Tumor necrosis factor-α in systemic lupus erythematosus: Structure, function and therapeutic implications (Review)

FARID GHORBANINEZHAD[1*], PATRIZIA LEONE[2*], HAJAR ALEMOHAMMAD[3**], BASIRA NAJAFZADEH[3**], NILOUFAR SADAT NOURBAKHSH[4], MARCELLA PRETE[2], ELEONORA MALERBA[2], HOSSEIN SAEEDI[1], NEDA JALILI TABRIZI[1], VITO RACANELLI[2] and BEHZAD BARADARAN[1,5]

[1]Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, East Azerbaijan 5165665811, Iran; [2]Department of Biomedical Sciences and Human Oncology, 'Aldo Moro' University of Bari Medical School, I-70124 Bari, Italy; [3]Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, East Azerbaijan 5166616471; [4]Department of Genetics, Faculty of Basic Sciences, Kazerun Branch, Islamic Azad University, Kazerun, Fars 7319846451; [5]Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, East Azerbaijan 5166614766, Iran

Received December 1, 2021; Accepted January 5, 2022

DOI: 10.3892/ijmm.2022.5098

Abstract. Tumor necrosis factor-α (TNF-α) is a pleiotropic pro-inflammatory cytokine that contributes to the pathophysiology of several autoimmune diseases, such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus (SLE). The specific role of TNF-α in autoimmunity is not yet fully understood however, partially, in a complex disease such as SLE. Through the engagement of the TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), both the two variants, soluble and transmembrane TNF-α, can exert multiple biological effects according to different settings. They can either function as immune regulators, impacting B-, T- and dendritic cell activity, modulating the autoimmune response, or as pro-inflammatory mediators, regulating the induction and maintenance of inflammatory processes in SLE. The present study reviews the dual role of TNF-α, focusing on the different effects that TNF-α may have on the pathogenesis of SLE. In addition, the efficacy and safety of anti-TNF-α therapies in preclinical and clinical trials SLE are discussed.

Correspondence to: Professor Vito Racanelli, Department of Biomedical Sciences and Human Oncology, 'Aldo Moro' University of Bari Medical School, Piazza Giulio Cesare 11, I-70124 Bari, Italy
E-mail: vito.racanelli1@uniba.it

Professor Behzad Baradaran, Immunology Research Center, Tabriz University of Medical Sciences, Golgasht Street, Tabriz, East Azerbaijan 5165665811, Iran
E-mail: baradaranb@tbzmed.ac.ir

*,**Contributed equally

Key words: systemic lupus erythematosus, tumor necrosis factor-α, tumor necrosis factor receptor, autoimmune disease

Contents

1. Introduction

Tumor necrosis factor-α (TNF-α) is a complex cytokine that impacts various physiological and pathological conditions. It can function as an immune regulator, contributing to the development and function regulation of B-cells, T-lymphocytes and dendritic cells, as a pro-inflammatory mediator, modulating the generation and preservation of inflammatory processes, or as an apoptotic inducer, promoting cell death (1,2). TNF-α is involved in the pathogenesis of numerous autoimmune disorders, such as rheumatoid arthritis (RA) (3), inflammatory bowel disease (4,5), psoriatic arthritis (6) and multiple sclerosis (7,8); however, its role in systemic lupus erythematosus (SLE) disease remains unclear. From the genetic point of view, several investigations have demonstrated a link between the TNF-α gene polymorphism and the susceptibility to SLE (9-11). Furthermore, there is a strong connection between TNF-α gene expression and clinical manifestations in patients with SLE (12).

Furthermore, TNF-α is a growth factor for B-lymphocytes, which can produce large quantities of TNF-α in an autocrine loop (13-15). Serum levels of TNF-α have been discovered to

be high in patients with SLE and have been linked to disease activity and several systemic manifestations, such as SLE-related cardiovascular disease and lupus nephritis (12,16-20). The dysregulation of TNF-α is clearly linked to tissue destruction observed in lupus organ disease, to the death of lymphocytes and to the impaired clearance of apoptotic cells, resulting in the presentation of self-antigens and autoantibody formation (21). However, TNF-α has pro-apoptotic and anti-apoptotic properties, depending on the underlying contextual circumstances (22-24). Treatment with anti-TNF drugs or recombinant TNF has been demonstrated to have conflicting results in murine models of SLE. As previously demonstrated, TNF-competent New Zealand Black (NZB) mice displayed an autoimmune phenotype, whereas TNF-deficient New Zealand Black (NZB) mice developed severe lupus-like disease (25,26).

