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Establishment of CRISPR/Cas9-based murine models to study the impact of NF-kB pathway mutations on chronic lymphocytic leukemia growth, survival and resistance to treatment

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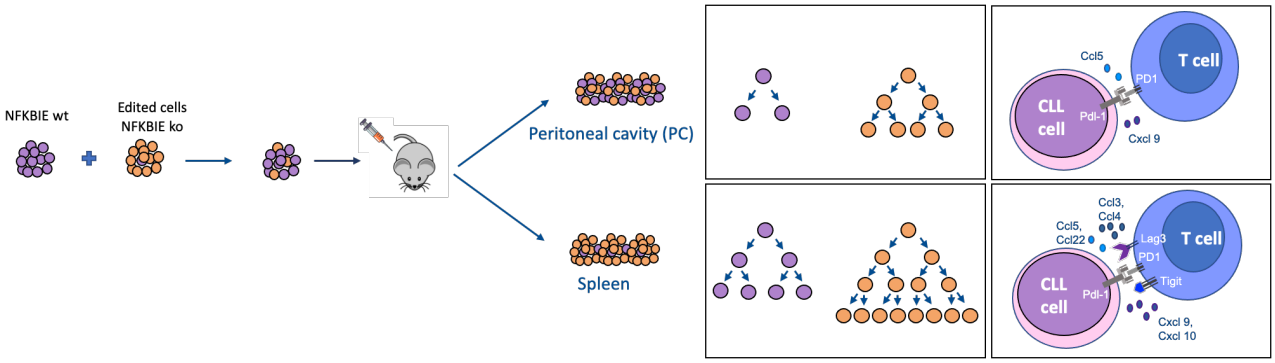
Graphical Abstract

Mechanisms that select NFKBIE-mutated murine CLL cells in different anatomical compartments.



Abstract

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in western countries. The disease is caused by the malignant transformation of a subset of autoreactive B lymphocytes with a particular immunophenotype. Strong evidence exists that the disease is driven by the combined effects of signals generated by B cell receptor (BCR) and other microenvironmental stimuli that interact with various recurrent genetic lesions.

Inactivating mutations in NF-kB pathway genes, such as the NF-kB inhibitor NFKBIE, are among the more frequent genetic lesions in CLL. However, the role of these genetic lesions in CLL pathogenesis and treatment resistance is still largely unknown. To this end we generated transplantable murine leukemias with inactivating NFKBIE mutations and we investigated their impact on leukemia growth and response to treatment. The NFKBIE mutations were introduced by CRISPR/Cas9 editing in two leukemia lines derived from the Eμ-TCL1 murine CLL model. These cell lines were recently established by our group (Chakraborty et al, Blood 2021) and are characterized by spontaneous *in vitro* proliferation that is BCR-dependent but independent of other microenvironmental signals. Here, we performed *in vitro* competition experiments with mixed cells with wild-type and mutated NFKBIE. Interestingly, we observed no change in the mutant allele frequency (MAF) in culture, suggesting that NFKBIE mutations do not affect the spontaneous *in vitro* growth of these leukemia cells. However, repeated stimulation with CpG-DNA, TNFα, anti-IgM or autoantigen resulted in a significant increase in MAF, suggesting that NFKBIE mutations provide a growth advantage to certain microenvironmental signals. Remarkably, using *in vivo* competition experiments performed in wild-type mouse recipients, we demonstrated that NFKBIE-mutated cells are preferentially selected in the spleen, implying different interactions of the malignant cells with the tumor microenvironment in different anatomical compartments.

As mentioned, the mechanism(s) underlying treatment resistance in CLL are still partially understood. In particular, the BCR inhibitor ibrutinib (IBR), which has emerged as the most effective therapeutic option in CLL, induces clinical responses in the majority of patients, but a substantial proportion subsequently shows disease progression. Because mutations in other NF-kB pathway genes have been associated with resistance to IBR in mantle cell lymphoma, we investigated whether NFKBIE mutations can also affect the response to IBR treatment. Interestingly, we noted that *in vitro* IBR inhibits proliferation of NFKBIE-mutated cells significantly less compared to wild-type NFKBIE cells while, *in vivo*, we observed positive selection of NFKBIE-mutated cells in mice treated with IBR

compared to controls. To validate these findings in the clinical setting, we investigated the impact of NFKBIE mutations in a cohort of 229 IBR- treated CLL patients, among which 13.5% had mutated NFKBIE. Kaplan-Meier analysis showed a trend towards reduced progression-free survival and significantly reduced overall survival for the NFKBIE-mutated cases, further suggesting that NFKBIE-mutations reduce the sensitivity to BTK inhibitor treatment.

Finally, we observed that NFKBIE-mutated cells remain sensitive to other BCR inhibitors, such as the PI3K inhibitor idelalisib and the SYK inhibitor fostamatinib. Collectively, these data demonstrate that NFKBIE mutations can reduce the response to IBR treatment and suggest that such cases may benefit more from treatment with a PI3K or SYK inhibitor.

1. INTRODUCTION

1.1. Chronic Lymphocytic Leukemia

1.1.1. Definition

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative malignancy that is characterized by clonal expansion of mature, CD5 positive, B lymphocytes in blood, bone marrow and lymphoid tissues. The diagnosis of CLL requires the presence of ≥ 5000 monoclonal B lymphocytes/μL in the peripheral blood for the duration of at least 3 months; the malignant cells express CD5, CD19, CD22 and CD23, and reduced levels of membrane immunoglobulin (Ig), CD20 and CD79B compared to those found on normal B-cells (*Chiorazzi et al., 2005*).

CLL is the most common type of adult leukemia in Western countries where it accounts for ~ 40% of all leukemia diagnosis (*Young et al., 2017*) while it is less common in Asia and relatively rare in Japan and Korea (*Kipps et al., 2017b*). There is also a marked difference between the incidence in men (6.8 cases per 100,000/year) and women (3.5 cases per 100,000/year) (*Howlader et al., 2016*).

The clinical course of the disease is heterogenous. In the majority of the cases, CLL shows an indolent clinical course and patients may not require therapy for many years or never require it. However, approximately one third of CLL patients display an aggressive disease course characterized by progressive lymphadenopathy, splenomegaly, anemia and thrombocytopenia, as well as frequent infections as a consequence of impairment of the immune system. Another serious complication which affects around 2-10% of CLL patients is Richter transformation or Richter syndrome (RS), which represents the transformation of CLL in a more aggressive lymphoma, most commonly diffuse-large B-cell lymphoma (DLBCL). RS is associated with very rapid disease progression, limited therapeutic options and generally poor survival (*Ghamlouch et al., 2017*).

1.2. Pathogenesis

CLL presents a tingled pathogenetic process in which different actors play an important role. Genetic alterations, B cell receptor signaling, microenvironmental interactions and immune deficiency have a complex interplay in driving the disease. Moreover, CLL has a strong heritability as highlighted in family studies which show that first-degree relatives of patients with CLL have a 2 to 8-fold increased risk of developing the disease (*Berndt et al., 2016*). Genome wide association studies (GWAS) have identified alleles at 43 susceptibility loci, mostly mapping to non-coding regions of the genome (*Speedy et al., 2014; Berndt et al., 2016; Law etal 2017*). Recently, meta-analysis of GWAS datasets revealed that 93% of the risk loci reside in active promoters or enhancers. This leads to altered expression of more than 30 genes involved in immune response, cell survival or WNT signaling, through increased binding affinity of different transcription factors, including FOX, NFAT and TCF/LEF family members (*Speedy et al., 2014*). However, despite these progresses, the factors that determine predisposition to CLL still remain largely unknown.

1.2.1. Cell of origin

The cell of origin is, by definition, the non-malignant cell from which the malignant transformation originates. Hence, it becomes important to identify the cell of origin of any type of malignancy to find out the alterations in the cell that trigger the malignant transformation. Thanks to the increased knowledge of B cell biology and differentiation, several cell types have been proposed as putative cells of origin of CLL (*Bosch & Dalla-Favera, 2019*).

The immunoglobulin (IG) gene structure analyses discovered that CLL patients can be distributed in two different subgroups based on the presence, or absence, of somatic mutations in the immunoglobulin heavy chain variable region (IGHV) genes, which encode part of the B cell receptor (BCR). The acquisition of somatic mutations depends on the transition of the B lymphocyte through the germinal centers (GC) of secondary lymphoid organs, which is the anatomical site in the lymph nodes where B cells experience somatic hypermutation and become selected based on increased antigen affinity (*Klein et al., 2001*). According to this, the two subgroups have been defined as unmutated CLL (U- CLL), with 98% or more sequence homology with the corresponding consensus germline immunoglobulin heavy chain variable

(IGHV) gene sequence, and mutated CLL (M-CLL), with less than 98% IGHV gene sequence homology (*Fais et al., 1998*). Clinically, patients with U-CLL typically exhibit aggressive disease, while patients with M-CLL present slower disease progression and longer survival (*Damle et al., 1999; Hamblin et al., 1999*).

Comparative gene expression profiling of CLL specimens and normal human B cells has revealed that both CLL subtypes originate from an antigen experienced CD27+ B cell. Specifically, the M-CLL subset derives from a CD27+ CD5+ post-germinal center (GC) B cell, whereas the UM-IGVH subset originates from a CD27- CD5+ pre-germinal center (GC) B cell, which might arise from pre-GC naïve B cells or from a separate lineage of precursor B cells, probably in a GC-independent and T cell-independent process (*Klein et al., 2001; Seifert et al., 2012*). However, despite the importance of IGHV gene mutations in CLL, the distinction of mutated and unmutated CLL does not fully reflect the heterogeneity of the disease (*Stamatopoulos et al., 2017*).

As the available IG gene sequence data increased, it became clear that patients with M-CLL and those with U-CLL have a highly restricted repertoire of IG genes, suggesting a role for antigen selection in the pathogenesis of the disease. However, it has been shown that in approximately one-third of CLL cases, particularly those with U-CLL, the leukemic cells express quasi-identical BCRs characterized by the presence of highly similar and sometimes identical variable heavy complementarity determining region 3 (VH-CDR3) sequences that are often associated with identical IGHV and immunoglobulin light chain variable (IGLV) gene combinations (*Stamatopoulos et al., 2017*). U-CLL cells tend to express low-affinity, polyreactive and self-reactive BCRs while BCRs expressed by M-CLL cells have a much more restricted antigen-specificity (*Agathangelidis et al., 2012*).

It has been suggested that early genetic and epigenetic events, which lead to the development of CLL, occur in hematopoietic stem cells (HSCs). In support of this theory, it has been observed that in some patents that have undergone allogeneic HSC transplantation (HSCT), pre-malignant lymphoid cells were transmitted from the donor to the recipient and eventually lead to CLL development (*Husby et al., 2017*). To reinforce this finding, it has been noted that HSCs purified from bone marrow of CLL patients and transplanted in immunodeficient mice were able to engraft and generate accumulations of oligoclonal mature CD5+ B cells with IG gene rearrangements that were different from those of the CLL clones of the HSC donors (*Kikushige et al., 2011*). Finally, genome sequencing studies have reported the presence of specific genetic lesions involved in lymphoid tumors (e.g., NOTCH1, SF3B1, MYD88 genes) in purified HSC derived

from CLL patients (*Damm et al., 2014*). However, the hypothesis that the initial genetic lesions favoring CLL development occur in HSCs remain controversial, also because of the difficulty in purifying CLL-free HSC cells from the bone marrow (*Damm et al., 2014*). Overall, the cell of origin of CLL is a subject of continued debate, both in terms of the cell type, in which the first genetic lesion occurs (HSCs versus mature B cells), and of the mature B cell type (pre-GC, post-GC or GC-independent) from which the clonal expansion of overt CLL can originate.

1.2.2. Cytogenetic and copy number alterations

With fluorescent *in situ* hybridization (FISH), it has been possible to detect different genomic aberrations in CLL. More than 80% of patients carry at least one of the four most relevant chromosomal alterations which are trisomy 12, 13q deletion [del(13q)], 11q deletion [del(11q)] and 17p deletion [del(17p)] (*Haferlach et al., 2007*). However, 20-35% of the CLL cases have other aberrations that could not be detected by FISH. Using chromosome banding analysis, it has been possible to find out these other aberrations, including chromosome translocations that could not be detected by FISH (*Haferlach et al., 2007*).

The most common cytogenetic aberration is the del(13q14) reported in > 50% of patients, generally monoallelic (~ 80%) and usually found in all cells of the malignant clone, suggesting its role in the early stages of CLL development (*Klein et al., 2010; Landau et al., 2015a*). The size of 13q14 deletion is variable across patients but with a minimal deleted region that contains two long non-coding RNA genes (DLEU2 and DLEU1) and the miRNA gene cluster miR-15a/16-1, which physiologically regulates the expression of certain apoptosis inhibitors and cell cycle regulators (*Kalachikov et al., 1997; Migliazza et al., 2001; Calin et al., 2002; Hammarsund et al., 2004*). *In vitro* studies have highlighted that the main mechanisms by which miR15A and miR16-1 exert their pathogenetic roles in B cells is through deregulation of the cell cycle and apoptosis, specifically by modulating the expression of the anti-apoptotic gene BCL2 and of genes involved in the G0/G1-S transition, inducing CCND2, CCND3, CDK4 and CDK6) (*Cimmino et al., 2005; Klein et al., 2010*).

As mentioned above, trisomy 12 is another recurrent cytogenetic abnormality present in CLL, which has been found in ~ 15% of patients with CLL at diagnosis and frequently associated with an atypical lymphocyte morphology (*Kipps et al., 2017*). It is considered as a driver mutation occurring in early stage of the disease even if its functional mechanism contributing to CLL

pathogenesis is still unknown (*Ghamlouch et al., 2017*). From a clinical point of view, it is important also to highlight that even if trisomy 12 has been classified as intermediate-risk genetic lesion, in co-occurrence with NOTCH1 mutation has been associated with poor outcomes and greater risk for the transformation into an aggressive form of lymphoma, the Richter syndrome (*Balatti et al., 2012; DelGiudice et al., 2012; Chigrinova et al., 2013*).

As regards the del(11q), it is usually found at the time of diagnosis in ~ 6-20% of CLL cases. Del(11q) typically results in deletion of the tumor-suppressor gene ATM (*Kipps et al., 2017*) however, in some patients could affect also the BIRC3 gene at 11q22.2 locus, which is a negative regulator of the non-canonical NF-κB pathway (*Rossi et al., 2013*).

Finally, 17p deletions typically involve the entire short arm of chromosome 17 and inevitably involve the TP53 gene, one of the most important tumor suppressor genes (*Döhner et al., 1995*). It is present at different frequencies in CLL depending on the clinical stage of the disease, ranging from 1% up to 20% in chemorefractory disease (*Stilgenbauer et al., 2014*). Del(17p13) is generally associated with inactivation of both alleles of the tumor suppressor gene TP53, even though the mono-allelic inactivation of TP53 is itself an adverse prognostic marker (*Zenz et al., 2010*).

All the cytogenetic aberrations discussed above have been associated with different prognosis and classified in five distinct categories which have been identified through the use of FISH: 13q deletion, trisomy 12, 11q deletion, 17p deletion and "normal" FISH (*Döhner et al., 2000*). Generally, patients with 13q14 deletions only are associated with a favorable prognosis but they are still divided into two different groups: type I deletion, which encompasses the DLEU2/miR-15a/16-1 cluster but not the retinoblastoma (RB1) gene, and the type II deletion that includes RB1 and is associated with a more aggressive disease (*Ouillette et al., 2011*). The trisomy 12 instead, correlates with intermediate outcome (*Ghamlouch et al., 2017*) while CLL patients carrying 11q or 17p deletions exhibit a poor outcome with a rapid progression and short survival (*Greipp et al., 2013; Stilgenbauer et al., 2014*). In terms of "normal" FISH, almost 20% of cases with no genetic aberrations detected have been reported to carry complex karyotypes which has been defined as composed of ≥ 3 abnormalities and has been associated with an unfavorable prognosis, short time to treatment and poor response to treatment (*Jain et al., 2015; Herling et al., 2016*). The complex karyotypes have been recognized as an independent predictor of poor outcome of Ibrutinib-based therapy (*Jain et al., 2015*). In addition, patients with both complex karyotypes and TP53 aberrations present a particularly short survival (*Herling et al., 2016*).

1.2.3. Somatic gene mutations

With whole-exome and whole-genome sequencing, it has been possible to identify the most common somatic genetic alterations associated with CLL pathogenesis, elucidating the underlying molecular mechanisms and activated pathways implicated in the development of CLL (*Bosch & Dalla Favera, 2019*). In general, CLL tumors accumulate around 2,500 somatic mutations with a clear difference between M-CLL and U-CLL (3,000 vs 2,000 somatic mutations on average, respectively) (*Delgado et al., 2020*). The mutational landscape of the disease is significantly heterogeneous, with only a few genes mutated in more than 5% of patients at diagnosis (NOTCH1, SF3B1, TP53 and ATM). The recurrent genetic alterations involve different cell pathways including cell cycle regulation and DNA damage repair (TP53, ATM, CCND2, CDKN1B, CDKN2A), ribosomal RNA processing, chromatin modifiers (CHD2, SETD2, KMT2D, ASKL1), B cell receptor (BCR) and Toll-like receptor (TLR) signaling (EGR2, BCOR, MYD88 TLR2, IKZF3), NOTCH1 signaling (NOTCH1, FBXW7), NF-κB pathway (BIRC3, NFKB2, NFKBIE, TRAF2, TRAF3), WNT pathway, B cell-associated transcription factors regulation (EGR2 or BRAF) and RNA splicing and metabolism (SF3B1, XPO1, U1, DDX3X, RPS15) (*Damm et al., 2014; Fabbri et al., 2011; Puente et al., 2011*) (Figure 1).

CLL is a dynamic disease in which the leukemic cells adapt themselves to the biological pressure imposed from outside. Indeed, different studies have demonstrated that large clonal shifts can occur in the neoplastic cell population following chemotherapy, indicating that such genetic changes provide a strong fitness advantage in the setting of therapy (*Landau et al., 2015*). Interestingly, mutations observed in CLL cells of patients treated with standard chemotherapy are distinct from those observed in CLL cells of patients treated with ibrutinib, suggesting that mutations associated with the resistance to novel therapeutic agents are different from those associated with standard chemotherapy (*Burger et al., 2016*).

Several driver mutations mentioned above have been characterized in their functional role. Specifically, deletions in the 11q22-23 chromosomal region are found in 20% of CLL patients at diagnosis and are associated with U-CLL subtype. This lesion, generally monoallelic, encloses the ataxia telangiectasia-mutated (ATM) tumor suppressor gene which encodes a protein that is crucial for the cellular response to DNA damage (*Shilloh et al., 2013*). It phosphorylates several key proteins that trigger activation of the DNA damage checkpoint, leading to cell cycle arrest, DNA repair or apoptosis. Several of its target proteins are tumor suppressors, including p53, CHK2, BRCA1, NBS1 and H2AX (*Shilloh et al., 2013*). In addition to deletions, the ATM gene can also be

inactivated through somatic mutations in CLL. Clonal ATM mutations confer different outcomes compared to subclonal mutations, with the former associated with a shorter overall survival (OS) after first line treatment (*Skowronska et al., 2012; Nadeu et al., 2016*).

As previously reported, chromosomal deletion 17p typically involves the entire short arm of chromosome 17 and invariably encompasses the locus of the tumor suppressor gene TP53 (*Zenz et al., 2010*). TP53 encodes for the tumor protein 53, which is described as "the guardian of the genome" because of its role in conserving genome stability and preventing mutations. Specifically, the tumor protein 53 is an ubiquitous transcription factor that is responsible for complex pivotal regulatory functions that promote DNA repair and prevent tumor formation through several mechanisms. It activates DNA repair proteins on DNA damage recognition and arrests cellular growth by holding the cell cycle at the G1/S regulation point. It can initiate apoptosis if DNA damage proves to be irreparable and, finally, it is essential for the senescence response to short telomeres. Overall, it is activated by DNA damage and cellular stress (e.g., hypoxia, oncogene overexpression) and, as a transcription factor, it regulates the expression of many genes that further direct cell fate, either to the cell cycle arrest, DNA repair and/or apoptosis (*Catherwood et al., 2019*). Other mechanisms that can inactivate TP53 are somatic mutations or overexpression of MDM2, a TP53-specific ubiquitin ligase that participates in the regulation of TP53 activity by mediating its degradation. Consistent with the increased genomic instability caused by the inactivation of TP53, TP53- inactivated CLL cells carrying TP53 mutations, del17p or MDM2 overexpression display a higher degree of genomic complexity compared to CLL cells lacking TP53 mutations, del17p or MDM2 dysregulation (*Yu et al., 2017*). Finally, TP53 inactivation is linked to DNA-damaging agent's resistance (chemotherapy or radiotherapy) and unfavorable overall survival (OS) (*Bosch & Dalla Favera, 2019*).

Another driver mutation involves the NOTCH1 transcription factor. NOTCH1 has emerged as the most mutated gene in CLL patients at diagnosis. The frequency of NOTCH1 mutations in CLL varies between 6 and 12% at initial diagnosis (*Rossi et al., 2012*). NOTCH1 encodes for a transmembrane receptor that, after ligand binding, undergoes conformational changes and proteolytic cleavage that enable the migration of its intracellular portion (ICN1) to the nucleus (*Kopan & Ilagan, 2009*). In CLL, NOTCH1 mutations remove the PEST domain of the NOTCH1 protein, preventing proteasomal degradation of ICN1 by the ubiquitin ligase F-box/WD repeat-containing protein 7 (FBXW7) (*Fabbri et al., 2011*). The consequence of deregulated ICN1 expression is the activation of NOTCH1 transcriptional program, which involves many genes that

regulate cell survival and proliferation (*Rosati et al., 2009*). Moreover, NOTCH1 mutations have been associated with decreased CD20 surface expression, which may partially explain why NOTCH1-mutated CLL patients show reduced benefit from anti-CD20-based therapies (*Pozzo et al., 2016*).

Sequencing studies have also revealed recurrent mutations affecting the splicing factor 3b subunit 1 (SF3B1), a key component of the spliceosome machinery, with a frequency of 10-15% in CLL at the time of the diagnosis and associated with more aggressive disease and reduced survival. SF3B1 encodes a crucial component of the U2 snRNP and acts in the initial phases of RNA splicing (*Shin et al., 2004*). These mutations are heterozygous missense events, mapping to the C-terminus of the protein. The consequence of SF3B1 mutations in CLL might be linked to genomic stability and epigenetic modification. (*Quesada et al., 2012; Wan et al., 2013*).

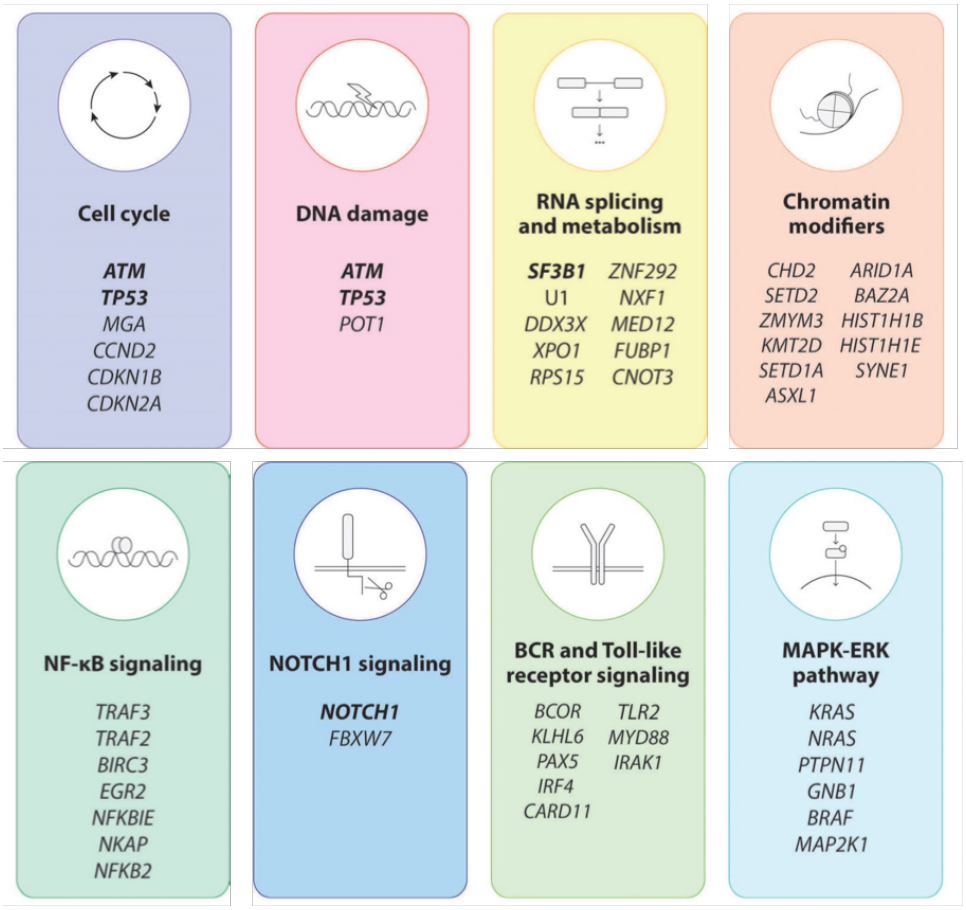


Figure 1. Genes and pathways that are frequently mutated in chronic lymphocytic leukemia. The figure here reported shows the principal molecular pathways that are disrupted by mutations in chronic lymphocytic leukemia. Genes with greater frequency mutations (>5%) in newly diagnosed patients are indicated in bold (Delgado et al., 2020).

1.2.4. Genetic lesions leading to NF-κB activation

One of the most recurrently mutated pathways in CLL is the Nuclear factor-κB (NF-κB) pathway. NF-κB signaling plays an essential role in regulating cardinal cellular processes including cell survival, proliferation and inflammation that are also closely linked to cancer progression (*Mansouri L et al., 2016*). For this reason, it is not surprising that deregulations in NF-κB signaling contribute to tumor development and evolution (*Hanahan & Weinberg, 2011*). In certain B-cell malignancies the NF-κB pathway is constitutively activated due to recurrent genetic events that directly affect the pathway or its upstream mediators (*Staudt, 2010*). In addition, aberrant stimulation derived from the microenvironment through different surface receptors, such as the B-cell receptor (BCR), Toll-like receptors (TRL) and CD40, contribute to lymphoma development through downstream activation of NF-κB (*Mansouri et al., 2016*).

In the context of CLL, NF-κB alterations undeniably play a role in to the pathophysiology of the disease. However, with the exception of NFKBIE and BIRC3, genetic lesions in most of the other affected NF-kB pathway genes, such as TRAF3, IKBKB, NFKB1, RELA and NFKBIB, are infrequent and are seen in less than 1% of the cases (*Puente et al., 2011; Mansouri et al., 2016; Knisbacher et al., 2022*).

1.2.5. The NF-κB signaling pathway

The NF-kB family consists of five members: NF-kB1 (p105/p50), NF-kB2 (p100/p52), RelA (p65), RelB and c-Rel which mediate transcription of target genes by binding to a specific DNA element (kB enhancer). NF-kB proteins form various homo- and hetero-dimers that are associated with distinct patterns of transcriptional activation or repression (*Oeckinghaus & Ghosh, 2009*). Generally, in unstimulated cells the inactive NF-kB heterodimers are sequestered in the cytoplasm by IkB proteins, which include different members IkBα, IkBβ, IkBδ and IkBε (*Liu et al., 2011*). These proteins contain 6-7 ankyrin repeats that bind to the Rel-homology domains (RHD) of the NF-kB transcription factors (*Gosh S et al*, 1998). Upon inducible IkB degradation, the heterodimeric NF-kB transcription factors are released and translocate to the nucleus where they promote the expression of different target genes.

The activation of NF-kB involves two distinct signalling pathways, the canonical pathway (or classical) and non-canonical pathway (or alternative). From a functional point of view, the

canonical pathway is implicated in immune responses while the non-canonical pathway appears to be involved in a supplementary signalling axis that cooperates with the former pathway in the regulation of specific functions of the adaptive immune system (*Sun & Liu, 2011*). The canonical pathway is activated by numerous microenvironmental signals, including proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), Toll-like receptor (TLR) ligands, or by antigen-receptor stimulation. Triggering of this pathway results in the activation of the IKK complex, which consists of the kinases IKKα, IKKβ and IKKγ (*Oeckinghaus et al., 2011*). The IKKβ kinase phosphorylates the IkB proteins, inducing their degradation and the release of the sequestered homo- or hetero-dimers of p65, c-Rel, p50 and p52, which can then translocate into the nucleus and induce gene transcription (*Gosh et al., 2002*).

The canonical NF-kB pathway is mainly activated in response to signals originating from cell surface receptors, such as B-cell receptor (BCR), T-cell receptor (TCR), as well as Toll-like receptor (TLR) superfamily and cytokine receptors, including the tumor necrosis factor receptor (TNFR) superfamily members and interleukin 1 receptor (IL-1R) families (*Oeckinghaus et al., 2011*). Moreover, it is known that different pathogens can trigger the NF-kB canonical pathway through specific TLRs. Specifically, Gram-negative bacteria activate TLR4 through the production of lipopolysaccharide (LPS), TLR2 recognizes Gram-positive microbial products, TLR5 is more specialized in identifying bacterial flagellins while TLR9 recognizes non-methylated bacterial DNA and TLR3 is activated by viruses double-strand RNA (ds) (*Hemmi et al., 2000; Alexopoulou et al., 2001; Medzhitov et al., 2001*). The engagement of all these TLRs result in NF-kB activation, with NF-kB dimers translocation, and subsequent induction of NF-kB target genes (*Medzhitov et al., 2001*) (Figure2). The translocation of NF-kB dimers, mostly p50-RelA, into the nucleus result in the transcription of genes encoding cytokines, chemokines and adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-19) and endothelial-leukocyte adhesion molecule 1 (ELAM), enzymes that produce secondary inflammatory mediators and inhibitors of apoptosis (*Gosh et al., 1998*). All these molecules are fundamental components of the innate immune response.

Differently, the activation of the non-canonical pathway requires the phosphorylation and polyubiquitination of NF-kB2/p100 homodimers at two C-terminal sites with subsequent degradation of the C-terminal half (*Senftleben et al., 2001*). This process is closely dependent on IKKα, and it leads to the release of the p52 polypeptide and consequent nuclear translocation which occurs most commonly in association with RelB (*Dejardin et al., 2002*). The non-canonical

NF-kB pathway responds to a specific group of stimuli including ligands of tumor necrosis factor (TNF) receptor superfamily, such as CD40 ligand, B cell-activating factor (BAFF), lympho-toxin β (LTβ), receptor activator nuclear factor-kB ligand (RANKL) and CD30L (*Oeckinghaus et al., 2011; Sun, 2011; Gasparini et al., 2014*).

Signal-induced non-canonical NF-kB pathway activation is also subject to negative regulation mediated by BIRC3 (Baculoviral IAP Repeat Containing 3), which is a member of the inhibitor of apoptosis protein (IAP) family that negatively regulates the non-canonical pathway by co-operating with TRAF3 and TRAF2 in the negative regulation of MAP3K14 (Figure 2).

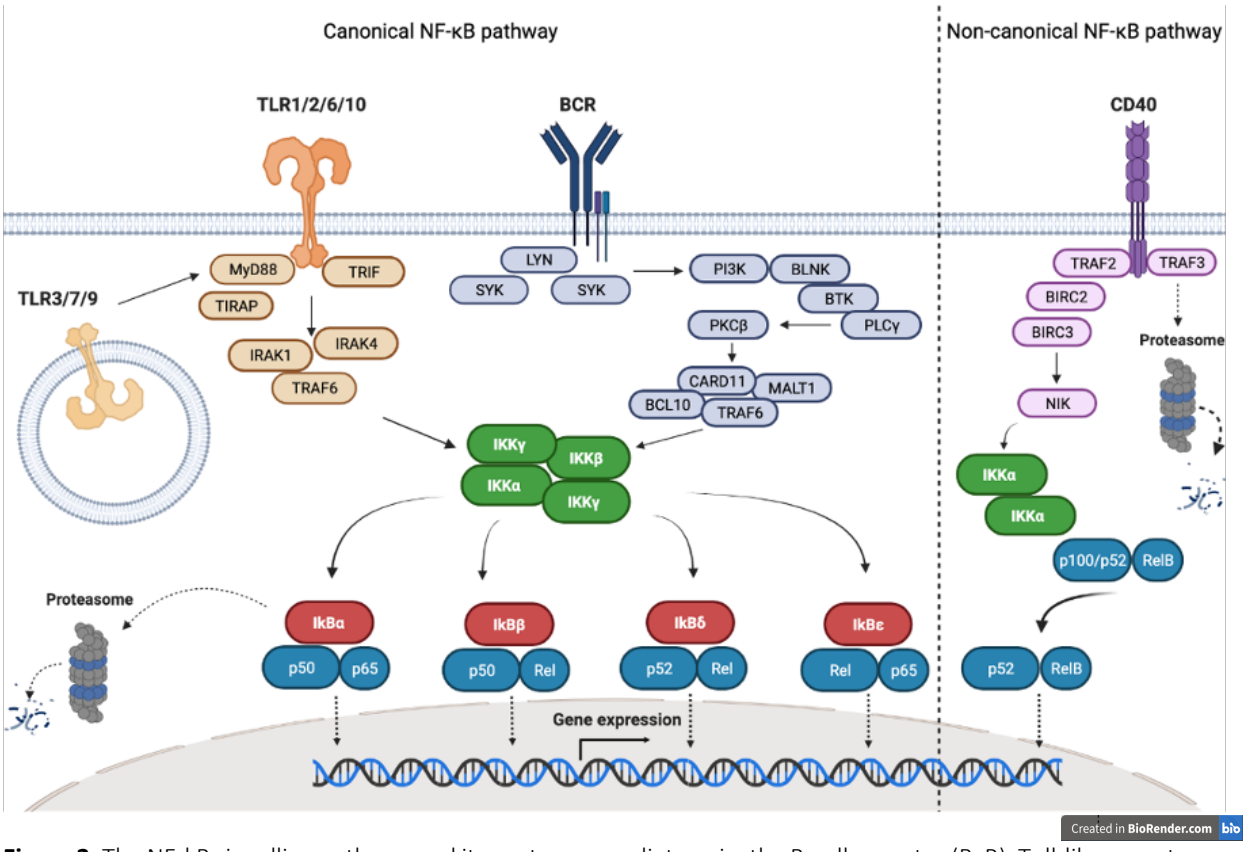


Figure 2. The NF-kB signalling pathway and its upstream mediators, i.e the B-cell receptor (BcR), Toll-like receptor (TRL)and CD40 signaling. Stars indicates recurrent gene mutations in CLL.

1.2.6. Genetic lesions resulting in increased NF-κB pathway activity in CLL

Several genetic lesions found in patients with CLL seem to converge on the activation of the NF-κB transcriptional complex (*Bosch & Dalla Favera, 2019*). As reported above, the BIRC3 gene encodes for a member of the IAP family that negatively regulates the non-canonical NF-κB pathway, by co-operating with TRAF3 and TRAF2 in the negative regulation of MAP3K14.

Inactivating mutations of BIRC3 have shown to be associated with constitutive activation of NF-κB signalling in CLL cells. The frequency of BIRC3 mutations at the time of diagnosis varies and tends to increase amongst chemo-refractory cases and advanced clinical stages (*Rossi et al., 2012; Ghamlouch et al., 2017*). Monoallelic BIRC3 nonsense mutations have been found in < 5% of CLL patients at diagnosis and result in the removal of the C-terminal RING finger domain of the BIRC3 protein, leading to constitutive activation of NF-κB pathway (*Rossi et al., 2011; Rossi et al., 2012*). Of note, the BIRC3 locus is located close to the ATM locus on 11q thus, in case of 11q deletion, BIRC3 abnormalities are strongly associated with ATM ones (*Ghamlouch et al., 2017*). In addition, studies conducted on other types of B cell malignancies suggested that BIRC3 mutations may be associated with refractoriness to the BTK inhibitor ibrutinib (*Rossi et al., 2012*). Other mutations that affect the NF-κB pathway involve the MYD88 gene. This gene encodes for a cytosolic protein adaptor for interleukin-1 receptor (IL-1R) and Toll-like receptors (TLRs) and both these pathways converge in NF-κB activation. MYD88 protein associates with the TLR/IL-1R intracellular TIR domain resulting in the assembly of the Myddosome, a multiprotein complex composed of MyD88, IRAK4, and IRAK2, which further activates the serine/threonine kinase IRAK1 through IRAK4-dependent phosphorylation. IRAK1 promotes recruitment of TRAF6, an E3 ubiquitin ligase that subsequently ubiquitinates and activates TAK1, which in turn mediates phosphorylation and activation of the IKK complex. Activated IKK complex mediates the phosphorylation of IκB by inducing its ubiquitination and degradation, driving nuclear NF-κB translocation that promotes cell survival and proliferation (*Loiarro et al., 2010; Ngo et al., 2011; Mansouri et al., 2016*). Mutations in MYD88 has been observed at low frequencies (3-5%) in CLL patients (*Landau et al., 2015; Puente et al., 2015*). The most common MYD88 mutation (p.L265P) is a missense mutation, which leads to increased binding of MYD88 to IRAK1, resulting in downstream activation of the NF-κB pathway (*Ngo et al., 2011; Puente et al., 2011*). However, except for aberrations in MYD88, mutations in other molecules involved in TLR pathway signal transduction, such as TLR2, TLR5, TLR6, IRAK1, IRAK2 and IRAK4, are rarely found in CLL (<1%) (*Puente et al., 2011; Quesada et al., 2011; Wanget al., 2011*).

Finally, the NF-κB inhibitor I-kappa-B-epsilon (NFKBIE) gene, which encodes a negative regulator of the canonical NF-κB signaling pathway IκBε, was recently found mutated in CLL. It has been observed that NFKBIE mutations are more frequent in CLL patients with advanced disease and with other poor-prognostic markers. The most common NFKBIE gene mutation is a 4-bp frameshift deletion which leads to the truncation of the ankyrin repeat domain and loss of IκBε

inhibitory function. In fact, CLL cases carrying mutated NFKBIE show decreased levels of IκBε expression with consequently reduced IκBε-p65 interaction and increased p65 phosphorylation and nuclear translocation. Mutations in NFKBIE have also been detected in other B cell malignancies such as diffuse large B-cell lymphoma (DLBCL) (4.5%), mantle cell lymphoma (5%) and splenic marginal lymphoma (2%) (*Mansouri et al., 2015*).

1.3. B-cell receptor signaling

The B cell receptor (BCR) is a transmembrane signaling complex present on the cell surface of normal lymphocytes which plays a key role in B cell development, differentiation and immune function. Intracellular events following BCR triggering are mediated through a signaling transduction cascade that involve a complex network of membrane-proximal kinases and phosphatases, adaptor proteins and transcription factors, that belong to various downstream signaling pathways including the MAPK/ERK, PI3K/AKT/mTOR, and NF-kB pathways. All these signaling pathways lead to the expression of genes involved in cellular responses such as metabolism regulation, proliferation, differentiation, cytoskeleton remodeling, adhesion, chemotaxis, migration, survival, anergy, or apoptosis (*Deglesne et al., 2006; Guarini et al., 2008; Burger & Chiorazzi, 2013; Efremov et al., 2020*). Consistently, dysregulated BCR signaling results in enhanced B cell survival and aberrant activation of B cell-mediated immune responses, leading to primary immunodeficiencies, autoimmune diseases and even B cell malignancies (*Dühren-von Minden et al., 2012; Young et al., 2015*).

1.3.1. BCR signaling in normal B lymphocytes

The BCR complex consists of a membrane-anchored ligand-binding surface immunoglobulin, either IgA, IgD, IgE, IgG or IgM, composed of two identical heavy chains and two light chains that are interconnected by disulfide bonds, coupled with the heterodimerized signal transduction subunits CD79A (or Igα) and CD79B (or Igβ), which are the first components involved in the signal transduction process. Of note, less than a few per cent of CLL cases express class-switched isotypes, most commonly IgG.

The B-cell receptor can be activated by antigen-dependent and antigen-independent mechanisms (*Herishanu et al., 2013; Yasuda et al., 2017*). When an antigen binds to the BCR it

induces a conformation change in the BCR signaling complex and re-organization of the actin cytoskeleton. This results in local convergence of adjacent BCR units with consequent assembly into micro-clusters (*Mattila et al., 2016*). These two early events recruit members of the SRC-family of tyrosine kinases (SFKs), such as LYN, that phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs) of CD79A and CD79B components. The phosphorylated ITAMs become a binding site for the spleen tyrosine kinase (SYK), which is promptly activated through a multistep phosphorylation process driven by SRC family kinases (*Mócsai et al., 2010*). Once activated, SYK propagates the BCR signal by phosphorylating the adaptor proteins BLNK, BCAP, and SHC, which constitute the molecular scaffold for the BCR signalosome, a multi-protein signaling complex (*Satpathy et al., 2015*). At this point, the BCR signal is further propagated by the phosphoinositide 3-kinase delta isoform (PI3Kδ), which can be recruited to the signalosome in two different manners. In fact, PI3Kδ can be directly recruited by BCAP or can be recruited by CD19, a BCR co-receptor which becomes activated when the tyrosine-protein kinase LYN phosphorylates its cytoplasmatic domain (*Aiba et al., 2008*). Subsequently, activated PI3Kδ phosphorylates the membrane phospholipid phosphatidylinositol-4,5-biphosphate (PIP2) and generates the second messenger molecule phosphatidylinositol-3,4,5-triphosphate (PIP3), that further recruits several important downstream signaling molecules, including the Bruton's tyrosine kinase (BTK) (Figure 3). BTK is activated by the signalosome through phosphorylation mediated by SRC family kinases so it can activate, in turn, the phospholipase Cγ2 (PLCγ2), which hydrolyses PIP2 to generate inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 generation results in calcium flux toward the cytosol and subsequent activation of the phosphatase calcineurin, which finally dephosphorylates and activates the transcription factor NFAT (*Antony et al., 2004*). In addition, calcium together with DAG activate protein kinase C (PKC), which phosphorylates the adaptor protein CARD11 and induces the formation of a multi-protein CARD11-BCL10-MALT1 (CBM) signaling complex which activates the transcription factor of NF-κB and the mitogen-activated protein (MAP) kinase JNK (*Blonska & Lin, 2009*). Among the key downstream signaling molecules recruited by the signalosome by PIP3 there is the serine/threonine kinase AKT, which targets numerous substrates involved in cell growth regulation and survival, such as FoxO transcription factors and the glycogen synthase kinase 3 (GSK3) (*Manning & Cantley, 2007*). Lastly, other signaling molecules that are recruited and activated downstream of the BCR are the mitogen-activated protein kinases ERK and p38, which promote B cell proliferation and survival (*Johnson & Lapadat, 2002*).

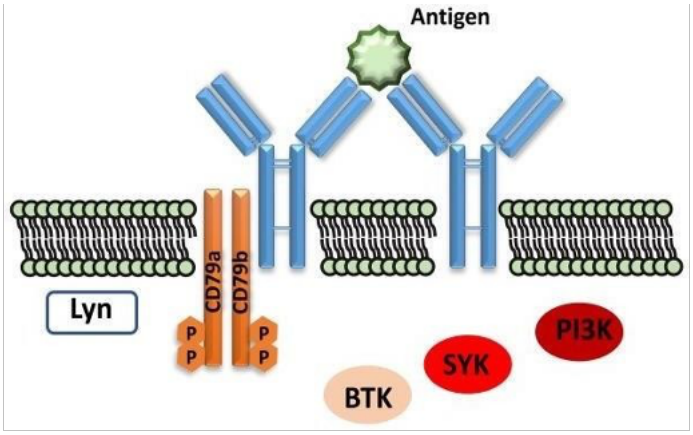


Figure 3. BCR complex and kinases involved in signal transduction: BCR receptor is composed of an extracellular portion, which binds the antigen and a signal transduction portion (CD79A and CD79B) that propagate the signal with a pro-survival and proliferative response.

Studies regarding BCR have highlighted the presence of both, negative and positive feedback mechanisms, that regulate the BCR signaling (*Shinohara et al., 2014*). On one side, the negative feedback system functions to prevent excessive intra-cellular signals while, on the other side, the positive feedback mechanism functions as on/off signal transduction switch characterized by an intrinsic activation threshold. This means that only a certain dose of antigen stimulation may induce a robust response in B cells. The presence of a threshold in antigen-triggered BCR signaling prevents B cell activation by low doses of self-antigen stimulation, which is a mechanism involved in maintaining peripheral B cell tolerance (*Yasuda et al., 2017*). The BCR signal is negatively modulated by various inhibitory B cell co-receptors including CD22, CD5, CD72, FCγRIIB, and SIGLEC10, but also different intra-cytoplasmatic phosphatases such as SHP1, PTPN22, SHIP1, and PTEN (Rhee & Veillette, 2012). SHP1 and PTPN22 terminate the BCR signal by dephosphorylating certain BCR-proximal signaling components, including CD79A, CD79B, SRC-family kinases (SFKs), SYK and BLNK. The complexity of the BCR signaling network is further increased by the existence of parallel activation pathways and by crosstalk between the various downstream signaling molecules (*Burger& Wiestner, 2018*).

Besides antigen-dependent BCR signaling, it has also been reported that the BCR constitutively sustains a tonic antigen-independent BCR signaling, which is transmitted through CD79A and CD79B heterodimers and activates the downstream PI3K, maintaining B cell survival (*Kraus et al., 2004*). This type of BCR signaling is supposed to be fundamental for normal B lymphocyte survival, as evidenced by the finding that *in vivo* ablation of BCR expression in mice causes rapid death of B cells (*Lam et al., 1997*).