Moreover, the disease was shown to be reversible by the administration of recombinant TNF; indeed, the early application of TNF in NZB/White (NZB/W) mice postponed the development of autoantibodies and lupus nephritis (25,27). In addition, TNF-blocking therapies have sometimes induced the production of antinuclear antibodies and IgM antibodies to double-stranded DNA in individuals with RA or Crohn's disease, suggesting the potential propensity of anti-TNF agents to stimulate pathogenic autoantibody production (28,29). These patients rarely exhibited a reversible drug-induced lupus-like syndrome (29). In this context, a critical view of the relevance of TNF in SLE is necessary. The present review article thus aimed to enhance the understanding of the functions of TNF-α in the pathogenesis of SLE and discuss the benefits associated with anti-TNF therapies in patients with SLE.

2. TNF-α: Structure and function

TNF-α, also known as cachectin, was first defined by Carswell *et al* (30) several decades ago as an endotoxin-inducing autoantibody molecule that leads to tumor necrosis. The human gene for TNF-α is located on the short arm of chromosome 6 between 6p21.1 and 6p21.3, which is within the human leukocyte antigen (HLA) class III region in humans (31). It includes exons, interrupted via 3 introns and is ~3 kb in length. Of note, >80% of the mature TNF-α sequence is encoded in exon 4. Exons 1 and 2 mainly include the sequence of leader peptides (32). In addition, multiple regulatory sites with sequences corresponding to the transcription factors, activator protein (AP-1/2), NF-κB and the cAMP-response element (CRE) have been identified on the 5'b-end of the TNF-α gene. TNF-α exists in two types, as a membrane-bound trimeric ligand (tmTNF) and as a soluble trimeric molecule (sTNF), each of which probably play a different physiological role. The sTNF-α is formed from tmTNF-α via the extracellular domain of the matrix metalloproteinase (MMP) TNF-α-converting enzyme (TACE). tmTNF-α can function as ligand-bound TNFR or as an intermediate receptor in transmitting external signals. The human TNF-α protein contains 233 amino acids with a predicted molecular weight of 25.6 kDa, which, following proteolytical cleavage by a specific protease, generates an active protein of 17 kDa. The hydrophobic transmembrane region includes 26-44 amino acids of the TNF-α pre-sequence, and the intracytoplasmic region comprises 50-76 amino acids (33). The soluble and membrane-bound forms function as biological homotrimers (similar to a triangular cone), each molecule interacting the other two substances. Each monomer includes two packed β-pleated sheets that are formed via eight antiparallel β-strands arranged in a β-jellyroll topology (34). It has also been reported that TNF-α undergoes post-translational alterations, including phosphorylation. The initial sequence of TNF-α indicates the existence of several phosphorylation consensus sites, providing a possible mechanism for regulating trimer formation and/or receptor binding. In addition, a previous study demonstrated that membrane-bound TNF-α was phosphorylated via creatine kinase (CKI) and dephosphorylated through phosphatase activation (35). TNF-α production has been detected in a wide range of cells, such as normal, malignant, hematopoietic and non-hematopoietic cells (36). Several factors can induce the production of TNF-α, including bacterial lipopolysaccharide (LPS, endotoxin), viral antigens, immune complexes, IL-1 and TNF-α itself via autocrine mechanisms. In addition, certain pathophysiological conditions, such as previous infection and inflammation, trauma, infarction and heart failure, can also induce the production of TNF-α (37,38). TNF-α performs its biological activities by interacting with two membrane-dependent receptors, TNF receptor (TNFR)1 and TNFR2, and via triggering a number of secondary proteins that elicit various responses in the cell, such as transcription factors, protein kinases and phospholipases (36,39-41).

It has been demonstrated that TNF-α functions as a multifunctional cytokine which plays a vital role in controlling inflammation, secondary and tertiary lymphoid tissue development, and immune regulation (42). The functional mechanisms of TNF-α are highly diverse and somewhat complex. This protein plays conflicting roles: On the one hand, it combats certain types of infections and, on the other hand, induces pathological complications. This may be due to the stimulation of various signaling pathways involved in diverse cellular reactions, such as survival, differentiation, cell proliferation and cell death (43). A recent study indicated that TNF-α deregulation was directly associated with chronic inflammation, autoimmune diseases and other pathologies, such as neuroinflammation (44). Therefore, understanding the exact mechanisms of action of the TNF-α signaling pathways may lead to the development of effective therapies for the treatment of immune diseases.

3. TNF receptors: TNFR1 and TNFR2

The TNFR1 gene (also known as p55, p60, CD120a or TNFRSF1A), located on chromosome 12p13, has 10 exons and produces a 60-kDa protein (45). TNFR2 (also known as p75, p80, CD120b or TNFRSF1B) encoded via the gene located on chromosome 1p36.2, consists of 10 exons and gives rise to a protein of 80 kDa (46,47). These receptors are membrane glycoproteins and members of the TNF receptor superfamily (48). They are crucial to the development and homeostasis of the immune and neurological systems, and ectodermal organs (49,50). The extracellular domain is very similar between these two receptors and consists of multiple cysteine-rich domains involved in ligand binding; however, the intracellular domains clearly differ; thus, they can activate different signaling pathways by interacting with a variety of cytosolic proteins (51). Receptors

are dependent on adapter proteins, including TNFR-associated death domain protein (TRADD), Fas-associated protein with death domain (FADD) and the TNFR-associated factor (TRAF)-1 to activate intracellular signaling pathways and induce a biological response. These proteins form a scaffold that allows other proteins to be absorbed to trigger the signaling pathway (52,53). TNFR1 expression has been observed in a number of cell types; however, TNFR2 expression has been observed in a small number of cells, such as T-cells and endothelial cells (54). TNF-α strongly binds to both receptors, and the differential engagement of the receptors is associated with distinct functions. sTNF interacts with both TNF receptors, while tmTNF mainly activates TNFR2 (51). TNFR2 has a lower affinity for TNF-α than for TNFR1, suggesting that TNFR2 can momentarily bind and can subsequently be release, playing a role in amplifying or synergizing TNFR1 signaling (55,56). The stimulation of TNFR1 is responsible for several biological effects of TNF-α, such as cytotoxicity and proliferation. The activation of TNFR1 stimulates various cellular responses, such as the induction of proliferation processes, apoptosis, or necroptosis, depending on the cell type and environmental conditions (56). TNFR1, in its cytoplasmic part, has a death domain (DD) related to TNF-α-mediated cytotoxicity, while TNFR2 lacks this domain (57). The engagement of TNF with TNFR1 leads to the successive formation of two different TNF receptor signaling complexes (complex I and complex II) that are separated both temporally and spatially. Complex I induces the expression of anti-apoptotic genes, which inhibit cell death processes mainly by activating transcription factors, such as NF-κB, whereas the second signaling pathway (complex II) leads to apoptosis or necroptosis (1). Compared to TNFR1, knowledge of TNFR2 signaling pathways is limited. Since TNFR2 lacks the DD, it cannot directly induce cell death. In contrast to the functions of TNFR1, which is able to induce inflammation or apoptotic responses, TNFR2 engagement significantly enhances cell stimulation, migration and propagation (58). The binding of TRAF2 to TNFR2 activates the canonical and non-canonical NF-κB signaling pathways (59). However, TNFR is able to activate NF-κB slowly, although with a longer activation time compared to TNFR (60). In addition, it has been shown that TNFR2 can induce cell survival (61). Other researchers have indicated that TNFR2 is required for antigen-associated differentiation and T-cell survival. TNFR2 regulates several adhesion molecules, including intercellular adhesion molecule-1 and selectin-E, which are central molecules in angiogenesis (62).

4. Downstream signaling of the TNF and TNFR axis

TNF signaling appears to be quite complex and can cover various downstream signaling pathways. TNFR1 is triggered through both membrane-bound and soluble TNF (51) (Fig. 1). The TNFR1 cytoplasmic DD allows interactions with other DD-containing proteins, including TRADD, E3 ubiquitin ligases, cellular inhibitor of apoptosis protein (cIAP)1/2, the receptor-interacting serine/threonine-protein kinase (RIPK)1 and TRAF2, resulting in complex I signaling (52,53). In turn, polyubiquitinated RIPK1 and cIAP1/2 proteins have a crucial function in the uptake of other proteins, such as the TGF-β-activated kinase 1 (TAK1) in the TAK1-binding protein (TAB)2/3 complex and the linear ubiquitin chain assembly complex (LUBAC), respectively (63,64). LUBAC can polyubiquitinate numerous molecules, such as LUBAC itself and NF-κB essential modulator (NEMO) in the IκB kinase (IKK) complex comprised of IKK1/IKKα, IKK2/IKKβ and NEMO/IKKγ (64,65). Furthermore, TAK1 phosphorylates IκB, a prerequisite for its ubiquitylation and proteasome degradation. NF-κB then translocates to the nucleus and prompts the transcription of target genes involved in inflammation and cell survival (64). In addition, TAK1 in complex with TAB2/TAB3 can also induce the triggering of AP-1 transcription factor through the phosphorylation of MAP kinases, such as cJun NH2-terminal kinase (JNK) and p38 (66,67). This signaling pathway activates the transcription of various pro-inflammatory genes. Moreover, TNF-TNFR1 interaction can activate other signaling pathways involved in programmed cell death, such as apoptosis and necroptosis through complex II and IIb signaling, respectively (68,69). In this case, the separation of RIPK1 and TRADD from complex I leads to the instability of complex I and in the formation of complex II, which includes FADD, cellular FLICE-inhibitory protein and pro-caspase-8 molecules, thus inducing apoptosis (70). In addition, when caspase is inhibited, the interaction of TNF with TNFR1 induces the formation of complex IIb, leading to the activation of the cell death pathway known as necroptosis. Complex IIb consists of the phosphorylated molecules, RIPK1 and RIPK3, and mixed lineage kinase domain-like pseudokinase (MLKL). Thereafter, MLKL oligomerization occurs, and phosphorylated MLKL is translocated to the plasma membrane, which is disrupted to stimulate necroptosis (71). In contrast to TNFR1, the interaction of TNFR2 with TNF (Fig. 2) causes the direct recruitment of TRAF1 or TRAF2 together with cIAP1/2 and LUBAC molecules (72,73). Subsequently, this signaling pathway may, similar to the TNFR1 signaling pathway, recruit the TAK1/TAB2/TAB3 and NEMO/IKKα/β complexes, resulting in the downstream stimulation of the canonical NF-κB pathway (60). Alternatively, the only membrane-bound TNF and non-soluble TNF trimers can activate, via TNFR2, the non-canonical NF-κB pathway via the TRAF2/cIAP1/2 complex interaction, resulting in the accumulation of NF-κB-inducing kinase (NIK). NIK phosphorylates the NF-κB precursor protein p100, thus eliciting its proteasomal proteolysis to p52, which results in the transcription of p52/RelB-containing NF-κB heterodimer (74,75). Under normal conditions, the basal level of NIK is maintained at a low level by TRAF3, which induces NIK ubiquitination and constitutive degradation by the proteasome. In response to tmTNF, NIK becomes stabilized due to TRAF3 degradation, and its accumulation activates non-canonical NF-κB signaling, resulting in autoimmune and inflammatory diseases (75).