1.3.2. BCR signalling in CLL lymphocytes

In CLL, the BCR pathway is constitutively active, and two mechanisms have been hypothesised as the causes of this constitutive activation. The first one is the antigen- dependent BCR signalling, which is the classical mechanism of BCR activation, and it is triggered by binding to an external antigen. The U-CLL cells typically express BCRs which bind with low affinity to autoantigens that are generated during apoptosis or oxidation including dsDNA and ssDNA, non-muscle myosin heavy chain IIA (MYHIIA), vimentin, filamin B, Sm, cofilin-1, oxidized lipoproteins and molecular motifs exposed on apoptotic cells (*Catera et al., 2008*). The interaction of these antigens with the leukemic BCRs results in an intermittent BCR signal, similar to that induced by crosslinking the BCR with anti-IgM. Specifically, the expression of anti-apoptotic and cell cycle regulatory proteins such Mcl-1, CCND2 and CDK4 has been demonstrated to be induced by anti-IgM, which may contribute to the progression of the illness by boosting CLL cell survival and proliferation (*Deglesne PA et al. 2006; Guarini A et al. 2008*).

The second mechanism, known as cell-autonomous BCR signalling, was discovered as an unique feature of CLL BCRs and implicates intermolecular interactions between the CDR3 of one BCR and internal immunoglobulin motifs located in nearby BCRs expressed on the same cell which result in a continuous low intensity BCR signal (*Dühren-von Minden M et al. 2012*). The kinases LYN, SYK, PI3K, BTK, and PKC, which are situated immediately downstream of the BCR, appear to have increased basal activity as a result of this signal (*Gobessi S et al. 2009; Efremov DG et al. 2014*) (Figure 4).

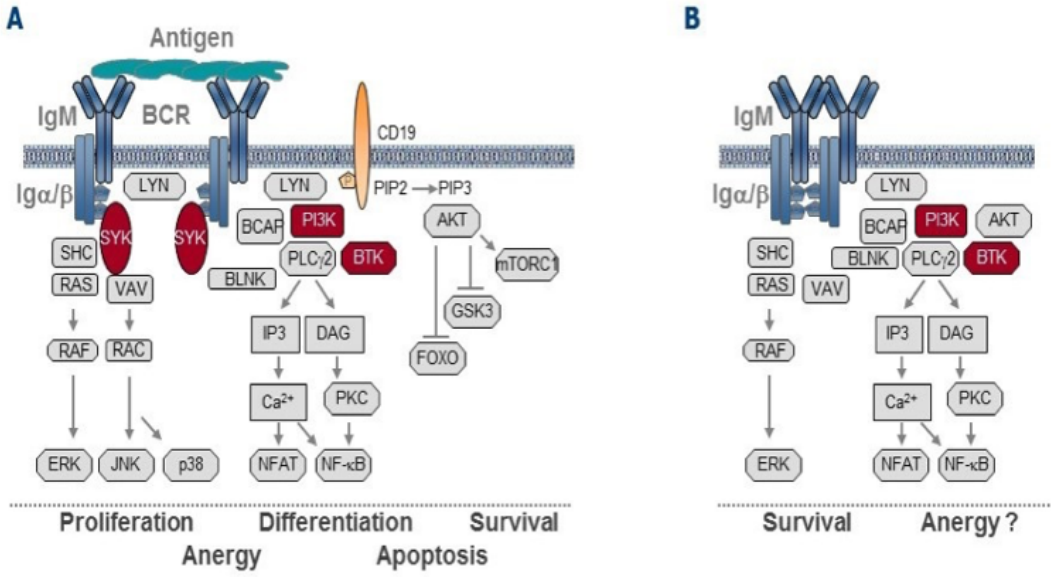


Figure 4. Two types of BCR signals generated in CLL B cells. A) Antigen- dependent BCR signal generated by crosslinking of neighbouring BCRs by an external self- or foreign antigen or an antigen surrogate such as anti-IgM antibodies. **B)** Cell-autonomous BCR signal generated by an intra-molecular interaction between the HCDR3 and FR2 region of the same smIg (*Efremov DG et al. 2014*).

The evidence that CLL pathogenesis is strongly influenced by the signals generated by these two different mechanisms have been provided in the study conducted by Iacovelli et al., using the well-established Eμ-TCL1 transgenic mouse model of CLL, in which they investigated the capacity of different antigen-BCR and BCR-BCR interactions to induce leukemia (*Iacovelli et al., 2015*). The Eμ-TCL1 transgenic mouse model is characterized by the overexpression of the TCL1 oncogene in the B cell compartment that predisposes adult mice to develop CD5+/IgM+ CLL like leukemia. The oncogenic progression is promoted by TCL1 through factors involved in regulation of cell-cycle, proliferation, and survival (*Laine J et al. 2000; Stachelscheid et al. 2022*). These mice were crossed with mice expressing different transgenic BCRs, including BCRs with cell-autonomous activity and BCRs specific for various foreign or self-antigens. B cells expressing transgenic BCRs that were activated by low-affinity extrinsic autoantigens and/or cell-autonomous interactions entered the leukemogenic process and became CLL cells, although, regardless of antigen form, leukemias did not develop in B cells expressing high-affinity BCRs. These findings indicate that both antigen-dependent and cell-autonomous BCR interactions cooperate in CLL pathogenesis.

The different clinical behavior of patients carrying somatic mutations in the clonal IGHV genes (M-CLL) compared to patients with no mutations in the IGHV sequence (U-CLL) provides additional evidence for the BCR's key role in CLL pathogenesis and progression. As already reported, patients

with U-CLL present a more aggressive disease and a shorter survival compared with patients with M-CLL which exhibit a more indolent disease and a longer survival (*Damle R et al. 1999; Hamblin et al. 1999*). These clinical differences are thought to be the result of U-CLL greater responsiveness to BCR stimulation or the different antigen specificity between U-CLL and M-CLL. Specifically, U-CLL cells express poly-reactive low-affinity BCRs capable of recognising and binding multiple autoantigens, resulting in chronic BCR pathway activation (*Burger at al. 2013*). In M-CLL, since these BCRs do not typically exhibit poly- or auto-reactivity, the mechanism of BCR activation in M-CLL is less clear (*Herve M et al. 2005*). The BCR pathway may be activated primarily by cell-autonomous BCR interactions in this subset, leading to the generation of continuous low-amplitude signals that increase CLL cell survival but have no effect on CLL proliferation (*Chiorazzi N and Efremov D. 2013*). Gene expression profiling studies found that freshly isolated CLL B cells express high levels of genes induced by BCR engagement, providing evidence for in vivo BCR pathway activation. BCR target genes were particularly enriched in CLL cells isolated from lymph nodes, indicating that CLL cells are constantly exposed to antigen in vivo. Furthermore, higher levels of BCR target genes were found in U-CLL cells compared to M-CLL cells, implying that U-CLL cells are more frequently exposed to antigenic stimuli *(Herishanu Y et al. 2011*). Moreover, approximately 30% of CLL cases express "quasi-identical" BCRs, known as "stereotyped" BCRs, indicating that BCRs with specific antigen-binding capacities are selected. This adds to the evidence that BCR-dependent mechanisms select and drive the propagation of malignant clones in a significant proportion of CLL cases (*Agathangelidis A et al. 2012*). However, the clinical activity of BCR inhibitors provides the most compelling evidence for the BCR pathway's importance in CLL.

Contrary to normal B-cells, *in vitro* BCR activation is insufficient to stimulate CLL cell proliferation, despite the BCR pathway being critical in the pathogenesis and development of CLL, implying that additional signals from the microenvironment are required for the proliferation of CLL cells and influence the course of the disease.

1.4. Tumor microenvironment

Based on findings from *in vitro* studies and in *vivo* models, CLL is a prime example of a B cell malignancy crucially dependent for survival and proliferation on signals derived from the microenvironment. CLL cells receive such signals when they enter in secondary lymphoid organs (SLOs). These signals include interactions between malignant B cells within the so-called tumor microenvironment composed of various cell-types such as T-cells, monocyte-derived nurse-like cells, mesenchymal stromal cells, extracellular matrix components and soluble factors that can promote the growth of the malignant cells. CLL cells repeatedly cycle between peripheral blood (PB) and SLOs by following chemokine gradients, where they form "proliferation centers" in which they are activated through survival signals from surrounding cells (*Herishanu et al., 2011; Kipps et al., 2017*). Importantly, the evidence that CLL proliferation only takes place in SLOs proliferation center indicates the lack of additional growth and survival signals outside of these micro-anatomical compartments (*Chiorazzi & Ferrarini, 2006*). When CLL cells isolated from peripheral blood (PB) of patients are cultured *in vitro*, they typically experience spontaneous apoptosis, but this can be avoided by soluble molecules or by co-culturing with other cell types that are present in the tumour microenvironment indicating that, *in vivo*, there are signals that support the survival and growth of CLL cells. Contrarily, *in vitro* BCR engagement on CLL cells only leads to low-level activation without induction of proliferation, despite of the strong evidence for a crucial role of BCR signaling in driving CLL proliferation and disease progression *in vivo*. This indicate that BCR-induced CLL proliferation *in vivo* likely requires additional costimulatory signals that are missing *in vitro*. Consistently, to induce proliferation upon *in vitro* stimulation it is necessary to co-stimulate the other receptors that are known to mediate interactions between CLL cells and the accessory cells, such as CD40 or BAFF-R, in combination with TLRs or cytokine receptors, by stimulating CLL cells with various cytokines and chemokines, like interleukin-4 (IL-4), interleukin-15 (IL-15), interleukein-21 (IL-21) and CXCL12, or molecules expressed on cells in the microenvironment, such as CD40L, Jagged, BAFF, VCAM1 (*Pascutti et al., 2013*) (Figure 5).

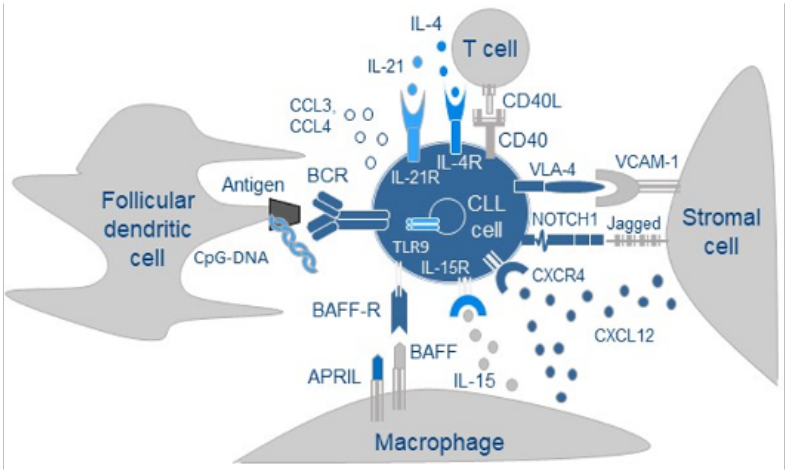


Figure 5. Crosstalk between malignant B cells and microenvironmental cells: Mesenchymal stromal cells express above all CXCL12, whereas NLCs express CXCL12 and CXCL13 and both cells attract CLL cells CXCR4 and CXCR5, expressed on CLL cell surface. The integrin VLA-4 (CD49d) is involved in establish cell-cell adhesion with the stromal cells. CLL cells can recruit CD40+ T cells, present in proliferating centers, through interaction with CD40 on CLL cell surface. These interactions promote CLL survival and induce proliferation.

1.4.1. Role of tumor microenvironment in CLL proliferation

As already mentioned, within the proliferation centers CLL cells are in intimate contact with non-malignant accessory cells including CD40L-presenting CD4+ T cells, monocyte-derived nurse-like cells, mesenchymal stromal cells (MSCs) and extracellular matrix (ECM) factors (*Burger et al., 2000; Patten et al., 2008; Burger et al., 2009*).

T-cells play an important role in the CLL lymph node microenvironment, and T cells/T-cell factors provide signals that promote CLL cell survival and proliferation. CLL cells drive T cells towards the proliferating centers by releasing the chemokines C-C motif ligand 3 (CCL3), C-C motif ligand 4 (CCL4) and C-C motif ligand 22 (CCL2) and are in close contact with activated CD4+ T cells (*Ghia et al., 2002; Burger et al., 2009*). CLL cells and activated CD4+ T cells interact via CD40-CD40L axis engagement and it has been shown that *in vitro* stimulation through the T-cell factor CD40L reduces the spontaneous apoptosis of the CLL leukemia cells (*Scielzo et al. 2011*). In addition to CD40L, IL-4 and IL-21 are other two cytokines secreted by T cells that are involved in CLL proliferation and survival. Gene Set Enrichment Analysis (GSEA) revealed that IL-4 target genes are more abundant in lymph node-derived CLL cells than in peripheral blood CLL cells, indicating that IL-4 stimulates CLL cells in lymphoid tissues (*Dancescu et al. 1992; Aguilar-Hernandez et al. 2016*). Moreover, it has been observed that *in vitro* IL-4 supports CLL cell survival without inducing cell division. On the other hand, IL-21 is produced mainly by follicular T helper cells and

significantly enhances the effects of CD40L/IL4 stimulation promoting CLL cell proliferation (*Pascutti et al. 2013*). Consistent with the role of cytokines in enhancing CD40-mediated proliferation, CD40 stimulation in combination with IL-21 or IL-4 is sufficient to induce CLL proliferation *in vitro* (*Pascutti et al., 2013*). In addition, it has been reported that the growth of primary CLL cells in immune-deficient mice also requires the presence of activated autologous T cells. providing additional evidence of the relevance of T cell signals *in vivo* (*Bagnara et al., 2011*).

Nurse like cells (NLCs) derive from monocytes and they are another important component of the microenvironment as they protect CLL cells from spontaneous and drug-induced apoptosis. NLCs interact with CLL cells by secreting chemokines CXCL12 (SDF-1α) and CXCL13 which attract CLL cells expressing the corresponding receptors CXCR4 and CXCR5 into the protective tissue niches (*Burger et al., 2000; Binder et al., 2010*). The binding of CXCL12 to CXCR4 activates the MAP kinase/AKT pathway, which is critical for CLL cell survival and regulation of leukemia cell adhesion. In the Eμ-TCL1 mouse model, the hyper activation of CXCR4 signalling has been linked to accelerated leukaemia development and CLL transformation into aggressive lymphoma (*Lewis et al. Leukemia 2021*). Furthermore, NLCs support the survival and the proliferation of the leukemic cells through the release of the B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), both belonging to the TNF superfamily members (*Burger et al., 2000; Nishio et al., 2005; Endo et al., 2007; Audrito et al., 2015*).

Another important component of the tumor microenvironment are the mesenchymal stromal cells (MSCs). MSCs provides structural and functional support to CLL cells through the production of chemokines, cytokines, pro-angiogenic factors, and direct cell-cell contact (*Panayiotidis et al., 1996*).

1.4.2. TLR signaling

Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs) that activate the innate immune response by sensing pathogen associated molecular patterns (PAMPs), which are conserved structural components of viruses, bacteria and fungi, or damage associated molecular patterns (DAMPs), which are structural components of damaged or apoptotic cells. TLRs are present on various immune cells, including B lymphocytes, and primarily take part in the innate immune response (*Muzio et al., 2012*). The majority of TLRs are type I transmembrane proteins that contain three structural domains: a leucine-rich repeats (LRRs) motif, a transmembrane

domain, and a cytoplasmic Toll/IL-1 receptor (TIR) domain. The LRR domain is responsible for recognition of PAMPs or DAMPs, whereas the TIR domain is responsible for signal propagation. The TLR family consists of ten members (TLR1-TLR10) that are variably expressed in different cell types. TLR1, TLR2, TLR6 and TLR10 are expressed on the cell surface, while TLR7, TLR8, and TLR9 are expressed intracellularly.

Stimulation of CLL cells in vitro with CpG oligonucleotides, which represent a surrogate ligand for TLR9, leads to the activation of several downstream signalling pathway, including MAPK/ERK, PI3K/AKT and NF-kB, and induction of CLL cell proliferation (*Jahrsdörfer et al., 2001, Longo et al, Leukemia 2007).* However, the extent to which TLR signals contribute to CLL cell proliferation in vivo is still uncertain. Gene expression profiling studies have shown enrichment of TLR9-target genes in lymph node CLL cells, suggesting that the leukemic cells may be exposed to TLR signals in the proliferating lymph node compartment. However, in a recent study we showed that genetic inactivation of the TLR-pathway by CRISPR/Cas9 editing in murine TCL1-derived CLL cells or human Richter syndrome patient-derived xenograft cells does not affect the growth of the transplanted cells in murine models, arguing against a major role for TLR-derived signals in driving the proliferation of the malignant cells *in vivo* (*Martines et al., 2022*).

1.5. Prognosis

Due to CLL clinical course variability, it is imperative to have robust clinical and molecular hallmarks to stratify patients into subsets with distinctive clinical outcomes and to identify patients who are likely to progress that require early treatment soon after diagnosis. This requirement is even more warranted in CLL given its heterogeneity in life expectancy, ranging from a few years to more than 15 years in some cases. For this reason, patients with an established diagnosis of CLL should undergo risk stratification. The requirement for intuitive and easy-to-use in clinical practice prognostic systems have encouraged the development of multivariable prognostic scores and nomograms combining clinical, genetic and molecular variables (*Rossi et al., 2013; Bosch & Dalla Favera, 2019*). The most reliable is the chronic lymphocytic leukemia International Prognostic Index (CLL-IPI).

1.5.1. Clinical staging system

Two clinical staging systems are widely used to divide patients with CLL into three broad prognostic groups (low, intermediate and high risk): the Rai staging system and the Binet classification (the latter is most commonly used in Europe) (*Rai et al., 1975; Binet et al., 1977*). These staging systems are basedon physical examination and standard laboratory tests (CBC) and do not involve imaging studies. Both classifications rely upon lymphadenopathy and number of enlarged lymph nodes, splenomegaly and hepatomegaly, degree of lymphocytosis, hemoglobin concentration and thrombocyte count. However, the clinical staging systems are unable of predicting disease progression in CLL patients with early-stage disease.

1.5.2. Prognostics factor and predictive markers

Over the past decades, advances in understanding CLL genetics and molecular biology have led to identification of biomarkers associated with increased risk of disease progression and decreased survival, providing prognostic information complementary to the clinical staging systems, and enhancing our capacity to assess prognosis and therapy for patients (*Landau et al., 2015; Puente et al., 2015; Kipps et al., 2017*).

Clinical features that are associated with unfavorable prognosis are male sex, ≥65 years of age, poor performance status due to medical comorbidities, high serum levels of β2-microglobulin (>3.5 mg/L), high serum concentrations of thymidine kinase, a high absolute lymphocyte count (>50,000 cells per μL), lymphocyte count doubling time shorter than 12 months, ibrutinib resistance, as well as early relapse after first-line chemotherapy or chemoimmunotherapy (*Damle et al., 1999; Hamblin et al., 1999; Rassenti et al., 2004*).

Cytogenetic and molecular features that negatively influence the prognosis are TP53 mutations, IGHV genes mutational status, presence of del(17p) or del(11q), complex karyotype (i.e., the presence of three or more chromosomal aberrations) and the expression of surrogates of the IGHV genes mutational status, such as tyrosine protein kinase ZAP70 cytoplasmatic expression, CD49d or CD38 membrane expression (*Damle et al., 1999; Hamblin et al., 1999; Rassenti et al., 2004*). Interestingly, some of these biomarkers has also been found to predict response, and eventually resistance, to both chemoimmunotherapy and targeted therapy, and to provide information on the likelihood that a patient will benefit from a specific treatment (*Bosch & Dalla Favera, 2019*). Deletions of chromosome 17 and mutations of TP53 are currently considered the strongest CLL prognostic marker

as their presence is reported to negatively influence overall survival (OS) and predict an aggressive disease course with refractoriness to the standard chemoimmunotherapy regimen fludarabine-cyclophosphamide-rituximab (FCR) (*Zenz et al., 2010*).

As IGHV genes mutational status remains stable throughout the disease course, it is particularly suitable as a prognostic marker. As stated above, U-CLL patients are characterized by high-risk genetic lesions occurrence, an increased propensity to undergo clonal evolution and an association with an unfavorable overall survival (OS) (*Damle et al., 1999; Hamblin et al., 1999; Puente et al., 2015*).

Finally, among recurrently mutated genes in CLL associated with clinical progression, gain-of-function mutations in NOTCH1 and SF3B1 and loss-of- function mutations in BIRC3 are found to confer a shorter overall survival (OS) and to correlate with chemo-refractoriness (*Puente et al., 2011; Quesada et al., 2011*). A possible explanation for NOTCH1-mutated CLL cells refractoriness to anti-CD20 monoclonal antibodies is the low CD20 expression reported in NOTCH1 mutated CLL cases (*Ghamlouch et al., 2017*). The prognostic relevance of many gene mutations including NFKBIE, MYD88, SAMHD1, XPO1, RPS15, POT1, BRAF and EGR2 mutations is still unclear (*Bosch & Dalla Favera, 2019*). Importantly, most prognostic and predictive markers (such as IGHV mutational status) have been identified in patients treated with chemo- immunotherapy regimens and thus might have different value in patients treated with novel targeted agents. For this reason, different prognostic indexes are needed for patients receiving these new therapies (*Bosch & Dalla Favera, 2019*).

1.5.3. Indications for treatment

The criteria to initiate therapy rely on the Rai and Binet clinical staging systems and on the presence of disease-related signs and symptoms. As stated above, most newly diagnosed patients present an asymptomatic early-stage disease (Rai 0; Binet A) or intermediate-stage disease (Rai stage I or stage II; Binet stage B). Solid evidence exists that these patients do not benefit from early treatment and should be monitored until development of symptomatic disease or evidence of disease progression (*Kipps et al., 2017*). Patients with advanced-stage disease (Rai stage III and IV; Binet stage C) and patients with symptomatic or active disease, defined as presence of signs of progressive marrow failure (anemia or thrombocytopenia, or both), symptomatic splenomegaly or lymphadenopathy and autoimmune anemia or autoimmune thrombocytopenia not responding to corticosteroids, need treatment. Other reasonable indications for treatment could also be disease-related symptoms and rapidly

progressive lymphocytosis (a lymphocyte doubling time <6 months) (*Hallek et al, 2018*).

1.6. Treatment

Treatment options for CLL patients include chemotherapy, a combination of chemotherapy and immunotherapy (chemoimmunotherapy), novel agents targeting signaling pathways involved in CLL cells growth and/or survival (such as BCR signaling inhibitors and BCL-2 inhibitors), immune-modulatory drugs, immune checkpoint inhibitors, allogenic hematopoietic stem cell transplantation (HSCT) and CAR T-cell therapy. Even though CLL is still an incurable disease, thanks to the large number of treatment options, nowadays we might be able to achieve more durable remissions for most patients by using combinations of novel targeted drugs, with or without chemoimmunotherapy, which synergically target different B cell signaling pathways involved in CLL cell survival and proliferation (*Hallek et al, 2018; Kipps et al., 2017*).

1.6.1. Chemotherapy and Chemoimmunotherapy

Until very recently, relatively few therapeutic options were available for patients with CLL. These included chemotherapy and combination of chemotherapy and immunotherapy (chemoimmunotherapy). For many years cytostatic agents were the only drugs available for treatment of CLL patients. The alkylating agent chlorambucil was the standard first line treatment for CLL until phase 3 studies demonstrated an improved overall response rate (ORR) and prolonged progression-free survival (PFS) in patients treated with the purine analogue fludarabine (*Rai KR et al. 2000*). Sub-sequent studies showed that the ORR and PFS can be further improved by combining fludarabine with cyclophosphamide (*O'Brien et al. 2001*). A major step forward was the addition of the monoclonal anti-CD20 antibody rituximab to the fludarabine/cyclophosphamide combination, resulting in an even more effective regimen. This FCR regimen was the first to show an improvement in overall survival (OS) and has since become standard first line therapy for CLL (*Hallek et al. 2010*). However, the FCR regimen is associated with significant myelosuppression and a high rate of early and late infections, which is why it is unsuitable for most elderly patients and patients with co-morbidities (*Tam et al. 2008*). Of note, high rates of therapy-related adverse events have encouraged the development of less toxic treatment regimens, which are characterized by

fludarabine and cyclophosphamide dose reduction or by fludarabine replacement with pentostatin, cladribine, or bendamustine (*Eichhorst et al., 2009*). However, these alternative regimens appeared to be either less effective than FCR or had similar toxicity.

1.6.2. BCR signaling inhibitors

The identification of the BCR as a major driver in various B cell malignancies resulted in the clinical testing and approval of multiple drugs that selectively target and inhibit molecules involved in propagating the BCR signal. Three main classes of drugs have demonstrated efficacy, and some were recently approved for CLL treatment. These drug classes are Bruton's tyrosine kinase (BTK) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors and SYK tyrosine kinase inhibitors. The primary target of these drugs in the malignant B cells is the BCR, but these agents have much broader effects and also target other interactions that take place in the tumor microenvironment. Indeed, part of their biological activity has been attributed to their capacity to interfere with other intracellular signaling pathways that regulate leukemic cell migration, proliferation and survival, such as CD40, BAFF, IL-4, CXCR4 and TLR signaling pathways (*Slinger et al., 2017*). In addition, they can interfere with signaling through molecules that cooperatively regulate the tissue homing of B cells, such as chemokine receptors and integrins (*de Rooij et al., 2012*). Furthermore, as the expression of BTK and PI3Kδ is not restricted to neoplastic cells, these kinase inhibitors target BTK and PI3Kδ in non-tumor cells within the tumor microenvironment, such as macrophages, modulating their function (*Gunderson et al., 2016*). Since the selectivity of first-generation agents is not high, they can target not only their designated kinase but also related kinases. In particular, ibrutinib has been shown to inhibit the inducible T cell kinase (ITK) which, in turn, could partially explain some of the activity of this drug but also may contribute to increased sensitivity to certain infections (*Dubovsky et al., 2013*). Hence, more selective second-generation BCR signaling inhibitors have been developed more recently.

The previously described effects on cell homing receptors have two important implications for the mechanism of action of BCR signaling inhibitors. Firstly, they mobilize CLL cells from SLOs into the peripheral blood inducing redistribution lymphocytosis, which results in rapid reduction in lymphadenopathy associated with a concomitant and transient increase in absolute leukemia cells count. Importantly, redistribution lymphocytosis does not cause any adverse symptoms and tends to resolve over time, therefore, it should not be regarded as a sign of progression (*Kipps et*

al., 2017). Secondly, the displacement of CLL cells from tumor microenvironmental niches in SLOs further deprive them of growth and survival signals coming from microenvironmental cells, resulting in anoikis and subsequent clearance of apoptotic debris by local phagocytic cells. Anoikis is a particular form of programmed cell death in which leukemia cells "die by neglect". It results from CLL cells detachment from their supportive tissue environment which aborts survival signals through the BCR and other receptors such as CD40, BAFF-R, TLRs, chemokine receptors and integrins (*de Rooij et al., 2012*) (Figure 6).

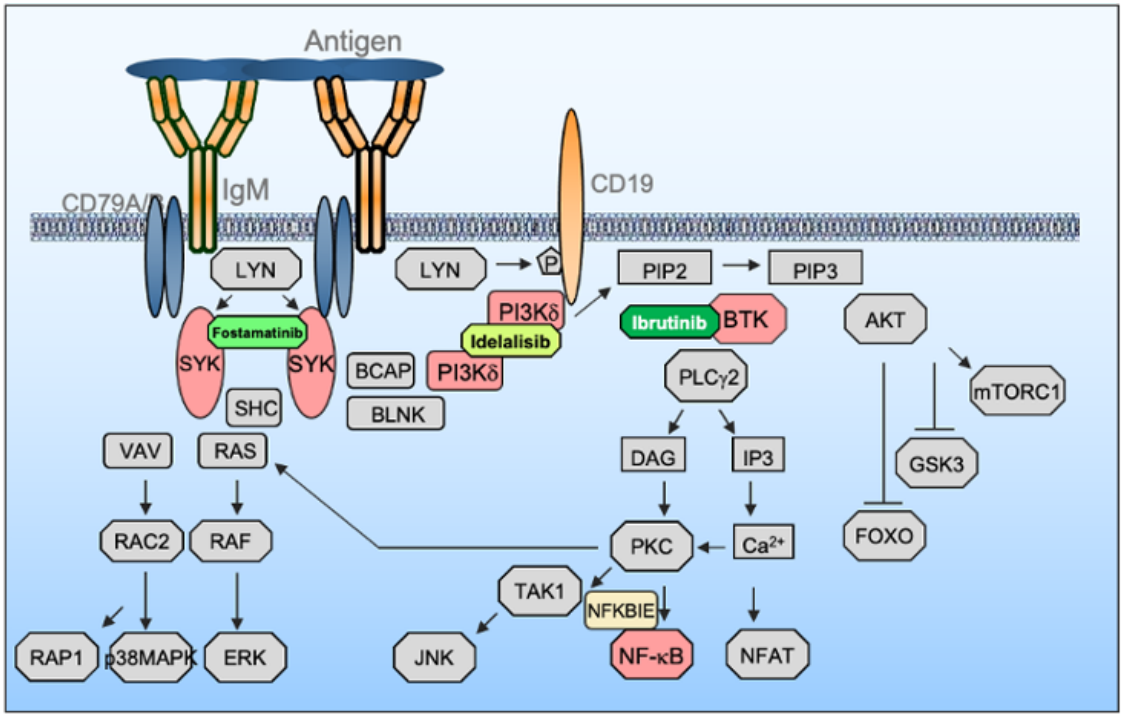


Figure 6. Inhibitors of BCR downstream signaling molecules: Fostamatinib inhibits the kinase SYK; Idelalisib is a PI3kδ inhibitor and Ibrutinib is the BTK inihibitor.

BTK inhibitors - Ibrutinib is an orally available irreversible small- molecule inhibitor of BTK, which bind covalently to the sulfhydryl group of cysteine 481 in the active site of BTK, resulting in the irreversible inhibition of its kinase activity and, thus, in a strong inhibition of the BTK/PLCγ2/PKC/NF-κB axis, which in turn leads to reduction in CLL cell proliferation and survival. In addition, inhibitory effects on chemokine receptors and adhesion molecules regulating CLL lymphocyte chemotaxis, homing and adhesion to extracellular matrix or to adjacent cells have also been reported. These lead to inhibition of CLL cell migration from the blood into the lymphoid tissues, resulting in abrogation of the supportive effects deriving from the

microenvironment and thereby halting disease progression, both *in vivo* and *in vitro* (*de Rooij et al., 2012*). Even though ibrutinib targets simultaneously two key pathogenic pillars of CLL, antigen- driven BCR signaling and microenvironmental interactions, it is not sufficient to eradicate the disease, as stopping treatment reverses remission. Importantly, ibrutinib is active against CLL subtypes with genetic lesions traditionally associated with resistance to chemoimmunotherapy, specifically TP53 or SF3B1 lesions. Accordingly, unlike patients treated with chemoimmunotherapy, analysis of clonal dynamics in patients treated with ibrutinib did not reveal the expansion of clones displaying SF3B1 or TP53 mutations (*Landau et al., 2015*). Besides targeted BTK inhibition, ibrutinib might also inhibit other kinases including ITK, TEC, EGFR, JAK3, ErbB, and SRC family kinases. Inhibition of these off-target kinases has been shown to cause ibrutinib side effects, which include fatigue, diarrhea, bleeding, ecchymoses, rash, arthralgia, myalgia, increased blood pressure and atrial fibrillation. Finally, with the aim of reducing ibrutinib off- target activity and consequent adverse clinical effects, more selective second-generation BTK inhibitors have recently been developed, including acalabrutinib, zanubrutinib, and tirabrutinib (*Byrd et al., 2016; Wu et al., 2016*).

PI3Kδ inhibitors - Idelalisib is an orally available reversible small-molecule inhibitor of PI3Kδ, with greater selectivity for the δ isoform of the catalytic subunit (PI3Kδ), which is specifically expressed in the hematopoietic compartment (*Efremov et al., 2020*). Both *in vitro* and *in vivo* studies showed that similarly to ibrutinib, idelalisib inhibits downstream BCR signaling, affecting leukemia cell survival and proliferation, and disrupts the migration and homing of CLL cells, affecting the essential crosstalk between CLL cells and their microenvironment accessory-cells (*Okkenhaug et al., 2016*). However, treatment with idelalisib has been associated with a toxicity profile characterized by autoimmune complications, hepatotoxicity, and increased risk of opportunistic infections, that have reduced its use in the clinical setting (*Lampson et al., 2016*). With the aim of reducing idelalisib's adverse clinical effects, several second-generation PI3Kδ inhibitors have recently been developed and explored in clinical trials, including duvelisib (PI3Kγ/δ inhibitor), copanlisib (PI3Kα/δ) and umbrasilib (TGR-1202). Some of them have been recently approved or entered advanced stages of clinical development and have shown promising clinical data in terms of response rates and safety profiles.

SYK inhibitors - Fostamatinib, an oral SYK inhibitor, was the first BCR inhibitor that was tested in preclinical studies and in a clinical trial of patients with B cell malignancies (*Gobessi et al, Leukemia 2009; Suljagic et al, Blood 2010, Friedberg et al, Blood 2010*). Despite the encouraging preclinical and clinical data, this drug did not undergo further clinical development in CLL, although it was recently approved for the treatment of immune thrombocytopenic purpura. However, other inhibitors of SYK are being developed and have shown promising results in clinical trials against B-cell malignancies, including chronic lymphocytic leukemia (*Burger & Wiestner, 2018*).

1.6.3. BCL-2 inhibitors

Bcl-2 is the principal member of the Bcl-2 family proteins, which are critical regulators of apoptosis and function immediately upstream of mitochondria. Structurally, BCL-2 family proteins share conserved BCL-2 homology (BH) domains and are classified into anti- and pro-apoptotic members, that are further subdivided into "multidomain" proteins, which contain four BH domains (BH1 to BH4), and "BH3-only" proteins, which contain only the BH3 domain. Among multidomain proteins, the pro-apoptotic multidomain members BAX and BAK function as mitochondrial executioners and directly open pores in the mitochondrial outer membrane, resulting in the release of the apoptogenic factors (such as cytochrome c and Smac/DIABLO). However, the anti-apoptotic multidomain members BCL-2, BCL-XL and MCL-1 inhibit the pore formation by directly binding BAX and BAK. BH3-only proteins are critical for initiating apoptosis, since acting immediately upstream of multidomain member, they activate BAX and BAK. Accordingly, the overexpression of BCL-2 oncogene in CLL cells is associated with evasion of apoptosis, leading to resistance to chemotherapy.

Venetoclax is a BCL-2 homology domain 3 (BH3) mimetic, which selectively blocks BCL-2 protein function, acting similarly to the BH3-only proteins that are physiologic antagonists of BCL-2. This drug is highly potent in inducing apoptosis in CLL cells and mediates this effect primarily by diminishing the capacity of BCL-2 to sequester the pro-apoptotic molecule BCL-2-interacting mediator of cell death (BIM), which activates BAX and BAK (*Del Gaizo Moore et al., 2007*). As evaluated by flow cytometry analyses, venetoclax is more potent compared to BCR signaling inhibitors in inducing minimal residual disease (MRD) negative remissions, which are generally not

observed using PI3K and BTK inhibitors (*Hallek et al., 2018*). In addition, venetoclax is highly active in CLL patients carrying TP53 aberrations (del17p and/or TP53 gene mutations), which is consistent with its p53-independent mechanism of action (*Stilgenbauer et al., 2016*). Toxicities of venetoclax include gastrointestinal disturbances, neutropenia and tumor lysis syndrome (*Roberts et al., 2016*).

1.6.4. Resistance to novel targeted agents

Despite the impressive clinical efficacy of the novel targeted agents, some patients fail to respond whereas others develop resistance. In particular, it has been reported that some patients achieve deep responses to BCR inhibitors, whereas some do not respond at all when they first receive treatment. It has also been observed that among those who respond, many eventually develop resistance to the drugs under ongoing treatment. Considering these two categories of patients, resistance to BCR inhibitors can be divided into primary and secondary. The mechanisms responsible for primary resistance have still not been well characterized but are believed to result from adoptive changes in the kinome resulting in greater activation of compensatory pathways that substitute for the BCR signal. Instead, secondary resistance to BCR inhibitors is usually associated with mutations that affect the kinase inhibitor binding site, such as Cys481Ser (BTKC481S), which prevent the covalent binding of ibrutinib to the BTK active site (*Woyach et al., 2014*). In addition, mutations in the BTK SH2 domain (BTKT316A) were also reported to be responsible for ibrutinib resistance (*Sharma et al., 2016*). Moreover, other mutations allowing escape from treatment include gain-of-function mutations in PLCγ2, a downstream target of BTK, which allow for BCR-mediated signaling independent of BTK inhibition (*Woyach et al., 2014*). In particular, mutations in PLCγ2 gene were identified as non-synonymous substitutions occurring in exon 19 (P664S and R665W), exon 20 (S707Y) and exon 24 (L845F) or a 6- nucleotide deletion in exon 20 (c.2120-2125del) which led to the deletion of S707 and A708 (*Ahn etal., 2017*).

Little is known about the potential molecular mechanisms of resistance to idelalisib. However, gain- of-function mutations and subsequent upregulation in other members of the PI3K pathway and MYC amplification could be possible mechanisms of resistance (*Cheah & Fowler, 2016*).

Mutations in BCL-2 that reduce venetoclax binding affinity have emerged as an important mechanism of resistance to this drug (*Blombery et al., 2018*). However, other genetic lesions, such as mutations in BTG1, deletions of CDKN2A/B and amplification of MCL-1 have also been implicated

in venetoclax resistance [33,34]. In addition, survival signals derived from the BCR, T cells and TLRs have been shown to confer venetoclax resistance by modulating the expression of the antiapoptotic proteins MCL-1, BCL-xL and/or BFL-1 (*Bojarczuk et al., 2016*).

1.6.5. Future Treatments

Several therapies, such as new drugs and treatment modalities that can modulate the immune system, including immune checkpoint inhibitors, are currently being studied in clinical trials for the treatment of CLL patients. Immune checkpoints are proteins present on the surface of antigen-presenting cells that are able to regulate the immune response by sending co-stimulatory or co-inhibitory signals to receptors present on T cells and other immune effector cells. The finding that cancer cells can avoid immune detection and destruction by aberrantly expressing immune checkpoints, has led to the development of immune checkpoint inhibitors, which are currently being used for the treatment of certain solid tumors and Hodgkin lymphoma (*Sharma et al., 2015*).

The most significant cognate receptor implicated in the inhibition of cellular immune activation is the immune checkpoint receptor PD-1, along with its ligands PD-L1 and PD-L2. High quantities of PD-L1 and PD-L2 are expressed by CLL cells, which have the ability to inhibit effector T cells that express PD-1 and cause them to become exhausted (i.e., no longer functional) (*Ramsay et al., 2012*). T cell exhaustion in CLL is also influenced by the lymphocyte activation gene 3 protein and the T cell immunoglobulin mucin receptor 3 (TIM3, also known as HAVCR2). TIM3 inhibits the function of type 1 helper T cells and type 1 CD8+ T cells by inducing cell death in response to ligand binding (*Monney et al., 2002*). In addition to PD1 and TIM3, exhausted T cells can express a variety of others cell surface inhibitory molecules. In fact, it has been reported that exhausted T cells can co-express PD1 with other inhibitory receptors such as lymphocyte activation gene 3 protein (LAG3), CD244, CD160, CTLA4 and TIGIT (*Blackburn et al., 2009*).

Checkpoint inhibitors have been shown in preclinical studies in mouse models to reactivate immune effector cells, resulting in anti-leukemia activity (*McClanahan et al., 2015; Roessner et al., 2020*). However, recent phase I/II trials of immune checkpoint inhibitors in relapsed CLL patients have not shown much clinical activity, which could be attributed to the highly immunosuppressive nature of CLL cells and/or the highly 'exhausted' phenotype of T cells in patients with CLL (*Kipps et al., 2017)*.

2. Aims of the project

The main objectives of this thesis are to:

1. Characterize the effect of inactivating mutations in NFKBIE on the growth of transformed leukemia cells derived from the Eμ-TCL1 transgenic mouse model;

2. Investigate how leukemic cells with NFKBIE mutations respond to various microenvironmental signals (BCR, CD40, TLR and BAFF-R signals);

3. Investigate whether NFKBIE mutations confer resistance to BCR inhibitors.

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3. Material and Methods

3.1. CRISPR/Cas9 editing of murine CLL cells

Previously established immortalized leukemia B-cells, derived from the Eμ-TCL1 transgenic mouse model of CLL (Chakraborty et al., 2021), were used for generating NFKBIE mutant murine CLL cells. Cells were thawed and cultured in RPMI-1640 supplemented with 10% heat-inactivated FBS, 100U/mL penicillin, 0.1mg/mL streptomycin, 2mM L-glutamine, 1mM sodium pyruvate (Invitrogen), and 1M CpG-1668 (InvivoGen) for 20 hours prior to CRISPR/Cas9 editing with the Alt-R system (Integrated DNA Technologies). A predesigned NFKBIE cr-RNAs (1.5 μM) was combined with 1.5 M ATTO 550-labeled tracr-RNA, 0.75 M recombinant Cas9 protein, and 1.5 μM Alt-R Cas9 electroporation enhancer in 5 L nuclease-free duplex buffer to create the Cas9 ribonucleoprotein (RNP) complex that targets the NFKBIE gene (all from Integrated DNA Technologies). Following that, the Cas9 RNP complex was electroporated into $6x10^6$ leukemic cells suspended in 100μl Mouse B cell Nucleofector solution using the Amaxa Nucleofector II device and the Z-001 program (Lonza). The sequence of the NFKBIE cr-RNA is shown in Table 1.

Table 1. Nucleotide sequences of cr-RNAs used in this study.

Name of the Gene	cr-RNA sequences	PAM Sequence
NFKBIE (Mus musculus)	AGTGATTCACGAAGCCCCGT	CGG

3.2. DNA extraction and PCR amplification of the CRISPR/Cas9 targeted region

The Cas9 editing efficiency was evaluated by amplicon capillary electrophoresis on a 3500 Genetic Analyzer (Applied Biosystems) of polymerase chain reaction (PCR) fragments spanning the region of genomic DNA around the targeted site as described elsewhere (*Chakraborty et al, Blood 2021*). Briefly, DNA was extracted using the KAPA Express Extract kit (Sigma Aldrich) from Eμ-TCL1 cells that had previously been purified with the EasySep Mouse CD19 Positive Selection Kit (Stem cell Technologies). The samples were then heated for 10 minutes at 75 °C for lysis and for 5 minutes at 95 ° C to inactivate the enzyme. As a PCR template, a 2 μl DNA extract was used.

Based on the following Table 2, a PCR master mix was prepared with the correct volume of each reaction component.

The following PCR conditions were used: denaturation at 95°C for 10 minutes followed by repeated cycles at 95°C 15 sec/64°C 15 sec/72°C 20 sec for 40 times, and extension at 72° for 10 min. Table 3 provides the sequence of the primers used to amplify the CRISPR/Cas9 targeted area.

Table 2. PCR master mix.

	Volume (50 ul)
PCR buffer 10x	5 ml
MgCl2	3 ml
Forward primer	0.5 ml
Reverse primer	0.5 ml
Ampli Taq Gold polymerase	0.25 ml
DNA	2 ml
DNase free water	38.75 ml

Table 3. Primers sequences used to measure the editing efficiency of Cas9 via fragment length analysis.

Name of the Gene	(5'-3') Forward Primer	(5'-3') Reverse Primer
NFKBIE (Mus musculus)	TATCACCTCTGACCTGGGCTC	TCTGAATGTCCAGGACTTCCTG

3.3. Agarose gel electrophoresis of DNA

Size fractionation of PCR products was performed through electrophoresis in 2% (w/v) agarose gel (Invitrogen) prepared in TBE 1X (89 mM Tris; 89 mM Boric acid; 2 mM EDTA; pH 8.3), containing 1µl of SYBR safe/10 ml agarose gel (Thermo Scientific). DNA size markers and PCR samples were loaded onto the gel and ran at 80 mA in TBE 1X buffer. UV transilluminator equipment was used to see the PCR results, and a Gel Doc EZ imager was used to record the image (BioRad).

3.4. In vitro cell proliferation assays

For the *in vitro* BrdU proliferation assay of murine Em-TCL1 cells, 1x106 cells were treated, or not, with Ibrutinib at two different concentrations: 0.2 mM and 1 mM for 24h and 48h prior to addition of 10µM BrdU. The duration of BrdU incorporation prior to harvesting is indicated in the figure legends. Cells were harvested, labelled with the fixable viability dye eFluor 780, fixed with 2% paraformaldehyde, permeabilized with a solution of 3 M HCl and 2% Tween 20, neutralised with 0.1M sodium borate buffer pH 9.0, and stained with anti-BrDU-V450 antibody (BD Horizon, cat. #563445).

3.5. Flow cytometry analysis

Single cell suspensions were prepared from spleens by grinding the tissue through 70 µm cell strainers (BD Biosciences) and ACK-lysing buffer (Thermo Fisher) was used to lyse erythrocytes. Cells from peritoneal cavity were obtained by lavage which were not further processed.

Following that, cell surface proteins were stained in phosphate-buffered saline (PBS) with 1% fetal calf serum and 0.1% sodium azide for 30 min at 4 °C.

The subsequent antibodies were used:

- CD5-anti-mouse-PE (BD Pharmingen, cat. #553023)
- CD19-anti-mouse-APC (BD Pharmingen, cat. #561738)
- CD11b-anti-mouse-APC (Miltenyi, cat. #130-098-088)
- F4/80-anti-mouse-FITC (Biorad, cat. #MCA497FA)
- CD45.2-anti-mouse-BV421 (BD Pharmingen, cat. #562895)
- LAG-3-anti-mouse-BV650 (BD Pharmingen, cat. #125227)

• TIGIT-anti-mouse-BV421 (BD Pharmingen, cat. #142111)
• PD-1 (CD279)-anti-mouse-BV421 (BD Pharmingen, cat. #135217)
• CD4-anti-mouse-FITC (BD Pharmingen, cat. #116003)
• CD8a-anti-mouse-APC (BD Pharmingen, cat. #100711)
• PD-L1-anti-mouse-PerCP-eFluor 710 (Invitrogen, cat. #46-5982-80)
• Tim3-anti-mouse-PerCP-eFluor 710 (Invitrogen, cat. # 46-3109-42)

Data were acquired on a FACS Celesta (BD Biosciences) and analysed using FlowJo software (FlowJo, Ashland, OR, USA).