In contrast to the common belief that TNFR1 signaling triggers apoptosis and TNFR2 signaling promotes pro-survival, there is increasing evidence to indicate that exclusive TNFR2 stimulation can induce apoptosis (despite the fact that TNFR2 does not contain a DD) through crosstalk among the two receptors and TRAFs, which are involved in initiating TNFR1 and TNFR2 signaling (60). Moreover, TNFR2 can enhance TNFR1-mediated apoptosis, despite the enhanced NF-κB activation (22,76-80). The upregulation of TNFR2 induces proteasomal degradation and the consequent depletion of

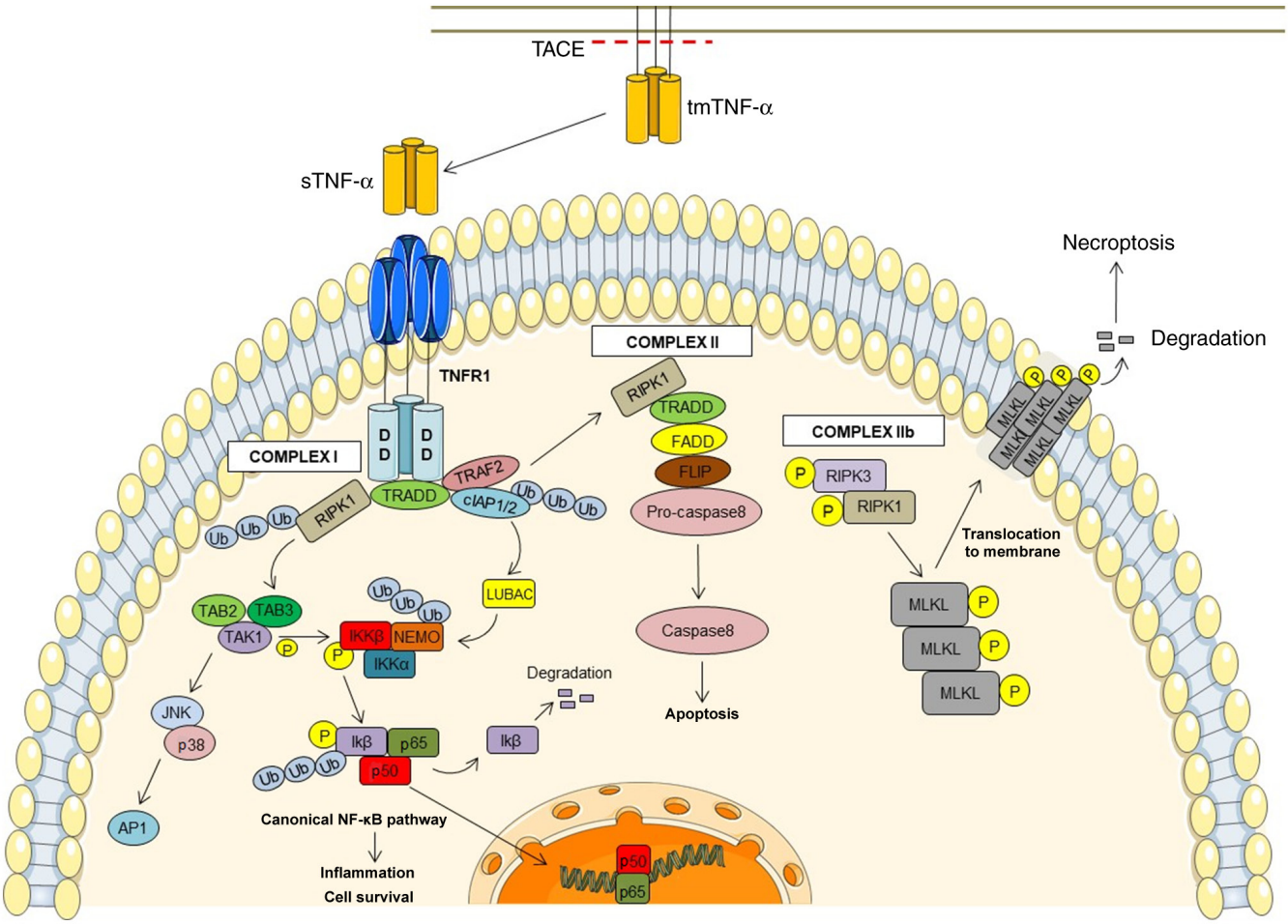

Figure 1. TNFR1 signaling pathway. TNF, tumor necrosis factor; TNFR, TNF receptor; TACE, TNF-α-converting enzyme; sTNF-α, soluble form of TNF-α; tmTNF-α, membrane-bound trimeric ligand form of TNF-α; AP1, activator protein 1; TAK1, TGF-β-activated kinase 1; TAB, TAK1-binding protein; RIPK1, receptor-interacting serine/threonine-protein kinase 1; TRADD, TNFR-associated death domain protein; TRAF2, TNFR-associated factor 2; cIAP, cellular inhibitor of apoptosis protein; FLIP, FLICE-inhibitory protein; MLKL, mixed lineage kinase domain-like pseudokinase.

TRAF2 (77,78). Upon the activation of TNF, a member of the MAPK kinase family termed apoptosis signal-regulating kinase-1 is activated by TRAF2, and induces p38 and JNK activation (81). This pathway is triggered by stress stimuli and results in the regulation of apoptosis and inflammatory cytokine expression (66).

5. Role of TNF-α and TNFRs in autoimmune diseases

TNF-α is associated with the pathogenesis of various autoimmune diseases (Fig. 3), such as RA (3), inflammatory bowel disease, including ulcerative colitis and Crohn's disease (4,5), psoriatic arthritis (6) and multiple sclerosis (8). Along with IL-1β, TNF-α is involved in the onset and progression of RA (82). Elevated levels of TNF-α have been detected in the synovial fluid and synovium of patients with RA (82), causing local inflammation and 'pannus' structure formation, leading to tissue necrosis, cartilage erosion and bone destruction (82). In this context, synovial fibroblasts secrete IL-1β, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, MMP-1 and MMP-3, and receptor activator of nuclear factor-kB ligand, an osteoclastogenic cytokine, resulting in recruitment of immune cells (B-cells, T-cells, macrophages and neutrophils) and the perpetuation of the production of pro-inflammatory cytokines and mediators, such as IL-2, IL-1β and TNF-α (82-84). Several studies using mouse models have demonstrated the interplay between TNF-α and IL-1β *in vivo*, and their crucial function in the onset and evolution of RA (85-88). In addition, TNF-α reduces the frequency and function of regulatory T-cells in autoimmune-prone mice (89) and in patients with RA, and this effect has been shown to be reverted by TNF-α blockade (90).

A similar role is played by TNF-α in the gastrointestinal tract in patients with ulcerative colitis and Crohn's. TNF-α activates macrophages, enhances the T-cell response, induces the expression of adhesion molecules by the vascular endothelium, and the recruitment of neutrophils to local sites of inflammation, promotes tissue remodeling, edema and granuloma formation (4,5). TNF-α-dependent inflammation is extended through triggered NF-κβ-dependent pathways, which provide the release of MMPs with the consequent degradation of the mucosa and ulceration (91).

In patients with psoriatic arthritis, elevated levels of TNF-α stimulate DCs and macrophages to secrete high amounts of TNF-α and IL-23, promoting the differentiation of naive T-cells into Th17 cells, with the consequent overproduction of the pro-inflammatory cytokine, IL-17. IL-17 and TNF-α trigger the NF-κB signaling pathway, leading to