3.6. Immunoblotting analysis

For total protein extracts, cells were washed in ice-cold PBS, pelleted, and lysed in a protease- and phosphatase-inhibiting RIPA lysis buffer (10 mM Tris-HCl, pH 7.4, 5 mM EDTA, 150 mM NaCl, 0.1% SDS, 0.1% sodium deoxycholate) (Sigma-Aldrich). Total cell lysates were kept on ice for 30 minutes, mixed every 10 minutes, and then centrifuged in a benchtop centrifuge (Eppendorf) at 16000xg for 20 minutes at 4°C.

Nuclear and cytoplasmic protein extracts were extracted with NE-PER Nuclear and Cytoplasmic Extraction Reagents as per protocol (Thermo Scientific, cat. 78833).

The RC DC Protein Assay (Bio-Rad) was used to quantify the protein concentration within each cell lysate. In the presence of 1X SDS loading buffer (200mM Tris-HCl pH 6.8, 400mM DTT, 8% SDS, 0.4% Bromophenol blue, 40% glycerol), 15–40 mg of protein lysates was denatured by heating for 5 minutes at 95°C. Table 4 outlines how SDS PAGE gels were created.

Components	Resolving Gel 8% (10 ml)	Stacking Gel (5 ml)
30% Acrylamide mix	2.7 ml	830 ml
Tris-HCl pH 8.8	2.5 ml	-
Tris-HCl pH 6.8	-	630 ml
Ammonium persulphate	100 ml	50 ml
SDS 10%	100 ml	50 ml
TEMED	10 ml	5 ml
H2O	4.6 ml	3.4 ml

The protein samples were separated by SDS-PAGE and transferred on Immobilon-P polyvinylidene difluoride membranes (Millipore). Membranes were then blotted at 4°C in the presence of 5% non-fat dry milk with the following antibodies:

- anti-NFKBIE (Sigma Aldrich, cat. #HPA005941)
- c-Rel (Cell Signalling, cat. #12707S)
- Total-p65 (Cell Signalling, cat. D14E12)
- NF-kappaB2 p100/p52 (Cell Signalling, cat. #4882S)
- NF-kappaB1 p105/p50 (Cell Signalling, cat. #13586S)
- PARP (Cell Signalling, cat. #9542S)
- GAPDH (Santa Cruz, cat. #sc-365062)

Immunodetection was done on an ALLIANCE LD2 chemiluminescence Imaging System (Cleaver Scientific Ltd., Warwickshire, UK), using ECL Plus enhanced-chemiluminescence detection reagents (GE Healthcare, Chicago, IL, USA).

3.7. In vivo experiments with murine models

All animal procedures were performed under a protocol approved by the Italian Ministry of Health (no. 347/2017-PR). CRISPR/Cas9-edited Em-TCL1 leukaemia cells were transferred into 2-3 months old NSG or C57BL/6 mice via intraperitoneal injection of $1x10^7$ cells.

For the *in vivo* treatment experiments, C57BL/6 mice were treated with ibrutinib at a daily dose of 25 mg/kg. The drug was administered in 2 divided doses by intraperitoneal injection as described elsewhere (*Sasi et al., 2019*).

3.8. RNA preparation and sequencing

Total RNA was extracted with RNeasy Micro Kit (Quiagen) following manufacturer recommendations. RNA integrity was examined with the Bioanalyzer 2100 (Agilent). RNA sequencing has been performed by Macrogen, Inc. The RNA-seq libraries were prepared according to the standard Illumina protocol with the mRNA-seq Illumina TruSeq. cDNA libraries were checked for quality and quantified using the DNA-1000 kit (Agilent) on a 2100 Bioanalyzer. Each library was sequenced with the NovaSeq 6000 sequencer to obtain 2x100bp reads.

3.9. Bioinformatics methods

RNA sequencing was performed in quadruplicate for *in vivo* samples and in triplicate for *in vitro* ones. Raw sequences files' quality was checked via FastQC (v0.11.9, http://www.bioinformatics.babraham.ac.uk/projects/fastqc/). Transcript quantification was conducted with SALMON (version v1.8) using Transcriptome index with decoys, starting from GRCm39 genome version (accessed on June 2022). The generated transcript counts were analyzed using DESeq2 package. The normalized count matrix (obtained from variance stabilizing transformation (VST) method as implemented in DESeq2 package) was used to explore high-dimensional data property with Principal Component Analysis (PCA) coupled with a dimensionality reduction algorithm used in the DESeq2 package. Differentially expressed transcripts (DETs) were selected with a *p-adjusted* cut off of 0.05 and a log2 Fold Change value greater than 1 (up-regulated DETs) or lower than -1 (down-regulated DETs). *P-value* was adjusted for multiple testing using the Benjamini–Hochberg (BH) correction with a false discovery rate (FDR)≤0.05. DETs were then analyzed with a hierarchical clustering method, using correlation distance. Visualization of log2-normalized values and clustering was obtained thanks to pheatmap package, while visualization of DETs in volcano plots were acquired using the EnhancedVolcano package. Functional annotation was performed for all the comparisons and for feature list of interest, whose results were visualized with ggplot2 and ggpubr packages, with ggballoonplot functions. In particular, clusterProfiler was utilized for Gene Ontology analysis, Reactome, and gProfiler2 for other databases.

3.10. Statistical analysis

Data are expressed as means ±SD. As indicated in the figure legends, differences in leukemia cell numbers, % proliferating cells, % viable cells, and mutant allele frequency were assessed using the t test, Mann-Whitney rank sum test, or one-way repeated measures ANOVA. The Kaplan-Meier method was used to calculate survival curves and medians. The SigmaStat Version 3.1 programme was used for all statistical analyses (Systat Software). P values are shown in the figures.

4. RESULTS

4.1. Introduction of inactivating NFKBIE mutations in immortalized Eμ-TCL1 leukemia cells by CRISPR/Cas9 editing

The NF-kB inhibitor-e (NFKBIE) gene, which encodes IkBε, a negative regulator of the canonical NF-kB signaling pathway, was found recurrently mutated in CLL (*Mansouri L et al., 2015*). However, the involvement of this lesion in leukemogenesis and treatment resistance in CLL are still poorly understood. To better understand the role of NFKBIE in CLL, we first targeted the exon 2 of NFKBIE gene by nucleofection-mediated delivery of a ribonucleoprotein (RNP) complex containing recombinant Cas9 and a NFKBIE guide RNA (gRNA) in immortalized leukemia B-cells derived from the Eμ-TCL1 transgenic mouse model of CLL (Figure 7A). This cell line was recently established by our group by introducing inactivating genetic lesions in the TP53, CDKN2A and CDKN2B genes (TCL1-355-TKO), which genetic lesions typically co-occur in Richter transformation. The TCL1-355-TKO cells express a BCR reactive with the autoantigen phosphatidylcholine (PtC), which is a membrane phospholipid that is exposed on the surface of apoptotic cells and has been shown to drive the expansion of murine TCL1 leukemia cells with such antigen specificity (*Iacovelli et al., 2015*). The TCL1-355-TKO cells spontaneously proliferate in vitro but remain BCR dependent, as evidenced by the rapid block of their proliferation in the presence of a BCR inhibitor and their selective loss in vitro and in vivo following genetic disruption of the IgM constant region gene (*Chakraborty et al, Blood 2021*). However, these cells remain responsive to other putative microenvironmental stimuli, such as the Toll-like receptor 9 ligand CpG DNA, which induces an increase in the proliferation rate following in vitro stimulation.

To evaluate the effect of knockdown, we analyzed cells from three independent experiments by amplicon capillary electrophoresis and nucleotide sequencing analysis of the CRISPR/Cas9-targeted region (Figure 7B and 7C, respectively). Both approaches revealed an editing efficiency of 85-100% in the three lines that were generated. Consistent with this finding, the immunoblotting assay showed no detectable IkBe protein expression in any of the three TCL1-355-TKO NFKBIE-ko lines that were established (Figure 7D).

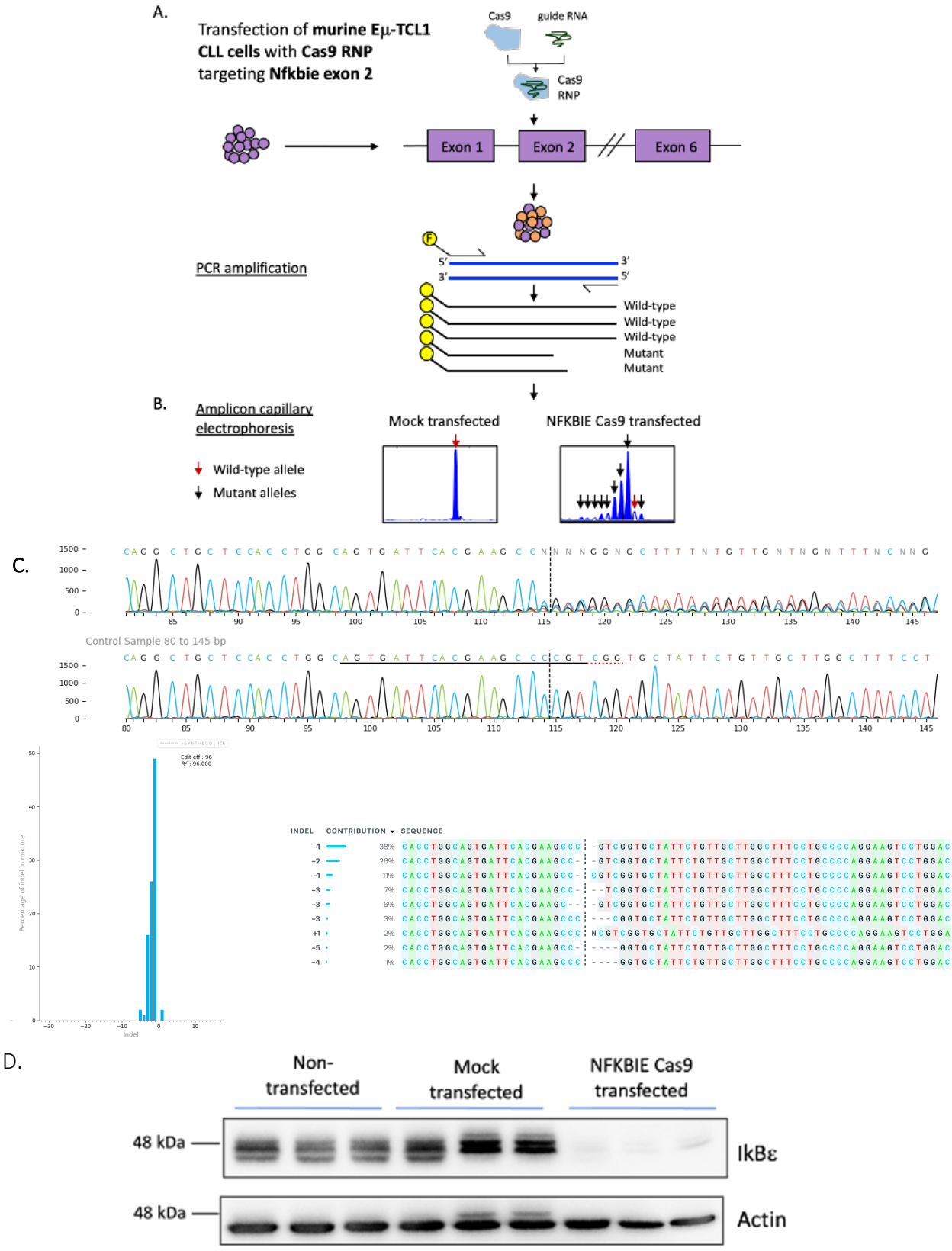


Figure 7. Generation of Eμ-TCL1 leukemia cells with NFKBIE knockdown. **A)** Schematic representation of the CRISPR/Cas9 procedure to target NFKBIE gene in Eμ-TCL1-derived murine CLL B-cells. **B)** Indel analysis by FLA of NFKBIE-targeted leukemia cells. **C)** Nucleotide sequencing of CRISPR/Cas9-targeted region. **D)** Immunoblotting analysis of NFKBIE protein expression in TCL1 leukemia cells with NFKBIE ko in three different technical replicates.

4.2. No effect of NFKBIE mutation on growth of immortalized TCL1 leukemia cells *in vitro*

Unlike normal B cells, CLL cells do not proliferate *in vitro* upon engagement of the BCR, although they can be induced to proliferate by other microenvironmental signals. However, the acquired capacity of the TCL1 355 TKO cell line to spontaneously proliferate gave us the possibility to study the effect of NFKBIE mutations *in vitro*.

To investigate whether NFKBIE mutations can confer a growth advantage to TCL1 leukemia cells *in vitro*, we conducted competition experiments with mixed cultures of cells with wild-type and mutated NFKBIE which allowed us to study the effect of this mutation on cell proliferation *in vitro*.

Analysis of the clonal composition after 2 weeks in culture revealed no change in the mutant allele frequency, suggesting that NFKBIE mutations do not affect the spontaneous in vitro growth of the immortalized leukemia cells (Figure 8).

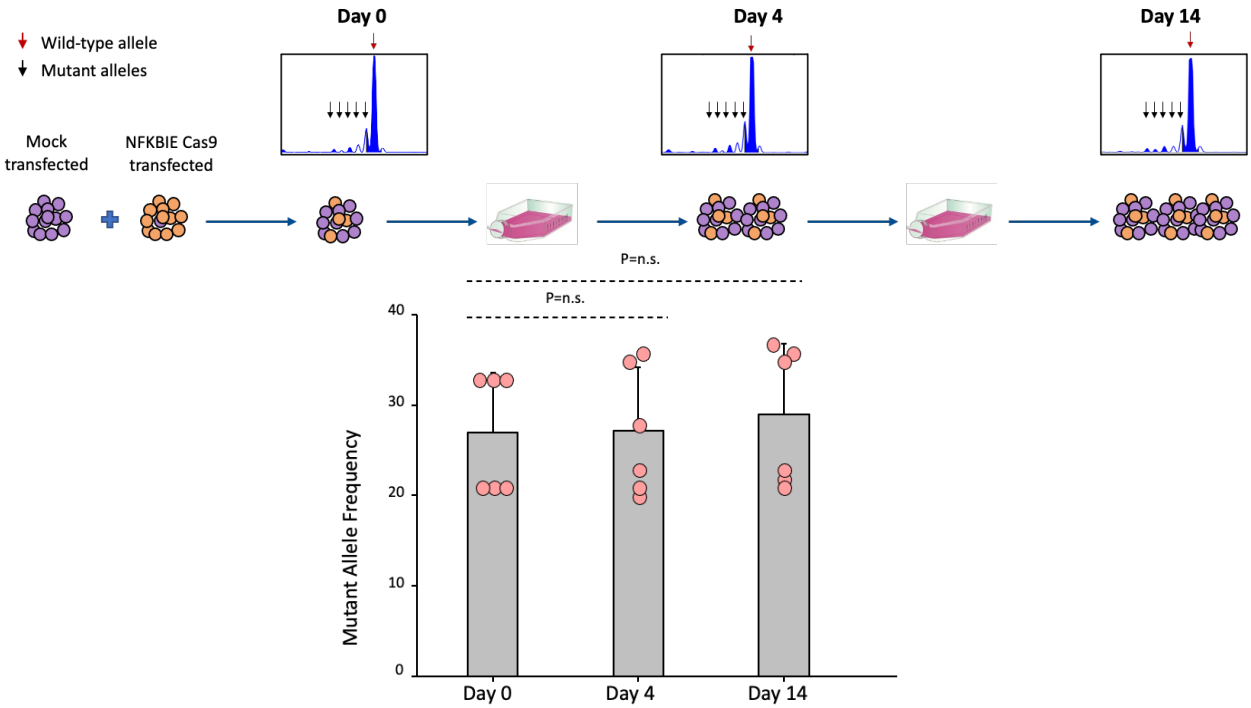


Figure 8. Generation of Eμ-TCL1 leukemia cells with NFKBIE knockdown. Mutant allele frequency (MAF) analysis during in vitro culturing. NFKBIE knockout and wild type TCL1 leukemia cells were mixed at a 1:2 ratio and cultured for 14 days. DNA was isolated at the indicated time points for indel analysis by amplicon capillary electrophoresis. Summary of the data is shown in the panel below and the analysis of the samples from the 1:2 mixture in the panel above. Statistical analysis was done using One Way RM ANOVA with Tukey test for multiple comparisons.

4.3. NFKBIE-mutated leukemia cells are positively selected by microenvironmental signals that activate the canonical NF-kB pathway

To further understand the impact of NFKBIE mutations in response to the different stimuli present in the microenvironment we set up several *in vitro* competition experiments. Mixtures of cells with mutated and wild type NFKBIE alleles were stimulated or not with **PtC**, anti-**IgM**, **CpG-DNA**, tumor necrosis factor alpha (**TNF-α**), CD40 ligand (**CD40L**) and B cell Activating Factor (**BAFF**) for 14 days. A significant increase in mutant allele frequency was observed following repeated stimulation through the TLR, BCR or TNF receptor with CpG-DNA, anti-IgM, phosphatydilcholine or TNF-α, respectively, which are all involved in NF-kB signaling activation through the canonical pathway. Interestingly, no increase in mutant allele frequency was noted following CD40L or BAFF stimulation, both involved in the activation of the non-canonical NF-kB pathway, suggesting that NFKBIE mutations provide a growth advantage only when cells are exposed to microenvironmental signals that activate the canonical NF-kB pathway (Figure 9).

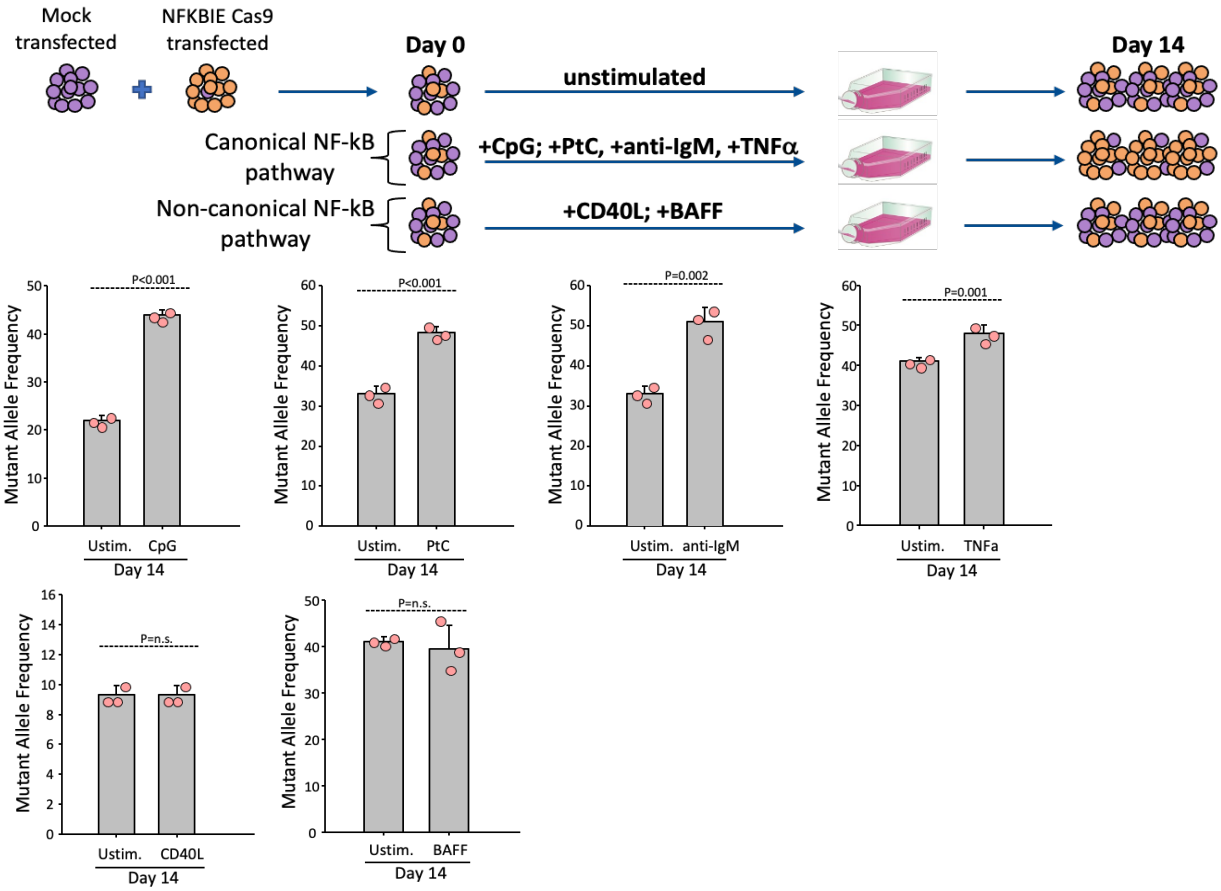


Figure 9. Generation of Eμ-TCL1 leukemia cells with NFKBIE knockdown. Mutant allele frequency (MAF) analysis during in vitro culturing in presence or not of PtC, anti-IgM, CpG-DNA, TNF-α, CD40L and BAFF. NFKBIE knockout and wild type TCL1 leukemia cells were mixed at a 1:2 ratio and cultured for 14 days. DNA was isolated at the indicated time points for indel analysis by amplicon capillary electrophoresis. Summary of the data is shown in the panel below. Statistical analysis was done using One Way RM ANOVA with Tukey test for multiple comparisons.

4.4. p65 and p52 nuclear translocation is increased in NFKBIE-mutated TCL1 leukemia cells following CpG stimulation

The previous experiment showed that stimulation with various stimuli resulted in the selection of NFKBIE mutant alleles, with greatest selection observed following stimulation with CpG-DNA. Therefore, to determine why NFKBIE mutations can confer a growth advantage to leukemic cells following CpG-DNA stimulation, we performed a time course immunoblotting analysis of nuclear and cytoplasmic protein extracts derived from NFKBIE mutated and wild type cells stimulated with CpG-DNA for 1h, 3h or 5h. Interestingly, CpG-stimulated NFKBIE mutated cells showed significantly greater nuclear levels of NF-kB subunits p65 and p52 compared to CpG-stimulated NFKBIE wild type cells, suggesting that aberrant regulation of the transcriptional activity of these subunits could be responsible for the growth advantage of the NFKBIE mutated cells. In contrast, no differences were observed with respect to the nuclear levels of Rel and p50, suggesting that the nuclear translocation of these subunits is not affected by the absence of IkBε protein (Figure 10)

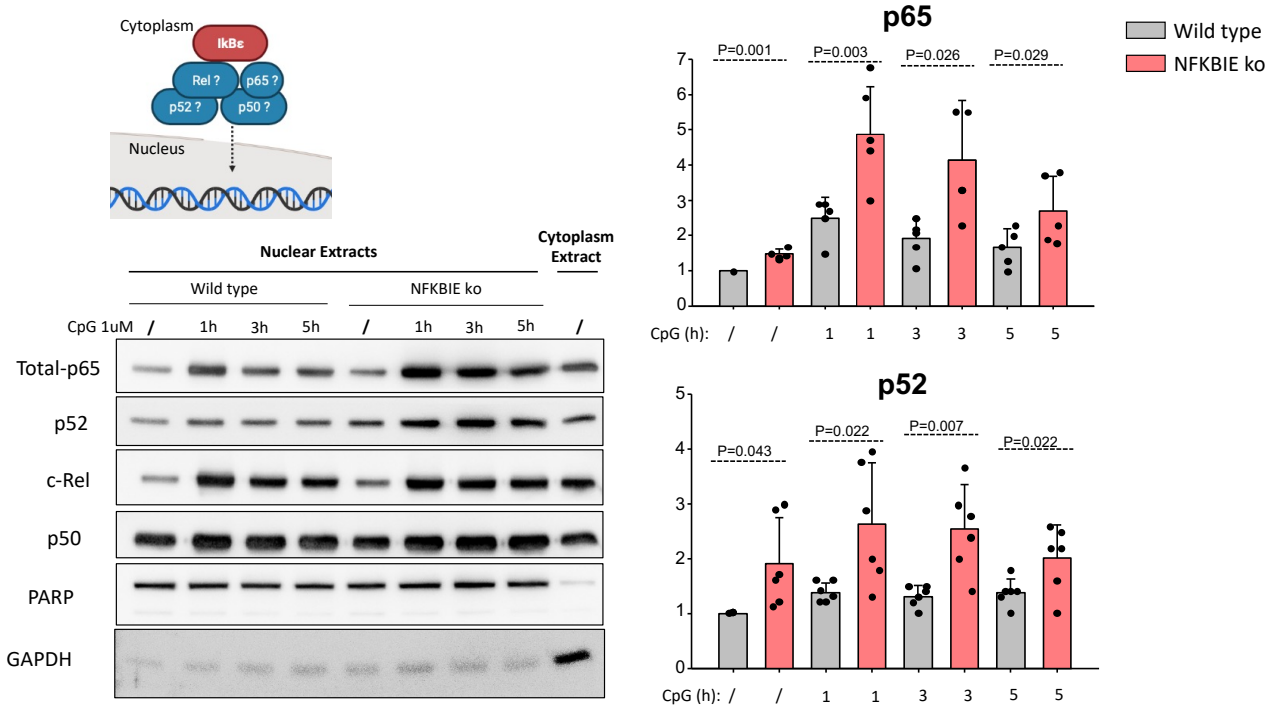


Figure 10. Immunoblotting analysis of NF-kB transcriptional factors following CpG-DNA stimulation. Nuclear and cytoplasmic protein extracts from NFKBIE mutated and wild type leukemic cells after were extracted after 1h, 3h or 5h of CpG-DNA stimulation with NE-PER kit. Statistical analysis done with One Way Repeated Measures ANOVA and Tukey test for multiple comparisons.

4.5. NFKBIE-mutated TCL1-355 TKO CLL cells are differently selected in different anatomical compartments

The previous *in vitro* experiments showed that NFKBIE mutations provide a growth advantage when the leukemic cells are exposed to certain microenvironmental signals. To determine whether NFKBIE-mutated cells are also selected by microenvironmental signals in vivo, we transplanted mixtures of cells with mutated and wild type NFKBIE alleles by intraperitoneal injection in wild type mouse recipients and investigated the clonal composition 3 weeks later through MAF analysis of cells isolated from the peritoneal cavity, blood and spleen of the transplanted mice. We observed a significant enrichment of NFKBIE mutant alleles in all three compartments of the recipient mice compared to injected cells. However, leukemia cells isolated from the spleen and peripheral blood showed a significantly greater increase in MAF compared to leukemia cells isolated from the peritoneal cavity, indicating that the quality or the quantity of the microenvironmental signals that select the NFKBIE-mutated cells is different between these two compartments (Figure 11).

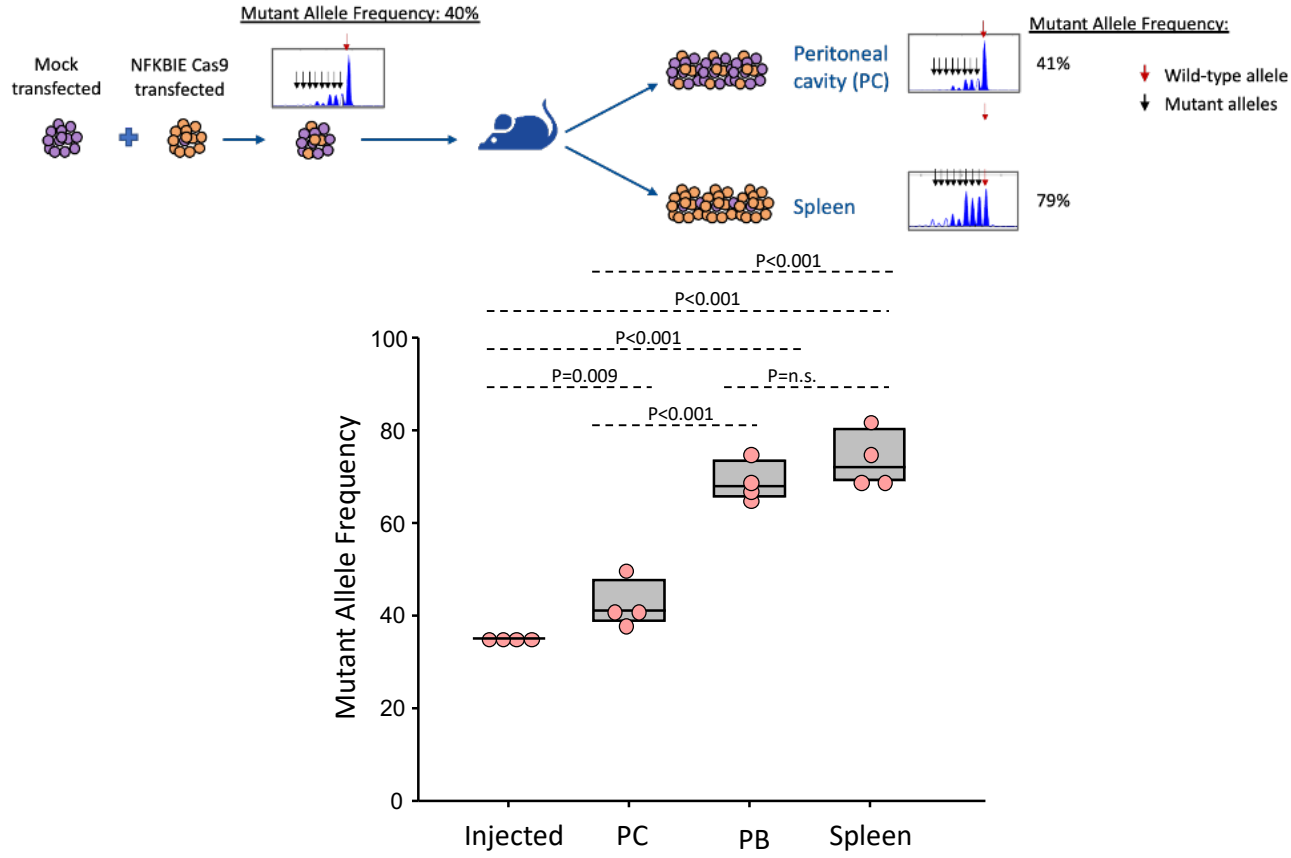


Figure 11. In vivo competition experiment of NFKBIE knockout and wild type TCL1 leukemia cells. MAF analysis was evaluated during in vivo adoptively transferred leukemia. NFKBIE and wild type CLL cells were mixed ad 1:2 ratio and injected intraperitoneally in 8 wil type mice recipient. After leukemia expansion, CLL cells were isolated, purified and DNA was extracted for MAF analysis by amplicon capillary electrophoresis.

The results of the above described experiment pointed to a crucial role of the microenvironment in the selection of NFKBIE mutant alleles. To further investigate how NFKBIE mutations are selected in vivo, we conducted the same experiment in immunodeficient NSG mice, which are characterized by lack of mature T, B and NK cells. A mixture of NFKBIE mutated and wild type cells was inoculated intraperitoneally in 5 NSG recipient mice. Four weeks later, CLL cells collected from peritoneal cavities and spleens were purified and analyzed. MAF analysis again revealed a significant enrichment of NFKBIE mutant alleles in CLL cells collected from peritoneal cavities and spleens compared to the injected cells. However, unlike the previous experiment conducted in wild type mice, we observed no significant difference in the NFKBIE mutant allele frequency between CLL cells harvested from peritoneal cavity and spleen, suggesting a potential role for immune cells in the selection of NFKBIE-mutated CLL cells (Figure 12). That notwithstanding, in vivo BrdU labeling experiments showed a higher percentage of BrdU-positive cells both in the spleen and peritoneal cavity of mice that had received NFKBIE-mutated compared to NFKBIE-wild type cells, suggesting that the greater expansion of NFKBIE-mutated cells was also a result of their greater proliferative rate *in vivo*.

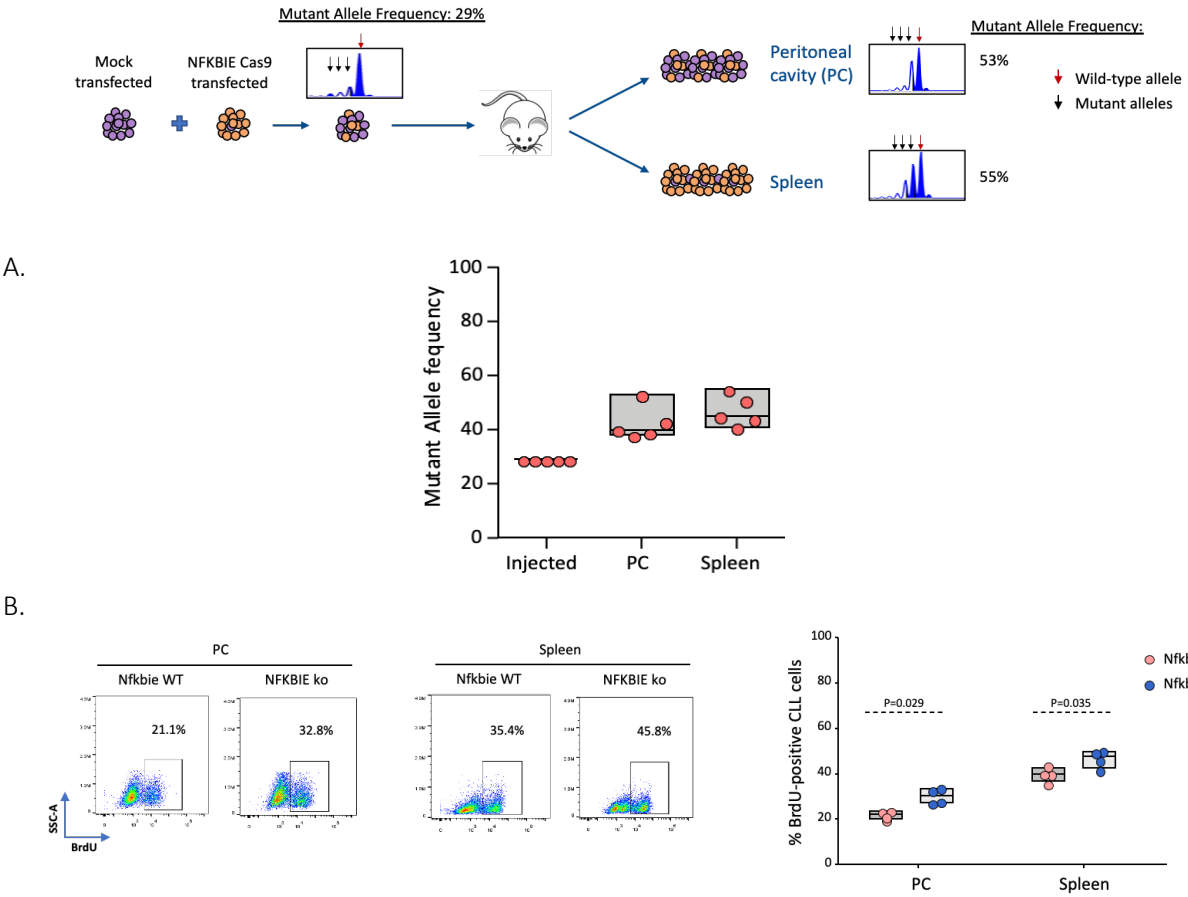


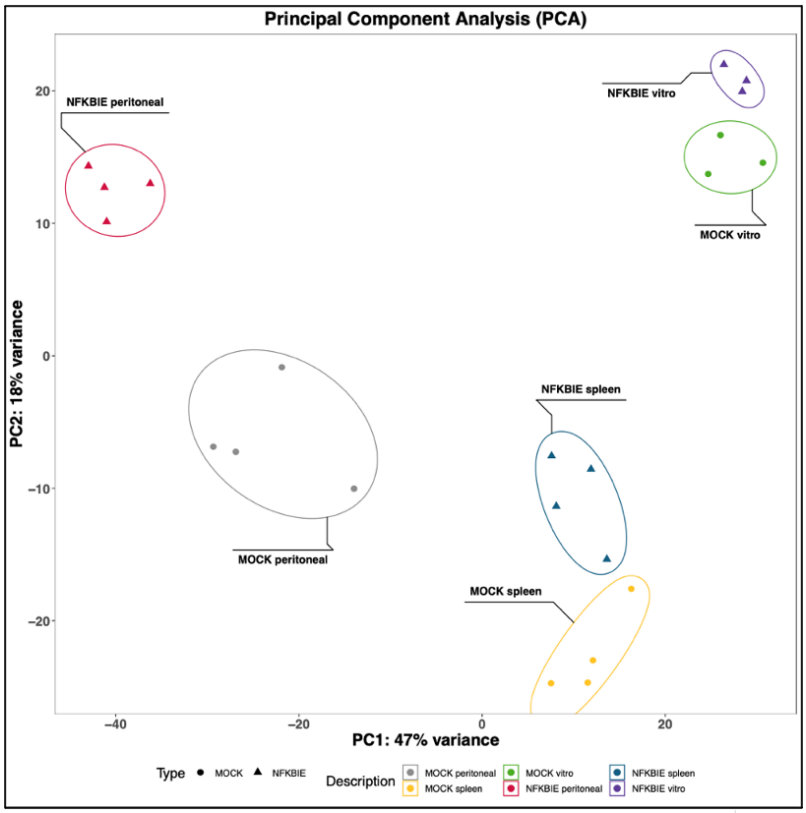
Figure 12. In vivo competition experiment of NFKBIE knockout and wild type TCL1 leukemia cells. MAF analysis was evaluated during in vivo adoptively transferred leukemia. NFKBIE and wild type CLL cells were mixed ad 1:3 ratio and injected intraperitoneally in 5 NSG mice recipient. After leukemia expansion, CLL cells were isolated, purified and DNA was extracted for MAF analysis by amplicon capillary electrophoresis.

4.6. RNA-Seq analysis of NFKBIE-mutated and NFKBIE-wild type cells **shows evident tissue-based differences**

To investigate the mechanism through which NFKBIE mutations confer a growth advantage to the leukemic cells *in vivo*, we characterized by RNA-seq analysis the transcriptional landscape of NFKBIE-mutated and NFKBIE-wild type TCL1 CLL cells propagated under i*n vivo* and *in vitro* conditions. For this purpose, NFKBIE-wild type and NFKBIE-mutated TCL1-355 TKO cells were first expanded by propagating them individually for 21 days in C57BL/6 mice and then separately transferred via intraperitoneal injection in two different groups of C57/BL6 recipient mice ($5x10^7$ cells/mouse, 5 mice per group). The leukemic cells were recovered after 10 days from the spleen and peritoneal cavity of the transplanted mice and 4 samples from each group were analyzed by RNA sequencing. Importantly, CLL cells were not purified in these experiments to retain the non-leukemic elements from the microenvironment, which ranged from 5-15% of the cells in each individual sample. In parallel, we analyzed NFKBIE-mutated and NFKBIE-wild type TCL1-355 TKO cells, each isolated from three different mice and separately cultured for two weeks prior to RNA isolation, to determine the impact of the NFKBIE mutation on the transcriptional profile of unstimulated cells *in vitro*.

Principal Component Analysis (PCA) clearly separated the *in vitro* from the *in vivo* condition, which in turn showed evident tissue-based differences. Moreover, the NFKBIE-wild type and NFKBIE-mutated samples clustered distinctly in each of the three investigated conditions (Figure 13A). Differential gene expression analysis showed a total of 774 transcripts that were downregulated and 491 transcripts that were upregulated in the spleens of mice with NFKBIE mutations compared to those without (Figure 13B). In the peritoneal cavity, we found 938 transcripts that were downregulated and 1711 upregulated, while in the *in vitro* condition, we observed downregulation of 99 transcripts and upregulation of 87 transcripts in the NFKBIE-mutated samples (Figure 13B).

A.



B.

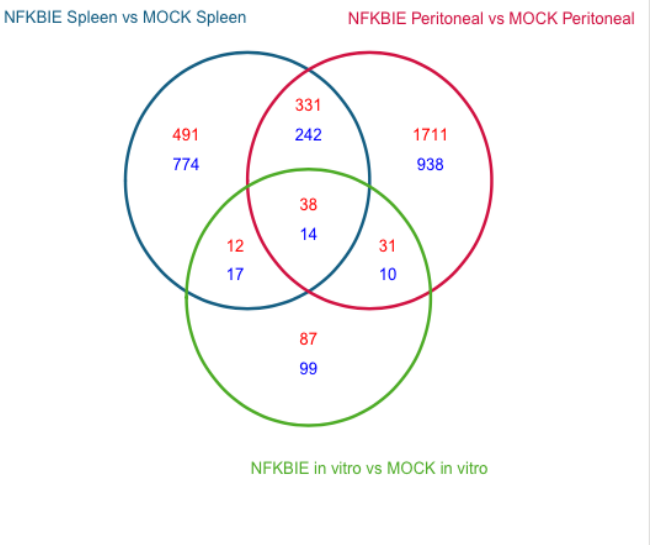


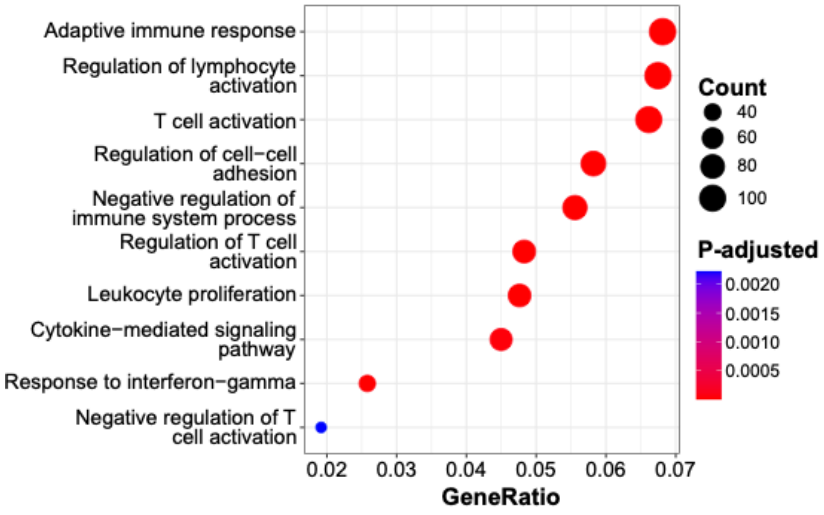
Figure 13. RNA-seq analyses. A. Principal Component Analysis (PCA) of the transcript expression counts (log2 vst-method normalized counts) for the 22 samples, showing the first versus the second PC. PC1 shows 47% variance and PC2 18%. Each dot represents a MOCK sample, each triangle is a NFKBIE sample. Every condition groups together with same type samples and indeed it can be observed that the *in vitro* condition is separated from the *in vivo*, which in turn clearly shows tissue-based differences. **B.** Venn of differentially expressed transcripts (DETs), the numbers in each circle represent the number of DETs between the different comparisons while the ones overlapping are for mutual DETs (NFKBIE Spleen vs MOCK Spleen in red, NFKBIE Peritoneal vs MOCK Peritoneal in green, NFKBIE in vitro vs MOCK in vitro in blue). The numbers in red represent up-regulated DETs, blue numbers are relative to the down-regulated portion.

4.7. NFKBIE mutations in CLL induce different antitumor immune response and increased T cell exhaustion *in vivo*

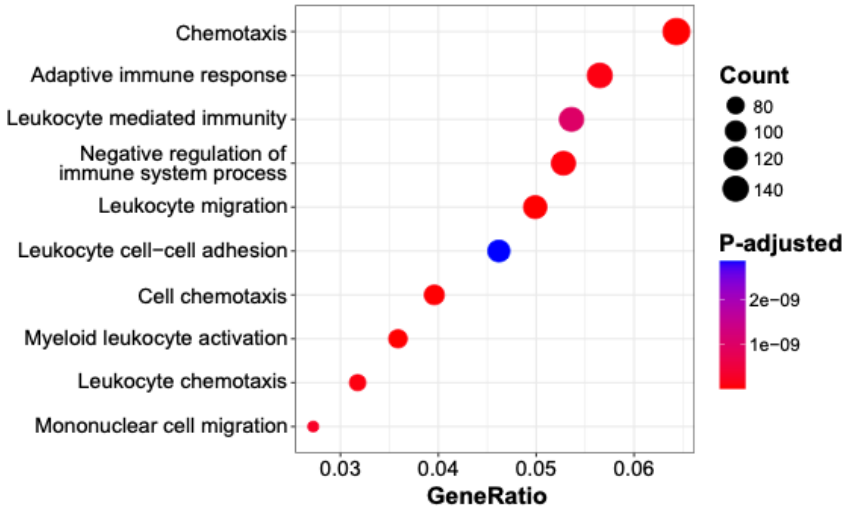
Gene set enrichment analysis of the differentially expressed transcripts (DETs) in spleens of mice receiving NFKBIE-mutated or NFKBIE-wild type cells revealed that most of the top 10 significantly overrepresented gene ontology terms were related to adaptive immune response, regulation of T cell activation and regulation of cell-cell adhesion (Figure 14 and Appendix 1). In contrast, the most differentially expressed pathways in cells isolated from the peritoneal cavity were related to chemotaxis and leukocyte migration, whereas those *in vitro* involved lymphocyte activation and proliferation, B cell mediated immunity and MHC class II protein complex assembly (Figure 14).

A more detailed inspection of the differentially expressed genes in the spleen revealed enrichment of various cytokines and chemokines that are involved in recruitment of T cells and macrophages, such as Ccl3, Ccl4, Ccl5, Ccl22, Cxcl10, Csf1, Tnfα and Ifnα, as well as inhibitory immune checkpoint molecules, such as CD274 (Pd-l1), Tigit, Lag3 and Pdcd1 (Pd1) (Figure 15). Except for TNFα, none of these molecules were differentially expressed between the NFKBIE-mutated and NFKBIE-wild type cells in the in vitro condition, suggesting that they are induced by signals from the microenvironment. Consistent with this possibility, only some of these molecules were differentially expressed in PC cells of mice that had received NFKBIE-mutated compared to NFKBIE-wild type tumors (Figure 15). Altogether these findings raised the hypothesis that NFKBIE mutations in CLL induce a different antitumor immune response with increased T cells exhaustion.