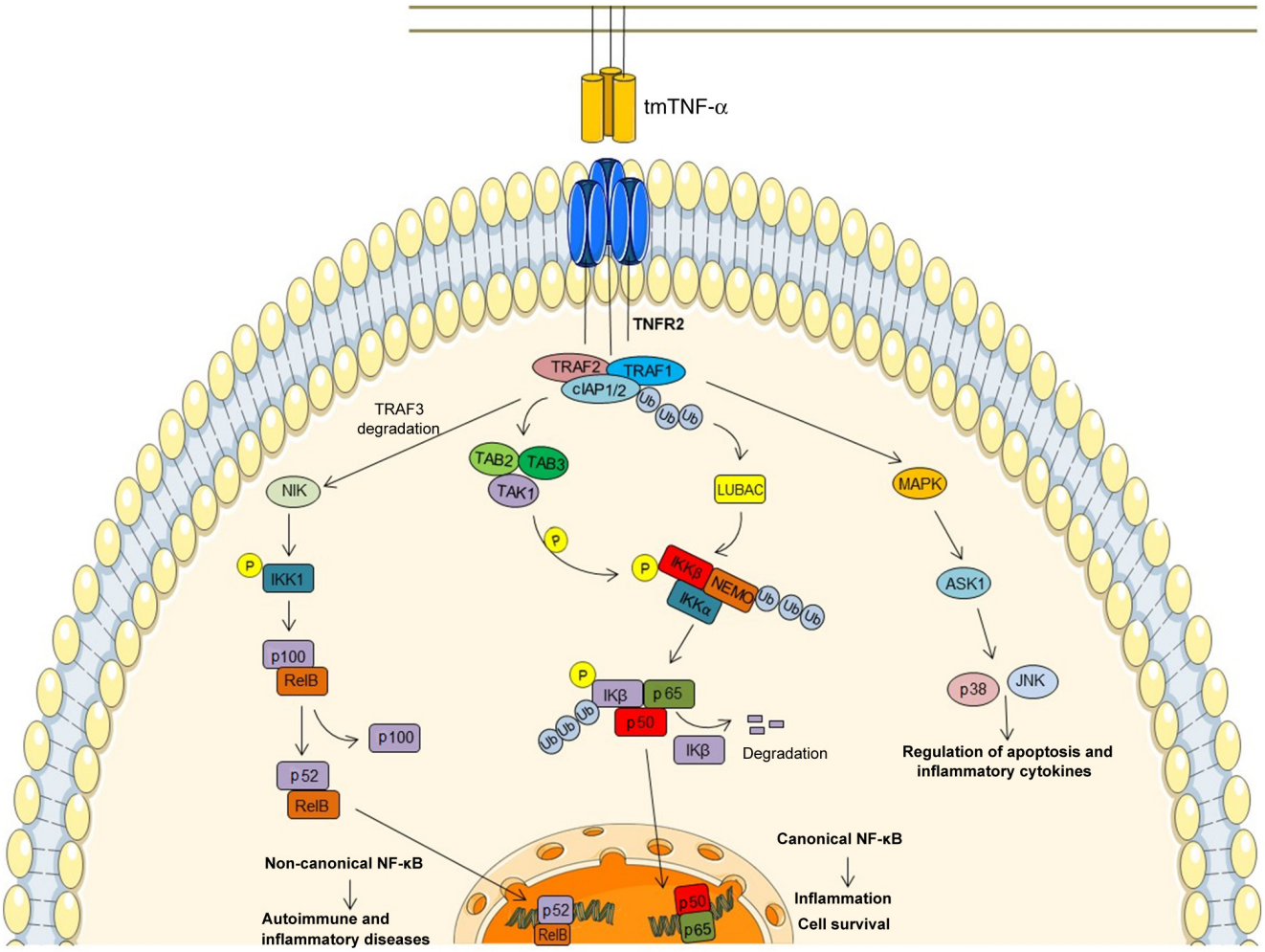

Figure 2. TNFR2 signaling pathway. TNF, tumor necrosis factor; TNFR, TNF receptor; tmTNF-α, membrane-bound trimeric ligand form of TNF-α; IKK, IκB kinase; NIK, NF-κB-inducing kinase; TRAF, TNFR-associated factor; TAK1, TGF-β-activated kinase 1; TAB, TAK1-binding protein; cIAP, cellular inhibitor of apoptosis protein; LUBAC, linear ubiquitin chain assembly complex; NEMO, NF-κB essential modulator; ASK1, apoptosis signal-regulating kinase-1.

keratinocyte activation and proliferation, the recruitment of inflammatory cells, epidermal hyperplasia and microabscess development (92).

There is also emerging evidence to support the involvement of TNF-α in the pathogenesis of SLE, which is discussed in the following section (Fig. 3).