A. Spleen



B. Peritoneal Cavity (PC)



C. In vitro

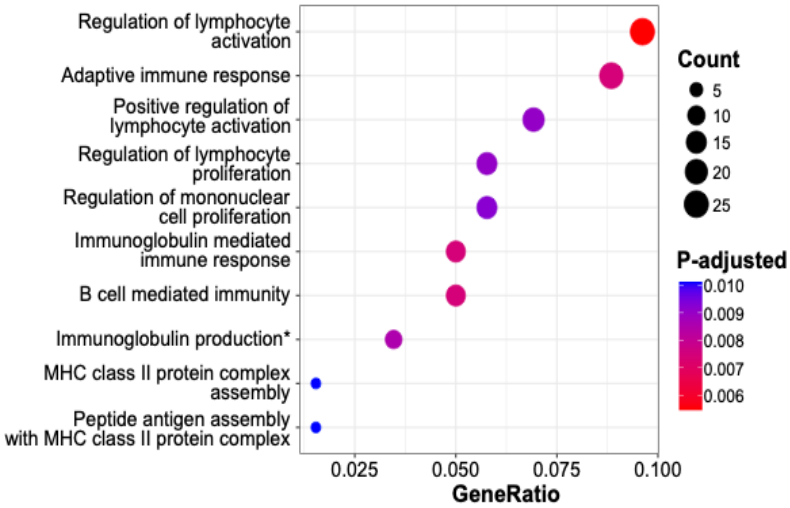
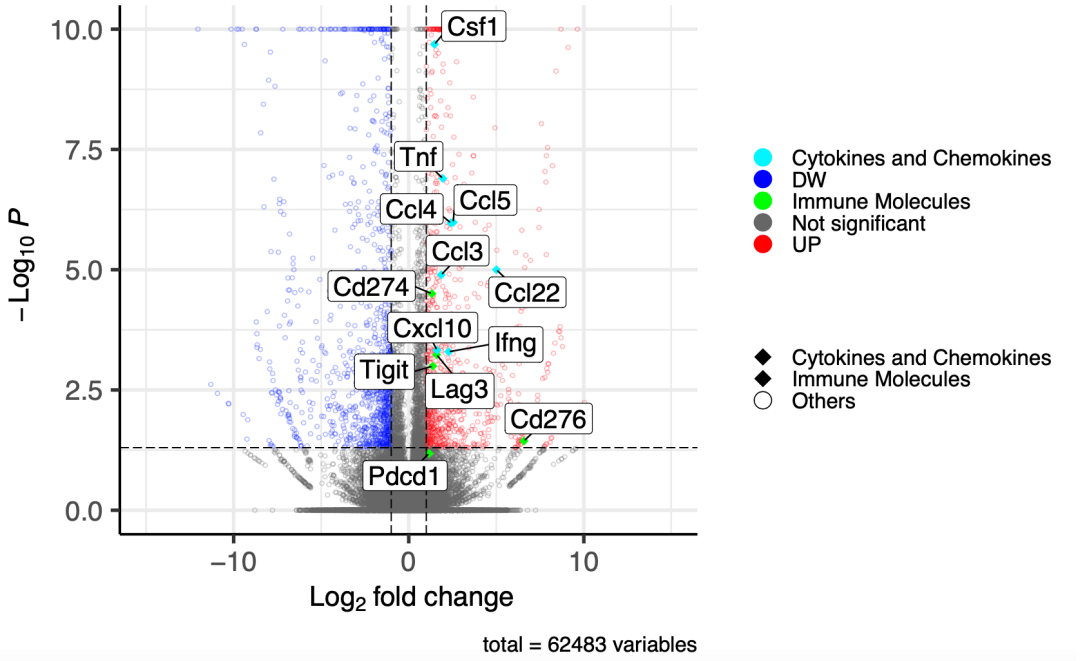


Figure 14. Gene ontology analyses. Top ten Gene Ontology terms based on the Gene Ratio (x-axis), which is ratio between the transcripts of the transcripts set found to be enriched for that specific term and the total transcripts in the set. In each row, the dots represent the enriched up-regulated biological terms. The size of each dot is proportional to the number of the transcripts enriched in the term, while the color of the dots is the p-adjusted value, spanning from red to blue.

Spleen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Ccl22
Cxcl10
Ifng
Tigit
Lag3
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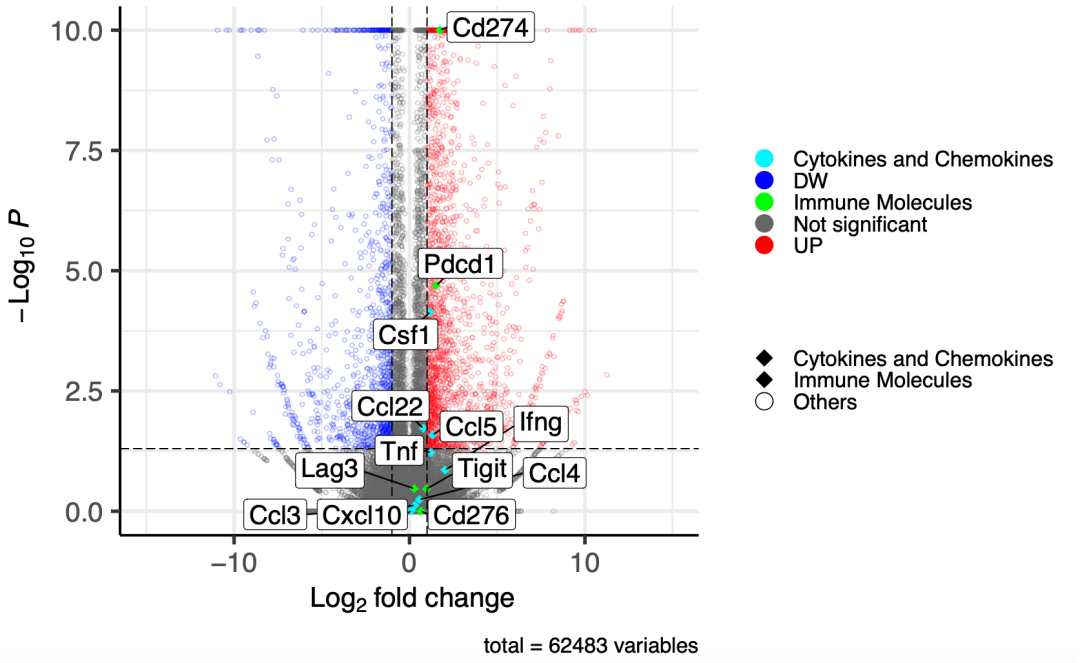
Others

PC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Ccl22
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Ifng
Tnf
Lag3
Tigit
Ccl4
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In vitro

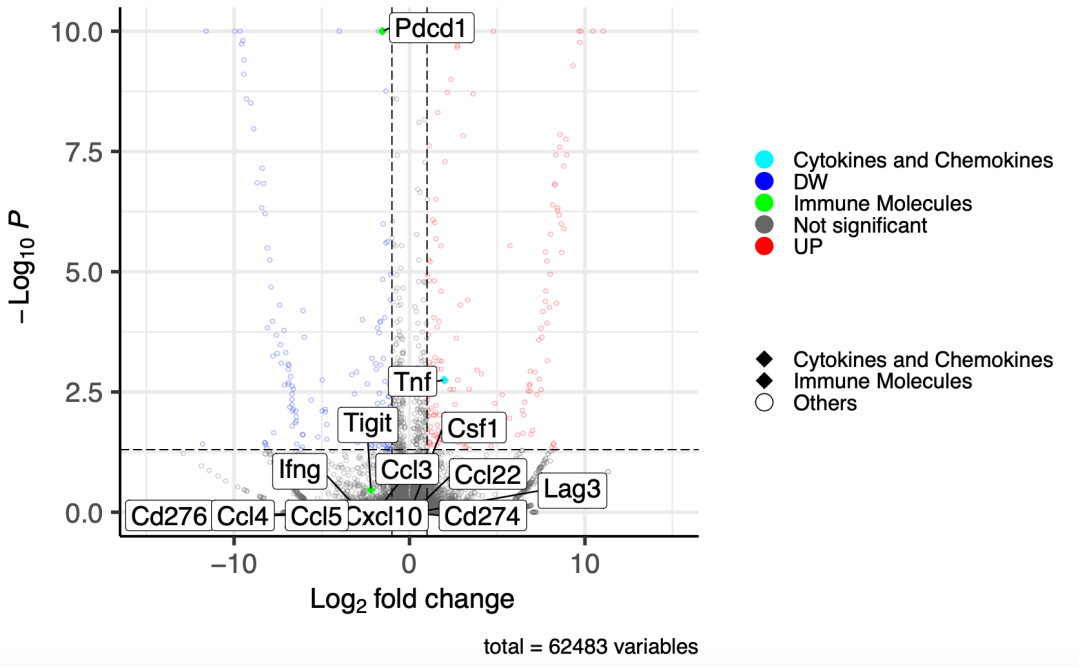
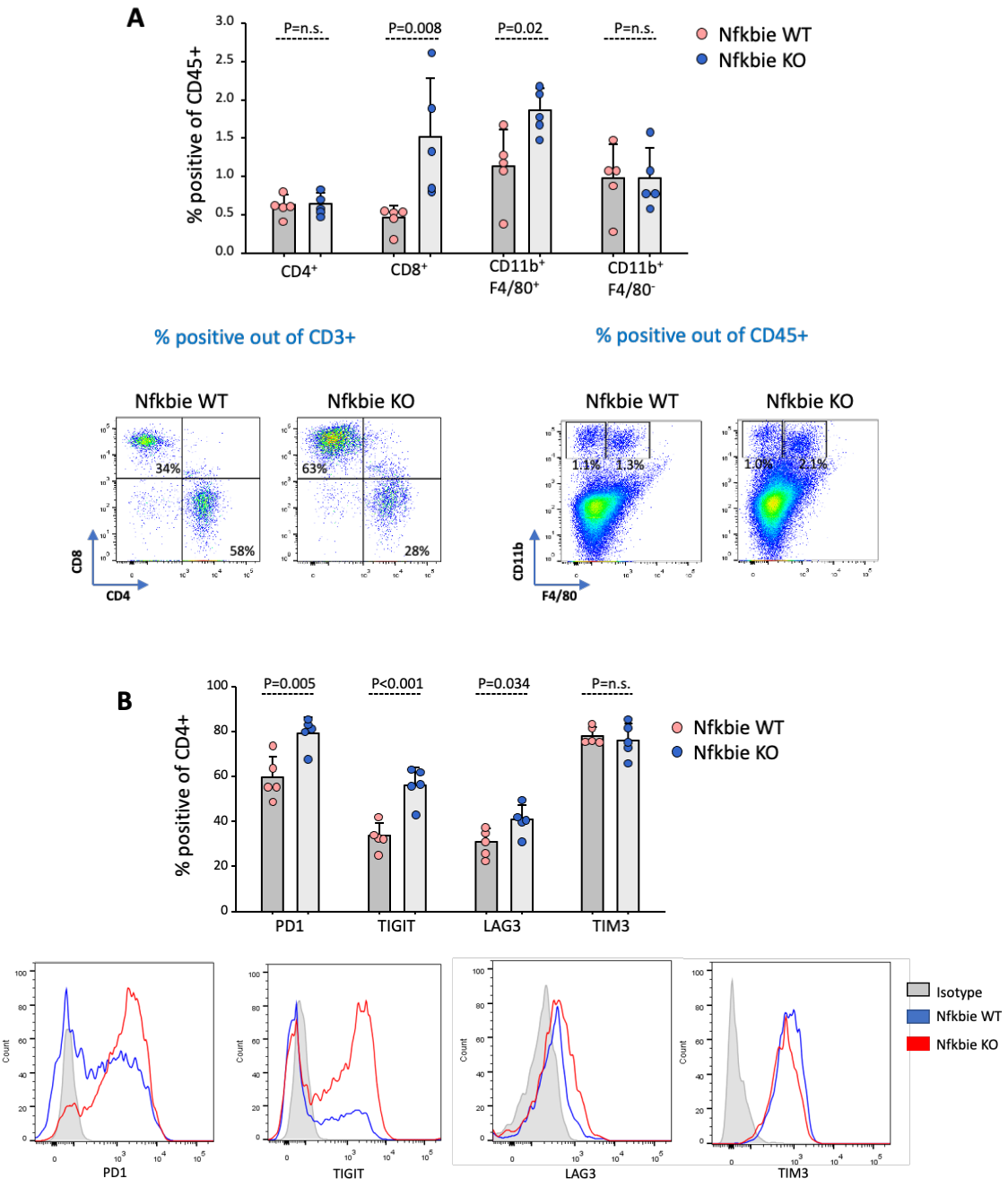


Figure 15. Volcano plots highlighting significant differentially expressed transcripts in the spleen, peritoneal cavity and *in vitro*. Significantly up-regulated transcripts shown in red ($p<0.05$, fold change≥ 1, significantly down-regulated transcripts shown in blue ($p<0.05$, fold change≤ -1); black dots represent non-differentially expressed transcripts. Left volcano shows significant differentially expressed transcripts. Cytokines and Chemokines significant differentially expressed transcripts are highlighted in light blue. Immune checkpoint significant differentially expressed transcripts are highlighted in green.

The findings from the RNA-seq analysis raised the possibility that NFKBIE mutations are preferentially selected in the spleens of transplanted mice because they affect the antitumor immune response. To further validate this possibility, we analyzed by flow cytometry the different cell populations in spleens of mice transplanted with NFKBIE-mutated or NFKBIE-wild type TCL1-355 TKO cells. We observed a significant increase in the number of CD8+ T cells which resulted in the inversion of the CD4+/CD8+ ratio in spleens of mice receiving NFKBIE-mutated compared with NFKBIE-wild type cells (Figure 16A). A smaller but significant increase was also observed in the percentage of CD11b+F4/80+ monocytes.

In addition, we noted increased expression of the immune checkpoints PD1 and TIGIT on CD4+ and CD8+ T cells and LAG3 on CD4+ T cells recovered from spleens with NFKBIE-mutated CLL cells compared to spleens with NFKBIE-wild type CLL cells (Figure 16B and C). In contrast, no difference was observed in the expression of TIM3, suggesting that the NFKBIE mutation affects the expression of some but not all inhibitory checkpoint molecules. We also observed greater

expression of PD-L1, PD1 and LAG3 on the NFKBIE-mutated leukemic cells, whereas TIGIT and TIM3 were not expressed (Figure 16D).



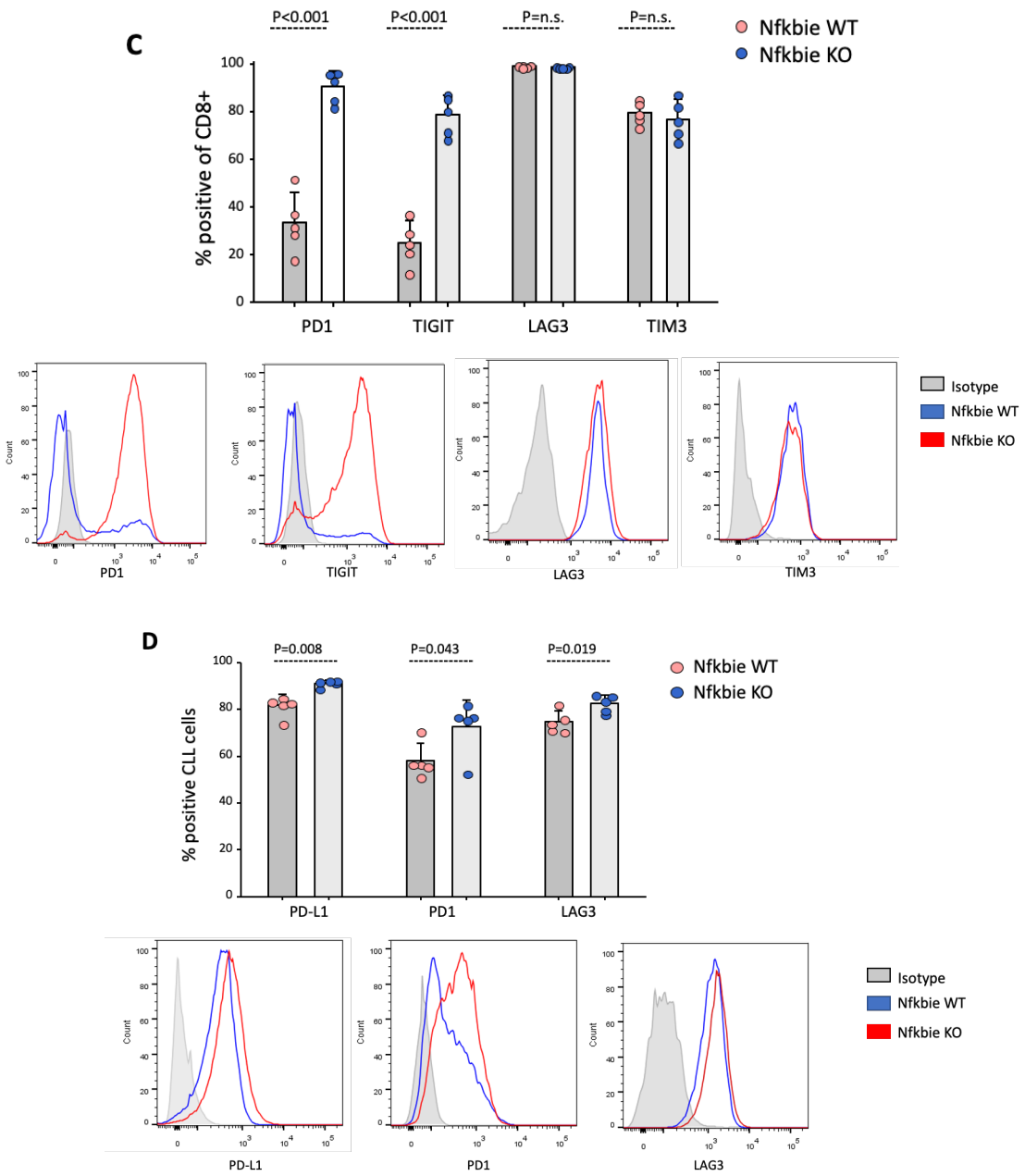


Figure 16. NFKBIE mutations in CLL induce different antitumor immune response and increased T cell exhaustion in vivo. A) Flow cytometry analysis of CD4 CD8 T cells and CD11b F4/80 monocytes in spleens of mice receiving NFKBIE-mutated or NFKBIE-wild type cells. B) Flow cytometry analysis of Immune checkpoint expression on CD4+ T cells NFKBIE-mutated or wild type cells collected from the spleen. C) Immune checkpoint expression analysis on CD8+ T cells in spleens of mice receiving NFKBIE-mutated or NFKBIE-wild type cells performed by flow cytometry. D) Flow cytometry analysis of inhibitory checkpoint molecules expression on NFKBIE-mutated or WT CLL cells isolated from spleen.

4.8. NFKBIE-mutated TCL1 leukemia cells are less sensitive to inhibition of proliferation by Ibrutinib *in vitro*

The mechanism(s) underlying resistance to novel targeted therapies, such as the BTK inhibitor ibrutinib, are still only partially understood. Acquired mutations of BTK and PLCG2 are present in 50-80% of patients that progress on ibrutinib and have been shown to prevent the binding of ibrutinib to BTK or to allow for BTK-independent activation of PLCG2. However, the mechanisms responsible for ibrutinib resistance in the remaining patients are still unknown. In addition, in many patients the BTK and PLCG2 mutations are present in only a minor subclone at the time of progression, suggesting that multiple mechanisms of ibrutinib resistance may operate in the same patient.

Because mutations in NF-kB pathway genes have been associated with resistance to Ibrutinib in mantle cell lymphoma, we next investigated whether NFKBIE mutations can affect the response to ibrutinib treatment (*Rahal et al., 2014 Wu et al., 2016*). We therefore first tested the effect of ibrutinib on the proliferation of the NFKBIE wild type and NFKBIE mutated cells in vitro by BrdU incorporation analysis. In these experiments ibrutinib was used at two different concentrations, one below (0.2 μM) and one above the maximal plasma concentration achievable in patients (1 μM). At both concentrations, ibrutinib inhibited to a significantly lesser extent the proliferation of cells with mutated NFKBIE compared to cells with wild type NFKBIE, suggesting that the NFKBIE-mutated cells are less sensitive to ibrutinib treatment (Figure 17).

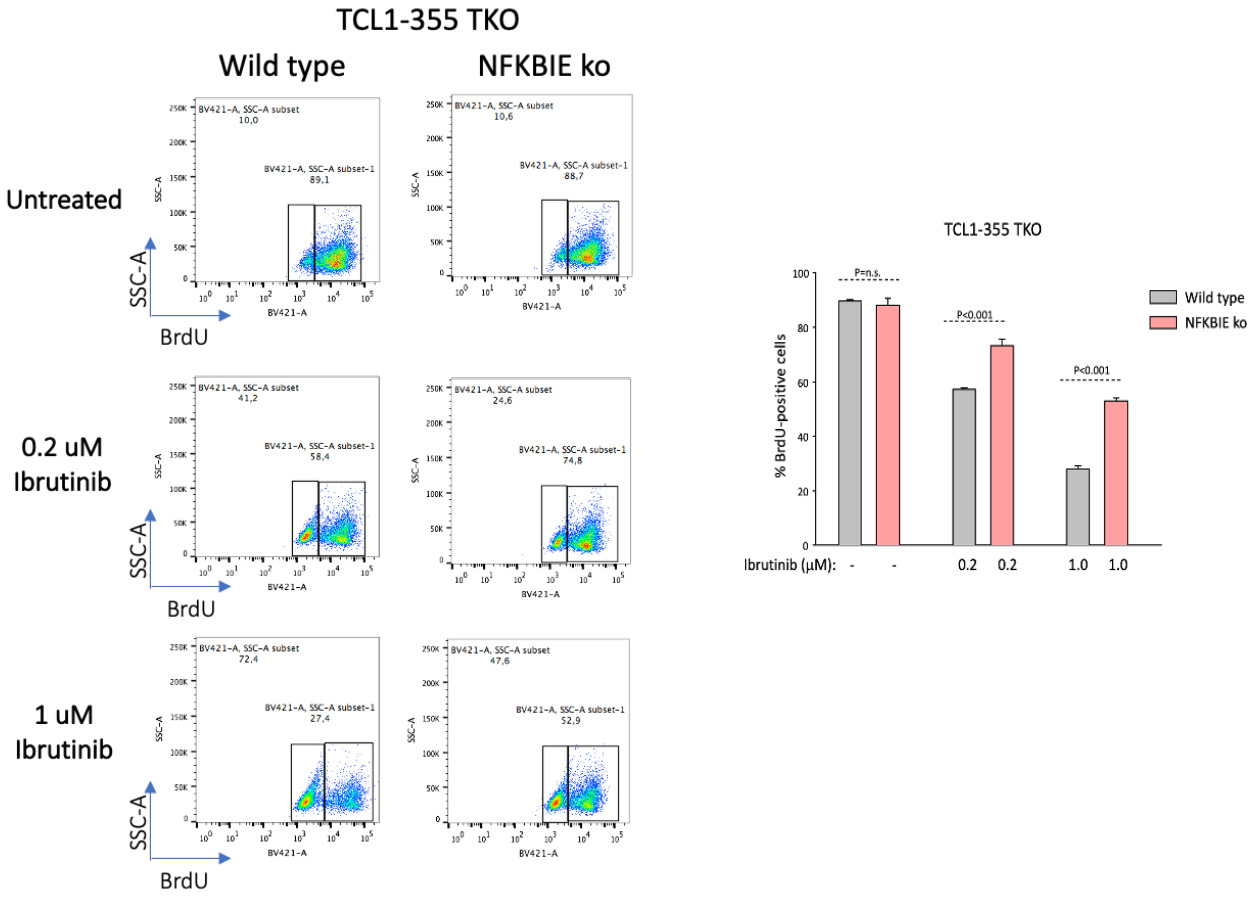


Figure 17. Analysis of proliferation and BCR inhibitor sensitivity of NFKBIE mutated CLL cells. Analysis of BrdU incorporation in TCL1 NFKBIE ko cells treated with ibrutinib. The analysis was done after 48 hours in culture, BrdU was present in the culture medium during the last 14 hours. Graph shows summary of results from 3 independent experiments. Significance of differences with respect to untreated cells was evaluated with the paired *t* test.

4.9. NFKBIE-mutated TCL1 leukemia cells are positively selected by ibrutinib *in vitro*

To further validate the findings from the BrdU-incorporation experiments showing reduced sensitivity of NFKBIE-mutated cells to ibrutinib treatment, we conducted *in vitro* competition experiments by mixing NFKBIE wild type and mutated cells and treating them with ibrutinib or control vehicle for two weeks. Consistent with the previous finding, the *in vitro* competition experiments showed positive selection of NFKBIE-mutated cells in the presence of ibrutinib, as evidenced by the significant increase in mutant allele frequency at day 7 and day 14 of culture (Figure 18).

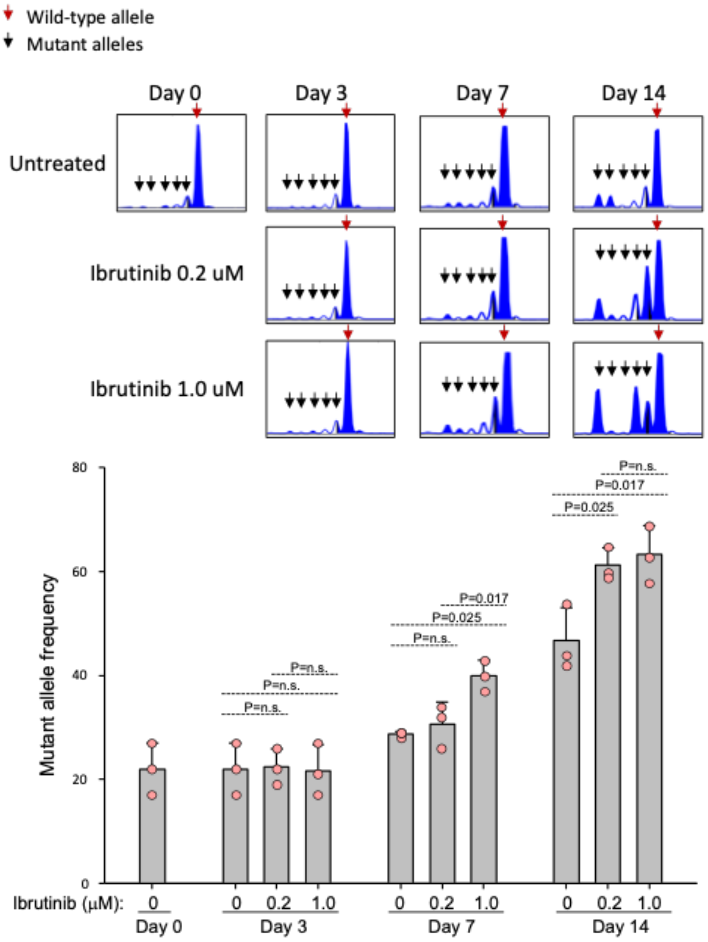


Figure 18. Changes in NFKBIE mutant allele frequency during ibrutinib treatment in vitro. NFKBIE knockout and wild type TCL1 leukemia cells were mixed at a 1:3, 1:4 and 1:5 ratio and cultured in the presence or absence of ibrutinib (0.2 or 1.0 μM). DNA was isolated at the indicated time points for indel analysis by amplicon capillary electrophoresis. Summary of the data is shown in the left panel and the analysis of the samples from the 1:4 mixture in the right panels. Statistical analysis was done using One Way RM ANOVA with Holm-Sidak test for multiple comparisons.

4.10. Inhibition of Total-p65 and p52 nuclear translocation by ibrutinib is reduced in NFKBIE-mutated TCL1 leukemia cells

To better understand the mechanism through which mutations in the NFKBIE gene confer resistance to ibrutinib, we investigated the nuclear translocation of NF-kB transcription factors in NFKBIE mutated and wild type leukemic cells following treatment with ibrutinib via immunoblotting analysis. Ibrutinib-treated NFKBIE-mutated cells showed greater nuclear levels of the NF-kB subunits p65 and p52 compared to ibrutinib-treated wild type cells, suggesting that the aberrant regulation of the transcriptional activity of these subunits could be responsible for the growth advantage of the NFKBIE-mutated cells. In contrast, no differences were observed with respect to the nuclear levels of

Rel and p50, suggesting that the nuclear translocation of these subunits is not affected by the absence of the IkBε protein (Figure 19).

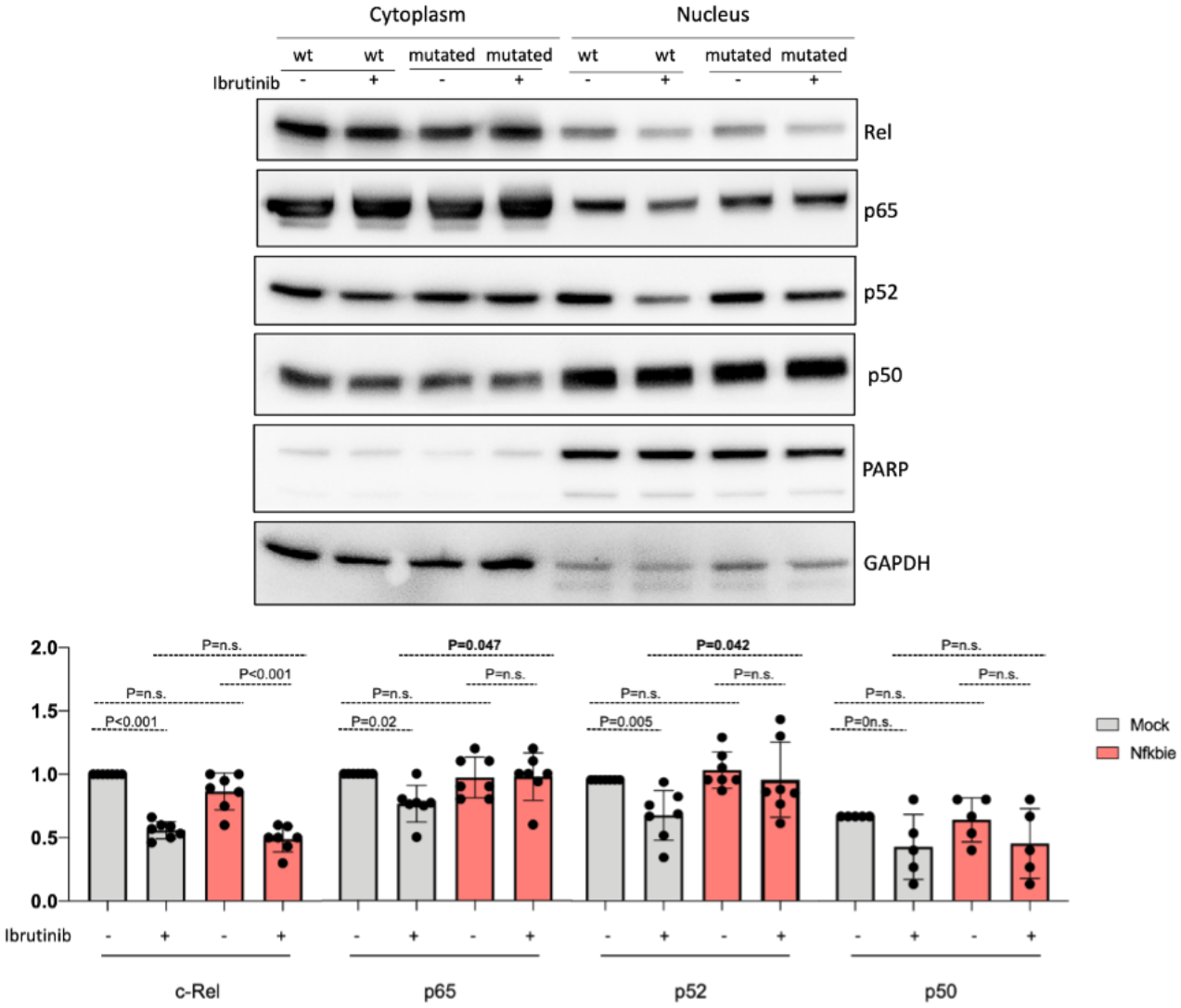


Figure 19. Immunoblotting analysis of NF-kB transcriptional factors following ibrutinib treatment. Nuclear and cytoplasmic protein extracts from NFKBIE mutated and wild type leukemic cells after were extracted after 22h of ibrutinib treatment with NE-PER kit. Statistical analysis done with One Way Repeated Measures ANOVA and Tukey test for multiple comparisons

4.11. NFKBIE-mutated TCL1 leukemia cells are positively selected by ibrutinib *in vivo*

The greater resistance of NFKBIE-mutated cells to ibrutinib was further validated by *in vivo* competition experiments. Mixed cultures of cells with wild-type and mutated NFKBIE were inoculated intraperitoneally in syngeneic C57BL/6 mice and after 3 days mice were treated with ibrutinib or vehicle control. MAF analysis of leukemic cells isolated from peritoneal cavity (PC), peripheral blood (PB), and spleen showed a significantly greater increase in NFKBIE mutant allele frequency in mice treated with ibrutinib compared to controls in all three investigated compartments after 2 weeks of treatment (Figure 20).

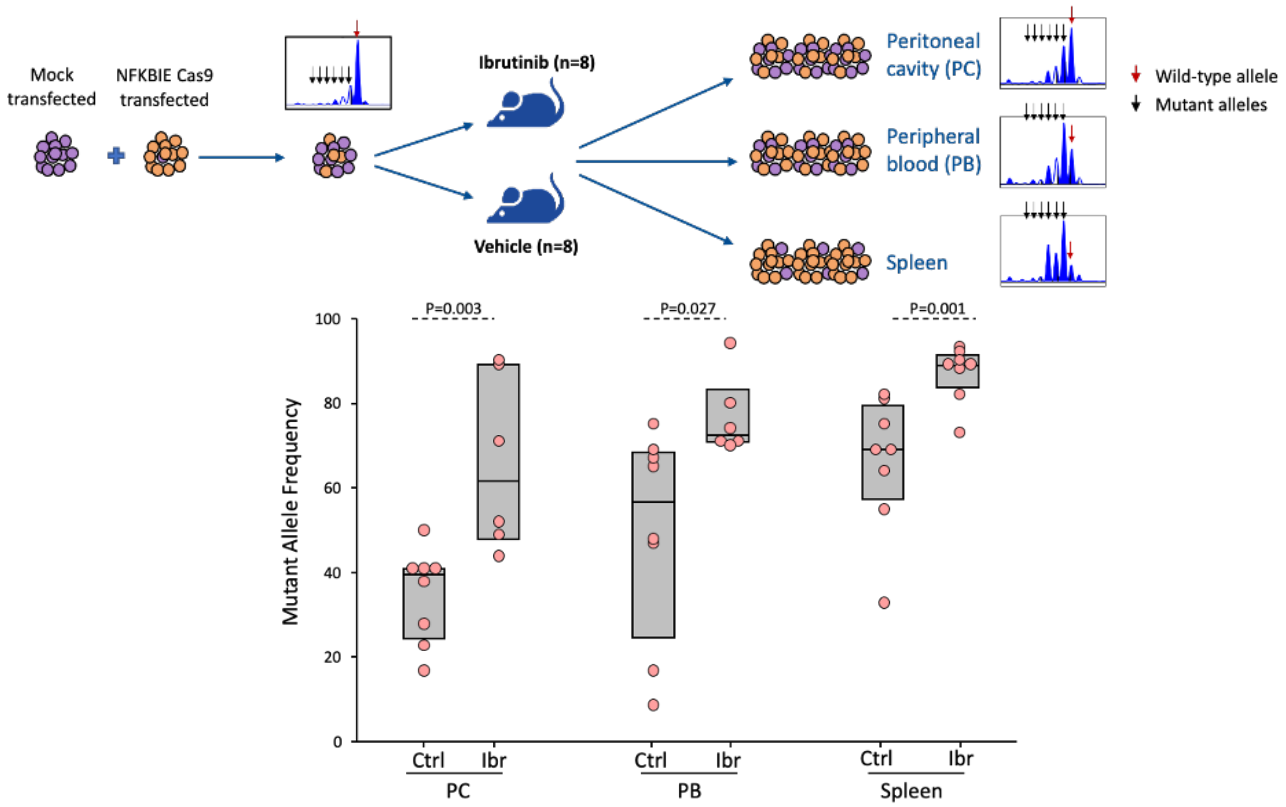


Figure 20. MAF analysis during *in vivo* ibrutinib treatment. NFKBIE knockout and wild type TCL1 leukemia cells were mixed at a 1:3 ratio and injected in 16 wild-type mice, 8 treated with ibrutinib and 8 with vehicle control. After leukemia expansion, CLL cells were isolated, purified and DNA was extracted from peritoneal cavity (PC), peripheral blood (PB) and spleen (SP) for MAF analysis by amplicon capillary electrophoresis.

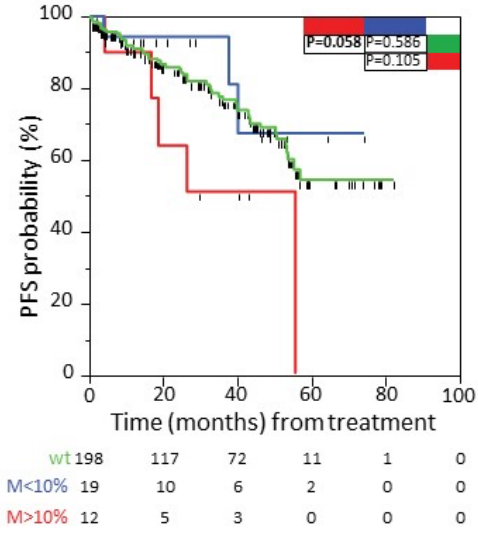
4.12. Ibrutinib-treated NFKBIE-mutated patients have reduced overall survival compared to ibrutinib-treated NFKBIE wild type patients

To validate these findings in the clinical setting, we investigated the presence of NFKBIE mutations in a cohort of 229 ibrutinib-treated CLL patients. Mutations in NFKBIE were detected in pre-treatment samples from 13.5% of the patients, among whom 5.2% had a variant allele frequency of >10% and 8.3% had a variant allele frequency of <10% (Figure 21A). Kaplan-Meier survival curves calculated from the beginning of ibrutinib treatment showed a trend towards reduced progression-free survival for the NFKBIE-mutated patients with variant allele frequency more than 10% (Figure 21B), along with a significantly reduced overall survival for the whole cohort of NFKBIE-mutated patients when low-VAF and high-VAF patients are combined (Figure 21C).

A

NFKBIE status	Number of cases	%
Wild Type (wt)	198/229	**86.5%**
NFKBIE mutated VAF>10% (M>10%)	12/229	5.2%
NFKBIE mutated VAF<10% (M<10%)	19/229	8.3%
Total NFKBIE mutated (M)	31/229	**13.5%**

B.



C.

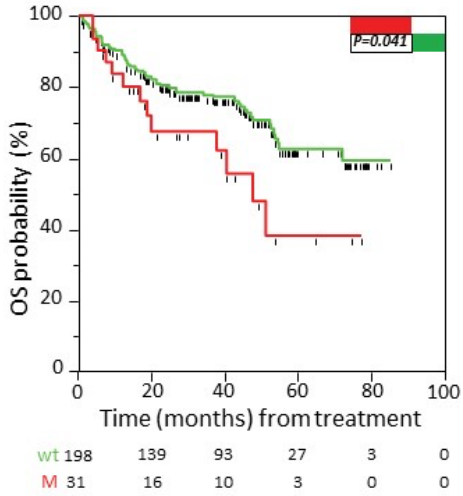


Figure 21. Kaplan Meier survival analysis from initiation of ibrutinib treatment in CLL patients segregated based on NFKBIE mutations. **A.** Number and percentage of cases with NFKBIE mutations. **B.** Progression-free survival of the investigated patients. Green color indicates unmutated cases (n=198), blue color indicates NFKBIE-mutated cases with a VAF<10% (n=12), and red color indicates cases with a VAF>10% (n=19). **C.** Overall survival of NFKBIE-wild type (green color) and NFKBIE-mutated cases (red color).

4.13. NFKBIE-mutated TCL1 leukemia cells remain sensitive to PI3K and SYK inhibitors

We next investigated whether leukemic cells with mutated NFKBIE remain sensitive to other BCR inhibitors. For this purpose, we tested their growth in the presence of the PI3K inhibitor idelalisib or the SYK inhibitor fostamatinib, both approved for clinical use. These drugs were investigated because their targets are positioned upstream of BTK and would therefore be expected to inhibit a broader range of signaling pathways downstream of the BCR compared to ibrutinib (Figure 6). In contrast to ibrutinib, both drugs inhibited the proliferation of NFKBIE-mutated cells in vitro, with a greater effect observed with idelalisib (Figure 22A). Moreover, in vitro competition experiments showed no change in the proportion of NFKBIE-mutated cells in the presence of idelalisib over a period of 14 days in culture, further suggesting that NFKBIE mutations do not confer resistance to treatment with a PI3K or SYK inhibitor (Figure 22B).

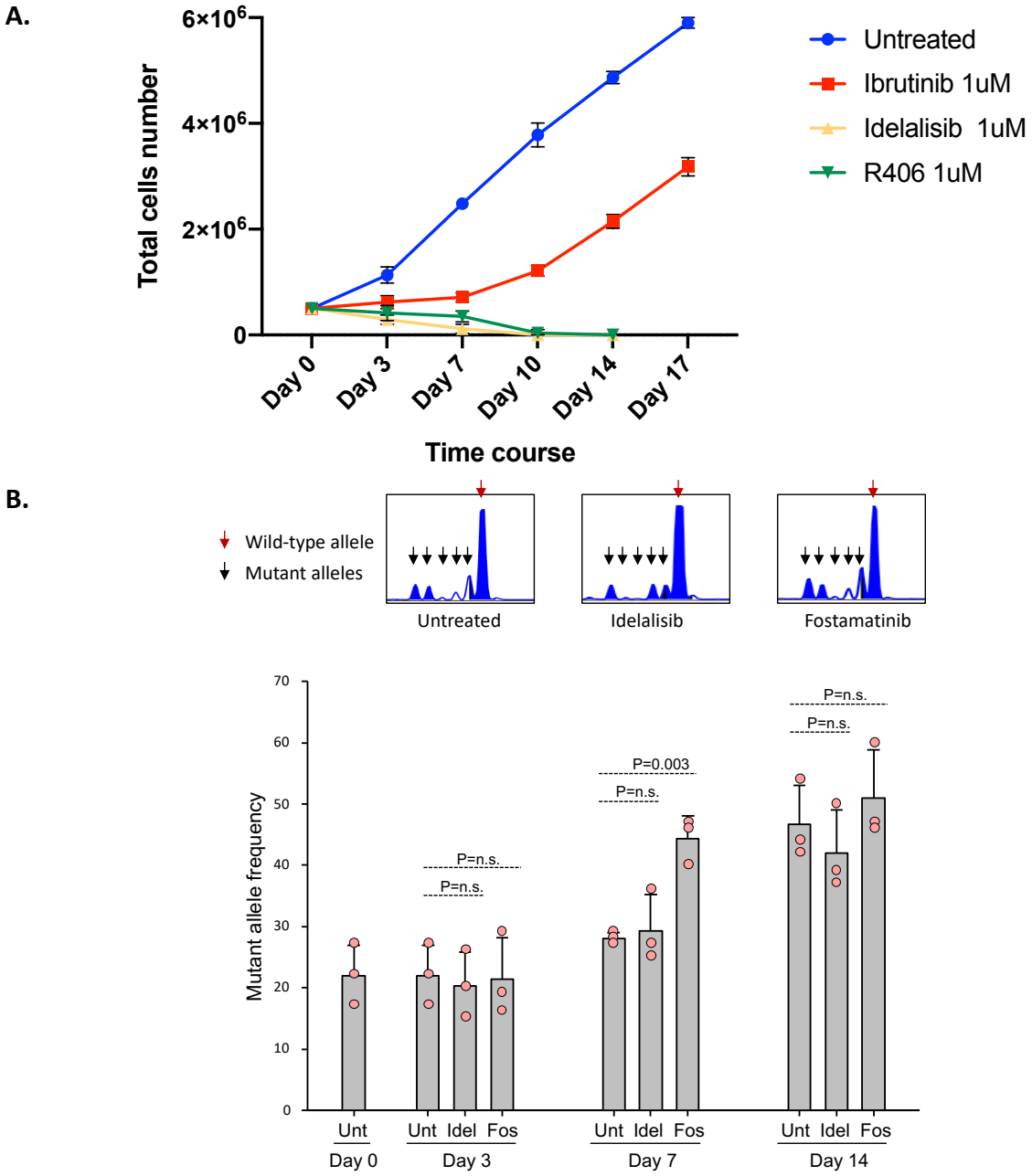


Figure 22. Changes in NFKBIE MAF during fostamatinib and idelalisib treatment *in vitro*. NFKBIE knockout and wild type TCL1 leukemia cells were mixed at a 1:3 ratio and cultured in the presence or absence of idelalisib or fostamatinib (1.0 uM). DNA was isolated at the indicated time points for indel analysis by amplicon capillary electrophoresis. Summary of the data is shown in the left panel and the analysis of the samples from the 1:4 mixture in the right panels. Statistical analysis was done using One Way RM ANOVA with Holm-Sidak test for multiple comparisons.