6. Systemic lupus erythematosus and TNF-α

SLE is a systemic autoimmune disease featured by heterogeneous clinical manifestations and immunological abnormalities. Its pathogenesis remains poorly understood, and even though the etiology of SLE is undetermined, multiple elements are associated with disease development, including genetic (93-95), epigenetic (96), immunoregulatory (97), ethnic (98), hormonal (99) and environmental factors (100-103). The role TNF-α in the pathogenesis of SLE is controversial; some investigators have found that TNF-α confers SLE susceptibility (10,11,18,104), while others have described a protective role of TNF-α in patients with SLE (105,106). Multiple have studies indicated that TNF-α, along with other cytokines, such as IFN-α, IL-12, IL-4, IL-10, IL-6, A proliferation-inducing ligand (APRIL) and B cell-activating factor, IL-17 and IL-21 are the main SLE-related cytokines (107-111). In particular, Svenungsson *et al* (19,20) emphasized the high triglyceride and low HDL levels as disease activity markers, and the elevated levels of TNF-α/TNFR in patients with SLE, as well as the link between inflammation, dyslipoproteinemia and cardiovascular disease in patients with SLE. Furthermore, an increased TNF-α concentration has been observed in the blood and in the inflamed kidneys of patients with SLE (112-116). Further studies have also demonstrated a significant genetic relation between TNF-α promoter polymorphism and SLE susceptibility (9-11,117-121). Increased levels of TNF-α have been found to be associated with disease severity in patients with SLE (18,107,122). Higher serum levels of TNF-α and its soluble receptors have been observed in patients with SLE with active disease compared with SLE patients with inactive disease (122). Moreover, patients with SLE with high TNF-α levels present T-lymphocytes which are more susceptible to apoptosis than T-cells from healthy controls (104). This enhanced TNF-α-induced apoptosis increases the autoantigen load, promoting autoimmune responses in patients with SLE (104). This enhanced TNF-α-induced apoptosis also increases the load of autoantigens, promoting autoimmune responses in patients with SLE (104).