5. Discussion

The NF-kB pathway is constitutively activated in patients with Chronic Lymphocytic Leukemia and thus plays a significant role in disease development and progression. Mutations in the NFKBIE gene are among the more common genetic lesions in CLL, reported at frequencies ranging from 3% to 11% of untreated CLL patients (*Damm et al., 2014; Brieghel et al., 2020; Mansouri et al., 2023*). Transcriptome analysis of paired peripheral blood and lymph node (LN) CLL samples revealed prominent activation of the NF-kB pathway in most LN CLL cells from patients (*Herishanu et al., 2011; Sun et al., 2022*). The constitutive NF-kB activity can be reduced by treatment with a BTK or SYK inhibitor, implying that the NF-kB pathway is abnormally activated in the majority of CLL cases by external signals received in the LN microenvironment (*Herman et al., 2013; Herman et al.,2014*). However, the role of NFKBIE genetic lesions in CLL pathogenesis and treatment resistance is still largely unknown.

The data presented in this thesis show that the introduction of NFKBIE genetic lesions in previously established autoreactive leukemia cell line which can spontaneously proliferate *in vitro* (*Chakraborty et al., 2021*) does not confer growth advantage to the leukemic cells *in vitro*. However, repeated BCR, TLR or TNFR stimulation of these cells with anti-IgM, PtC, CpG-DNA or TNFα, respectively, results in 2-3 fold increase in MAF, suggesting that NFKBIE mutations provide a growth advantage when the cells are exposed to certain microenvironmental signals. This possibility was additionally supported by our *in vivo* competition experiments showing increased NFKBIE mutant allele frequencies in spleen of recipient mice compared to peritoneal cavity, indicating that NFKBIE-mutated CLL cells are differently selected by microenvironmental signals in different anatomical compartment. Consistent with this possibility, previous studies have shown that NFKBIE-deficient mouse B1 and marginal zone B cells (MZB) hyperproliferate in response to T-cell independent stimuli, such as the TLR agonist CpG and LPS or anti-IgM (*Alves et al., 2014; Della Valle et al., 2020*). However, the mechanism causing growth advantage of NFKBIE mutated leukemic cells following certain simulation is still unknown. Ablation of IκBε in murine B cells has been reported to have a role in limiting cRel and p65-containing dimers in a stimulus-specific manner (*Alves et al., 2014*). Moreover, in NFKBIE mutated CLL cases, the reduced expression of IκBε protein levels have been reported to result in increased phosphorylation and nuclear translocation of p65, suggesting greater activation of this subunit (*Mansouri et al., 2015*). Here, to further define the mechanism involved in the selection of NFKBIE mutated cells following exposure to certain stimuli, I performed a time course immunoblotting analysis of nuclear

and cytoplasmic protein extracts derived from NFKBIE mutated and wild type cells stimulated with CpG-DNA. In accordance with the study of Mansouri et al, CpG-stimulated NFKBIE mutated cells showed significantly greater nuclear translocation of the NF-kB subunits p65 and p52, suggesting that aberrant regulation of the transcriptional activity of these subunits could be responsible for the growth advantage of the NFKBIE-mutated cells.

CLL is a B-cell malignancy characterized by substantial immune system alterations and defects, as well as a strong reliance on the microenvironment niche. It is known that blood samples of CLL patients exhibit an increased number of T cells with an inversion of the CD4/CD8 ratio (*Nunes et al., 2012; Elston et al., 2020; Roessner et al., 2020*). In line with this observation, we showed a significant increase in the number of CD8+ T cells which resulted in the inversion of the CD4+/CD8+ ratio, along with a significant increase in the number of macrophages in spleens of mice receiving NFKBIE-mutated cells compared with NFKBIE-wild type cells. Different studies have reported that the increased expression of exhaustion markers, such as PD-1, TIM-3, LAG-3, CD160, CD244, CTLA-4 and TIGIT, on CD8+ and/or CD4+ T-cells in CLL patient samples leads to the loss of T-cell function and reduced immune anti-tumor response (*Nunes et al., 2012; Brusa et al., 2013; Riches et al., 2013; Motta et al., 2005; Novak et al., 2015; Wu et al., 2016; Taghiloo et al., 2017; Hanna et al., 2019, Catakovic et al., 2017, Arruga et al., 2020, Hajiasghar-Sharbaf et al., 2021*). However, the individual effect that recurrent genetic mutations exert on the tumor immune microenvironment in CLL is still unknown and requires further study. A major novelty of this thesis is the finding that NFKBIE-mutated cells induce multiple changes in the tumor microenvironment that can contribute to escape from immune surveillance. In particular, we demonstrated that NFKBIE mutations cause the overexpression of PD-L1 on the malignant B cells, and result in increased expression of the immune checkpoints PD-1 and TIGIT on CD4+ and CD8+ T cells and LAG3 on CD4+ T cells, suggesting that they promote T cell exhaustion and immune evasion. The mechanism how NFKBIE mutations in CLL cells affect the expression of immune checkpoint receptors on T cells is still not clear but is likely related to increased expression of some of the multitude of immunoregulatory cytokines and chemokines that were overexpressed by the NFKBIE-mutated CLL cells, such as Ccl3, Ccl4, Ccl5, Ccl22, Cxcl10, Csf1, Tnfα and Ifnγ.

Recently, a study by Mangolini et al. reported that NOTCH1 mutations may also facilitate immune evasion of the malignant B cells by up- regulating PD-L1 and silencing of the entire HLA-class II locus via epigenetic regulation of the transcriptional co-activator CIITA (*Mangolini et al., 2022*). In addition, increased expression of PD-1 on CD8+ T cells, but not of CD4+ T cells, was observed in the NOTCH1

positive samples, indicating terminal differentiation and exhaustion of CD8+ cells. Although similar, these effects are not identical to the ones we observed in the NFKBIE-mutated tumors, where we did not observe a downregulation of MHC class II genes while observing changes in the expression of PD-1 and other exhaustion markers on CD4+ T cells. These findings suggest that the mechanisms of immune evasion of the malignant B cells driven by NFKBIE gene mutations are different from the ones driven by NOTCH1 mutations.

Altogether, the findings of this thesis show that the NFKBIE-mutated cells have a growth advantage because of two distinct mechanisms: first, these cells were found to respond more strongly to microenvironmental stimuli that activate the canonical NF-kB pathway, resulting in greater positive selection in vivo, and second, the mutated cells induced multiple changes in the tumor microenvironment that can potentially allow for escape from immune surveillance. Both of these findings are novel, but particularly the second observation is unexpected and opens new avenues for research, because it suggests that certain genetic lesions may contribute to disease progression by dampening the anti-tumor immune response.

Another major finding of this thesis is the observation that NFKBIE mutations can confer resistance to treatment with the BTK inhibitor ibrutinib. This drug has emerged as the most effective therapeutic option in CLL, inducing clinical responses in the majority of patients. However, a substantial proportion subsequently shows disease progression. Mechanism of resistance to ibrutinib has been associated to acquired mutations in BTK, which prevent the binding of ibrutinib to BTK, and mutations in PLCG2 that allow the activation of PLCG2 despite the inhibition of BTK (*Woyach et al., 2014; Furman et al., 2014*). Although these mutations have been reported in 50% to 80% of patients that progress to ibrutinib, at the time of progression the percentage of cells with these mutations is very low, suggesting that there are additional mechanisms implicated in ibrutinib resistance (*Woyach JA et al., 2014; Furman et al., 2014*). Mutations in NOTCH1 have been associated with impaired nodal response, shorter progression free survival (PSF) and overall survival (OS) in patients treated with ibrutinib compared with NOTCH1-wild type patients (*Del Poeta et al., 2021*). In addition, PFS and OS calculated from the start of ibrutinib treatment are reduced in CLL patients with concomitant TP53 mutation and deletion compared to TP53 wild type cases (*Brieghel C et al, 2021; Bomben et al, 2023*). Mutations that involve NF-kB pathway genes have been associated with resistance to Ibrutinib in another B cell malignancy, the mantle cell lymphoma (MCL) (*Rahal et al., 2014 Wu et al., 2016*). Here, I show that mutations in NFKBIE can represent another mechanism of ibrutinib resistance showing that NFKBIE-mutated TCL1 leukemia cells are less sensitive to inhibition of proliferation induced by

Ibrutinib, and that they are positively selected by this drug *in vitro*. This finding was additionally supported by our *in vivo* competition experiments showing significant increase in NFKBIE mutant allele frequencies in spleen, PC and peripheral blood of recipient mice that received ibrutinib compared to controls, indicating that NFKBIE mutations can confer greater resistance to ibrutinib treatment. Moreover, Ibrutinib treated NFKBIE-mutated cells showed significantly greater nuclear translocation of the NF-kB subunits p65 and p52, reinforcing the hypothesis that the aberrant regulation of the transcriptional activity of these two subunits could be responsible for the growth advantage and resistance to ibrutinib treatment of NFKBIE-mutated CLL cells.

In addition, the NFKBIE mutations have also been associated with greater resistance to chemoimmunotherapy in patients, as reported in the study of *Damm et al.* They reported that patients with NFKBIE mutations treated with chemoimmunotherapy exhibited shorter time to first treatment and shorter PFS (*Damm et al., 2014; Brieghel et al., 2020; Mansouri et al., 2023*). Here, we showed that mutations in NFKBIE gene are also associated with reduced overall survival in patients treated with ibrutinib carrying NFKBIE mutations, compared to NFKBIE wild type patients. Moreover, our *in vitro* experiments showed that NFKBIE-mutated CLL cells remain sensitive to the treatment with PI3K inhibitor idelalisib, and the SYK inhibitor fostamatinib, suggesting that NFKBIE mutations do not confer resistance to treatment with these other two BCR inhibitors, indicating that such drugs may represent an effective therapeutic option for CLL patients with NFKBIE mutations.

The main limitation of this thesis is that the experiments were performed with murine CLL cells, which may not entirely reflect the human situation. An alternative approach would have been to perform these experiments using patient-derived CLL or RS xenograft models. However, using only the latter approach, the impact of the NFKBIE mutations on the tumor microenvironment would have remined unnoticed. Nonetheless, the impact of NFKBIE mutations on response to ibrutinib treatment should be further validated in the PDX models and such efforts are ongoing.

6. Appendix

NFKBIE_vitro_vs_MOCK_vitro_egoALL_ABS_LFC1

ONTOLOGY	ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count	Symbols
BP	GO:0051249	regulation of lymphocyte activation	25/260	469/14199	1,73695E-06	0,005460967	0,005126742	25	Hmces;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Nod2;Il2ra;Zc3h12d;Inpp5d;Pik3r6;Icosl;Rasal3;Fanca;Slamf7;Cd22;Rhbdd3;Pla2g2d;Cd59a;Tbx21
BP	GO:0002250	adaptive immune response	23/260	439/14199	6,11254E-06	0,007446018	0,006990302	23	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Fyn;Gpr183;Cd4;Tnf;Lta;Mef2c;Tnfrsf13b;Nod2;C4bp;Lig4;Inpp5d;Relb;Aire;Icosl;Pdcd1;Slamf7;Prkcb;Tbx21
BP	GO:0016064	immunoglobulin mediated immune response	13/260	160/14199	7,73823E-06	0,007446018	0,006990302	13	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Tnf;Lta;Nod2;C4bp;Lig4;Inpp5d;Icosl;Tbx21
BP	GO:0019724	B cell mediated immunity	13/260	163/14199	9,47331E-06	0,007446018	0,006990302	13	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Tnf;Lta;Nod2;C4bp;Lig4;Inpp5d;Icosl;Tbx21
BP	GO:0002381	immunoglobulin production involved in immunoglobulin-mediated immune response	9/260	79/14199	1,35587E-05	0,008525685	0,008003891	9	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Nod2;Lig4;Icosl;Tbx21
BP	GO:0051251	positive regulation of lymphocyte activation	18/260	314/14199	1,97569E-05	0,009054584	0,008500419	18	Hmces;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Gpr183;Cd4;Mef2c;Cd6;Nod2;Il2ra;Inpp5d;Pik3r6;Icosl;Rasal3;Cd59a;Tbx21
BP	GO:0050670	regulation of lymphocyte proliferation	15/260	228/14199	2,01597E-05	0,009054584	0,008500419	15	H2-DMb2;H2-Ab1;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Il2ra;Zc3h12d;Inpp5d;Icosl;Rasal3;Cd22;Pla2g2d;Cd59a
BP	GO:0032944	regulation of mononuclear cell proliferation	15/260	231/14199	2,35044E-05	0,009237232	0,008671889	15	H2-DMb2;H2-Ab1;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Il2ra;Zc3h12d;Inpp5d;Icosl;Rasal3;Cd22;Pla2g2d;Cd59a
BP	GO:0002399	MHC class II protein complex assembly	4/260	11/14199	3,27632E-05	0,010123492	0,009503908	4	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1
BP	GO:0002503	peptide antigen assembly with MHC class II protein complex	4/260	11/14199	3,27632E-05	0,010123492	0,009503908	4	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1
BP	GO:0060402	calcium ion transport into cytosol	11/260	134/14199	3,54193E-05	0,010123492	0,009503908	11	Cacna1d;Fyn;Cd4;Ddit3;Akap5;Tmbim6;Bak1;Cxcr3;Chd7;Ffar1;Ryr3
BP	GO:0042110	T cell activation	23/260	498/14199	4,54418E-05	0,011905741	0,011177078	23	H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Fyn;Gpr183;Cd4;Cd6;Il2ra;Zc3h12d;Lig4;Relb;Pik3r6;Aire;Icosl;Rasal3;Fanca;Chd7;Slamf7;Pla2g2d;Cd59a;Tbx21
BP	GO:0070663	regulation of leukocyte proliferation	15/260	247/14199	5,10158E-05	0,012337975	0,011582859	15	H2-DMb2;H2-Ab1;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Il2ra;Zc3h12d;Inpp5d;Icosl;Rasal3;Cd22;Pla2g2d;Cd59a
BP	GO:0002920	regulation of humoral immune response	6/260	39/14199	6,99066E-05	0,015699027	0,014738205	6	H2-DMa;Tnf;Lta;Nod2;C4bp;Cd59a
BP	GO:1903037	regulation of leukocyte cell-cell adhesion	17/260	318/14199	8,03604E-05	0,016716758	0,015693648	17	Rela;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Tnf;Cd6;Il2ra;Zc3h12d;Pik3r6;Icosl;Rasal3;Pla2g2d;Cd59a;Tbx21
BP	GO:0046651	lymphocyte proliferation	16/260	290/14199	9,02336E-05	0,016716758	0,015693648	16	H2-DMb2;H2-Ab1;Fyn;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Il2ra;Zc3h12d;Inpp5d;Icosl;Rasal3;Cd22;Pla2g2d;Cd59a
BP	GO:1903039	positive regulation of leukocyte cell-cell adhesion	14/260	231/14199	9,27254E-05	0,016716758	0,015693648	14	Rela;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Tnf;Cd6;Il2ra;Pik3r6;Icosl;Rasal3;Cd59a
BP	GO:0032943	mononuclear cell proliferation	16/260	293/14199	0,00010176	0,016716758	0,015693648	16	H2-DMb2;H2-Ab1;Fyn;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Il2ra;Zc3h12d;Inpp5d;Icosl;Rasal3;Cd22;Pla2g2d;Cd59a
BP	GO:0002377	immunoglobulin production	13/260	208/14199	0,0001212	0,016716758	0,015693648	13	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Tnf;Nod2;Tmbim6;Nipal3;Lig4;Icosl;Cd22;Tbx21
BP	GO:0002696	positive regulation of leukocyte activation	18/260	362/14199	0,000124875	0,016716758	0,015693648	18	Hmces;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Gpr183;Cd4;Mef2c;Cd6;Nod2;Il2ra;Inpp5d;Pik3r6;Icosl;Rasal3;Cd59a;Tbx21
BP	GO:0002683	negative regulation of immune system process	19/260	395/14199	0,000125166	0,016716758	0,015693648	19	Tjp2;H2-Ab1;Cd47;Gfer;Tmem176a;Tnf;Tnfrsf13b;Nod2;Tmbim6;Il2ra;C4bp;Zc3h12d;Inpp5d;Pdcd1;Cd22;Rhbdd3;Pla2g2d;Cd59a;Tbx21
BP	GO:0002396	MHC protein complex assembly	4/260	15/14199	0,000127903	0,016716758	0,015693648	4	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1
BP	GO:0002501	peptide antigen assembly with MHC protein complex	4/260	15/14199	0,000127903	0,016716758	0,015693648	4	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1
BP	GO:0014015	positive regulation of gliogenesis	7/260	62/14199	0,00013262	0,016716758	0,015693648	7	Synj1;Rela;Egr2;Tnf;Lta;Actr3;Flt1
BP	GO:0060401	cytosolic calcium ion transport	11/260	155/14199	0,000132926	0,016716758	0,015693648	11	Cacna1d;Fyn;Cd4;Ddit3;Akap5;Tmbim6;Bak1;Cxcr3;Chd7;Ffar1;Ryr3
BP	GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	17/260	334/14199	0,000145679	0,01732932	0,01626872	17	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Cd4;Tnf;Lta;Mef2c;Nod2;C4bp;Lig4;Inpp5d;Relb;Aire;Icosl;Tbx21
BP	GO:0010522	regulation of calcium ion transport into cytosol	8/260	84/14199	0,00014882	0,01732932	0,01626872	8	Fyn;Cd4;Akap5;Tmbim6;Bak1;Cxcr3;Chd7;Ffar1
BP	GO:0050867	positive regulation of cell activation	18/260	381/14199	0,000235065	0,026394447	0,024779037	18	Hmces;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Gpr183;Cd4;Mef2c;Cd6;Nod2;Il2ra;Inpp5d;Pik3r6;Icosl;Rasal3;Cd59a;Tbx21
BP	GO:0070661	leukocyte proliferation	16/260	318/14199	0,000259601	0,027759657	0,026060693	16	H2-DMb2;H2-Ab1;Fyn;Gpr183;Cd4;Mef2c;Cd6;Tnfrsf13b;Il2ra;Zc3h12d;Inpp5d;Icosl;Rasal3;Cd22;Pla2g2d;Cd59a
BP	GO:0007159	leukocyte cell-cell adhesion	17/260	352/14199	0,000270951	0,027759657	0,026060693	17	Rela;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Tnf;Cd6;Il2ra;Zc3h12d;Pik3r6;Icosl;Rasal3;Pla2g2d;Cd59a;Tbx21
BP	GO:0002922	positive regulation of humoral immune response	4/260	18/14199	0,000274576	0,027759657	0,026060693	4	H2-DMa;Tnf;Lta;Nod2
BP	GO:0022407	regulation of cell-cell adhesion	19/260	421/14199	0,000282541	0,027759657	0,026060693	19	Epcam;Rela;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Tnf;Mbp;Cd6;Il2ra;Zc3h12d;Pik3r6;Icosl;Rasal3;Pla2g2d;Cd59a;Tbx21
BP	GO:0050863	regulation of T cell activation	16/260	322/14199	0,000298548	0,028443508	0,02670269	16	H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Cd6;Il2ra;Zc3h12d;Pik3r6;Icosl;Rasal3;Fanca;Pla2g2d;Cd59a;Tbx21
BP	GO:0002698	negative regulation of immune effector process	9/260	118/14199	0,000317153	0,029174416	0,027388865	9	Cd47;Gfer;Tnf;Nod2;Tmbim6;C4bp;Cd22;Cd59a;Tbx21
BP	GO:0014013	regulation of gliogenesis	8/260	94/14199	0,000324779	0,029174416	0,027388865	8	Synj1;Rela;Egr2;Tnf;Lta;Actr3;Atf5;Flt1
BP	GO:0002923	regulation of humoral immune response mediated by circulating immunoglobulin	4/260	19/14199	0,000342819	0,029939483	0,028107108	4	Tnf;Lta;Nod2;C4bp
BP	GO:0002449	lymphocyte mediated immunity	16/260	330/14199	0,00039183	0,033294966	0,031257226	16	Hmces;H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Gfer;Tnf;Lta;Nod2;C4bp;Lig4;Inpp5d;Pik3r6;Aire;Icosl;Tbx21
BP	GO:0019886	antigen processing and presentation of exogenous peptide antigen via MHC class II	4/260	20/14199	0,000422393	0,034758728	0,032631402	4	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1
BP	GO:0022409	positive regulation of cell-cell adhesion	14/260	268/14199	0,000431167	0,034758728	0,032631402	14	Rela;H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Tnf;Cd6;Il2ra;Pik3r6;Icosl;Rasal3;Cd59a
BP	GO:0050870	positive regulation of T cell activation	12/260	208/14199	0,000457747	0,035978943	0,033776937	12	H2-DMa;H2-DMb2;H2-Ab1;Cd47;H2-Eb1;Cd4;Cd6;Il2ra;Pik3r6;Icosl;Rasal3;Cd59a
BP	GO:0002437	inflammatory response to antigenic stimulus	6/260	57/14199	0,00059063	0,045291246	0,042519303	6	Tnf;Lta;Cd6;Nod2;Il2ra;Pla2g2d
CC	GO:0042613	MHC class II protein complex	4/262	12/14331	4,81479E-05	0,017766593	0,017766593	4	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1
MF	GO:0023026	MHC class II protein complex binding	5/259	13/14018	2,36201E-06	0,001164469	0,001141222	5	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Cd4
MF	GO:0023023	MHC protein complex binding	5/259	23/14018	5,30757E-05	0,013083155	0,012821967	5	H2-DMa;H2-DMb2;H2-Ab1;H2-Eb1;Cd4

NFKBIE_peritoneal_vs_MOCK_peritoneal_egoALL_ABS_LFC1

ONTOLOGY	ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count	Symbols
BP	GO:0006935	chemotaxis	156/2425	463/14199	8,49347E-19	4,86761E-15	3,96511E-15	156	[illegible]
BP	GO:0042330	taxis	156/2425	467/14199	2,12846E-18	6,09909E-15	4,96826E-15	156	[illegible]
BP	GO:0050900	leukocyte migration	121/2425	329/14199	3,73508E-18	7,13524E-15	5,8123E-15	121	[illegible]
BP	GO:0002274	myeloid leukocyte activation	87/2425	217/14199	5,44839E-16	7,80618E-13	6,35884E-13	87	[illegible]
BP	GO:0060326	cell chemotaxis	96/2425	258/14199	4,93209E-15	5,65316E-12	4,60502E-12	96	[illegible]
BP	GO:0002683	negative regulation of immune system process	128/2425	395/14199	3,58268E-14	3,42206E-11	2,78758E-11	128	[illegible]
BP	GO:0030595	leukocyte chemotaxis	77/2425	196/14199	9,40662E-14	7,70134E-11	6,27344E-11	77	[illegible]
BP	GO:0002250	adaptive immune response	137/2425	439/14199	1,18037E-13	8,45589E-11	6,88809E-11	137	[illegible]
BP	GO:0071674	mononuclear cell migration	66/2425	160/14199	3,8196E-13	2,43223E-10	1,98128E-10	66	[illegible]
BP	GO:0002443	leukocyte mediated immunity	130/2425	423/14199	1,73802E-12	9,96058E-10	8,1138E-10	130	[illegible]
BP	GO:0007159	leukocyte cell-cell adhesion	112/2425	352/14199	5,51001E-12	2,87071E-09	2,33846E-09	112	[illegible]
BP	GO:0097529	myeloid leukocyte migration	72/2425	192/14199	8,397E-12	4,01026E-09	3,26673E-09	72	[illegible]
BP	GO:0070661	leukocyte proliferation	103/2425	318/14199	1,21782E-11	5,36872E-09	4,37331E-09	103	[illegible]
BP	GO:0002696	positive regulation of leukocyte activation	113/2425	362/14199	1,72195E-11	6,83961E-09	5,57148E-09	113	[illegible]
BP	GO:0030335	positive regulation of cell migration	144/2425	498/14199	1,79016E-11	6,83961E-09	5,57148E-09	144	[illegible]
BP	GO:0050867	positive regulation of cell activation	117/2425	381/14199	2,4332E-11	8,71543E-09	7,09951E-09	117	[illegible]
BP	GO:0032943	mononuclear cell proliferation	96/2425	293/14199	2,96123E-11	9,98282E-09	8,13191E-09	96	[illegible]
BP	GO:0002460	adaptive immune response based on somatic recomb	105/2425	334/14199	5,68911E-11	1,81135E-08	1,47551E-08	105	[illegible]
BP	GO:0042110	T cell activation	142/2425	498/14199	7,44257E-11	2,24491E-08	1,82869E-08	142	[illegible]
BP	GO:0046651	lymphocyte proliferation	94/2425	290/14199	9,24393E-11	2,64885E-08	2,15773E-08	94	[illegible]
BP	GO:0002697	regulation of immune effector process	113/2425	372/14199	1,12523E-10	3,07081E-08	2,50146E-08	113	[illegible]
BP	GO:0045785	positive regulation of cell adhesion	125/2425	425/14199	1,20247E-10	3,13244E-08	2,55166E-08	125	[illegible]
BP	GO:0070663	regulation of leukocyte proliferation	83/2425	247/14199	1,58525E-10	3,95003E-08	3,21766E-08	83	[illegible]
BP	GO:0022409	positive regulation of cell-cell adhesion	88/2425	268/14199	1,74262E-10	4,16123E-08	3,3897E-08	88	[illegible]
BP	GO:0002685	regulation of leukocyte migration	71/2425	200/14199	2,14544E-10	4,83375E-08	3,93753E-08	71	[illegible]
BP	GO:0042098	T cell proliferation	75/2425	216/14199	2,19294E-10	4,83375E-08	3,93753E-08	75	[illegible]
BP	GO:0032944	regulation of mononuclear cell proliferation	78/2425	231/14199	4,35559E-10	9,24514E-08	7,5311E-08	78	[illegible]
BP	GO:0022407	regulation of cell-cell adhesion	122/2425	421/14199	5,61049E-10	1,11144E-07	9,05373E-08	122	[illegible]
BP	GO:0030855	epithelial cell differentiation	134/2425	475/14199	5,62413E-10	1,11144E-07	9,05373E-08	134	[illegible]
BP	GO:0050866	negative regulation of cell activation	70/2425	201/14199	7,51952E-10	1,43648E-07	1,17016E-07	70	[illegible]
BP	GO:0042119	neutrophil activation	23/2425	37/14199	1,04579E-09	1,93336E-07	1,5749E-07	23	[illegible]
BP	GO:0002263	cell activation involved in immune response	86/2425	269/14199	1,25161E-09	2,24155E-07	1,82595E-07	86	[illegible]
BP	GO:0050670	regulation of lymphocyte proliferation	76/2425	228/14199	1,41654E-09	2,46005E-07	2,00394E-07	76	[illegible]
BP	GO:0032496	response to lipopolysaccharide	81/2425	250/14199	1,87955E-09	3,16815E-07	2,58075E-07	81	[illegible]
BP	GO:0002366	leukocyte activation involved in immune response	84/2425	265/14199	3,07416E-09	5,03371E-07	4,10042E-07	84	[illegible]
BP	GO:0051249	regulation of lymphocyte activation	130/2425	469/14199	3,4276E-09	5,45655E-07	4,44485E-07	130	[illegible]
BP	GO:0002237	response to molecule of bacterial origin	84/2425	268/14199	5,56659E-09	8,62219E-07	7,02356E-07	84	[illegible]
BP	GO:0050727	regulation of inflammatory response	91/2425	299/14199	6,64061E-09	1,00151E-06	8,1582E-07	91	[illegible]
BP	GO:0042129	regulation of T cell proliferation	62/2425	178/14199	6,89507E-09	1,01322E-06	8,25362E-07	62	[illegible]
BP	GO:0002449	lymphocyte mediated immunity	98/2425	330/14199	7,19731E-09	1,03119E-06	8,40001E-07	98	[illegible]
BP	GO:0002703	regulation of leukocyte mediated immunity	82/2425	262/14199	9,09449E-09	1,26938E-06	1,03402E-06	82	[illegible]
BP	GO:0043410	positive regulation of MAPK cascade	116/2425	412/14199	9,3027E-09	1,26938E-06	1,03402E-06	116	[illegible]
BP	GO:0036230	granulocyte activation	24/2425	43/14199	9,56434E-09	1,27473E-06	1,03838E-06	24	[illegible]
BP	GO:0071675	regulation of mononuclear cell migration	42/2425	104/14199	1,49593E-08	1,94845E-06	1,58719E-06	42	[illegible]
BP	GO:1903037	regulation of leukocyte cell-cell adhesion	94/2425	318/14199	1,87341E-08	2,38589E-06	1,94352E-06	94	[illegible]
BP	GO:0051251	positive regulation of lymphocyte activation	93/2425	314/14199	2,00633E-08	2,49962E-06	2,03617E-06	93	[illegible]
BP	GO:0050920	regulation of chemotaxis	63/2425	187/14199	2,25129E-08	2,74514E-06	2,23617E-06	63	[illegible]
BP	GO:0032103	positive regulation of response to external stimulus	111/2425	397/14199	2,93237E-08	3,50113E-06	2,85199E-06	111	[illegible]
BP	GO:0002253	activation of immune response	89/2425	299/14199	3,12112E-08	3,63635E-06	2,96214E-06	89	[illegible]
BP	GO:0002819	regulation of adaptive immune response	67/2425	205/14199	3,17253E-08	3,63635E-06	2,96214E-06	67	[illegible]
BP	GO:0002687	positive regulation of leukocyte migration	50/2425	137/14199	3,53019E-08	3,96696E-06	3,23145E-06	50	[illegible]
BP	GO:0070371	ERK1 and ERK2 cascade	82/2425	270/14199	4,09044E-08	4,50814E-06	3,67229E-06	82	[illegible]
BP	GO:0002695	negative regulation of leukocyte activation	61/2425	182/14199	4,64211E-08	5,01961E-06	4,08893E-06	61	[illegible]
BP	GO:0019221	cytokine-mediated signaling pathway	98/2425	342/14199	5,1752E-08	5,49242E-06	4,47408E-06	98	[illegible]
BP	GO:1903131	mononuclear cell differentiation	117/2425	429/14199	5,57823E-08	5,81251E-06	4,73482E-06	117	[illegible]
BP	GO:0050870	positive regulation of T cell activation	67/2425	208/14199	5,98336E-08	6,12333E-06	4,98801E-06	67	[illegible]
BP	GO:0001525	angiogenesis	120/2425	444/14199	6,4997E-08	6,52559E-06	5,31569E-06	120	[illegible]
BP	GO:0070372	regulation of ERK1 and ERK2 cascade	77/2425	251/14199	6,60416E-08	6,52559E-06	5,31569E-06	77	[illegible]
BP	GO:0032611	interleukin-1 beta production	38/2425	94/14199	6,95614E-08	6,75689E-06	5,5041E-06	38	[illegible]
BP	GO:0034341	response to interferon-gamma	47/2425	128/14199	7,26444E-08	6,93875E-06	5,65225E-06	47	[illegible]
BP	GO:0050863	regulation of T cell activation	93/2425	322/14199	7,38805E-08	7,08206E-06	5,76898E-06	93	[illegible]
BP	GO:1903039	positive regulation of leukocyte cell-cell adhesion	72/2425	231/14199	8,68121E-08	8,01286E-06	6,5272E-06	72	[illegible]
BP	GO:0071219	cellular response to molecule of bacterial origin	62/2425	189/14199	8,80841E-08	8,01286E-06	6,5272E-06	62	[illegible]
BP	GO:0032612	interleukin-1 production	42/2425	110/14199	1,0023E-07	8,97533E-06	7,31122E-06	42	[illegible]
BP	GO:0070665	positive regulation of leukocyte proliferation	52/2425	149/14199	1,03309E-07	9,10869E-06	7,41986E-06	52	[illegible]
BP	GO:0002698	negative regulation of immune effector process	44/2425	118/14199	1,12343E-07	9,68185E-06	7,88675E-06	44	[illegible]
BP	GO:0001818	negative regulation of cytokine production	80/2425	267/14199	1,13189E-07	9,68185E-06	7,88675E-06	80	[illegible]
BP	GO:0002688	regulation of leukocyte chemotaxis	41/2425	107/14199	1,26448E-07	1,0657E-05	8,68107E-06	41	[illegible]
BP	GO:0009611	response to wounding	110/2425	403/14199	1,33064E-07	1,1052E-05	9,00289E-06	110	[illegible]
BP	GO:0032102	negative regulation of response to external stimulus	92/2425	322/14199	1,53025E-07	1,25283E-05	1,02055E-05	92	[illegible]
BP	GO:0050777	negative regulation of immune response	56/2425	167/14199	1,60046E-07	1,29187E-05	1,05234E-05	56	[illegible]
BP	GO:0071216	cellular response to biotic stimulus	67/2425	213/14199	1,64695E-07	1,31093E-05	1,06787E-05	67	[illegible]
BP	GO:0097530	granulocyte migration	47/2425	132/14199	2,11982E-07	1,64868E-05	1,3431E-05	47	[illegible]
BP	GO:0032946	positive regulation of mononuclear cell proliferation	48/2425	136/14199	2,14565E-07	1,64868E-05	1,3431E-05	48	[illegible]
BP	GO:0007599	hemostasis	51/2425	148/14199	2,15758E-07	1,64868E-05	1,3431E-05	51	[illegible]
BP	GO:0071222	cellular response to lipopolysaccharide	59/2425	181/14199	2,29466E-07	1,73035E-05	1,40953E-05	59	[illegible]
BP	GO:0007596	blood coagulation	50/2425	145/14199	2,7615E-07	2,05535E-05	1,67427E-05	50	[illegible]
BP	GO:1990266	neutrophil migration	41/2425	110/14199	3,04981E-07	2,24083E-05	1,82536E-05	41	[illegible]
BP	GO:0050671	positive regulation of lymphocyte proliferation	47/2425	134/14199	3,53145E-07	2,56186E-05	2,08687E-05	47	[illegible]
BP	GO:0042742	defense response to bacterium	69/2425	226/14199	3,82996E-07	2,74369E-05	2,23499E-05	69	[illegible]
BP	GO:0051345	positive regulation of hydrolase activity	122/2425	468/14199	4,23738E-07	2,99808E-05	2,44221E-05	122	[illegible]
BP	GO:0050817	coagulation	50/2425	147/14199	4,45007E-07	3,11017E-05	2,53351E-05	50	[illegible]
BP	GO:1903555	regulation of tumor necrosis factor superfamily cytoki	55/2425	169/14199	6,17115E-07	4,23954E-05	3,45349E-05	55	[illegible]
BP	GO:0042102	positive regulation of T cell proliferation	38/2425	101/14199	6,21395E-07	4,23954E-05	3,45349E-05	38	[illegible]
BP	GO:0006909	phagocytosis	71/2425	238/14199	6,91087E-07	4,65956E-05	3,79563E-05	71	[illegible]
BP	GO:0050878	regulation of body fluid levels	78/2425	270/14199	8,25329E-07	5,49995E-05	4,48021E-05	78	[illegible]
BP	GO:0071706	tumor necrosis factor superfamily cytokine productio	56/2425	175/14199	9,02783E-07	5,94695E-05	4,84433E-05	56	[illegible]
BP	GO:0007162	negative regulation of cell adhesion	79/2425	276/14199	1,05184E-06	6,85012E-05	5,58005E-05	79	[illegible]
BP	GO:0002831	regulation of response to biotic stimulus	93/2425	340/14199	1,11215E-06	7,16148E-05	5,83367E-05	93	[illegible]
BP	GO:0002822	regulation of adaptive immune response based on so	59/2425	189/14199	1,17022E-06	7,39919E-05	6,02731E-05	59	[illegible]
BP	GO:0032651	regulation of interleukin-1 beta production	34/2425	88/14199	1,17488E-06	7,39919E-05	6,02731E-05	34	[illegible]
BP	GO:0006959	humoral immune response	54/2425	168/14199	1,20325E-06	7,47936E-05	6,09262E-05	54	[illegible]
BP	GO:0050921	positive regulation of chemotaxis	43/2425	123/14199	1,21372E-06	7,47936E-05	6,09262E-05	43	[illegible]
BP	GO:0051250	negative regulation of lymphocyte activation	51/2425	156/14199	1,34043E-06	8,17235E-05	6,65712E-05	51	[illegible]
BP	GO:0002573	myeloid leukocyte differentiation	65/2425	216/14199	1,44532E-06	8,65535E-05	7,05057E-05	65	[illegible]
BP	GO:0032652	regulation of interleukin-1 production	38/2425	104/14199	1,44986E-06	8,65535E-05	7,05057E-05	38	[illegible]
BP	GO:0002275	myeloid cell activation involved in immune response	34/2425	89/14199	1,59199E-06	9,30989E-05	7,58376E-05	34	[illegible]
BP	GO:0030593	neutrophil chemotaxis	34/2425	89/14199	1,59199E-06	9,30989E-05	7,58376E-05	34	[illegible]
BP	GO:0032680	regulation of tumor necrosis factor production	53/2425	166/14199	1,89205E-06	0,000109528	8,92208E-05	53	[illegible]
BP	GO:0050729	positive regulation of inflammatory response	43/2425	125/14199	1,98269E-06	0,000113628	9,25601E-05	43	[illegible]
BP	GO:0006875	cellular metal ion homeostasis	120/2425	472/14199	2,07327E-06	0,000117643	9,58309E-05	120	[illegible]
BP	GO:0001503	ossification	85/2425	308/14199	2,16034E-06	0,000121381	9,88761E-05	85	[illegible]
BP	GO:0070374	positive regulation of ERK1 and ERK2 cascade	54/2425	171/14199	2,21402E-06	0,00012319	0,000100349	54	[illegible]
BP	GO:0006691	leukotriene metabolic process	13/2425	20/14199	2,39284E-06	0,000131859	0,000107411	13	[illegible]
BP	GO:0019724	B cell mediated immunity	52/2425	163/14199	2,42133E-06	0,000132159	0,000107655	52	[illegible]
BP	GO:0002886	regulation of myeloid leukocyte mediated immunity	26/2425	61/14199	2,44785E-06	0,000132346	0,000107808	26	[illegible]
BP	GO:0001906	cell killing	59/2425	193/14199	2,49396E-06	0,000133578	0,000108812	59	[illegible]
BP	GO:0032640	tumor necrosis factor production	54/2425	172/14199	2,69851E-06	0,000143196	0,000116646	54	[illegible]
BP	GO:0002704	negative regulation of leukocyte mediated immunity	28/2425	69/14199	3,2858E-06	0,000171699	0,000139865	28	[illegible]
BP	GO:0042060	wound healing	85/2425	311/14199	3,29557E-06	0,000171699	0,000139865	85	[illegible]
BP	GO:0002690	positive regulation of leukocyte chemotaxis	32/2425	84/14199	3,43229E-06	0,000177212	0,000144355	32	[illegible]
BP	GO:0030098	lymphocyte differentiation	101/2425	386/14199	3,4792E-06	0,00017803	0,000145021	101	[illegible]
BP	GO:0043312	neutrophil degranulation	10/2425	13/14199	3,59378E-06	0,000181174	0,000147583	10	[illegible]
BP	GO:0007229	integrin-mediated signaling pathway	33/2425	88/14199	3,6355E-06	0,000181174	0,000147583	33	[illegible]
BP	GO:0042116	macrophage activation	33/2425	88/14199	3,6355E-06	0,000181174	0,000147583	33	[illegible]
BP	GO:0051047	positive regulation of secretion	78/2425	280/14199	3,82219E-06	0,000188836	0,000153824	78	[illegible]
BP	GO:0045765	regulation of angiogenesis	71/2425	249/14199	4,21935E-06	0,000206676	0,000168356	71	[illegible]
BP	GO:0032963	collagen metabolic process	35/2425	97/14199	5,16444E-06	0,000250825	0,00020432	35	[illegible]
BP	GO:0002699	positive regulation of immune effector process	74/2425	264/14199	5,26717E-06	0,000253665	0,000206633	74	[illegible]
BP	GO:0071621	granulocyte chemotaxis	38/2425	109/14199	5,34739E-06	0,000255382	0,000208032	38	[illegible]
BP	GO:1900744	regulation of p38MAPK cascade	18/2425	36/14199	5,69413E-06	0,000269695	0,000219691	18	[illegible]
BP	GO:0032872	regulation of stress-activated MAPK cascade	53/2425	172/14199	6,13967E-06	0,000288413	0,000234939	53	[illegible]
BP	GO:0070664	negative regulation of leukocyte proliferation	33/2425	90/14199	6,40121E-06	0,00029378	0,00023931	33	[illegible]
BP	GO:1900046	regulation of hemostasis	23/2425	53/14199	6,40769E-06	0,00029378	0,00023931	23	[illegible]
BP	GO:1905517	macrophage migration	23/2425	53/14199	6,40769E-06	0,00029378	0,00023931	23	[illegible]
BP	GO:0032635	interleukin-6 production	48/2425	151/14199	6,4958E-06	0,000295456	0,000240676	48	[illegible]
BP	GO:0072676	lymphocyte migration	35/2425	98/14199	6,72788E-06	0,000303602	0,000247312	35	[illegible]
BP	GO:0016064	immunoglobulin mediated immune response	50/2425	160/14199	7,20324E-06	0,000322514	0,000262717	50	[illegible]
BP	GO:0035456	response to interferon-beta	24/2425	57/14199	7,65527E-06	0,000340096	0,000277039	24	[illegible]
BP	GO:1901342	regulation of vasculature development	71/2425	253/14199	7,75983E-06	0,000341637	0,000278295	71	[illegible]
BP	GO:1902105	regulation of leukocyte differentiation	78/2425	285/14199	7,80919E-06	0,000341637	0,000278295	78	[illegible]
BP	GO:0032675	regulation of interleukin-6 production	46/2425	144/14199	8,68367E-06	0,000377016	0,000307114	46	[illegible]
BP	GO:0002283	neutrophil activation involved in immune response	12/2425	19/14199	9,21697E-06	0,000397161	0,000323524	12	[illegible]
BP	GO:0048705	skeletal system morphogenesis	54/2425	179/14199	1,00404E-05	0,000429415	0,000349798	54	[illegible]
BP	GO:1902563	regulation of neutrophil activation	10/2425	14/14199	1,06408E-05	0,000450072	0,000366624	10	[illegible]
BP	GO:0070302	regulation of stress-activated protein kinase signaling	53/2425	175/14199	1,06805E-05	0,000450072	0,000366624	53	[illegible]
BP	GO:0032874	positive regulation of stress-activated MAPK cascade	39/2425	116/14199	1,08517E-05	0,00045395	0,000369784	39	[illegible]
BP	GO:0030193	regulation of blood coagulation	22/2425	51/14199	1,14071E-05	0,000473723	0,000385891	22	[illegible]
BP	GO:0036336	dendritic cell migration	14/2425	25/14199	1,17072E-05	0,000482692	0,000393196	14	[illegible]
BP	GO:0045123	cellular extravasation	28/2425	73/14199	1,18577E-05	0,000485403	0,000395405	28	[illegible]
BP	GO:0002821	positive regulation of adaptive immune response	43/2425	133/14199	1,20488E-05	0,000489727	0,000398927	43	[illegible]
BP	GO:0006956	complement activation	26/2425	66/14199	1,3796E-05	0,000556796	0,000453561	26	[illegible]
BP	GO:0008544	epidermis development	67/2425	239/14199	1,43683E-05	0,000572929	0,000466703	67	[illegible]
BP	GO:0002444	myeloid leukocyte mediated immunity	35/2425	101/14199	1,43957E-05	0,000572929	0,000466703	35	[illegible]
BP	GO:0031349	positive regulation of defense response	74/2425	272/14199	1,65383E-05	0,000653661	0,000532467	74	[illegible]
BP	GO:0070304	positive regulation of stress-activated protein kinase	39/2425	118/14199	1,70427E-05	0,000668986	0,00054495	39	[illegible]
BP	GO:0032945	negative regulation of mononuclear cell proliferation	31/2425	86/14199	1,79518E-05	0,000695149	0,000566262	31	[illegible]
BP	GO:0050672	negative regulation of lymphocyte proliferation	31/2425	86/14199	1,79518E-05	0,000695149	0,000566262	31	[illegible]
BP	GO:0055074	calcium ion homeostasis	98/2425	386/14199	1,86866E-05	0,000718743	0,000585482	98	[illegible]
BP	GO:0072507	divalent inorganic cation homeostasis	104/2425	415/14199	1,89547E-05	0,000724197	0,000589924	104	[illegible]
BP	GO:0034113	heterotypic cell-cell adhesion	21/2425	49/14199	2,02937E-05	0,000770221	0,000627415	21	[illegible]
BP	GO:1900745	positive regulation of p38MAPK cascade	13/2425	23/14199	2,11823E-05	0,000798655	0,000650577	13	[illegible]
BP	GO:0001501	skeletal system development	102/2425	407/14199	2,26819E-05	0,000849607	0,000692082	102	[illegible]
BP	GO:0071396	cellular response to lipid	103/2425	412/14199	2,30971E-05	0,000854747	0,000696269	103	[illegible]
BP	GO:0043313	regulation of neutrophil degranulation	8/2425	10/14199	2,32413E-05	0,000854747	0,000696269	8	[illegible]
BP	GO:0019884	antigen processing and presentation of exogenous an	18/2425	39/14199	2,32665E-05	0,000854747	0,000696269	18	[illegible]
BP	GO:0048002	antigen processing and presentation of peptide antig	25/2425	64/14199	2,38415E-05	0,000870291	0,000708932	25	[illegible]
BP	GO:0038066	p38MAPK cascade	20/2425	46/14199	2,46591E-05	0,000894438	0,000728601	20	[illegible]
BP	GO:0031098	stress-activated protein kinase signaling cascade	61/2425	216/14199	2,68194E-05	0,000961601	0,000783311	61	[illegible]
BP	GO:0051403	stress-activated MAPK cascade	59/2425	207/14199	2,68463E-05	0,000961601	0,000783311	59	[illegible]
BP	GO:0050673	epithelial cell proliferation	90/2425	351/14199	2,70858E-05	0,000964155	0,000785392	90	[illegible]
BP	GO:0002764	immune response-regulating signaling pathway	95/2425	375/14199	2,73466E-05	0,000967429	0,000788059	95	[illegible]
BP	GO:0090132	epithelium migration	71/2425	262/14199	2,80001E-05	0,000984471	0,000801941	71	[illegible]
BP	GO:0030316	osteoclast differentiation	34/2425	100/14199	2,98918E-05	0,0010424	0,00084913	34	[illegible]
BP	GO:0150076	neuroinflammatory response	24/2425	61/14199	3,00115E-05	0,0010424	0,00084913	24	[illegible]
BP	GO:0002478	antigen processing and presentation of exogenous pe	16/2425	33/14199	3,08903E-05	0,001059909	0,000863392	16	[illegible]
BP	GO:0032692	negative regulation of interleukin-1 production	16/2425	33/14199	3,08903E-05	0,001059909	0,000863392	16	[illegible]
BP	GO:0046328	regulation of JNK cascade	40/2425	125/14199	3,12441E-05	0,001059909	0,000863392	40	[illegible]
BP	GO:0002706	regulation of lymphocyte mediated immunity	57/2425	199/14199	3,12554E-05	0,001059909	0,000863392	57	[illegible]
BP	GO:0090130	tissue migration	71/2425	263/14199	3,20607E-05	0,001080821	0,000880427	71	[illegible]
BP	GO:0045576	mast cell activation	25/2425	65/14199	3,25125E-05	0,00108331	0,000882455	25	[illegible]
BP	GO:1903556	negative regulation of tumor necrosis factor superfam	25/2425	65/14199	3,25125E-05	0,00108331	0,000882455	25	[illegible]
BP	GO:0050818	regulation of coagulation	22/2425	54/14199	3,37865E-05	0,001119253	0,000911733	22	[illegible]
BP	GO:0002548	monocyte chemotaxis	20/2425	47/14199	3,6077E-05	0,001182448	0,000963212	20	[illegible]
BP	GO:0043087	regulation of GTPase activity	80/2425	306/14199	3,61475E-05	0,001182448	0,000963212	80	[illegible]
BP	GO:0022408	negative regulation of cell-cell adhesion	55/2425	191/14199	3,63132E-05	0,001182448	0,000963212	55	[illegible]
BP	GO:0002707	negative regulation of lymphocyte mediated immunit	23/2425	58/14199	3,77142E-05	0,001221131	0,000994722	23	[illegible]
BP	GO:0007204	positive regulation of cytosolic calcium ion concentrat	69/2425	255/14199	3,79926E-05	0,001223235	0,000996436	69	[illegible]
BP	GO:0002495	antigen processing and presentation of peptide antig	13/2425	24/14199	3,8992E-05	0,00124146	0,001011282	13	[illegible]
BP	GO:0090025	regulation of monocyte chemotaxis	13/2425	24/14199	3,8992E-05	0,00124146	0,001011282	13	[illegible]
BP	GO:0009913	epidermal cell differentiation	46/2425	152/14199	4,05636E-05	0,001284363	0,001046231	46	[illegible]
BP	GO:0030217	T cell differentiation	74/2425	279/14199	4,19073E-05	0,001319618	0,001074949	74	[illegible]
BP	GO:0001667	ameboidal-type cell migration	92/2425	365/14199	4,46798E-05	0,001399234	0,001139803	92	[illegible]
BP	GO:0010631	epithelial cell migration	70/2425	261/14199	4,56101E-05	0,001420607	0,001157214	70	[illegible]
BP	GO:0045600	positive regulation of fat cell differentiation	22/2425	55/14199	4,72997E-05	0,001465267	0,001193593	22	[illegible]
BP	GO:0060284	regulation of cell development	114/2425	473/14199	4,82009E-05	0,001485159	0,001209797	114	[illegible]
BP	GO:0030195	negative regulation of blood coagulation	16/2425	34/14199	4,91331E-05	0,001505784	0,001226598	16	[illegible]
BP	GO:0001819	positive regulation of cytokine production	108/2425	444/14199	5,07099E-05	0,001545841	0,001259229	108	[illegible]
BP	GO:1903038	negative regulation of leukocyte cell-cell adhesion	42/2425	136/14199	5,12917E-05	0,001555307	0,001266939	42	[illegible]
BP	GO:0007254	JNK cascade	45/2425	149/14199	5,17012E-05	0,001559473	0,001270333	45	[illegible]
BP	GO:0045668	negative regulation of osteoblast differentiation	18/2425	41/14199	5,33602E-05	0,001595249	0,001299476	18	[illegible]
BP	GO:1903706	regulation of hemopoiesis	90/2425	357/14199	5,3444E-05	0,001595249	0,001299476	90	[illegible]
BP	GO:0019722	calcium-mediated signaling	46/2425	154/14199	5,79336E-05	0,001720297	0,001401338	46	[illegible]
BP	GO:0050868	negative regulation of T cell activation	39/2425	124/14199	5,99957E-05	0,001767119	0,001439479	39	[illegible]
BP	GO:0030099	myeloid cell differentiation	97/2425	392/14199	6,04354E-05	0,001767119	0,001439479	97	[illegible]
BP	GO:0072503	cellular divalent inorganic cation homeostasis	97/2425	392/14199	6,04354E-05	0,001767119	0,001439479	97	[illegible]
BP	GO:0023035	CD40 signaling pathway	10/2425	16/14199	6,09748E-05	0,001769292	0,00144125	10	[illegible]
BP	GO:0042130	negative regulation of T cell proliferation	26/2425	71/14199	6,11272E-05	0,001769292	0,00144125	26	[illegible]
BP	GO:0006874	cellular calcium ion homeostasis	92/2425	368/14199	6,19589E-05	0,001784355	0,00145352	92	[illegible]
BP	GO:0048247	lymphocyte chemotaxis	19/2425	45/14199	6,40816E-05	0,001828223	0,001489254	19	[illegible]
BP	GO:0002446	neutrophil mediated immunity	17/2425	38/14199	6,41202E-05	0,001828223	0,001489254	17	[illegible]
BP	GO:0030449	regulation of complement activation	11/2425	19/14199	6,93451E-05	0,001957718	0,001594739	11	[illegible]
BP	GO:0150146	cell junction disassembly	11/2425	19/14199	6,93451E-05	0,001957718	0,001594739	11	[illegible]
BP	GO:0035458	cellular response to interferon-beta	20/2425	49/14199	7,38422E-05	0,002057515	0,001676034	20	[illegible]
BP	GO:0046633	alpha-beta T cell proliferation	20/2425	49/14199	7,38422E-05	0,002057515	0,001676034	20	[illegible]
BP	GO:0031589	cell-substrate adhesion	80/2425	312/14199	7,41165E-05	0,002057515	0,001676034	80	[illegible]
BP	GO:0007015	actin filament organization	97/2425	394/14199	7,43161E-05	0,002057515	0,001676034	97	[illegible]
BP	GO:0032720	negative regulation of tumor necrosis factor productio	24/2425	64/14199	7,4889E-05	0,002063407	0,001680833	24	[illegible]
BP	GO:0050819	negative regulation of coagulation	16/2425	35/14199	7,62262E-05	0,002080249	0,001694552	16	[illegible]
BP	GO:1900047	negative regulation of hemostasis	16/2425	35/14199	7,62262E-05	0,002080249	0,001694552	16	[illegible]
BP	GO:0010632	regulation of epithelial cell migration	57/2425	205/14199	7,77772E-05	0,002112518	0,001720838	57	[illegible]
BP	GO:0046330	positive regulation of JNK cascade	30/2425	88/14199	8,12724E-05	0,002197038	0,001789688	30	[illegible]
BP	GO:0071363	cellular response to growth factor stimulus	116/2425	489/14199	8,49843E-05	0,002286597	0,001862642	116	[illegible]
BP	GO:0045766	positive regulation of angiogenesis	45/2425	152/14199	8,76617E-05	0,002336693	0,001903449	45	[illegible]
BP	GO:1904018	positive regulation of vasculature development	45/2425	152/14199	8,76617E-05	0,002336693	0,001903449	45	[illegible]
BP	GO:0002824	positive regulation of adaptive immune response bas	39/2425	126/14199	8,85918E-05	0,002343309	0,001908838	39	[illegible]
BP	GO:0052547	regulation of peptidase activity	83/2425	328/14199	8,94842E-05	0,002343309	0,001908838	83	[illegible]
BP	GO:0002437	inflammatory response to antigenic stimulus	22/2425	57/14199	8,95454E-05	0,002343309	0,001908838	22	[illegible]
BP	GO:0002820	negative regulation of adaptive immune response	22/2425	57/14199	8,95454E-05	0,002343309	0,001908838	22	[illegible]
BP	GO:0061900	glial cell activation	19/2425	46/14199	9,18234E-05	0,002392	0,001948502	19	[illegible]
BP	GO:0002285	lymphocyte activation involved in immune response	53/2425	188/14199	9,22903E-05	0,002393285	0,001949548	53	[illegible]
BP	GO:0032602	chemokine production	33/2425	101/14199	9,49196E-05	0,00241583	0,001967913	33	[illegible]
BP	GO:0071677	positive regulation of mononuclear cell migration	23/2425	61/14199	9,53085E-05	0,00241583	0,001967913	23	[illegible]
BP	GO:1990868	response to chemokine	23/2425	61/14199	9,53085E-05	0,00241583	0,001967913	23	[illegible]
BP	GO:1990869	cellular response to chemokine	23/2425	61/14199	9,53085E-05	0,00241583	0,001967913	23	[illegible]
BP	GO:0001774	microglial cell activation	17/2425	39/14199	9,5689E-05	0,00241583	0,001967913	17	[illegible]
BP	GO:0002920	regulation of humoral immune response	17/2425	39/14199	9,5689E-05	0,00241583	0,001967913	17	[illegible]
BP	GO:0051480	regulation of cytosolic calcium ion concentration	73/2425	281/14199	9,66413E-05	0,002429171	0,001978781	73	[illegible]
BP	GO:0002064	epithelial cell development	52/2425	184/14199	9,98377E-05	0,00249856	0,002035304	52	[illegible]
BP	GO:0045655	regulation of monocyte differentiation	9/2425	14/14199	0,000106767	0,002660355	0,002167101	9	[illegible]
BP	GO:0031341	regulation of cell killing	38/2425	123/14199	0,000113317	0,002805027	0,002284949	38	[illegible]
BP	GO:0002347	response to tumor cell	18/2425	43/14199	0,000113715	0,002805027	0,002284949	18	[illegible]
BP	GO:1903034	regulation of response to wounding	41/2425	136/14199	0,000114041	0,002805027	0,002284949	41	[illegible]
BP	GO:0002504	antigen processing and presentation of peptide or pol	13/2425	26/14199	0,000115721	0,002824173	0,002300546	13	[illegible]
BP	GO:0007423	sensory organ development	102/2425	423/14199	0,000115992	0,002824173	0,002300546	102	[illegible]
BP	GO:0006898	receptor-mediated endocytosis	59/2425	217/14199	0,000116298	0,002824173	0,002300546	59	[illegible]
BP	GO:0072678	T cell migration	22/2425	58/14199	0,00012122	0,002931273	0,002387789	22	[illegible]
BP	GO:0071887	leukocyte apoptotic process	36/2425	115/14199	0,00012607	0,003035754	0,002472898	36	[illegible]
BP	GO:0019886	antigen processing and presentation of exogenous pe	11/2425	20/14199	0,000130324	0,003125052	0,002545639	11	[illegible]
BP	GO:0060395	SMAD protein signal transduction	25/2425	70/14199	0,000134232	0,003205338	0,00261104	25	[illegible]
BP	GO:0001649	osteoblast differentiation	46/2425	159/14199	0,000134791	0,00320534	0,002611041	46	[illegible]
BP	GO:0051606	detection of stimulus	41/2425	137/14199	0,000136298	0,003227775	0,002629317	41	[illegible]
BP	GO:0031346	positive regulation of cell projection organization	90/2425	366/14199	0,000139158	0,003281959	0,002673454	90	[illegible]
BP	GO:0070098	chemokine-mediated signaling pathway	20/2425	51/14199	0,000143143	0,00336209	0,002738728	20	[illegible]
BP	GO:0007411	axon guidance	47/2425	164/14199	0,000146854	0,003409416	0,00277728	47	[illegible]
BP	GO:0097485	neuron projection guidance	47/2425	164/14199	0,000146854	0,003409416	0,00277728	47	[illegible]
BP	GO:0002768	immune response-regulating cell surface receptor sig	61/2425	228/14199	0,000146942	0,003409416	0,00277728	61	[illegible]
BP	GO:0032642	regulation of chemokine production	31/2425	95/14199	0,0001567	0,003621172	0,002949774	31	[illegible]
BP	GO:0018108	peptidyl-tyrosine phosphorylation	70/2425	271/14199	0,000160301	0,003689502	0,003005435	70	[illegible]
BP	GO:0002507	tolerance induction	14/2425	30/14199	0,000162806	0,003732175	0,003040196	14	[illegible]
BP	GO:0032609	interferon-gamma production	38/2425	125/14199	0,000164763	0,003761988	0,003064482	38	[illegible]
BP	GO:1903532	positive regulation of secretion by cell	68/2425	262/14199	0,000169752	0,003860513	0,00314474	68	[illegible]
BP	GO:0034109	homotypic cell-cell adhesion	25/2425	71/14199	0,000173962	0,003925108	0,003197358	25	[illegible]
BP	GO:0043299	leukocyte degranulation	25/2425	71/14199	0,000173962	0,003925108	0,003197358	25	[illegible]
BP	GO:0006816	calcium ion transport	84/2425	339/14199	0,00017465	0,003925176	0,003197413	84	[illegible]
BP	GO:0007389	pattern specification process	80/2425	320/14199	0,000181711	0,004067914	0,003313686	80	[illegible]
BP	GO:0050678	regulation of epithelial cell proliferation	75/2425	296/14199	0,000183071	0,004082413	0,003325497	75	[illegible]
BP	GO:0097201	negative regulation of transcription from RNA polyme	8/2425	12/14199	0,000184469	0,004097643	0,003337903	8	Dnajb1;Tmbim6;Sirt2;Cited2;Jun;Ppp1r15a;Nck2;Nfe2l1
BP	GO:0001933	negative regulation of protein phosphorylation	78/2425	311/14199	0,000195062	0,004306399	0,003507954	78	[illegible]
BP	GO:0061045	negative regulation of wound healing	20/2425	52/14199	0,000195618	0,004306399	0,003507954	20	[illegible]
BP	GO:0032649	regulation of interferon-gamma production	35/2425	113/14199	0,000196121	0,004306399	0,003507954	35	[illegible]
BP	GO:0051271	negative regulation of cellular component movement	66/2425	254/14199	0,000202635	0,004432437	0,003610624	66	[illegible]
BP	GO:0045667	regulation of osteoblast differentiation	34/2425	109/14199	0,00020696	0,004509839	0,003673674	34	[illegible]
BP	GO:0002888	positive regulation of myeloid leukocyte mediated im	12/2425	24/14199	0,000212631	0,004615864	0,003760041	12	C3;Itgb2l;Spi1;Ptafr;Fcgr1;Itgam;Arg1;Cd177;Itgb2;Tyrobp;Fcgr3;Ddx58
BP	GO:0002761	regulation of myeloid leukocyte differentiation	36/2425	118/14199	0,000223626	0,00483623	0,00393955	36	[illegible]
BP	GO:0018212	peptidyl-tyrosine modification	70/2425	274/14199	0,00022793	0,004908	0,003998013	70	[illegible]
BP	GO:0061041	regulation of wound healing	32/2425	101/14199	0,000228657	0,004908	0,003998013	32	[illegible]
BP	GO:1903975	regulation of glial cell migration	10/2425	18/14199	0,000238946	0,005109702	0,004162317	10	Trem2;Fubp1;P2rx4;Fas;Gpr183;Lrp1;Vim;P2ry12;Csf1;Cx3cr1
BP	GO:0098742	cell-cell adhesion via plasma-membrane adhesion mo	40/2425	136/14199	0,000245274	0,005225517	0,004256659	40	[illegible]
BP	GO:0030216	keratinocyte differentiation	30/2425	93/14199	0,000249446	0,005283586	0,004303961	30	[illegible]
BP	GO:1902107	positive regulation of leukocyte differentiation	48/2425	172/14199	0,000250765	0,005283586	0,004303961	48	[illegible]
BP	GO:1903708	positive regulation of hemopoiesis	48/2425	172/14199	0,000250765	0,005283586	0,004303961	48	[illegible]
BP	GO:0002705	positive regulation of leukocyte mediated immunity	46/2425	163/14199	0,000253152	0,005314334	0,004329009	46	[illegible]
BP	GO:0030225	macrophage differentiation	17/2425	42/14199	0,000285207	0,005965408	0,004859368	17	[illegible]
BP	GO:1903035	negative regulation of response to wounding	24/2425	69/14199	0,000287872	0,005999246	0,004886932	24	[illegible]
BP	GO:0007178	transmembrane receptor protein serine/threonine ki	72/2425	286/14199	0,000299392	0,00621672	0,005064084	72	[illegible]
BP	GO:0003128	heart field specification	7/2425	10/14199	0,000311551	0,00644585	0,005250732	7	Robo1;Lrp2;Mef2c;Ext1;Rbpj;Axin2;Bmp2
BP	GO:0033003	regulation of mast cell activation	18/2425	46/14199	0,000314249	0,006478281	0,005277149	18	[illegible]
BP	GO:0030336	negative regulation of cell migration	61/2425	234/14199	0,000315406	0,006478827	0,005277594	61	[illegible]
BP	GO:0002757	immune response-activating signal transduction	58/2425	220/14199	0,000320083	0,006506267	0,005299947	58	[illegible]
BP	GO:0050730	regulation of peptidyl-tyrosine phosphorylation	58/2425	220/14199	0,000320083	0,006506267	0,005299947	58	[illegible]
BP	GO:0048771	tissue remodeling	43/2425	151/14199	0,000320148	0,006506267	0,005299947	43	[illegible]
BP	GO:0019882	antigen processing and presentation	33/2425	107/14199	0,000321583	0,006512338	0,005304892	33	[illegible]
BP	GO:0043030	regulation of macrophage activation	19/2425	50/14199	0,000336755	0,006795583	0,005535621	19	[illegible]

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4	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
5	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
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8	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
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14	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
15	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
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18	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
19	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
20	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
21	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
22	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
23	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
24	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
25	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
26	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
27	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
28	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
29	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
30	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
31	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
32	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
33	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
34	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
35	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
36	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
37	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
38	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
39	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
40	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
41	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
42	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
43	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
44	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
45	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
46	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
47	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
48	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
49	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
50	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
51	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
52	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
53	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
54	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
55	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
56	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
57	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
58	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
59	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
60	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
61	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
62	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
63	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
64	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
65	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
66	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
67	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
68	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
69	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
70	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
71	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
72	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
73	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
74	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
75	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
76	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
77	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
78	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
79	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
80	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
81	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
82	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
83	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
84	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
85	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
86	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
87	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
88	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
89	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
90	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
91	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
92	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
93	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
94	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
95	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
96	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
97	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
98	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
99	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
100	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000

1	0.0000%	difficulties of architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
2	0.0000%	difficulties of architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
3	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
4	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
5	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
6	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
7	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
8	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
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14	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
15	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
16	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
17	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
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92	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
93	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
94	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
95	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
96	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
97	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
98	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
99	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%
100	0.0000%	difficulties of the architectural professionals in an open...	1	0.0000%	0.0000%	0.0000%

NFKBIE_spleen_vs_MOCK_spleen_egoALL_ABS_LFC1

ONTOLOGY	ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count	Symbols
BP	GO:0002250	adaptive immune response	103/1512	439/14199	3,84034E-15	2,0734E-11	1,87853E-11	103	Trbc2;Ighe;Ighg3;Treml4;Cyrib;Hmces;Aicda;Btla;Ifng;Il7r;Clec4n;Cd274;Cd8b1;Parp3;Cd8a;H2-DMa;Tap1;Sh2d1a;H2-Ob;Ptk2b;H2-Aa;H2-Eb1;Fas;C1ra;Il27ra;Gpr183;C3;Syk;Cd4;Lag3;Ccr7;Adgre1;C2;Prdm1;Tsc1;Lilrb4a;Il9r;Pagr1a;Mfsd6;Tnf;Lta;Otud7b;Hspa8;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;Serpina3g;6030468B19Rik;Nfkb2;Cd55b;Thoc1;Swap70;Lyst;Pirb;Csf2rb2;Csf2rb;Icam1;Lig4;Nras;Inpp5d;Cd86;Tnfsf4;Stx11;Prf1;Tnfaip3;C1qb;C1qc;C1qa;Cd3e;Enpp1;Arg1;Gzmb;Ctla4;Lax1;Cd46;Zbtb7b;Cr2;Jchain;Irf1;Zap70;Mcoln1;Aire;Icosl;Nfkbid;Rnf19b;H2-K1;H2-Oa;Bach2;Ptprc;Rab27a;Cd79b;Slamf7;Slc11a1;Sit1;Cd40;Slamf6;Il18bp;Myo1g;Il21r;Tbx21;Eif2ak4
BP	GO:0051249	regulation of lymphocyte activation	102/1512	469/14199	8,74814E-13	2,36156E-09	2,13961E-09	102	Trbc2;Ighe;Ighg3;Tigit;Vcam1;Zbtb16;Nfam1;Cd83;Cyrib;Lck;Hmces;Il15;Btla;Ifng;Il7r;Cd274;Sox12;Parp3;H2-DMa;Axl;H2-Ob;Id2;Slc39a10;H2-Aa;H2-Eb1;Fas;Il27ra;Gpr183;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Prdm1;Sh3kbp1;Lilrb4a;Pagr1a;Lst1;Cav1;Il6st;Fgr;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Clec2i;Cd276;Thoc1;Lgals8;Hsph1;Lyst;Il15ra;Klrc1;Runx3;Hmgb3;Flot2;Mmp14;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Cd3e;Arg1;Tnfrsf4;Ctla4;Tcf7;Pik3r6;Lax1;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Tyrobp;Nfkbid;Gm5150;H2-Oa;Ptprc;Dtx1;Slamf7;Cd22;Slamf8;Sit1;Spta1;Cd40;Il1a;Prkar1a;Sirpa;Pla2g2f;Pla2g2d;Xbp1;Cd300a;Prnp;Tbx21;Ccl5
BP	GO:0002460	adaptive immune response based on somatic recombination of i	77/1512	334/14199	3,14978E-11	5,66855E-08	5,13579E-08	77	Trbc2;Ighe;Ighg3;Treml4;Cyrib;Hmces;Aicda;Ifng;Il7r;Clec4n;Cd274;Parp3;Cd8a;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Fas;C1ra;Il27ra;C3;Cd4;Ccr7;C2;Lilrb4a;Il9r;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Nfkb2;Cd55b;Thoc1;Swap70;Lyst;Pirb;Csf2rb2;Csf2rb;Icam1;Lig4;Nras;Inpp5d;Tnfsf4;Stx11;Prf1;Tnfaip3;C1qb;C1qc;C1qa;Enpp1;Arg1;Gzmb;Cd46;Zbtb7b;Cr2;Irf1;Aire;Icosl;Nfkbid;H2-K1;H2-Oa;Bach2;Ptprc;Rab27a;Slc11a1;Cd40;Slamf6;Il18bp;Myo1g;Il21r;Tbx21
BP	GO:0051251	positive regulation of lymphocyte activation	72/1512	314/14199	1,80028E-10	1,6415E-07	1,48722E-07	72	Trbc2;Ighe;Ighg3;Vcam1;Zbtb16;Cd83;Cyrib;Lck;Hmces;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;Axl;H2-Ob;Slc39a10;H2-Aa;H2-Eb1;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Prdm1;Sh3kbp1;Lilrb4a;Pagr1a;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Lgals8;Hsph1;Lyst;Il15ra;Klrc1;Runx3;Flot2;Mmp14;Inpp5d;Cd86;Tnfsf4;Cd3e;Tnfrsf4;Pik3r6;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Tyrobp;Nfkbid;Gm5150;H2-Oa;Ptprc;Spta1;Cd40;Il1a;Sirpa;Xbp1;Tbx21;Ccl5
BP	GO:0042110	T cell activation	100/1512	498/14199	1,92646E-10	1,6415E-07	1,48722E-07	100	Tigit;Vcam1;Zbtb16;Cd83;Psmb10;Cyrib;Lck;Il15;Btla;Ifng;Il7r;Clec4a1;Ebi3;Cd274;Sox12;Nkg7;Cd8a;H2-DMa;Bcl11a;H2-Ob;H2-Aa;H2-Eb1;Fas;Il27ra;Gpr183;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Prdm1;Tsc1;Lilrb4a;Bcl2a1d;Cav1;Il6st;Gja1;Cd6;Il4i1;Il4i1b;Itgal;Lmbr1l;Lcp1;Thy1;Cd55b;Il2ra;Clec2i;Cd276;Lgals8;Hsph1;Runx3;Flot2;Icam1;Zc3h12d;Lig4;Cd86;Tnfsf4;Stx11;Cdkn2a;Cd3e;Mpzl2;Jaml;Enpp1;Arg1;Tnfrsf4;Ctla4;Tcf7;Pik3r6;Lax1;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Aire;Icosl;Nfkbid;Ccnd3;Gm5150;H2-Oa;Ptprc;Rab27a;Dtx1;Slamf7;Slc11a1;Sit1;Spta1;Il1a;Prkar1a;Slamf6;Sirpa;Pla2g2f;Pla2g2d;Xbp1;Cd300a;Prnp;Tbx21;Ccl5;Eif2ak4
BP	GO:0050863	regulation of T cell activation	73/1512	322/14199	2,33028E-10	1,6415E-07	1,48722E-07	73	Tigit;Vcam1;Zbtb16;Cd83;Cyrib;Lck;Il15;Btla;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Prdm1;Lilrb4a;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Clec2i;Cd276;Lgals8;Hsph1;Runx3;Flot2;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Ctla4;Tcf7;Pik3r6;Lax1;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Nfkbid;Gm5150;H2-Oa;Ptprc;Dtx1;Sit1;Spta1;Il1a;Prkar1a;Sirpa;Pla2g2f;Pla2g2d;Xbp1;Cd300a;Prnp;Tbx21;Ccl5
BP	GO:0002449	lymphocyte mediated immunity	74/1512	330/14199	2,9811E-10	1,6415E-07	1,48722E-07	74	Trbc2;Ighe;Ighg3;Treml4;Cyrib;Hmces;Aicda;Ifng;Il7r;Cd96;Parp3;Nkg7;Cd8a;H2-DMa;Tap1;Sh2d1a;H2-Ob;H2-Aa;H2-Eb1;Fas;C1ra;Il27ra;C3;Serpinb9d;Lag3;C2;Lilrb4a;Il9r;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Cd55b;Thoc1;Swap70;Lyst;Klrc1;Pirb;Csf2rb2;Csf2rb;Icam1;Lig4;Inpp5d;Tnfsf4;Stx11;Prf1;C1qb;C1qc;C1qa;Enpp1;Arg1;Gzmb;Pik3r6;Cd46;Cr2;Aire;Icosl;Rnf19b;H2-K1;H2-Oa;Ptprc;Rab27a;Slc11a1;Cd40;Slamf6;Myo1g;Il21r;Tbx21
BP	GO:0022407	regulation of cell-cell adhesion	88/1512	421/14199	2,98201E-10	1,6415E-07	1,48722E-07	88	Tigit;Vcam1;Zbtb16;Epcam;Plpp3;Cd83;Cyrib;Lck;Il15;Btla;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Myo10;Tnfsf9;Ptpn2;Syk;Ptk2;Cd4;Lag3;Ccr7;Efna5;Ptger3;Lilrb4a;Tnf;Cd9;Bmp6;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Adipoq;Lgals8;Swap70;Hsph1;Runx3;Flot2;Icam1;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Cd3e;Arg1;Ctla4;Pik3r6;Lax1;Cd46;Zbtb7b;Slc4a1;Podxl;Irf1;Zap70;Src;Icosl;Fstl3;Nfkbid;Gm5150;Il1rn;H2-Oa;Ptprc;Dtx1;Ccr5;Spta1;Il1a;Prkar1a;Sirpa;F11r;Pla2g2f;Pla2g2d;Xbp1;Cd300a;Prnp;Tbx21;Ccl5
BP	GO:0002683	negative regulation of immune system process	84/1512	395/14199	3,13685E-10	1,6415E-07	1,48722E-07	84	Tigit;Acod1;Trib1;Btla;Cd200;Ifng;Il7r;Cd96;Cd274;Col3a1;Parp3;Axl;Tap1;Sh2d1a;H2-Ob;Id2;H2-Aa;Fas;Il27ra;Ptpn2;Serpinb9d;Lag3;Abr;Prdm1;Lilrb4a;Lst1;Tnf;Gpr55;Smpdl3b;Fcrl5;Fgr;Il4i1;Il4i1b;Thy1;Tmbim6;Cd55b;Il2ra;Clec2i;Cd276;Adipoq;Prdm16;Thoc1;Runx3;Hmgb3;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;C1qc;Zbtb46;Enpp3;Arg1;Tnfrsf4;Isg15;Ctla4;Lax1;Cd46;Zbtb7b;Cr2;Rabgef1;Irf1;Grn;Padi2;Tyrobp;Fstl3;Nfkbid;Dgkz;H2-Oa;Ptprc;Dtx1;Oas3;Oas1a;Cd22;Slamf8;Ifi204;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21;Tnfaip6
BP	GO:0070661	leukocyte proliferation	72/1512	318/14199	3,29557E-10	1,6415E-07	1,48722E-07	72	Csf1r;Vcam1;Psmb10;Il15;Btla;Ifng;Il7r;Ebi3;Cd274;Slc39a10;Cd180;H2-Aa;Il27ra;Gpr183;Tnfsf9;Syk;Ptk2;Cd4;Hells;Ccr7;Prdm1;Lilrb4a;Il9r;Lst1;Il6st;Gja1;Cd6;Il4i1;Il4i1b;Itgal;Lmbr1l;Cd55b;Il2ra;Clec2i;Cd276;St6gal1;Csf2rb2;Csf2rb;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Impdh1;Enpp3;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Cr2;Csf1;Irf1;Zap70;Icosl;Tyrobp;Ccnd3;Ptprc;Cd22;Slc11a1;Spta1;Cd40;Il1a;Prkar1a;Slamf6;Pla2g2f;Pla2g2d;Cd300a;Prnp;Ccl5
BP	GO:0032943	mononuclear cell proliferation	68/1512	293/14199	3,34441E-10	1,6415E-07	1,48722E-07	68	Csf1r;Vcam1;Psmb10;Il15;Btla;Ifng;Il7r;Ebi3;Cd274;Slc39a10;Cd180;H2-Aa;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Hells;Ccr7;Prdm1;Lilrb4a;Il9r;Lst1;Il6st;Gja1;Cd6;Il4i1;Il4i1b;Itgal;Lmbr1l;Cd55b;Il2ra;Clec2i;Cd276;St6gal1;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Impdh1;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Cr2;Csf1;Irf1;Zap70;Icosl;Tyrobp;Ccnd3;Ptprc;Cd22;Slc11a1;Spta1;Cd40;Il1a;Prkar1a;Slamf6;Pla2g2f;Pla2g2d;Cd300a;Prnp;Ccl5
BP	GO:0034341	response to interferon-gamma	39/1512	128/14199	6,31943E-10	2,84322E-07	2,576E-07	39	Acod1;Ifng;H2-Aa;H2-Eb1;Tlr2;Gbp8;Gbp9;Gbp10;Gbp6;Ptpn2;Capg;Stat1;H2-Q7;H2-Q9;Ciita;Tgtp1;Ccl22;Rab20;Stx11;Actg1;Gbp5;Gbp3;Gbp2b;Gbp2;Arg1;Irf1;Ubd;Vamp8;Igtp;Irgm2;Slc11a1;Cd40;Sirpa;Ifitm1;Ifitm3;Ccl5;Ccl3;Ccl4;Kynu
BP	GO:1903037	regulation of leukocyte cell-cell adhesion	71/1512	318/14199	8,39062E-10	3,48469E-07	3,15718E-07	71	Tigit;Vcam1;Zbtb16;Cd83;Cyrib;Lck;Il15;Btla;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Lilrb4a;Tnf;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Lgals8;Hsph1;Runx3;Flot2;Icam1;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Ctla4;Pik3r6;Lax1;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Nfkbid;Gm5150;H2-Oa;Ptprc;Dtx1;Spta1;Il1a;Prkar1a;Sirpa;Pla2g2f;Pla2g2d;Xbp1;Cd300a;Prnp;Tbx21;Ccl5
BP	GO:0050870	positive regulation of T cell activation	53/1512	208/14199	9,18992E-10	3,54403E-07	3,21094E-07	53	Vcam1;Zbtb16;Cd83;Cyrib;Lck;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Tnfsf9;Syk;Cd4;Ccr7;Lilrb4a;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Lgals8;Hsph1;Runx3;Flot2;Cd86;Tnfsf4;Cd3e;Pik3r6;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Nfkbid;Gm5150;H2-Oa;Ptprc;Spta1;Il1a;Sirpa;Xbp1;Ccl5
BP	GO:0070663	regulation of leukocyte proliferation	59/1512	247/14199	1,55379E-09	5,59259E-07	5,06697E-07	59	Csf1r;Vcam1;Il15;Btla;Ifng;Cd274;Slc39a10;H2-Aa;Il27ra;Gpr183;Tnfsf9;Syk;Ptk2;Cd4;Ccr7;Prdm1;Lilrb4a;Lst1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Cd55b;Il2ra;Clec2i;Cd276;St6gal1;Csf2rb2;Csf2rb;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Enpp3;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Csf1;Irf1;Zap70;Icosl;Tyrobp;Ptprc;Cd22;Spta1;Cd40;Il1a;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Ccl5
BP	GO:1902105	regulation of leukocyte differentiation	65/1512	285/14199	1,75648E-09	5,92702E-07	5,36998E-07	65	Csf1r;Zbtb16;Trib1;Nfam1;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;Axl;Id2;Ptk2b;H2-Aa;Fas;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Gfi1b;Prdm1;Lilrb4a;Tnf;Gpr55;Il4i1;Il4i1b;Tal1;Il2ra;Clec2i;Hsf1;Adipoq;Prdm16;Il15ra;Runx3;Hmgb3;Mmp14;Inpp5d;Car2;Prxl2a;Tnfsf4;Cdkn2a;C1qc;Zbtb46;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Csf1;Irf1;Zap70;Tyrobp;Fstl3;Nfkbid;H2-Oa;Ptprc;Dtx1;Slamf8;Xbp1;Tbx21;Ccl5;Ccl3;Tnfaip6
BP	GO:0002443	leukocyte mediated immunity	86/1512	423/14199	1,9953E-09	6,33682E-07	5,74126E-07	86	Trbc2;Ighe;Ighg3;Treml4;Cyrib;Hmces;Aicda;Ifng;Il7r;Cd96;Parp3;Nkg7;Cd8a;H2-DMa;Tap1;Sh2d1a;H2-Ob;H2-Aa;H2-Eb1;Fas;C1ra;Tlr2;Il27ra;C3;Syk;Serpinb9d;Lag3;Abr;C2;Lilrb4a;Il9r;Pagr1a;Tnf;Lta;Hspa8;Fgr;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Cd55b;Gata1;Thoc1;Swap70;Lyst;Klrc1;Pirb;Csf2rb2;Csf2rb;Icam1;Lig4;Inpp5d;Tnfsf4;Stx11;Prf1;C1qb;C1qc;C1qa;Enpp1;Arg1;Gzmb;Pik3r6;Cd46;Dnase1l3;Cr2;Rabgef1;Aire;Icosl;Tyrobp;Myo1f;Rnf19b;H2-K1;H2-Oa;Ptprc;Rab27a;Slc11a1;Cd40;Slamf6;Cd300a;Ncf1;Myo1g;Il21r;Tbx21
BP	GO:0046651	lymphocyte proliferation	65/1512	290/14199	3,69632E-09	1,10869E-06	1,00449E-06	65	Vcam1;Psmb10;Il15;Btla;Ifng;Il7r;Ebi3;Cd274;Slc39a10;Cd180;H2-Aa;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Hells;Ccr7;Prdm1;Lilrb4a;Il9r;Lst1;Il6st;Gja1;Cd6;Il4i1;Il4i1b;Itgal;Lmbr1l;Cd55b;Il2ra;Clec2i;Cd276;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Impdh1;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Cr2;Irf1;Zap70;Icosl;Tyrobp;Ccnd3;Ptprc;Cd22;Slc11a1;Spta1;Cd40;Il1a;Prkar1a;Slamf6;Pla2g2f;Pla2g2d;Cd300a;Prnp;Ccl5
BP	GO:0002253	activation of immune response	66/1512	299/14199	5,39035E-09	1,47592E-06	1,33721E-06	66	Trbc2;Ighe;Ighg3;Nfam1;Lck;Ifng;Clec4n;Zcchc3;Sting1;Cd8a;Sh2d1a;Slc39a10;C1ra;Tlr2;C3;Ptpn2;Syk;Ccr7;Cfb;C2;Usp46;Lilrb4a;Bcar1;Lcp2;Prkch;Bcl2a1d;Cd5l;Fcrl5;Ikbkg;Thy1;Cd55b;Clec2i;Cd276;Klrc1;Nras;C1qb;C1qc;C1qa;Fpr2;Cd3e;Cfp;Ctla4;Ermap;Lax1;Cd46;Cr2;Rabgef1;Zap70;Icosl;Tyrobp;Nfkbid;Dgkz;Plcg1;Plekha1;Ptprc;Cd79b;Cd22;Ifi204;Ifi211;Cd300a;Myo1g;Fcna;Prnp;Zbp1;Btnl10;Cacnb4
BP	GO:0022409	positive regulation of cell-cell adhesion	61/1512	268/14199	6,02817E-09	1,47592E-06	1,33721E-06	61	Vcam1;Zbtb16;Plpp3;Cd83;Cyrib;Lck;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Myo10;Tnfsf9;Syk;Cd4;Ccr7;Lilrb4a;Tnf;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Lgals8;Hsph1;Runx3;Flot2;Icam1;Cd86;Tnfsf4;Cd3e;Pik3r6;Cd46;Zbtb7b;Slc4a1;Podxl;Irf1;Zap70;Icosl;Fstl3;Nfkbid;Gm5150;H2-Oa;Ptprc;Ccr5;Spta1;Il1a;Sirpa;F11r;Xbp1;Ccl5
BP	GO:0007159	leukocyte cell-cell adhesion	74/1512	352/14199	6,12218E-09	1,47592E-06	1,33721E-06	74	Tigit;Vcam1;Zbtb16;Cd83;Cyrib;Lck;Il15;Btla;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Lilrb4a;Tnf;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Lgals8;Hsph1;Runx3;Flot2;Icam1;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Add2;Ctla4;Pik3r6;Lax1;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Nfkbid;Gm5150;Tnip1;H2-Oa;Ptprc;Dtx1;Spta1;Il1a;Prkar1a;Sirpa;F11r;Pla2g2f;Pla2g2d;Xbp1;Cd300a;Prnp;Tbx21;Ccl5
BP	GO:0032944	regulation of mononuclear cell proliferation	55/1512	231/14199	6,28749E-09	1,47592E-06	1,33721E-06	55	Csf1r;Vcam1;Il15;Btla;Ifng;Cd274;Slc39a10;H2-Aa;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Prdm1;Lilrb4a;Lst1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Cd55b;Il2ra;Clec2i;Cd276;St6gal1;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Csf1;Irf1;Zap70;Icosl;Tyrobp;Ptprc;Cd22;Spta1;Cd40;Il1a;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Ccl5
BP	GO:1903039	positive regulation of leukocyte cell-cell adhesion	55/1512	231/14199	6,28749E-09	1,47592E-06	1,33721E-06	55	Vcam1;Zbtb16;Cd83;Cyrib;Lck;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Tnfsf9;Syk;Cd4;Ccr7;Lilrb4a;Tnf;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Lgals8;Hsph1;Runx3;Flot2;Icam1;Cd86;Tnfsf4;Cd3e;Pik3r6;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Nfkbid;Gm5150;H2-Oa;Ptprc;Spta1;Il1a;Sirpa;Xbp1;Ccl5
BP	GO:0002696	positive regulation of leukocyte activation	75/1512	362/14199	9,38717E-09	2,11172E-06	1,91325E-06	75	Trbc2;Ighe;Ighg3;Vcam1;Zbtb16;Cd83;Cyrib;Lck;Hmces;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;Axl;H2-Ob;Slc39a10;H2-Aa;H2-Eb1;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Prdm1;Sh3kbp1;Lilrb4a;Pagr1a;Cav1;Il6st;Fgr;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Gata1;Lgals8;Hsph1;Lyst;Il15ra;Klrc1;Runx3;Flot2;Mmp14;Inpp5d;Cd86;Tnfsf4;Cd3e;Tnfrsf4;Pik3r6;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Tyrobp;Nfkbid;Gm5150;H2-Oa;Vamp8;Ptprc;Spta1;Cd40;Il1a;Sirpa;Xbp1;Tbx21;Ccl5
BP	GO:1903706	regulation of hemopoiesis	74/1512	357/14199	1,15401E-08	2,40357E-06	2,17767E-06	74	Csf1r;Zbtb16;Trib1;Nfam1;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;Axl;Id2;Ptk2b;H2-Aa;Fas;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Gfi1b;Prdm1;Stat1;Lilrb4a;Tnf;Gpr55;Senp1;Il4i1;Il4i1b;Tal1;Il2ra;Clec2i;Hsf1;Gata1;Adipoq;Prdm16;Il15ra;Runx3;Hmgb3;Rarg;Mmp14;Inpp5d;Car2;Prmt1;Prxl2a;Tnfsf4;Cdkn2a;Gpr171;C1qc;Zbtb46;Isg15;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Csf1;Irf1;Zap70;Tyrobp;Fstl3;Nfkbid;H2-Oa;Ptprc;Dtx1;Slamf8;Xbp1;Fam210b;Tbx21;Ccl5;Ccl3;Tnfaip6
BP	GO:0019724	B cell mediated immunity	43/1512	163/14199	1,15749E-08	2,40357E-06	2,17767E-06	43	Trbc2;Ighe;Ighg3;Hmces;Aicda;Ifng;Parp3;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Fas;C1ra;Il27ra;C3;C2;Il9r;Pagr1a;Tnf;Lta;Fcgr1;6030468B19Rik;Cd55b;Thoc1;Swap70;Pirb;Csf2rb2;Csf2rb;Lig4;Inpp5d;Tnfsf4;C1qb;C1qc;C1qa;Enpp1;Cd46;Cr2;Icosl;H2-Oa;Ptprc;Cd40;Il21r;Tbx21
BP	GO:0002695	negative regulation of leukocyte activation	46/1512	182/14199	1,54309E-08	3,08561E-06	2,79562E-06	46	Tigit;Btla;Cd200;Cd274;Parp3;Axl;Id2;H2-Aa;Fas;Ptpn2;Lag3;Abr;Prdm1;Lilrb4a;Lst1;Fgr;Il4i1;Il4i1b;Il2ra;Cd276;Thoc1;Runx3;Hmgb3;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Enpp3;Arg1;Ctla4;Lax1;Zbtb7b;Rabgef1;Irf1;Grn;Tyrobp;Nfkbid;Dtx1;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:0050866	negative regulation of cell activation	49/1512	201/14199	1,87015E-08	3,60605E-06	3,26714E-06	49	Tigit;Btla;Cd200;Cd274;Parp3;Axl;Id2;H2-Aa;Fas;Ptpn2;Lag3;Abr;Prdm1;Ptger3;Lilrb4a;Lst1;Cd9;Fgr;Il4i1;Il4i1b;Il2ra;Cd276;Thoc1;Runx3;Hmgb3;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Pdgfb;Tnfaip3;Enpp3;Arg1;Ctla4;Lax1;Zbtb7b;Rabgef1;Irf1;Grn;Tyrobp;Nfkbid;Dtx1;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:1902107	positive regulation of leukocyte differentiation	44/1512	172/14199	2,14289E-08	3,85649E-06	3,49404E-06	44	Csf1r;Zbtb16;Trib1;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;Axl;Id2;H2-Aa;Tnfsf9;Syk;Cd4;Ccr7;Gfi1b;Prdm1;Lilrb4a;Tnf;Il4i1;Il4i1b;Il2ra;Hsf1;Il15ra;Runx3;Mmp14;Inpp5d;Car2;Tnfsf4;Zbtb46;Pik3r6;Cd46;Zbtb7b;Csf1;Irf1;Zap70;Tyrobp;Nfkbid;Ptprc;Xbp1;Ccl5;Ccl3
BP	GO:1903708	positive regulation of hemopoiesis	44/1512	172/14199	2,14289E-08	3,85649E-06	3,49404E-06	44	Csf1r;Zbtb16;Trib1;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;Axl;Id2;H2-Aa;Tnfsf9;Syk;Cd4;Ccr7;Gfi1b;Prdm1;Lilrb4a;Tnf;Il4i1;Il4i1b;Il2ra;Hsf1;Il15ra;Runx3;Mmp14;Inpp5d;Car2;Tnfsf4;Zbtb46;Pik3r6;Cd46;Zbtb7b;Csf1;Irf1;Zap70;Tyrobp;Nfkbid;Ptprc;Xbp1;Ccl5;Ccl3
BP	GO:0051250	negative regulation of lymphocyte activation	41/1512	156/14199	2,82942E-08	4,92775E-06	4,46462E-06	41	Tigit;Btla;Cd274;Parp3;Axl;Id2;H2-Aa;Fas;Ptpn2;Lag3;Prdm1;Lilrb4a;Lst1;Fgr;Il4i1;Il4i1b;Il2ra;Cd276;Thoc1;Runx3;Hmgb3;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Arg1;Ctla4;Lax1;Zbtb7b;Irf1;Tyrobp;Nfkbid;Dtx1;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:0050867	positive regulation of cell activation	76/1512	381/14199	4,08894E-08	6,89881E-06	6,25043E-06	76	Trbc2;Ighe;Ighg3;Vcam1;Zbtb16;Cd83;Cyrib;Lck;Hmces;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;Axl;H2-Ob;Slc39a10;H2-Aa;H2-Eb1;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Prdm1;Sh3kbp1;Lilrb4a;Pagr1a;Cav1;Il6st;Fgr;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Il2ra;Cd276;Gata1;Lgals8;Hsph1;Lyst;Il15ra;Klrc1;Runx3;Flot2;Mmp14;Inpp5d;Cd86;Tnfsf4;Pdgfb;Cd3e;Tnfrsf4;Pik3r6;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Tyrobp;Nfkbid;Gm5150;H2-Oa;Vamp8;Ptprc;Spta1;Cd40;Il1a;Sirpa;Xbp1;Tbx21;Ccl5
BP	GO:0016064	immunoglobulin mediated immune response	41/1512	160/14199	6,1154E-08	1,00052E-05	9,06484E-06	41	Trbc2;Ighe;Ighg3;Hmces;Aicda;Ifng;Parp3;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;C1ra;Il27ra;C3;C2;Il9r;Pagr1a;Tnf;Lta;Fcgr1;6030468B19Rik;Cd55b;Thoc1;Swap70;Csf2rb2;Csf2rb;Lig4;Inpp5d;Tnfsf4;C1qb;C1qc;C1qa;Enpp1;Cd46;Cr2;Icosl;H2-Oa;Ptprc;Cd40;Il21r;Tbx21
BP	GO:0050670	regulation of lymphocyte proliferation	52/1512	228/14199	7,37867E-08	1,17169E-05	1,06157E-05	52	Vcam1;Il15;Btla;Ifng;Cd274;Slc39a10;H2-Aa;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Prdm1;Lilrb4a;Lst1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Cd55b;Il2ra;Clec2i;Cd276;Zc3h12d;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Tyrobp;Ptprc;Cd22;Spta1;Cd40;Il1a;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Ccl5