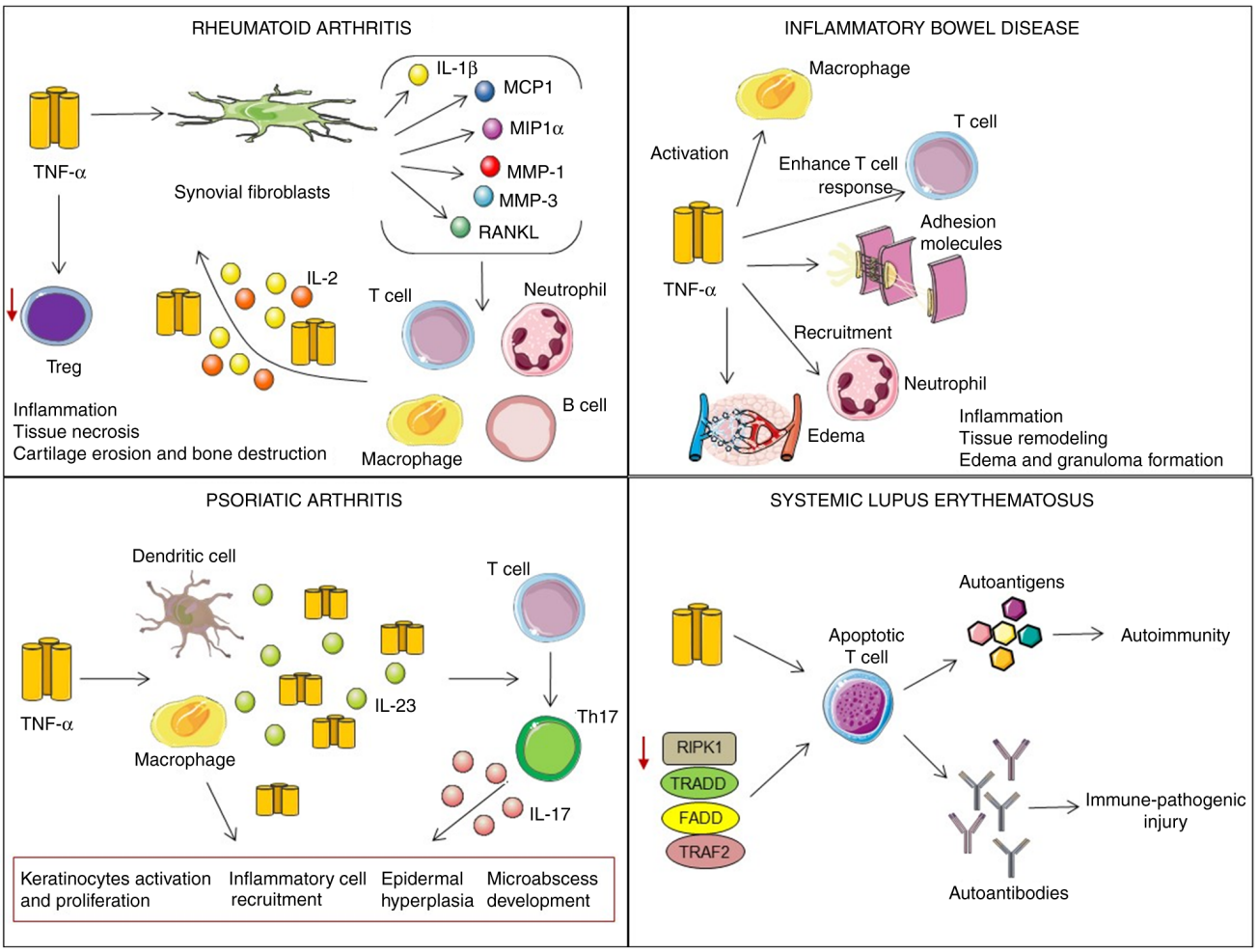

Figure 3. Role of TNF-α in systemic lupus erythematosus and other autoimmune diseases. TNF, tumor necrosis factor; Treg, regulatory T-cell; MCP1, monocyte chemoattractant protein-1; MIP1α, macrophage inflammatory protein-1α; MMP, matrix metalloproteinase; RANKL, receptor activator of nuclear factor-κB ligand; RIPK1, receptor-interacting serine/threonine-protein kinase 1; TRAF2, TNFR-associated factor 2; TRADD, TNFR-associated death domain protein; FADD, Fas-associated protein with death domain.

Moreover, genetic variation at TNF alpha induced protein 3 (TNFAIP3) and TNF superfamily member 4 (TNFSF4) have been associated with lymphocyte dysregulation and different SLE ethnic groups (123-126). Polymorphisms in TNFR2 may also play a role in the genetic susceptibility to SLE. A previous genotype analysis manifested that the existence of one 196R allele was sufficient for delivering SLE susceptibility in the Japanese population (127). Both TNFR1 and TNFR2 expression levels are highly enhanced in active the serum of patients with SLE (122,128,129), and sTNFRs are crucial modulators of the inflammatory responses in lupus nephritis (130,131). In Japanese patients, a mutation in exon 3 in position 61 of the tumor necrosis factor receptor superfamily 1A gene (TNFRSF1A) was shown to be associated with SLE. These patients were characterized by a high concentration of serum TNF, sTNFRSF1B and a low concentration of sTNFRSF1A (132).

On the contrary, some researchers have observed decreased levels of TNF-α in patients with SLE, particularly in patients with severe disease (105). Zhu *et al* (106) indicated that the expression levels of TNF-α adapter proteins TRADD, FADD, TRAF-2 and RIPK-1 in peripheral blood mononuclear cells were markedly diminished in patients with SLE and were negatively associated with the SLE activity index. Reduced levels of TNF-α adapter proteins have been shown to be related to advanced lymphocyte apoptosis and enormous autoantibody secretion, resulting in immune-pathogenic injury in patients with SLE (106). Moreover, several studies did not demonstrate any association between polymorphisms in the TNFR2 gene and SLE (133-135). Sullivan *et al* (135) analyzed