BP	GO:0042832	defense response to protozoan	17/1512	38/14199	8,60309E-08	1,32709E-05	1,20236E-05	17	Iigp1;Ifng;Nkg7;Gbp8;Gbp9;Gbp10;Gbp6;Lyst;Nras;Enpp1;Gbp3;Gbp2b;Gbp2;Arg1;Irgm2;Slc11a1;Cd40
BP	GO:0045619	regulation of lymphocyte differentiation	44/1512	181/14199	1,07456E-07	1,61155E-05	1,46009E-05	44	Zbtb16;Nfam1;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;Axl;Id2;H2-Aa;Fas;Tnfsf9;Ptpn2;Syk;Lag3;Ccr7;Prdm1;Lilrb4a;Il4i1;Il4i1b;Il2ra;Il15ra;Runx3;Hmgb3;Mmp14;Inpp5d;Tnfsf4;Cdkn2a;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Irf1;Zap70;Nfkbid;H2-Oa;Ptprc;Dtx1;Slamf8;Xbp1;Tbx21
BP	GO:0042098	T cell proliferation	49/1512	216/14199	2,07629E-07	3,02971E-05	2,74496E-05	49	Vcam1;Psmb10;Il15;Btla;Ifng;Ebi3;Cd274;H2-Aa;Il27ra;Tnfsf9;Syk;Cd4;Ccr7;Lilrb4a;Il6st;Gja1;Cd6;Il4i1;Il4i1b;Itgal;Lmbr1l;Cd55b;Il2ra;Clec2i;Cd276;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Tnfrsf4;Ctla4;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Ccnd3;Ptprc;Slc11a1;Spta1;Il1a;Prkar1a;Pla2g2f;Pla2g2d;Prnp;Ccl5
BP	GO:0019221	cytokine-mediated signaling pathway	68/1512	342/14199	2,40098E-07	3,41129E-05	3,09068E-05	68	Iigp1;Csf1r;Il15;Ifng;Il7r;Ebi3;Sting1;Prlr;Axl;Ptk2b;Il27ra;Ptpn2;Syk;Cd4;Ticam2;Stk39;Stat1;Il9r;Sphk1;Dok1;Tnf;Cav1;Il6st;Cdip1;Adipoq;Il15ra;Pirb;Ccl22;Csf2rb2;Csf2rb;Krt18;Il5ra;Pira2;Pdgfb;Il10ra;Arg1;Irf5;Isg15;Ackr3;Epor;Il2rb;Rabgef1;Csf1;Oasl2;Irf1;Padi2;Src;Cxcl9;Cxcl10;Il1rn;Ptprc;Igtp;Oas2;Oas3;Oas1a;Il11ra1;Il1a;Traf5;Lsm14a;Ifitm1;Ifitm3;Il21r;Pafah1b1;Traf1;Zbp1;Ccl5;Ccl3;Ccl4
BP	GO:0030098	lymphocyte differentiation	74/1512	386/14199	3,23457E-07	4,36621E-05	3,95586E-05	74	Ighe;Zbtb16;Nfam1;Cd83;Itm2a;Lck;Il15;Ifng;Il7r;Sox12;Cd8a;H2-DMa;Axl;Bcl11a;Id2;Ptk2b;H2-Aa;Fas;Gpr183;Tnfsf9;Ptpn2;Syk;Cd4;Hells;Lag3;Ccr7;Prdm1;Tsc1;Spib;Hdac9;Lilrb4a;Il9r;Bcl2a1d;Hdac7;Il4i1;Il4i1b;6030468B19Rik;Lmbr1l;Il2ra;Lgals8;Il15ra;Runx3;Hmgb3;Mmp14;Lig4;Inpp5d;Tnfsf4;Cdkn2a;Tnfaip3;Cd3e;Mpzl2;Enpp1;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Cr2;Irf1;Zap70;Aire;Nfkbid;H2-Oa;Ptprc;Dtx1;Cd79b;Cdh17;Il11ra1;Slamf8;Il1a;Slamf6;Pla2g2d;Xbp1;Tbx21
BP	GO:0042113	B cell activation	59/1512	284/14199	3,24157E-07	4,36621E-05	3,95586E-05	59	Trbc2;Ighe;Ighg3;Nfam1;Itm2a;Hmces;Aicda;Btla;Ifng;Il7r;Parp3;Bcl11a;Id2;Ptk2b;Slc39a10;Cd180;Fas;Il27ra;Gpr183;Ptpn2;Syk;Prdm1;Spib;Hdac9;Sh3kbp1;Lilrb4a;Il9r;Pagr1a;Hdac7;Fcrl1;Il4i1;6030468B19Rik;Thoc1;Lgals8;Swap70;Hmgb3;Mmp14;Lig4;Inpp5d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Enpp1;Tnfrsf4;Ctla4;Lax1;Cr2;Icosl;Tyrobp;Ptprc;Cd79b;Cdh17;Cd22;Slamf8;Cd40;Xbp1;Cd300a;Tbx21
BP	GO:0001562	response to protozoan	17/1512	41/14199	3,3157E-07	4,36621E-05	3,95586E-05	17	Iigp1;Ifng;Nkg7;Gbp8;Gbp9;Gbp10;Gbp6;Lyst;Nras;Enpp1;Gbp3;Gbp2b;Gbp2;Arg1;Irgm2;Slc11a1;Cd40
BP	GO:1903131	mononuclear cell differentiation	80/1512	429/14199	3,5634E-07	4,58067E-05	4,15016E-05	80	Ighe;Zbtb16;Nfam1;Cd83;Itm2a;Lck;Il15;Ifng;Il7r;Sox12;Cd8a;H2-DMa;Axl;Bcl11a;Id2;Ptk2b;H2-Aa;Fas;Gpr183;Tnfsf9;Ptpn2;Syk;Cd4;Hells;Lag3;Ccr7;Prdm1;Tsc1;Spib;Hdac9;Lilrb4a;Il9r;Bcl2a1d;Hdac7;Il4i1;Il4i1b;6030468B19Rik;Lmbr1l;Il2ra;Gata1;Lgals8;Il15ra;Pirb;Runx3;Hmgb3;Mmp14;Lig4;Inpp5d;Tnfsf4;Cdkn2a;Tnfaip3;Cd3e;Zbtb46;Mpzl2;Enpp1;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Cr2;Csf1;Irf1;Zap70;Aire;Nfkbid;Ubd;H2-Oa;Ptprc;Dtx1;Cd79b;Cdh17;Il11ra1;Slamf8;Ifi204;Il1a;Slamf6;Pla2g2d;Xbp1;Tbx21
BP	GO:0002768	immune response-regulating cell surface receptor signaling pathw	50/1512	228/14199	4,69889E-07	5,89984E-05	5,34535E-05	50	Trbc2;Ighe;Ighg3;Nfam1;Lck;Btla;Ifng;Clec4n;Cd8a;Sh2d1a;Slc39a10;Tlr2;Ptpn2;Syk;Ccr7;Usp46;Lilrb4a;Bcar1;Lcp2;Prkch;Bcl2a1d;Fcrl5;Ikbkg;Thy1;Clec2i;Cd276;Klrc1;Nras;Fpr2;Cd3e;Ctla4;Ermap;Lax1;Rabgef1;Zap70;Icosl;Tyrobp;Nfkbid;Dgkz;Plcg1;Plekha1;Ptprc;Cd79b;Cd22;Cd40;Cd300a;Myo1g;Prnp;Btnl10;Cacnb4
BP	GO:0042129	regulation of T cell proliferation	42/1512	178/14199	4,95985E-07	6,08596E-05	5,51398E-05	42	Vcam1;Il15;Btla;Ifng;Cd274;H2-Aa;Il27ra;Tnfsf9;Syk;Cd4;Ccr7;Lilrb4a;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Cd55b;Il2ra;Clec2i;Cd276;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Cd3e;Arg1;Ctla4;Cd46;Zbtb7b;Slc4a1;Irf1;Zap70;Icosl;Ptprc;Spta1;Il1a;Prkar1a;Pla2g2f;Pla2g2d;Prnp;Ccl5
BP	GO:0045621	positive regulation of lymphocyte differentiation	31/1512	114/14199	6,06318E-07	7,27447E-05	6,59079E-05	31	Zbtb16;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;Axl;H2-Aa;Tnfsf9;Syk;Ccr7;Prdm1;Lilrb4a;Il4i1;Il4i1b;Il2ra;Il15ra;Runx3;Mmp14;Inpp5d;Tnfsf4;Pik3r6;Cd46;Zbtb7b;Irf1;Zap70;Nfkbid;Ptprc;Xbp1
BP	GO:0002429	immune response-activating cell surface receptor signaling pathw	48/1512	219/14199	8,0614E-07	9,46163E-05	8,57238E-05	48	Trbc2;Ighe;Ighg3;Nfam1;Lck;Ifng;Clec4n;Cd8a;Sh2d1a;Slc39a10;Tlr2;Ptpn2;Syk;Ccr7;Usp46;Lilrb4a;Bcar1;Lcp2;Prkch;Bcl2a1d;Fcrl5;Ikbkg;Thy1;Clec2i;Cd276;Klrc1;Nras;Fpr2;Cd3e;Ctla4;Ermap;Lax1;Rabgef1;Zap70;Icosl;Tyrobp;Nfkbid;Dgkz;Plcg1;Plekha1;Ptprc;Cd79b;Cd22;Cd300a;Myo1g;Prnp;Btnl10;Cacnb4
BP	GO:0002764	immune response-regulating signaling pathway	71/1512	375/14199	9,08472E-07	0,000104238	9,44408E-05	71	Trbc2;Ighe;Ighg3;Treml4;Acod1;Nfam1;Lck;Btla;Ifng;Clec4n;Zcchc3;Cd8a;Sh2d1a;Slc39a10;Cd180;Ptprs;Tlr2;Ptpn2;Syk;Ccr7;Usp46;Lilrb4a;Bcar1;Nfkbil1;Lcp2;Prkch;App;Smpdl3b;Bcl2a1d;Cav1;Fcrl5;Ikbkg;Thy1;Clec2i;Cd276;Klrc1;Nras;Cd86;Slc15a2;Cd36;Tnfaip3;Cfp;Ctla4;Ermap;Lax1;Rabgef1;Zap70;Icosl;Cyba;Tyrobp;Nfkbid;Dgkz;Tnip1;Plcg1;Plekha1;Ptprc;Igtp;Oas3;Cd79b;Oas1a;Cd22;Cd40;Inava;Cd300a;Lsm14a;Myo1g;Prnp;Btnl10;Cacnb4
BP	GO:0002757	immune response-activating signal transduction	48/1512	220/14199	9,26727E-07	0,000104238	9,44408E-05	48	Trbc2;Ighe;Ighg3;Nfam1;Lck;Ifng;Clec4n;Cd8a;Sh2d1a;Slc39a10;Tlr2;Ptpn2;Syk;Ccr7;Usp46;Lilrb4a;Bcar1;Lcp2;Prkch;Bcl2a1d;Fcrl5;Ikbkg;Thy1;Clec2i;Cd276;Klrc1;Nras;Fpr2;Cd3e;Ctla4;Ermap;Lax1;Rabgef1;Zap70;Icosl;Tyrobp;Nfkbid;Dgkz;Plcg1;Plekha1;Ptprc;Cd79b;Cd22;Cd300a;Myo1g;Prnp;Btnl10;Cacnb4
BP	GO:0050764	regulation of phagocytosis	29/1512	105/14199	9,7684E-07	0,000107632	9,75161E-05	29	Il15;Ifng;Pten;Tlr2;Hck;C3;Syk;Ptk2;Ccr7;Abr;C2;Sphk1;Tnf;Hspa8;Fgr;Fcgr1;Adipoq;Il15ra;Cd36;Scarb1;Il2rb;Cyba;Abca7;Gm5150;Ptprc;Rab27a;Slc11a1;Sirpa;Cd300a
BP	GO:0050830	defense response to Gram-positive bacterium	23/1512	73/14199	1,05395E-06	0,000113806	0,00010311	23	Lyz2;Ifng;Il7r;Tlr2;Gbp8;Gbp9;Gbp10;Il27ra;Gbp6;Hck;Tnfaip8;Tnf;Lta;App;Scd1;Fgr;Mpeg1;Cd36;Gbp3;Gbp2b;Gbp2;Myo1f;Ncf1
BP	GO:0018108	peptidyl-tyrosine phosphorylation	55/1512	271/14199	1,73815E-06	0,000182886	0,000165698	55	Csf1r;Nedd9;Plpp3;Lck;Il15;Ifng;Clec4n;Prlr;Ptk2b;Agtr1a;Hck;Ptpn2;Syk;Ptk2;Cd4;Efna5;Lilrb4a;Il9r;Zfyve28;Ptpn4;App;Bmp6;Cav1;Il6st;Fgr;Htr2a;Thy1;Flt1;Hsf1;Gata1;Adipoq;Dyrk3;Hsph1;Clk1;Adra2a;Icam1;Cd36;Pdgfb;Cblc;Cd3e;Nrp1;Agrn;Lrp4;Reln;Irf1;Zap70;Src;Ptprc;Ptpn11;Gprc5b;Cd40;Cd300a;Ptpn1;Prnp;Ccl5
BP	GO:0070665	positive regulation of leukocyte proliferation	36/1512	149/14199	1,76145E-06	0,000182886	0,000165698	36	Csf1r;Vcam1;Il15;Ifng;Cd274;Slc39a10;Il27ra;Gpr183;Tnfsf9;Syk;Ptk2;Cd4;Ccr7;Il6st;Cd6;Itgal;Cd55b;Il2ra;Cd276;St6gal1;Csf2rb2;Csf2rb;Cd86;Tnfsf4;Cd3e;Tnfrsf4;Cd46;Slc4a1;Csf1;Zap70;Icosl;Ptprc;Spta1;Cd40;Il1a;Ccl5
BP	GO:0045785	positive regulation of cell adhesion	77/1512	425/14199	1,8809E-06	0,000191603	0,000173596	77	Nedd9;Vcam1;Zbtb16;Plpp3;Cd83;Cyrib;Lck;Il15;Ifng;Il7r;Cd274;Sox12;H2-DMa;H2-Ob;Ptk2b;H2-Aa;H2-Eb1;Il27ra;Myo10;Tnfsf9;Syk;Ptk2;Cd4;Ccr7;Tsc1;Lilrb4a;Tnf;Cav1;Il6st;Cd6;Il4i1;Il4i1b;Itgal;Thy1;Cd55b;Smoc1;Il2ra;Cd276;Dmd;Lgals8;Hsph1;Runx3;Flot2;Triobp;Hacd1;Icam1;Cd86;Tnfsf4;Cd36;Pdgfb;Fermt2;Cd3e;Nrp1;Pik3r6;Cd46;Zbtb7b;Slc4a1;Csf1;Podxl;Irf1;Zap70;Src;Icosl;Fstl3;Nfkbid;Gm5150;H2-Oa;Ptprc;Ptpn11;Hsd17b12;Ccr5;Spta1;Il1a;Sirpa;F11r;Xbp1;Ccl5
BP	GO:0042742	defense response to bacterium	48/1512	226/14199	2,08421E-06	0,000208382	0,000188797	48	Trbc2;Ighe;Ighg3;Iigp1;Lyz2;Aicda;Ifng;Il7r;Pten;Tlr2;Gbp8;Gbp9;Gbp10;Il27ra;Gbp6;Hck;Syk;Cd4;Tnfaip8;Tnf;Lta;App;Scd1;Fgr;Fcgr1;Mpeg1;Aqp1;Lyst;Cd36;Gbp3;Gbp2b;Gbp2;Isg15;Shc1;Jchain;Grn;Cyba;Myo1f;H2-K1;Igtp;Irgm2;Oas2;Oas3;Oas1a;Slpi;Slc11a1;Slamf8;Ncf1
BP	GO:0018212	peptidyl-tyrosine modification	55/1512	274/14199	2,47749E-06	0,0002432	0,000220343	55	Csf1r;Nedd9;Plpp3;Lck;Il15;Ifng;Clec4n;Prlr;Ptk2b;Agtr1a;Hck;Ptpn2;Syk;Ptk2;Cd4;Efna5;Lilrb4a;Il9r;Zfyve28;Ptpn4;App;Bmp6;Cav1;Il6st;Fgr;Htr2a;Thy1;Flt1;Hsf1;Gata1;Adipoq;Dyrk3;Hsph1;Clk1;Adra2a;Icam1;Cd36;Pdgfb;Cblc;Cd3e;Nrp1;Agrn;Lrp4;Reln;Irf1;Zap70;Src;Ptprc;Ptpn11;Gprc5b;Cd40;Cd300a;Ptpn1;Prnp;Ccl5
BP	GO:0030225	macrophage differentiation	16/1512	42/14199	2,83233E-06	0,000273067	0,000247403	16	Csf1r;Trib1;Il15;Ifng;Id2;Tlr2;Ptpn2;Cd4;Spib;App;Hsf1;Adipoq;C1qc;Zbtb46;Enpp1;Csf1
BP	GO:0002263	cell activation involved in immune response	54/1512	269/14199	3,04374E-06	0,0002883	0,000261205	54	Itm2a;Hmces;Aicda;Ifng;Parp3;Nkg7;Ptk2b;Cd180;Il27ra;Gpr183;Syk;Ccr7;Abr;Tsc1;Lilrb4a;Pagr1a;App;Fgr;Itgal;6030468B19Rik;Lcp1;Gata1;Thoc1;Lgals8;Swap70;Klrc1;Icam1;Lig4;Tnfsf4;Stx11;Tnfaip3;Enpp1;Enpp3;Cd46;Zbtb7b;Dnase1l3;Rabgef1;Irf1;Grn;Icosl;Tyrobp;Nfkbid;Myo1f;Vamp8;Ptprc;Rab27a;Cdh17;Slc11a1;Cd40;Slamf6;Xbp1;Cd300a;Tbx21;Eif2ak4
BP	GO:0071346	cellular response to interferon-gamma	28/1512	105/14199	3,18873E-06	0,000296827	0,00026893	28	Acod1;Ifng;Tlr2;Gbp8;Gbp9;Gbp10;Gbp6;Ptpn2;Capg;Stat1;H2-Q7;H2-Q9;Ccl22;Rab20;Stx11;Actg1;Gbp5;Gbp3;Gbp2b;Gbp2;Arg1;Irf1;Vamp8;Igtp;Sirpa;Ccl5;Ccl3;Ccl4
BP	GO:0035456	response to interferon-beta	19/1512	57/14199	3,53052E-06	0,000323072	0,000292709	19	Iigp1;Acod1;Sting1;Gbp6;Stat1;Tgtp1;Tgtp2;Gbp3;Gbp2b;Gbp2;Irf1;Htra2;Igtp;Irgm2;Oas1a;Ifi204;Ifi211;Ifitm1;Ifitm3
BP	GO:0050851	antigen receptor-mediated signaling pathway	41/1512	185/14199	3,74357E-06	0,000336859	0,0003052	41	Trbc2;Ighe;Ighg3;Nfam1;Lck;Ifng;Cd8a;Sh2d1a;Slc39a10;Ptpn2;Syk;Ccr7;Usp46;Lilrb4a;Bcar1;Lcp2;Prkch;Bcl2a1d;Fcrl5;Ikbkg;Thy1;Clec2i;Cd276;Nras;Cd3e;Ctla4;Ermap;Lax1;Zap70;Icosl;Nfkbid;Dgkz;Plcg1;Plekha1;Ptprc;Cd79b;Cd22;Cd300a;Prnp;Btnl10;Cacnb4
BP	GO:0002366	leukocyte activation involved in immune response	53/1512	265/14199	4,20077E-06	0,000371803	0,000336859	53	Itm2a;Hmces;Aicda;Ifng;Parp3;Nkg7;Ptk2b;Cd180;Il27ra;Gpr183;Syk;Ccr7;Abr;Tsc1;Lilrb4a;Pagr1a;Fgr;Itgal;6030468B19Rik;Lcp1;Gata1;Thoc1;Lgals8;Swap70;Klrc1;Icam1;Lig4;Tnfsf4;Stx11;Tnfaip3;Enpp1;Enpp3;Cd46;Zbtb7b;Dnase1l3;Rabgef1;Irf1;Grn;Icosl;Tyrobp;Nfkbid;Myo1f;Vamp8;Ptprc;Rab27a;Cdh17;Slc11a1;Cd40;Slamf6;Xbp1;Cd300a;Tbx21;Eif2ak4
BP	GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	36/1512	155/14199	4,68697E-06	0,000408145	0,000369786	36	Csf1r;Nedd9;Plpp3;Lck;Il15;Ifng;Clec4n;Ptk2b;Syk;Cd4;Efna5;App;Bmp6;Il6st;Htr2a;Hsf1;Gata1;Adipoq;Hsph1;Adra2a;Icam1;Cd36;Pdgfb;Cd3e;Nrp1;Agrn;Lrp4;Reln;Src;Ptprc;Ptpn11;Gprc5b;Cd40;Ptpn1;Prnp;Ccl5
BP	GO:0002285	lymphocyte activation involved in immune response	41/1512	188/14199	5,71629E-06	0,000489877	0,000443836	41	Itm2a;Hmces;Aicda;Ifng;Parp3;Nkg7;Ptk2b;Cd180;Il27ra;Gpr183;Ccr7;Tsc1;Lilrb4a;Pagr1a;Itgal;6030468B19Rik;Lcp1;Thoc1;Lgals8;Swap70;Klrc1;Icam1;Lig4;Tnfsf4;Stx11;Tnfaip3;Enpp1;Cd46;Zbtb7b;Irf1;Icosl;Nfkbid;Ptprc;Rab27a;Cdh17;Slc11a1;Cd40;Slamf6;Xbp1;Tbx21;Eif2ak4
BP	GO:0002312	B cell activation involved in immune response	25/1512	91/14199	5,96125E-06	0,000502887	0,000455624	25	Itm2a;Hmces;Aicda;Ifng;Parp3;Ptk2b;Cd180;Il27ra;Gpr183;Lilrb4a;Pagr1a;6030468B19Rik;Thoc1;Lgals8;Swap70;Lig4;Tnfsf4;Tnfaip3;Enpp1;Icosl;Ptprc;Cdh17;Cd40;Xbp1;Tbx21
BP	GO:0035458	cellular response to interferon-beta	17/1512	49/14199	6,19336E-06	0,00051443	0,000466082	17	Iigp1;Acod1;Sting1;Gbp6;Stat1;Tgtp1;Tgtp2;Gbp3;Gbp2b;Gbp2;Irf1;Htra2;Igtp;Irgm2;Oas1a;Ifi204;Ifi211
BP	GO:0045580	regulation of T cell differentiation	35/1512	151/14199	6,63374E-06	0,00054266	0,000491658	35	Zbtb16;Cd83;Lck;Il15;Ifng;Il7r;Sox12;H2-DMa;H2-Aa;Tnfsf9;Syk;Lag3;Ccr7;Prdm1;Lilrb4a;Il4i1;Il4i1b;Il2ra;Runx3;Tnfsf4;Cdkn2a;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Irf1;Zap70;Nfkbid;H2-Oa;Ptprc;Dtx1;Xbp1;Tbx21
BP	GO:0050869	negative regulation of B cell activation	14/1512	36/14199	8,94774E-06	0,000721028	0,000653262	14	Btla;Parp3;Id2;Fas;Prdm1;Lilrb4a;Thoc1;Hmgb3;Inpp5d;Cdkn2a;Tnfaip3;Ctla4;Tyrobp;Cd300a
BP	GO:0032946	positive regulation of mononuclear cell proliferation	32/1512	136/14199	1,17065E-05	0,000929459	0,000842105	32	Vcam1;Il15;Ifng;Cd274;Slc39a10;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Il6st;Cd6;Itgal;Cd55b;Il2ra;Cd276;St6gal1;Cd86;Tnfsf4;Cd3e;Tnfrsf4;Cd46;Slc4a1;Csf1;Zap70;Icosl;Ptprc;Spta1;Cd40;Il1a;Ccl5
BP	GO:0050730	regulation of peptidyl-tyrosine phosphorylation	45/1512	220/14199	1,20295E-05	0,000941268	0,000852804	45	Csf1r;Nedd9;Plpp3;Lck;Il15;Ifng;Clec4n;Ptk2b;Syk;Cd4;Efna5;Lilrb4a;Il9r;Zfyve28;App;Bmp6;Cav1;Il6st;Htr2a;Thy1;Hsf1;Gata1;Adipoq;Hsph1;Adra2a;Icam1;Cd36;Pdgfb;Cblc;Cd3e;Nrp1;Agrn;Lrp4;Reln;Irf1;Src;Ptprc;Ptpn11;Gprc5b;Cd40;Cd300a;Ptpn1;Prnp;Ccl5
BP	GO:0044406	adhesion of symbiont to host	8/1512	13/14199	1,27775E-05	0,000985509	0,000892887	8	Gbp9;Gbp6;Icam1;Scarb1;Gbp3;Gbp2b;Gbp2;Hsp90ab1
BP	GO:0050864	regulation of B cell activation	36/1512	162/14199	1,34547E-05	0,001023123	0,000926966	36	Trbc2;Ighe;Ighg3;Nfam1;Hmces;Btla;Ifng;Parp3;Id2;Ptk2b;Fas;Il27ra;Gpr183;Syk;Prdm1;Sh3kbp1;Lilrb4a;Pagr1a;Il4i1;Thoc1;Hmgb3;Mmp14;Inpp5d;Tnfsf4;Cdkn2a;Tnfaip3;Tnfrsf4;Ctla4;Tyrobp;Ptprc;Cd22;Slamf8;Cd40;Xbp1;Cd300a;Tbx21
BP	GO:0042102	positive regulation of T cell proliferation	26/1512	101/14199	1,41141E-05	0,001058358	0,000958889	26	Vcam1;Il15;Ifng;Cd274;Il27ra;Tnfsf9;Syk;Cd4;Ccr7;Il6st;Cd6;Itgal;Cd55b;Il2ra;Cd276;Cd86;Tnfsf4;Cd3e;Cd46;Slc4a1;Zap70;Icosl;Ptprc;Spta1;Il1a;Ccl5
BP	GO:0070664	negative regulation of leukocyte proliferation	24/1512	90/14199	1,57833E-05	0,001167314	0,001057605	24	Btla;Cd274;H2-Aa;Prdm1;Lilrb4a;Lst1;Il4i1;Il4i1b;Il2ra;Cd276;Zc3h12d;Inpp5d;Cd86;Cdkn2a;Enpp3;Arg1;Ctla4;Zbtb7b;Tyrobp;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp
BP	GO:1902106	negative regulation of leukocyte differentiation	25/1512	96/14199	1,65438E-05	0,001207026	0,001093584	25	Trib1;Ifng;Id2;Ptpn2;Lag3;Lilrb4a;Gpr55;Clec2i;Adipoq;Prdm16;Runx3;Hmgb3;Inpp5d;Cdkn2a;Tnfaip3;C1qc;Zbtb46;Ctla4;Zbtb7b;Irf1;Fstl3;Nfkbid;Dtx1;Tbx21;Tnfaip6
BP	GO:0006909	phagocytosis	47/1512	238/14199	2,03631E-05	0,001465874	0,001328105	47	Trbc2;Ighe;Ighg3;Treml4;Il15;Ifng;Axl;Pten;Tlr2;Hck;C3;Syk;Ptk2;Rhobtb2;4932438A13Rik;Ccr7;Abr;Ticam2;C2;Sphk1;Tnf;Hspa8;Fgr;Fcgr1;Itgal;Adipoq;Timd4;Lyst;Il15ra;Pld4;Rab20;Cd36;Scarb1;Il2rb;Cyba;Tyrobp;Pik3ca;Abca7;Gm5150;Ptprc;Rab27a;Slc11a1;Marco;Sirpa;Abca1;Cd300a;Myo1g
BP	GO:0043267	negative regulation of potassium ion transport	11/1512	25/14199	2,07992E-05	0,001477563	0,001338695	11	Kel;Bin1;Ptk2b;Pten;Ptger3;Stk39;Cav1;Htr2a;Atf4;Agrn;Nos1
BP	GO:0032945	negative regulation of mononuclear cell proliferation	23/1512	86/14199	2,23972E-05	0,00155029	0,001404587	23	Btla;Cd274;H2-Aa;Prdm1;Lilrb4a;Lst1;Il4i1;Il4i1b;Il2ra;Cd276;Zc3h12d;Inpp5d;Cd86;Cdkn2a;Arg1;Ctla4;Zbtb7b;Tyrobp;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp
BP	GO:0050672	negative regulation of lymphocyte proliferation	23/1512	86/14199	2,23972E-05	0,00155029	0,001404587	23	Btla;Cd274;H2-Aa;Prdm1;Lilrb4a;Lst1;Il4i1;Il4i1b;Il2ra;Cd276;Zc3h12d;Inpp5d;Cd86;Cdkn2a;Arg1;Ctla4;Zbtb7b;Tyrobp;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp
BP	GO:0045582	positive regulation of T cell differentiation	25/1512	98/14199	2,42513E-05	0,001636662	0,001482842	25	Zbtb16;Cd83;Lck;Ifng;Il7r;Sox12;H2-DMa;H2-Aa;Tnfsf9;Syk;Ccr7;Prdm1;Lilrb4a;Il4i1;Il4i1b;Il2ra;Runx3;Tnfsf4;Pik3r6;Cd46;Zbtb7b;Irf1;Zap70;Nfkbid;Ptprc;Xbp1
BP	GO:1903707	negative regulation of hemopoiesis	25/1512	98/14199	2,42513E-05	0,001636662	0,001482842	25	Trib1;Ifng;Id2;Ptpn2;Lag3;Lilrb4a;Gpr55;Clec2i;Adipoq;Prdm16;Runx3;Hmgb3;Inpp5d;Cdkn2a;Tnfaip3;C1qc;Zbtb46;Ctla4;Zbtb7b;Irf1;Fstl3;Nfkbid;Dtx1;Tbx21;Tnfaip6
BP	GO:0050868	negative regulation of T cell activation	29/1512	124/14199	3,33771E-05	0,002224726	0,002015637	29	Tigit;Btla;Cd274;H2-Aa;Ptpn2;Lag3;Lilrb4a;Il4i1;Il4i1b;Il2ra;Cd276;Runx3;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Arg1;Ctla4;Lax1;Zbtb7b;Irf1;Nfkbid;Dtx1;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:0002698	negative regulation of immune effector process	28/1512	118/14199	3,42623E-05	0,002231834	0,002022077	28	Il7r;Cd96;Parp3;Tap1;Serpinb9d;Abr;Lilrb4a;Tnf;Il4i1;Il4i1b;Tmbim6;Cd55b;Thoc1;Tnfsf4;Tnfaip3;Enpp3;Arg1;Cd46;Zbtb7b;Cr2;Rabgef1;Irf1;Grn;Ptprc;Cd22;Slamf8;Cd300a;Tbx21
BP	GO:0071280	cellular response to copper ion	7/1512	11/14199	3,43105E-05	0,002231834	0,002022077	7	Atp7b;Hsf1;Aqp1;Mt2;Mt1;Nfe2l2;Prnp
BP	GO:0002697	regulation of immune effector process	65/1512	372/14199	3,81472E-05	0,002451863	0,002221426	65	Cyrib;Hmces;Ifng;Il7r;Cd96;Parp3;Tap1;Sh2d1a;Tlr2;Il27ra;C3;Syk;Serpinb9d;Lag3;Ccr7;Abr;Lilrb4a;Pagr1a;Tnf;Lta;Hspa8;Fgr;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;Sema7a;6030468B19Rik;Tmbim6;Cd55b;Gata1;Thoc1;Klrc1;Cd86;Tnfsf4;Cd36;Tnfaip3;Enpp3;Arg1;Tnfrsf4;Pik3r6;Cd46;Zbtb7b;Dnase1l3;Cr2;Rabgef1;Irf1;Grn;Tyrobp;Nfkbid;H2-K1;Vamp8;Ptprc;Gprc5b;Cd22;Slamf8;Cd40;Slamf6;Xbp1;Inava;Cd300a;Ncf1;Tbx21
BP	GO:0019882	antigen processing and presentation	26/1512	107/14199	4,18237E-05	0,002656545	0,002406871	26	Treml4;Ifng;Clec4a1;H2-DMa;Psmb10;Tap1;H2-Ob;H2-Aa;H2-Eb1;Ccr7;Ctss;Mfsd6;Fcgr1;H2-Q7;H2-Q9;Abcb9;Icam1;Ctse;Psme2;Rab4a;Fcgr4;H2-K1;H2-Oa;Rab6a;Rab27a;Slc11a1
BP	GO:0022408	negative regulation of cell-cell adhesion	39/1512	191/14199	4,66504E-05	0,002928666	0,002653417	39	Tigit;Epcam;Btla;Cd274;H2-Aa;Ptpn2;Lag3;Ptger3;Lilrb4a;Cd9;Bmp6;Il4i1;Il4i1b;Il2ra;Cd276;Adipoq;Swap70;Runx3;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Arg1;Ctla4;Lax1;Zbtb7b;Podxl;Irf1;Nfkbid;Il1rn;Dtx1;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:0006875	cellular metal ion homeostasis	78/1512	472/14199	4,98224E-05	0,00309185	0,002801265	78	Hcrtr2;P2ry10;Kel;Lck;Slc1a3;Ifng;Ptk2b;Slc39a10;Cacna1d;Immt;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Atp7b;Ptger3;Camk2d;App;Gpr55;Bmp6;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Mcub;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Mt2;Mt1;Herpud1;Atp6v0a2;Nalf1;Cd36;Atf4;Fpr2;Sgk1;Ackr3;Ackr4;Epor;Atp1b1;Erfe;Kctd7;Mcoln1;Tmprss3;Cyba;Atp1b2;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Slc30a9;Slc11a1;Cd40;Abcb6;Il1a;Glrx3;Cox19;Atp2a3;Prnp;Ccl5;Ccl3;Ryr3;Cacnb4
BP	GO:0002381	immunoglobulin production involved in immunoglobulin-mediat	21/1512	79/14199	5,53859E-05	0,003347773	0,003033135	21	Hmces;Aicda;Ifng;Parp3;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Il27ra;Pagr1a;6030468B19Rik;Thoc1;Swap70;Lig4;Tnfsf4;Enpp1;Icosl;H2-Oa;Ptprc;Cd40;Tbx21
BP	GO:0050852	T cell receptor signaling pathway	28/1512	121/14199	5,54422E-05	0,003347773	0,003033135	28	Lck;Ifng;Cd8a;Sh2d1a;Ptpn2;Ccr7;Usp46;Lilrb4a;Lcp2;Bcl2a1d;Ikbkg;Thy1;Clec2i;Cd276;Nras;Cd3e;Ctla4;Ermap;Zap70;Icosl;Nfkbid;Dgkz;Plcg1;Ptprc;Cd300a;Prnp;Btnl10;Cacnb4
BP	GO:0044403	biological process involved in symbiotic interaction	41/1512	206/14199	5,58066E-05	0,003347773	0,003033135	41	Csf1r;Ifng;Trim30b;Axl;Ist1;Gbp9;Agtr1a;Gbp6;Cd4;Chmp7;Exoc7;Hspa8;Cav1;Mid2;Ciita;Thoc1;Icam1;Avpr1b;Grk2;Scarb1;Gbp3;Gbp2b;Gbp2;Arg1;Hsp90ab1;Nrp1;Napepld;Rrp1b;Brd4;Trim62;Vamp8;Tpcn1;Bcl2l11;Hpn;Cdk9;Ncf1;Siglec1;Ifitm1;Ifitm3;Ccl5;Eif2ak4
BP	GO:0001819	positive regulation of cytokine production	74/1512	444/14199	5,82179E-05	0,003431822	0,003109285	74	Csf1r;Tigit;Nfam1;Cd83;Cyrib;Il15;Cd200;Ifng;Clec4n;Cd274;Zcchc3;Sting1;Setd4;Tlr2;Il27ra;Agtr1a;Tnfsf9;C3;Syk;Ccr7;Ticam2;Stat1;Sphk1;Ltb;Tnf;Lta;App;Fgr;H2-Q9;Cd6;Sema7a;Cd55b;Cd276;Adipoq;Adra2a;Nras;Grk2;Tnfsf4;Cd36;Atf4;Cd3e;Gbp5;Irf5;Isg15;Cd46;Zbtb7b;Setd2;Irf1;Aire;Src;Icosl;Cyba;Tyrobp;Ptprc;Oas2;Oas3;Oas1a;Ptpn11;Ccr5;Gprc5b;Slc11a1;Ifi204;Ifi211;Cd40;Il1a;Slamf6;Tnfsf15;Xbp1;Inava;Cd300c2;Tbx21;Ccl5;Ccl3;Ccl4
BP	GO:0030099	myeloid cell differentiation	67/1512	392/14199	5,90311E-05	0,003431822	0,003109285	67	Csf1r;Zbtb16;Trib1;Alas1;Il15;Ifng;Id2;Ptk2b;Fas;Tlr2;Gpr183;Tnfsf9;Ptpn2;Cd4;Ccr7;Tgfbr3;Gfi1b;Spib;Stat1;Lilrb4a;Dnase2a;Tnf;App;Gpr55;Add1;Senp1;Ank1;Tal1;Actn1;Pml;Clec2i;Hsf1;Tet2;Gata1;Epb42;Adipoq;Prdm16;Dyrk3;Pirb;Hmgb3;Rarg;Inpp5d;Car2;Prmt1;Prxl2a;Flvcr1;Gpr171;C1qc;Zbtb46;Enpp1;Isg15;Slc4a1;Csf1;Sox6;Src;Tyrobp;Fstl3;Ubd;Rhag;Tcea1;Ptpn11;Ifi204;Pafah1b1;Fam210b;Ccl5;Ccl3;Tnfaip6
BP	GO:0050671	positive regulation of lymphocyte proliferation	30/1512	134/14199	5,91146E-05	0,003431822	0,003109285	30	Vcam1;Il15;Ifng;Cd274;Slc39a10;Il27ra;Gpr183;Tnfsf9;Syk;Cd4;Ccr7;Il6st;Cd6;Itgal;Cd55b;Il2ra;Cd276;Cd86;Tnfsf4;Cd3e;Tnfrsf4;Cd46;Slc4a1;Zap70;Icosl;Ptprc;Spta1;Cd40;Il1a;Ccl5
BP	GO:0050777	negative regulation of immune response	35/1512	167/14199	6,43859E-05	0,003698078	0,003350517	35	Acod1;Il7r;Cd96;Col3a1;Parp3;Tap1;Il27ra;Ptpn2;Serpinb9d;Abr;Lilrb4a;Smpdl3b;Il4i1;Il4i1b;Cd55b;Thoc1;Inpp5d;Tnfsf4;Tnfaip3;Enpp3;Arg1;Isg15;Cd46;Zbtb7b;Cr2;Rabgef1;Irf1;Grn;Ptprc;Oas3;Oas1a;Slamf8;Ifi204;Cd300a;Tbx21
BP	GO:0050766	positive regulation of phagocytosis	20/1512	75/14199	7,87633E-05	0,004440182	0,004022874	20	Il15;Ifng;C3;Ptk2;Ccr7;Abr;C2;Tnf;Hspa8;Fcgr1;Il15ra;Cd36;Il2rb;Cyba;Abca7;Gm5150;Ptprc;Rab27a;Slc11a1;Sirpa
BP	GO:0030217	T cell differentiation	51/1512	279/14199	7,89512E-05	0,004440182	0,004022874	51	Zbtb16;Cd83;Lck;Il15;Ifng;Il7r;Sox12;Cd8a;H2-DMa;Bcl11a;H2-Aa;Fas;Gpr183;Tnfsf9;Ptpn2;Syk;Cd4;Lag3;Ccr7;Prdm1;Tsc1;Lilrb4a;Bcl2a1d;Il4i1;Il4i1b;Lmbr1l;Il2ra;Runx3;Lig4;Tnfsf4;Cdkn2a;Cd3e;Mpzl2;Enpp1;Ctla4;Tcf7;Pik3r6;Cd46;Zbtb7b;Irf1;Zap70;Aire;Nfkbid;H2-Oa;Ptprc;Dtx1;Il1a;Slamf6;Pla2g2d;Xbp1;Tbx21
BP	GO:0002822	regulation of adaptive immune response based on somatic recon	38/1512	189/14199	8,21043E-05	0,004569911	0,004140411	38	Cyrib;Hmces;Ifng;Il7r;Clec4n;Cd274;Parp3;H2-DMa;Il27ra;C3;Cd4;Ccr7;Lilrb4a;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Cd55b;Thoc1;Tnfsf4;Tnfaip3;Arg1;Cd46;Zbtb7b;Cr2;Irf1;Nfkbid;H2-K1;Ptprc;Slc11a1;Cd40;Tbx21
BP	GO:0002478	antigen processing and presentation of exogenous peptide antig	12/1512	33/14199	8,51616E-05	0,004691709	0,004250762	12	Clec4a1;H2-DMa;Tap1;H2-Ob;H2-Aa;H2-Eb1;Ctss;Mfsd6;Fcgr1;Ctse;H2-K1;H2-Oa
BP	GO:0046688	response to copper ion	9/1512	20/14199	9,67493E-05	0,005276256	0,004780371	9	Atp7b;Hsf1;Aqp1;Mt2;Mt1;Cp;Nfe2l2;Il1a;Prnp
BP	GO:0002237	response to molecule of bacterial origin	49/1512	268/14199	0,000107498	0,005803822	0,005258354	49	Acod1;Trib1;Cyrib;Aicda;Ifng;Cd96;Cd274;Axl;Cd180;Tlr2;Gbp10;Gbp6;Ccr7;Abr;Prdm1;Ptger3;Stat1;Lilrb4a;Tnf;Nfkbil1;Bmp6;Noct;Cd6;Cd55b;Hsf1;Gata1;Pabpn1;Cd86;Tnfsf4;Cd36;Tnfaip3;Scarb1;Gbp2;Irf5;Cr2;Cxcl9;Tnip1;Cxcl10;Fcgr4;Nos1;Igtp;Slpi;Slc11a1;Il1a;Sirpa;Abca1;Xbp1;Inava;Ccl5
BP	GO:0007162	negative regulation of cell adhesion	50/1512	276/14199	0,000116527	0,006228988	0,005643561	50	Tigit;Epcam;Plet1;Btla;Cd274;Pten;H2-Aa;Ptpn2;Ptk2;Lag3;Efna5;Ptger3;Lilrb4a;Bcar1;Dscam;Cd9;Bmp6;Il4i1;Il4i1b;Il2ra;Cd276;Adipoq;Swap70;Runx3;Mmp14;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Tnfaip3;Arg1;Ctla4;Lax1;Zbtb7b;Plxnd1;Podxl;Irf1;Src;Nfkbid;Myo1f;Il1rn;Ptprc;Dtx1;Ptpn11;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:0019884	antigen processing and presentation of exogenous antigen	13/1512	39/14199	0,00012213	0,006464519	0,005856956	13	Clec4a1;H2-DMa;Tap1;H2-Ob;H2-Aa;H2-Eb1;Ctss;Mfsd6;Fcgr1;Ctse;Psme2;H2-K1;H2-Oa
BP	GO:0002712	regulation of B cell mediated immunity	18/1512	67/14199	0,000159503	0,008201477	0,007430667	18	Hmces;Ifng;Parp3;Il27ra;C3;Pagr1a;Tnf;Lta;Fcgr1;6030468B19Rik;Cd55b;Thoc1;Tnfsf4;Cd46;Cr2;Ptprc;Cd40;Tbx21
BP	GO:0002889	regulation of immunoglobulin mediated immune response	18/1512	67/14199	0,000159503	0,008201477	0,007430667	18	Hmces;Ifng;Parp3;Il27ra;C3;Pagr1a;Tnf;Lta;Fcgr1;6030468B19Rik;Cd55b;Thoc1;Tnfsf4;Cd46;Cr2;Ptprc;Cd40;Tbx21
BP	GO:0061097	regulation of protein tyrosine kinase activity	18/1512	67/14199	0,000159503	0,008201477	0,007430667	18	Csf1r;Nedd9;Ptpn2;Lilrb4a;Zfyve28;App;Cav1;Thy1;Hsph1;Adra2a;Pdgfb;Cblc;Agrn;Reln;Ptprc;Gprc5b;Ptpn1;Prnp
BP	GO:0071219	cellular response to molecule of bacterial origin	37/1512	189/14199	0,000179042	0,00911932	0,008262248	37	Acod1;Trib1;Cyrib;Aicda;Ifng;Cd274;Axl;Cd180;Tlr2;Gbp10;Gbp6;Prdm1;Stat1;Lilrb4a;Tnf;Nfkbil1;Bmp6;Cd6;Cd55b;Gata1;Pabpn1;Cd86;Tnfsf4;Cd36;Tnfaip3;Gbp2;Cr2;Cxcl9;Tnip1;Cxcl10;Fcgr4;Igtp;Il1a;Sirpa;Abca1;Xbp1;Ccl5
BP	GO:0045637	regulation of myeloid cell differentiation	38/1512	196/14199	0,000181548	0,009160553	0,008299606	38	Csf1r;Zbtb16;Trib1;Ifng;Id2;Ptk2b;Fas;Ptpn2;Cd4;Gfi1b;Stat1;Lilrb4a;Tnf;Gpr55;Senp1;Tal1;Clec2i;Hsf1;Gata1;Adipoq;Prdm16;Hmgb3;Rarg;Inpp5d;Car2;Prmt1;Prxl2a;Gpr171;C1qc;Zbtb46;Isg15;Csf1;Tyrobp;Fstl3;Fam210b;Ccl5;Ccl3;Tnfaip6
BP	GO:0072503	cellular divalent inorganic cation homeostasis	65/1512	392/14199	0,000186986	0,009305775	0,008431179	65	Hcrtr2;P2ry10;Kel;Lck;Ptk2b;Slc39a10;Cacna1d;Immt;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Atp7b;Ptger3;Camk2d;App;Gpr55;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Mcub;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Mt2;Mt1;Herpud1;Nalf1;Cd36;Atf4;Fpr2;Ackr3;Ackr4;Epor;Atp1b1;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Slc30a9;Slc11a1;Cd40;Atp2a3;Prnp;Ccl5;Ccl3;Ryr3;Cacnb4
BP	GO:0002831	regulation of response to biotic stimulus	58/1512	340/14199	0,000190585	0,009305775	0,008431179	58	Treml4;Acod1;Trib1;Il15;Ifng;Cd96;Clec4n;Cd274;Zcchc3;Sting1;Tap1;Sh2d1a;Cd180;Pten;Tlr2;C3;Serpinb1a;Ptpn2;Syk;Serpinb9d;Lag3;Srebf1;Prdm1;Stat1;Nfkbil1;Smpdl3b;Bmp6;Fgr;Il4i1;Il4i1b;Cd55b;Pml;Klrc1;Apobec3;Tnfaip3;Gbp5;Arg1;Isg15;Pik3r6;Irf1;Grn;Nfe2l2;Cyba;Tyrobp;Myo1f;Trim62;Igtp;Oas3;Oas1a;Slamf8;Ifi204;Ifi211;Slamf6;Lsm14a;Ncf1;Zbp1;Ccl5;Eif2ak4
BP	GO:0072507	divalent inorganic cation homeostasis	68/1512	415/14199	0,000191985	0,009305775	0,008431179	68	Hcrtr2;P2ry10;Kel;Lck;Ptk2b;Slc39a10;Cacna1d;Immt;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Atp7b;Ptger3;Camk2d;App;Gpr55;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Mcub;Tmc8;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Mt2;Mt1;Herpud1;Nalf1;Cd36;Atf4;Fpr2;Enpp1;Alpl;Ackr3;Ackr4;Epor;Atp1b1;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Slc30a9;Slc11a1;Cd40;Atp2a3;Prnp;Ccl5;Ccl3;Ryr3;Cacnb4
BP	GO:0030183	B cell differentiation	29/1512	136/14199	0,000193044	0,009305775	0,008431179	29	Ighe;Nfam1;Itm2a;Bcl11a;Id2;Ptk2b;Gpr183;Ptpn2;Syk;Prdm1;Spib;Hdac9;Lilrb4a;Il9r;Hdac7;Il4i1;6030468B19Rik;Lgals8;Hmgb3;Mmp14;Inpp5d;Tnfaip3;Enpp1;Cr2;Ptprc;Cd79b;Cdh17;Slamf8;Xbp1
BP	GO:1903038	negative regulation of leukocyte cell-cell adhesion	29/1512	136/14199	0,000193044	0,009305775	0,008431179	29	Tigit;Btla;Cd274;H2-Aa;Ptpn2;Lag3;Lilrb4a;Il4i1;Il4i1b;Il2ra;Cd276;Runx3;Zc3h12d;Cd86;Tnfsf4;Cdkn2a;Arg1;Ctla4;Lax1;Zbtb7b;Irf1;Nfkbid;Dtx1;Prkar1a;Pla2g2f;Pla2g2d;Cd300a;Prnp;Tbx21
BP	GO:0030853	negative regulation of granulocyte differentiation	6/1512	10/14199	0,000207498	0,009913985	0,008982227	6	Trib1;Adipoq;Prdm16;Inpp5d;C1qc;Zbtb46
BP	GO:0002819	regulation of adaptive immune response	39/1512	205/14199	0,000226458	0,01072496	0,009716983	39	Cyrib;Hmces;Ifng;Il7r;Clec4n;Cd274;Parp3;H2-DMa;Il27ra;C3;Cd4;Ccr7;Lilrb4a;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Cd55b;Thoc1;Tnfsf4;Tnfaip3;Arg1;Cd46;Zbtb7b;Cr2;Irf1;Nfkbid;H2-K1;Ptprc;Slc11a1;Cd40;Tbx21;Eif2ak4
BP	GO:0002761	regulation of myeloid leukocyte differentiation	26/1512	118/14199	0,000234794	0,010993409	0,009960201	26	Csf1r;Trib1;Ifng;Id2;Ptpn2;Cd4;Gfi1b;Lilrb4a;Tnf;Gpr55;Tal1;Clec2i;Hsf1;Adipoq;Prdm16;Inpp5d;Car2;Prxl2a;C1qc;Zbtb46;Csf1;Tyrobp;Fstl3;Ccl5;Ccl3;Tnfaip6
BP	GO:0002823	negative regulation of adaptive immune response based on soma	15/1512	52/14199	0,000236198	0,010993409	0,009960201	15	Il7r;Parp3;Il27ra;Lilrb4a;Il4i1;Il4i1b;Cd55b;Thoc1;Tnfsf4;Arg1;Cd46;Zbtb7b;Cr2;Ptprc;Tbx21
BP	GO:0002704	negative regulation of leukocyte mediated immunity	18/1512	69/14199	0,000238707	0,011012528	0,00997997	18	Il7r;Cd96;Parp3;Tap1;Serpinb9d;Abr;Lilrb4a;Il4i1;Il4i1b;Cd55b;Thoc1;Arg1;Cd46;Cr2;Rabgef1;Ptprc;Cd300a;Tbx21
BP	GO:0001906	cell killing	37/1512	193/14199	0,000276804	0,012664951	0,011474644	37	Ighg3;Lyz2;Cyrib;Ifng;Il7r;Nkg7;Tap1;Sh2d1a;C3;Syk;Serpinb9d;Lag3;Cd5l;Hspa8;Fgr;Fcgr1;H2-Q7;H2-Q9;Lyst;Klrc1;Ccl22;Stx11;Prf1;Arg1;Hsp90ab1;Gzmb;Pik3r6;Dnase1l3;Tyrobp;Cxcl9;Cxcl10;Rnf19b;H2-K1;Ptprc;Rab27a;Bcl2l11;Slamf6;Ncf1
BP	GO:0032611	interleukin-1 beta production	22/1512	94/14199	0,000282624	0,012822578	0,011617457	22	Ifng;Tlr2;Serpinb1a;Serpinb1b;Ccr7;Tnfaip8;Lilrb4a;Sphk1;Tnf;App;Pml;Gstp2;Cd36;Tnfaip3;Gbp5;Tyrobp;Ccr5;Ifi204;Ifi211;Sirpa;Inava;Ccl3
BP	GO:0032496	response to lipopolysaccharide	45/1512	250/14199	0,000289916	0,012943513	0,011727026	45	Acod1;Trib1;Aicda;Ifng;Cd96;Cd274;Axl;Cd180;Tlr2;Gbp10;Gbp6;Ccr7;Abr;Prdm1;Ptger3;Stat1;Lilrb4a;Tnf;Nfkbil1;Bmp6;Noct;Cd6;Cd55b;Hsf1;Gata1;Pabpn1;Cd86;Tnfsf4;Cd36;Tnfaip3;Scarb1;Gbp2;Irf5;Cr2;Cxcl9;Tnip1;Cxcl10;Fcgr4;Nos1;Igtp;Slpi;Slc11a1;Il1a;Sirpa;Abca1;Xbp1;Ccl5
BP	GO:0032651	regulation of interleukin-1 beta production	21/1512	88/14199	0,000290084	0,012943513	0,011727026	21	Ifng;Tlr2;Serpinb1a;Serpinb1b;Ccr7;Tnfaip8;Lilrb4a;Sphk1;Tnf;App;Pml;Gstp2;Cd36;Tnfaip3;Gbp5;Tyrobp;Ccr5;Ifi204;Ifi211;Sirpa;Inava;Ccl3
BP	GO:0071222	cellular response to lipopolysaccharide	35/1512	181/14199	0,000337375	0,01484503	0,013449831	35	Acod1;Trib1;Aicda;Ifng;Cd274;Axl;Cd180;Tlr2;Gbp10;Gbp6;Prdm1;Stat1;Lilrb4a;Tnf;Nfkbil1;Bmp6;Cd6;Cd55b;Gata1;Pabpn1;Cd86;Tnfsf4;Cd36;Tnfaip3;Gbp2;Cr2;Cxcl9;Tnip1;Cxcl10;Fcgr4;Igtp;Il1a;Sirpa;Abca1;Xbp1;Ccl5
BP	GO:0002573	myeloid leukocyte differentiation	40/1512	216/14199	0,000339081	0,01484503	0,013449831	40	Csf1r;Trib1;Il15;Ifng;Id2;Tlr2;Gpr183;Tnfsf9;Ptpn2;Cd4;Ccr7;Gfi1b;Spib;Lilrb4a;Tnf;App;Gpr55;Tal1;Clec2i;Hsf1;Gata1;Adipoq;Prdm16;Pirb;Inpp5d;Car2;Prxl2a;C1qc;Zbtb46;Enpp1;Csf1;Src;Tyrobp;Fstl3;Ubd;Ifi204;Pafah1b1;Ccl5;Ccl3;Tnfaip6
BP	GO:0050854	regulation of antigen receptor-mediated signaling pathway	17/1512	65/14199	0,000340949	0,01484503	0,013449831	17	Nfam1;Lck;Sh2d1a;Slc39a10;Ptpn2;Ccr7;Usp46;Lilrb4a;Prkch;Fcrl5;Ikbkg;Thy1;Dgkz;Ptprc;Cd22;Cd300a;Prnp
BP	GO:0060401	cytosolic calcium ion transport	31/1512	155/14199	0,000393364	0,016990163	0,015393355	31	Lck;Ptk2b;Cacna1d;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Camk2d;Cav1;Fcrl5;Htr2a;Mcub;Thy1;Tmbim6;Pml;Dmd;Nalf1;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Cacna1s;Ptprc;Xcr1;Ccr5;Rgs9;Atp2a3;Prnp;Ryr3
BP	GO:0045577	regulation of B cell differentiation	11/1512	33/14199	0,00040405	0,017313237	0,015686065	11	Nfam1;Id2;Syk;Prdm1;Lilrb4a;Il4i1;Hmgb3;Mmp14;Inpp5d;Slamf8;Xbp1
BP	GO:0045649	regulation of macrophage differentiation	8/1512	19/14199	0,000416995	0,017727204	0,016061126	8	Trib1;Id2;Ptpn2;Hsf1;Adipoq;C1qc;Zbtb46;Csf1
BP	GO:0002703	regulation of leukocyte mediated immunity	46/1512	262/14199	0,000443355	0,018700578	0,016943018	46	Cyrib;Hmces;Ifng;Il7r;Cd96;Parp3;Tap1;Sh2d1a;Il27ra;C3;Syk;Serpinb9d;Lag3;Abr;Lilrb4a;Pagr1a;Tnf;Lta;Hspa8;Fgr;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Cd55b;Gata1;Thoc1;Klrc1;Tnfsf4;Arg1;Pik3r6;Cd46;Dnase1l3;Cr2;Rabgef1;Tyrobp;H2-K1;Vamp8;Ptprc;Cd40;Slamf6;Cd300a;Tbx21
BP	GO:0071216	cellular response to biotic stimulus	39/1512	213/14199	0,000504736	0,021124577	0,019139199	39	Acod1;Trib1;Cyrib;Aicda;Ifng;Cd274;Axl;Cd180;Tlr2;Gbp10;Gbp6;Syk;Prdm1;Stat1;Lilrb4a;Tnf;Nfkbil1;Bmp6;Cd6;Cd55b;Gata1;Pabpn1;Cd86;Tnfsf4;Cd36;Tnfaip3;Gbp2;Cr2;Cxcl9;Tnip1;Cxcl10;Fcgr4;Igtp;Bcl2l11;Il1a;Sirpa;Abca1;Xbp1;Ccl5
BP	GO:0006874	cellular calcium ion homeostasis	60/1512	368/14199	0,000508909	0,021135393	0,019148998	60	Hcrtr2;P2ry10;Kel;Lck;Ptk2b;Slc39a10;Cacna1d;Immt;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Atp7b;Ptger3;Camk2d;App;Gpr55;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Mcub;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Herpud1;Nalf1;Cd36;Atf4;Fpr2;Ackr3;Ackr4;Epor;Atp1b1;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Cd40;Atp2a3;Prnp;Ccl5;Ccl3;Ryr3;Cacnb4
BP	GO:0055074	calcium ion homeostasis	62/1512	386/14199	0,000616942	0,025426473	0,023036784	62	Hcrtr2;P2ry10;Kel;Lck;Ptk2b;Slc39a10;Cacna1d;Immt;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Atp7b;Ptger3;Camk2d;App;Gpr55;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Mcub;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Herpud1;Nalf1;Cd36;Atf4;Fpr2;Enpp1;Alpl;Ackr3;Ackr4;Epor;Atp1b1;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Cd40;Atp2a3;Prnp;Ccl5;Ccl3;Ryr3;Cacnb4
BP	GO:0099068	postsynapse assembly	8/1512	20/14199	0,000630492	0,025788071	0,023364398	8	Pten;Ptprs;Nrxn2;Lrfn1;Sipa1l1;Nptxr;Lrp4;Reln
BP	GO:0051607	defense response to virus	44/1512	252/14199	0,000657921	0,02653715	0,024043075	44	Treml4;Acod1;Aicda;Il15;Ifng;Zcchc3;Sting1;Cd8a;Senp7;Pmaip1;Ticam2;Stat1;H2-Q9;Mid2;Zmynd11;Pml;Serinc5;Lyst;Ddx17;Cd86;Prf1;Apobec3;Itgax;Gbp2b;Irf5;Isg15;Setd2;Oasl2;Irf1;Cxcl9;Cxcl10;Vamp8;Ptprc;Oas2;Oas3;Oas1a;Ifi204;Cd40;Lsm14a;Ifitm1;Ifitm3;Zbp1;Ccl5;Eif2ak4
BP	GO:0045071	negative regulation of viral genome replication	14/1512	51/14199	0,000658636	0,02653715	0,024043075	14	Aicda;Tnf;Apobec3;Isg15;Srpk2;Oasl2;Oas2;Oas3;Oas1a;Slpi;Ifi204;Ifitm1;Ifitm3;Ccl5
BP	GO:0001818	negative regulation of cytokine production	46/1512	267/14199	0,00067663	0,027060185	0,024516953	46	Trib2;Tigit;Acod1;Cd83;Cd200;Ifng;Cd96;Clec4a1;Cd274;Axl;Ptprs;Tlr2;Il27ra;Serpinb1a;Serpinb1b;Lag3;Ccr7;Hdac9;Lilrb4a;Tnf;Nfkbil1;Otud7b;Hdac7;Flt1;Pml;Hsf1;Cd276;Adipoq;Gstp2;Inpp5d;Tnfsf4;Tnfaip3;Arg1;Tnfrsf4;Hsp90ab1;Rabgef1;Tyrobp;Anxa4;Ptprc;Oas3;Oas1a;Slc11a1;Atg9a;Sirpa;Prnp;Tbx21
BP	GO:0002437	inflammatory response to antigenic stimulus	15/1512	57/14199	0,000697676	0,027494552	0,024910496	15	Ighg3;C3;Ccr7;Lilrb4a;Tnf;Lta;Fcgr1;Cd6;Ak7;Il2ra;Il5ra;Icam1;Enpp1;Il1rn;Pla2g2d
BP	GO:0002820	negative regulation of adaptive immune response	15/1512	57/14199	0,000697676	0,027494552	0,024910496	15	Il7r;Parp3;Il27ra;Lilrb4a;Il4i1;Il4i1b;Cd55b;Thoc1;Tnfsf4;Arg1;Cd46;Zbtb7b;Cr2;Ptprc;Tbx21
BP	GO:0061098	positive regulation of protein tyrosine kinase activity	11/1512	35/14199	0,000713099	0,027762304	0,025153084	11	Csf1r;Nedd9;App;Hsph1;Adra2a;Pdgfb;Agrn;Reln;Gprc5b;Ptpn1;Prnp
BP	GO:0140546	defense response to symbiont	44/1512	253/14199	0,000716342	0,027762304	0,025153084	44	Treml4;Acod1;Aicda;Il15;Ifng;Zcchc3;Sting1;Cd8a;Senp7;Pmaip1;Ticam2;Stat1;H2-Q9;Mid2;Zmynd11;Pml;Serinc5;Lyst;Ddx17;Cd86;Prf1;Apobec3;Itgax;Gbp2b;Irf5;Isg15;Setd2;Oasl2;Irf1;Cxcl9;Cxcl10;Vamp8;Ptprc;Oas2;Oas3;Oas1a;Ifi204;Cd40;Lsm14a;Ifitm1;Ifitm3;Zbp1;Ccl5;Eif2ak4
BP	GO:0043266	regulation of potassium ion transport	17/1512	69/14199	0,000721836	0,027762304	0,025153084	17	Kel;Bin1;Ptk2b;Pten;Cacna1d;Ptger3;Klhl24;Stk39;Rapgef3;Cav1;Htr2a;Atf4;Agrn;Atp1b1;Atp1b2;Nos1;Prnp
BP	GO:0098698	postsynaptic specialization assembly	7/1512	16/14199	0,000734619	0,027762304	0,025153084	7	Pten;Ptprs;Nrxn2;Lrfn1;Sipa1l1;Nptxr;Reln
BP	GO:0002313	mature B cell differentiation involved in immune response	10/1512	30/14199	0,000738321	0,027762304	0,025153084	10	Itm2a;Ptk2b;Gpr183;Lilrb4a;6030468B19Rik;Lgals8;Tnfaip3;Enpp1;Cdh17;Xbp1
BP	GO:0045940	positive regulation of steroid metabolic process	10/1512	30/14199	0,000738321	0,027762304	0,025153084	10	Ifng;Agtr1a;Srebf1;Tnf;Bmp6;Scd1;Abcg4;Abcg1;Sec14l2;Il1a
BP	GO:0002762	negative regulation of myeloid leukocyte differentiation	13/1512	46/14199	0,000752701	0,027762304	0,025153084	13	Trib1;Ifng;Ptpn2;Lilrb4a;Gpr55;Clec2i;Adipoq;Prdm16;Inpp5d;C1qc;Zbtb46;Fstl3;Tnfaip6
BP	GO:0001660	fever generation	6/1512	12/14199	0,000755892	0,027762304	0,025153084	6	Ptger3;Tnf;Il1rn;Ccr5;Il1a;Ccl5
BP	GO:0045060	negative thymic T cell selection	6/1512	12/14199	0,000755892	0,027762304	0,025153084	6	Fas;Ccr7;Cd3e;Zap70;Aire;Ptprc
BP	GO:0097107	postsynaptic density assembly	6/1512	12/14199	0,000755892	0,027762304	0,025153084	6	Pten;Ptprs;Nrxn2;Lrfn1;Sipa1l1;Reln
BP	GO:0019722	calcium-mediated signaling	30/1512	154/14199	0,000764313	0,02788194	0,025261476	30	Vcam1;Cd8a;Bhlha15;Ptk2b;Cacna1d;Agtr1a;Syk;Cd4;Ccr7;Sphk1;Tnf;App;Itgal;Dmd;3425401B19Rik;Cd3e;Ackr3;Ackr4;Atp1b1;Zap70;Plcg1;Ksr2;Ptprc;Igtp;Xcr1;Ccr5;Cxcr6;Cd22;Prnp;Samd14
BP	GO:0002456	T cell mediated immunity	26/1512	127/14199	0,000777239	0,027987355	0,025356984	26	Treml4;Cyrib;Il7r;Cd8a;Lilrb4a;Hspa8;H2-Q7;H2-Q9;Il4i1;Il4i1b;Cd55b;Lyst;Icam1;Tnfsf4;Stx11;Prf1;Arg1;Gzmb;Cd46;Aire;H2-K1;Ptprc;Rab27a;Slc11a1;Myo1g;Tbx21
BP	GO:0006959	humoral immune response	32/1512	168/14199	0,000777571	0,027987355	0,025356984	32	Trbc2;Ighe;Ighg3;Acod1;Ifng;H2-DMa;Sh2d1a;C1ra;Gpr183;C3;Ccr7;Cfb;C2;Tnf;Lta;App;Cd5l;Cd55b;Ccl22;C1qb;C1qc;C1qa;Cfp;Cd46;Cr2;Jchain;Aire;Cxcl9;Cxcl10;Ptprc;Slpi;Fcna
BP	GO:0070588	calcium ion transmembrane transport	40/1512	225/14199	0,000789322	0,028222172	0,025569732	40	Bin1;Lck;Bhlha15;Ptk2b;Cacna1d;Sri;Agtr1a;Slc25a23;Ibtk;Pik3cg;Ptger3;Camk2d;Rapgef3;Fcrl5;Htr2a;Mcub;Thy1;Cacng7;Cacng6;Dmd;Nalf1;Atp1b1;Mcoln1;Cyba;Cbarp;Cxcl9;Plcg1;Cxcl10;Cacna1s;Tpcn1;Ptprc;Xcr1;Ccr5;Gem;Rgs9;Atp2a3;Prnp;Trpm5;Ryr3;Cacnb4
BP	GO:0060402	calcium ion transport into cytosol	27/1512	134/14199	0,000804248	0,028566683	0,025881864	27	Lck;Ptk2b;Cacna1d;Sri;Agtr1a;Cd4;Ibtk;Camk2d;Cav1;Fcrl5;Thy1;Tmbim6;Pml;Dmd;Nalf1;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Cacna1s;Ptprc;Xcr1;Ccr5;Prnp;Ryr3
BP	GO:0002637	regulation of immunoglobulin production	19/1512	82/14199	0,000816939	0,0286406	0,025948834	19	Hmces;Ifng;Parp3;Il27ra;Lilrb4a;Pagr1a;Tnf;6030468B19Rik;Tmbim6;Thoc1;Cd86;Tnfsf4;Tnfaip3;Tnfrsf4;Ptprc;Cd22;Cd40;Xbp1;Tbx21
BP	GO:0030101	natural killer cell activation	19/1512	82/14199	0,000816939	0,0286406	0,025948834	19	Il15;Nkg7;Axl;Id2;Prdm1;Lilrb4a;Fgr;Lyst;Il15ra;Klrc1;Stx11;Il2rb;Irf1;Tyrobp;Ptprc;Rab27a;Slamf7;Il11ra1;Slamf6
BP	GO:0016032	viral process	51/1512	307/14199	0,000844867	0,029225524	0,026478785	51	Csf1r;Vcam1;Aicda;Ifng;Trim30b;Ppid;Axl;Eif3a;Ist1;Agtr1a;Cd4;Chmp7;Stat1;Tnf;Hspa8;Cav1;Mid2;Ube2i;Pml;Ciita;Icam1;Avpr1b;Grk2;Apobec3;Hsp90ab1;Nrp1;Isg15;Epor;Srpk2;Oasl2;Rrp1b;Brd4;Trim62;Vamp8;Tpcn1;Oas2;Oas3;Oas1a;Slpi;Ifi204;Bcl2l11;Hpn;Cdk9;Siglec1;Ppia;Ifitm1;Ifitm3;Snf8;Zbp1;Ccl5;Eif2ak4
BP	GO:0007204	positive regulation of cytosolic calcium ion concentration	44/1512	255/14199	0,000847143	0,029225524	0,026478785	44	P2ry10;Lck;Ptk2b;Cacna1d;Sri;Agtr1a;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Ptger3;Camk2d;Gpr55;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Nalf1;Cd36;Fpr2;Ackr3;Ackr4;Epor;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Prnp;Ccl3;Ryr3
BP	GO:0002707	negative regulation of lymphocyte mediated immunity	15/1512	58/14199	0,000849862	0,029225524	0,026478785	15	Il7r;Cd96;Parp3;Tap1;Serpinb9d;Lilrb4a;Il4i1;Il4i1b;Cd55b;Thoc1;Arg1;Cd46;Cr2;Ptprc;Tbx21
BP	GO:0048002	antigen processing and presentation of peptide antigen	16/1512	64/14199	0,000863794	0,029338067	0,026580751	16	Clec4a1;H2-DMa;Tap1;H2-Ob;H2-Aa;H2-Eb1;Ctss;Mfsd6;Fcgr1;H2-Q7;H2-Q9;Abcb9;Ctse;H2-K1;H2-Oa;Slc11a1
BP	GO:1901653	cellular response to peptide	46/1512	270/14199	0,000864003	0,029338067	0,026580751	46	Camk2a;Vcam1;Trib3;Pten;Agtr1a;Ptpn2;Ptk2;Srebf1;Hdac9;Socs2;Bcar1;App;Cav1;Gja1;Hsf1;Adipoq;Nr4a1;Pkm;Icam1;Grk2;Car2;Cd36;Fpr2;Sgk1;Enpp1;Pklr;Pak1;Cpeb2;Gdf15;Zbtb7b;Erfe;Shc1;Irf1;Soga1;Zdhhc7;Src;Nfe2l2;Ccnd3;Ptpn11;Ywhag;Xbp1;Ptpn1;Grb10;Prnp;Mbd5;Nr4a2
BP	GO:0006816	calcium ion transport	55/1512	339/14199	0,00096081	0,032421341	0,029374245	55	Camk2a;Dnm1l;Bin1;Lck;Bhlha15;Ptk2b;Cacna1d;Sri;Agtr1a;Slc25a23;Cd4;Ibtk;Pik3cg;Ptger3;Camk2d;Rapgef3;Cav1;Fcrl5;Htr2a;Gja1;Mcub;Thy1;Cacng7;Cacng6;Tmbim6;Pml;Cacna1h;Dmd;Icam1;Nalf1;Pdgfb;Ramp1;Atp1b1;Mcoln1;Cyba;Cbarp;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Tpcn1;Ptprc;Xcr1;Ccr5;Gem;Rgs9;Orai2;Camk2b;Atp2a3;Prnp;Trpm5;Ccl5;Ryr3;Cacnb4
BP	GO:0045638	negative regulation of myeloid cell differentiation	18/1512	77/14199	0,000993436	0,033314054	0,030183057	18	Zbtb16;Trib1;Ifng;Ptk2b;Ptpn2;Lilrb4a;Gpr55;Clec2i;Adipoq;Prdm16;Hmgb3;Inpp5d;Prmt1;Gpr171;C1qc;Zbtb46;Fstl3;Tnfaip6
BP	GO:0045620	negative regulation of lymphocyte differentiation	14/1512	53/14199	0,000999812	0,033320884	0,030189245	14	Id2;Ptpn2;Lag3;Lilrb4a;Runx3;Hmgb3;Tnfsf4;Cdkn2a;Ctla4;Zbtb7b;Irf1;Nfkbid;Dtx1;Tbx21
BP	GO:0002706	regulation of lymphocyte mediated immunity	36/1512	199/14199	0,001019823	0,033612929	0,030453842	36	Cyrib;Hmces;Ifng;Il7r;Cd96;Parp3;Tap1;Sh2d1a;Il27ra;C3;Serpinb9d;Lag3;Lilrb4a;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;Il4i1;Il4i1b;6030468B19Rik;Cd55b;Thoc1;Klrc1;Tnfsf4;Arg1;Pik3r6;Cd46;Cr2;H2-K1;Ptprc;Cd40;Slamf6;Tbx21
BP	GO:0042130	negative regulation of T cell proliferation	17/1512	71/14199	0,001021026	0,033612929	0,030453842	17	Btla;Cd274;H2-Aa;Lilrb4a;Il4i1;Il4i1b;Il2ra;Cd276;Zc3h12d;Cd86;Cdkn2a;Arg1;Zbtb7b;Prkar1a;Pla2g2f;Pla2g2d;Prnp
BP	GO:0045088	regulation of innate immune response	39/1512	221/14199	0,001053222	0,034462078	0,031223738	39	Acod1;Cd96;Clec4n;Zcchc3;Sting1;Tap1;Sh2d1a;Tlr2;C3;Serpinb1a;Ptpn2;Syk;Serpinb9d;Lag3;Srebf1;Smpdl3b;Fgr;Klrc1;Tnfaip3;Gbp5;Arg1;Isg15;Pik3r6;Irf1;Grn;Nfe2l2;Tyrobp;Myo1f;Trim62;Igtp;Oas3;Oas1a;Slamf8;Ifi204;Ifi211;Slamf6;Lsm14a;Ncf1;Zbp1
BP	GO:0045066	regulatory T cell differentiation	12/1512	42/14199	0,001071277	0,034842329	0,031567698	12	Lck;Ifng;Sox12;Lag3;Lilrb4a;Il4i1;Il4i1b;Tnfsf4;Ctla4;Cd46;Irf1;Pla2g2d
BP	GO:0002526	acute inflammatory response	19/1512	84/14199	0,001114082	0,036017551	0,032632468	19	Ighg3;C3;Ccr7;Pik3cg;Ptger3;Tnf;Mylk3;Fcgr1;Cd6;F8;Adra2a;Icam1;Tnfsf4;Dnase1l3;Il1rn;Il1a;Pla2g2d;Ccl5
BP	GO:1901652	response to peptide	56/1512	349/14199	0,001132479	0,036250746	0,032843746	56	Camk2a;Vcam1;Trib3;Col3a1;Pten;Agtr1a;Ptpn2;Ptk2;Tgfbr3;Srebf1;Tsc1;Hdac9;Stat1;Socs2;Bcar1;App;Cav1;Serpina3f;Gja1;Serpina3g;Hsf1;Adipoq;Nr4a1;Pkm;Icam1;Grk2;Car2;Cd36;Tnfaip3;Fpr2;Sgk1;Enpp1;Pklr;Irf5;Pak1;Cpeb2;Gdf15;Zbtb7b;Erfe;Shc1;Irf1;Soga1;Zdhhc7;Src;Nfe2l2;Ccnd3;Nos1;Ptpn11;Ywhag;Xbp1;Inava;Ptpn1;Grb10;Prnp;Mbd5;Nr4a2
BP	GO:1901380	negative regulation of potassium ion transmembrane transport	7/1512	17/14199	0,001134724	0,036250746	0,032843746	7	Kel;Bin1;Pten;Ptger3;Stk39;Cav1;Agrn
BP	GO:0051480	regulation of cytosolic calcium ion concentration	47/1512	281/14199	0,001142284	0,036277611	0,032868087	47	Hcrtr2;P2ry10;Lck;Ptk2b;Cacna1d;Sri;Agtr1a;Cd4;Ibtk;Ccr7;Pik3cg;Gpr157;Ptger3;Camk2d;Gpr55;Cav1;Fcrl5;Il6st;Htr2a;Gja1;Thy1;Tmbim6;Cd55b;Pml;Gata1;Dmd;Swap70;Nalf1;Cd36;Fpr2;Ackr3;Ackr4;Epor;Mcoln1;Cyba;Cxcl9;Plcg1;Cxcl10;Nos1;Cacna1s;Ptprc;Xcr1;Ccr5;Cxcr6;Prnp;Ccl3;Ryr3
BP	GO:0009615	response to virus	50/1512	304/14199	0,00118235	0,037320509	0,033812969	50	Treml4;Acod1;Aicda;Il15;Ifng;Zcchc3;Sting1;Cd8a;Senp7;Pmaip1;Ticam2;Stat1;Tnf;H2-Q9;Mid2;Zmynd11;Pml;Serinc5;Tgtp1;Lgals8;Lyst;Ddx17;Cd86;Tnfsf4;Prf1;Apobec3;Itgax;Gbp2b;Irf5;Isg15;Setd2;Oasl2;Irf1;Rrp1b;Cxcl9;Cxcl10;Vamp8;Ptprc;Igtp;Oas2;Oas3;Oas1a;Ifi204;Cd40;Lsm14a;Ifitm1;Ifitm3;Zbp1;Ccl5;Eif2ak4
BP	GO:0042119	neutrophil activation	11/1512	37/14199	0,001196824	0,037564975	0,034036968	11	Il15;Syk;Abr;Stx11;Dnase1l3;Grn;Tyrobp;Myo1f;Fcgr4;Cd300a;Ccl5
BP	GO:0006956	complement activation	16/1512	66/14199	0,00123297	0,03847865	0,034862262	16	Trbc2;Ighe;Ighg3;C1ra;C3;Cfb;C2;Cd5l;Cd55b;C1qb;C1qc;C1qa;Cfp;Cd46;Cr2;Fcna
BP	GO:0043383	negative T cell selection	6/1512	13/14199	0,001277748	0,039646918	0,035920731	6	Fas;Ccr7;Cd3e;Zap70;Aire;Ptprc
BP	GO:0051345	positive regulation of hydrolase activity	71/1512	468/14199	0,001312363	0,040197033	0,036419145	71	Nedd9;Bin1;Lck;Cd200;Ifng;Pnlip;Asap1;Ptk2b;Slc39a10;Fas;Rgs16;Agtr1a;Pmaip1;Rasgrp2;Syk;Ccr7;Abr;Tsc1;Cradd;Stat1;Evi5;Tnf;Rapgef3;Diablo;App;Gpr55;Smcr8;Htr2a;Senp1;Thy1;Flt1;Ppp1r12a;Cyfip2;Pml;Hsf1;Sipa1l1;Ccl22;Sipa1l2;Icam1;Avpr1b;Grhl3;Cd86;Asap3;Cdkn2a;Rasgrp3;Rasgrf2;Fermt2;Psme2;Hsp90ab1;Agrn;Chn1;Grn;Rapgef6;Htra2;Ptprc;Rasgef1b;Ifi204;Bcl2l11;Cldn13;Cd40;F11r;Tnfsf15;Cd300a;Camk2b;Atp2a3;Hip1r;Rap1gap2;Ccl5;Ccl3;Ccl4;Tank
BP	GO:0002675	positive regulation of acute inflammatory response	8/1512	22/14199	0,001317813	0,040197033	0,036419145	8	C3;Ccr7;Pik3cg;Ptger3;Tnf;Fcgr1;Ccr5;Ccl5
BP	GO:1990776	response to angiotensin	8/1512	22/14199	0,001317813	0,040197033	0,036419145	8	Camk2a;Col3a1;Agtr1a;Cav1;Hsf1;Car2;Src;Nfe2l2
BP	GO:0036230	granulocyte activation	12/1512	43/14199	0,001344098	0,040716847	0,036936855	12	Il15;Syk;Abr;Stx11;Enpp3;Dnase1l3;Grn;Tyrobp;Myo1f;Fcgr4;Cd300a;Ccl5
BP	GO:0044057	regulation of system process	69/1512	454/14199	0,001453584	0,043843016	0,039722462	69	Bin1;Lck;Ifng;Ptk2b;Pten;Cacna1d;Mylk2;Mtg2;Sri;Agtr1a;Trip10;Ptk2;Srebf1;Ctss;Eno1b;Ptger3;Stk39;Camk2d;Gls;Sphk1;Abcb1a;App;Bmp6;Cav1;Fcgr1;Htr2a;Gja1;Flt1;Cacna1h;Begain;Aqp1;Faah;Adipoq;Dmd;Nr4a1;Adra2a;S1pr2;Icam1;Avpr1b;Grk2;Abcg2;Nptxr;Pdgfb;Itgax;Anpep;Tenm4;Agrn;Pak1;Reln;Fbxo32;Atp1b1;Shc1;Parp2;Src;Cyba;Dlgap3;Fcgr4;Nos1;Scn4a;Ptpn11;Prkag3;Il1a;Glrx3;Ren1;Cdk9;Ncf1;Hip1r;Pbx3;Tnni2
BP	GO:0002335	mature B cell differentiation	11/1512	38/14199	0,001524632	0,045477849	0,041203647	11	Itm2a;Ptk2b;Gpr183;Lilrb4a;6030468B19Rik;Lgals8;Tnfaip3;Enpp1;Cdh17;Slamf8;Xbp1
BP	GO:0045589	regulation of regulatory T cell differentiation	11/1512	38/14199	0,001524632	0,045477849	0,041203647	11	Lck;Sox12;Lag3;Lilrb4a;Il4i1;Il4i1b;Tnfsf4;Ctla4;Cd46;Irf1
BP	GO:0002824	positive regulation of adaptive immune response based on soma	25/1512	126/14199	0,001547895	0,045918063	0,041602488	25	Cyrib;Hmces;Ifng;Clec4n;Cd274;H2-DMa;Il27ra;C3;Cd4;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;6030468B19Rik;Cd55b;Tnfsf4;Nfkbid;H2-K1;Ptprc;Slc11a1;Cd40;Tbx21
BP	GO:0002821	positive regulation of adaptive immune response	26/1512	133/14199	0,001576664	0,046515896	0,042144134	26	Cyrib;Hmces;Ifng;Clec4n;Cd274;H2-DMa;Il27ra;C3;Cd4;Pagr1a;Tnf;Lta;Hspa8;Fcgr1;H2-Q7;H2-Q9;6030468B19Rik;Cd55b;Tnfsf4;Nfkbid;H2-K1;Ptprc;Slc11a1;Cd40;Tbx21;Eif2ak4
BP	GO:0008360	regulation of cell shape	28/1512	147/14199	0,001605444	0,047107657	0,042680188	28	Csf1r;Arhgap18;Parvb;Ptk2b;Myo10;Hck;Ptk2;Rhobtb2;Sh3kbp1;Lst1;Epb41l3;Fgr;Fmnl3;Arhgef18;Epb42;Icam1;Fermt2;Prag1;Kif3a;Myh10;Plxnd1;Mkln1;Spta1;Hpn;F11r;Ccl3;Gas7;Ermn
BP	GO:0002922	positive regulation of humoral immune response	7/1512	18/14199	0,00168745	0,049246162	0,044617798	7	Acod1;H2-DMa;C3;Ccr7;Tnf;Lta;Ptprc
CC	GO:0009897	external side of plasma membrane	94/1523	421/14331	1,29861E-12	8,23318E-10	7,91468E-10	94	Trbc2;Trgc1;Ighe;Ighg3;Vcam1;Cd83;Gypa;Plet1;Btla;Ifng;Il7r;Clec4a1;Ebi3;Clec4n;Cd274;Cd8b1;Cd8a;Prlr;H2-Aa;H2-Eb1;Fas;Tlr2;Il27ra;Cd4;Lag3;Ccr7;Tgfbr3;Adgre1;Efna5;Ly6a;Lilrb4a;Il9r;Tnf;Cd9;Il6st;Fcgr1;H2-Q7;H2-Q9;Cd6;Itgal;Sema7a;Thy1;Il2ra;Clec2i;Cd276;Klrc1;Pirb;Csf2rb2;Csf2rb;Krt18;Il5ra;Sdc1;Icam1;Pira2;Cd86;Abcg2;Cd36;Itgax;Anpep;Cd3e;Enpp3;Tnfrsf4;Ackr3;Ctla4;Ackr4;Ermap;Epor;Il2rb;Cr2;Abcg1;Icosl;Atp1b2;Cxcl9;Cxcl10;Fcgr4;H2-K1;Ptprc;Antxr2;Cd79b;Slamf7;Xcr1;Ccr5;Cxcr6;Il11ra1;Cd22;Cd40;Slamf6;Abca1;Art2b;Il21r;Fcna;Btnl10;Rtn4rl1;Thbd
CC	GO:0043230	extracellular organelle	23/1523	87/14331	2,65693E-05	0,00561498	0,005397764	23	Iigp1;Cd274;Asah2;Ist1;Sri;Gbp9;Gbp6;Cd9;Hspa8;Aqp1;Slc12a3;Icam1;Cd86;Anpep;Actg1;Gbp3;Gbp2b;Gbp2;Alpl;Podxl;Rab4a;Gprc5b;Abcb6
CC	GO:0065010	extracellular membrane-bounded organelle	23/1523	87/14331	2,65693E-05	0,00561498	0,005397764	23	Iigp1;Cd274;Asah2;Ist1;Sri;Gbp9;Gbp6;Cd9;Hspa8;Aqp1;Slc12a3;Icam1;Cd86;Anpep;Actg1;Gbp3;Gbp2b;Gbp2;Alpl;Podxl;Rab4a;Gprc5b;Abcb6
CC	GO:0015629	actin cytoskeleton	71/1523	434/14331	0,000138611	0,021969838	0,021119934	71	Vcam1;Parvb;Asap1;Cd274;Ndc1;Axl;Cnn3;Apbb3;Gas2l3;Myo10;Synpo2;Hck;Ptk2;Capg;Whrn;Tsc1;Bcar1;Sh3pxd2b;Tmsb15b2;Rapgef3;Abcb4;Mylpf;Mylk3;Espn;Add1;Stk17b;Capza2;Fgr;Myo3b;Lcp1;Flt1;Ppp1r12a;Actn1;Sipa1l1;Hnrnpc;Lpp;Dmd;Swap70;Flot2;Triobp;Coro1b;Inpp5d;Sptb;Crmp1;Fermt2;Nebl;Actg1;Gbp2;Add2;Dst;Pak1;Myh10;Myo1d;Cotl1;Src;Dennd2a;Cyba;Zfp268;Myo1f;Rtkn;Ptpn11;Nckap1;Spta1;Dctn3;Myo1g;Micall2;Tnni2;Samd14;Gas7;Bmf;Arpc5l
MF	GO:0140375	immune receptor activity	32/1494	117/14018	3,53903E-07	0,000334438	0,0003241	32	Il7r;Ebi3;Prlr;H2-Eb1;Il27ra;Cd4;Ccr7;Il9r;Mfsd6;Il6st;Fcgr1;Il2ra;Il15ra;Klrc1;Pirb;Csf2rb2;Csf2rb;Il5ra;Pira2;Fpr2;Il10ra;Ackr3;Ackr4;Epor;Il2rb;Cr2;Fcgr4;Xcr1;Ccr5;Cxcr6;Il11ra1;Il21r
MF	GO:0023023	MHC protein complex binding	11/1494	23/14018	7,78336E-06	0,003677638	0,00356396	11	Il7r;Cd8a;H2-DMa;H2-Ob;H2-Aa;H2-Eb1;Cd4;Klrc1;Pirb;Pira2;H2-Oa
MF	GO:0004896	cytokine receptor activity	23/1494	86/14018	2,2687E-05	0,007146392	0,006925493	23	Il7r;Ebi3;Prlr;Il27ra;Cd4;Ccr7;Il9r;Il6st;Il2ra;Il15ra;Csf2rb2;Csf2rb;Il5ra;Il10ra;Ackr3;Ackr4;Epor;Il2rb;Xcr1;Ccr5;Cxcr6;Il11ra1;Il21r
MF	GO:0005178	integrin binding	28/1494	131/14018	0,000240067	0,048148732	0,046660425	28	Vcam1;Plpp3;Col3a1;Ptpn2;Syk;Ptk2;Lilrb4a;Cd9;App;Itgal;Sema7a;Lcp1;Thy1;Actn1;Dmd;Lgals8;Mmp14;S1pr2;Icam1;Fermt2;Itgax;Jaml;Dst;Isg15;Src;Cdh17;F11r;Ppia
MF	GO:0008525	phosphatidylcholine transporter activity	8/1494	18/14018	0,000267706	0,048148732	0,046660425	8	Abcb1a;Abcb4;Pitpnm2;Mttp;Pitpnm1;Abcg1;Abca7;Abca1
MF	GO:0015026	coreceptor activity	9/1494	23/14018	0,000352186	0,048148732	0,046660425	9	Cd8b1;Cd4;Tgfbr3;Fcrl1;Pira2;Ackr3;Ramp1;Cxcr6;Cd22
MF	GO:0005044	scavenger receptor activity	11/1494	33/14018	0,000406961	0,048148732	0,046660425	11	Endou;Cd5l;Cd6;Lgals3bp;Cd36;Enpp1;Scarb1;Ackr3;Ackr4;Tmprss3;Marco
MF	GO:0019955	cytokine binding	26/1494	122/14018	0,000413507	0,048148732	0,046660425	26	Csf1r;Ebi3;Prlr;Il27ra;Cd4;Ccr7;Tgfbr3;Il9r;Il6st;Tmc8;Il2ra;Il5ra;Cd36;Ltbp1;Il10ra;Gbp2;Agrn;Ackr3;Ackr4;Il2rb;Il1rn;Xcr1;Ccr5;Cxcr6;Il11ra1;Il18bp
MF	GO:0005125	cytokine activity	28/1494	136/14018	0,000458559	0,048148732	0,046660425	28	Il15;Gdf3;Ifng;Ebi3;Tnfsf9;Ltb;Tnf;Lta;Bmp6;Wnt10b;6030468B19Rik;Ccl22;Gdf10;Tnfsf4;Gdf15;Csf1;Grn;Sectm1a;Cxcl9;Cxcl10;Il1rn;Wnt6;Wnt10a;Il1a;Tnfsf15;Ccl5;Ccl3;Ccl4

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