the frequency of genetic polymorphisms in the 3' untranslated region of the TNFR2 gene in patients with SLE and did not find an association, although the study examined only Caucasian patients. Furthermore, Chadha *et al* (134) did not find any association between TNFRSF14, TNFRSF8, TNFRSF1B locus and SLE in European-Caucasian families. In line with this, Al-Ansari *et al* did not find any connection between the TNFRII 196R allele and SLE neither in Spanish or in UK populations (133).

7. Blocking of TNF: Therapeutic approaches in SLE; animal models and clinical trials

Murine disease models are genetically homogeneous populations used to research disease initiation and progression (136). There are different mouse models for lupus; some of them develop lupus spontaneously [e.g., NZB/W F1hybrid mice,

Table I. FDA-approved TNF-α inhibitors.

Drug	Trade name	Type of agent	FDA approval data (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm)
Infliximab	Remicade®	Chimeric mouse/human mAb	August, 1998
Etanercept	Enbrel®	A human soluble TNF-α receptor	November, 1998
Adalimumab	Humira®	A fully human anti-TNF-α mAb	December, 2002
Certolizumab pegol	Cimzia®	A PEGylated, Fab'-only, recombinant humanized mAb	April, 2008
Golimumab	Simponi®	A human IgG1κ anti-TNF-α mAb	April, 2009

TNF-α, tumor necrosis factor-α; mAb, monoclonal antibody; PEG, polyethylene glycol.

Table II. Clinical trials of TNF-α/TNFR inhibition in SLE patients.

Intervention	Phase	Enrollment	Status	Study start date	National clinical trial no.
Infliximab + azathioprine	II/III	One participant	Terminated	September, 2006	NCT00368264
Etanercept + lupus treatment-standard of care + placebo	II	One participant	Terminated	February, 2008	NCT00447265
Etanercept	II	25 participants	Completed	February, 2016	NCT02656082
Etanercept	II	20 participants	Unknown	October, 2008	NCT00797784
Brentuximab vedotin + placebo	II	20 participants	Terminated	July, 2015	NCT02533570

medical research laboratory lymphoproliferation (MRL/lpr) mice, BXSB/Yaa mice], and in others, lupus is induced in the animals (e.g., pristane-induced lupus) (137). Due to the dual function of TNF-α (mediator of inflammation and regulator of autoimmunity), the efficacy of TNF-based therapies in SLE is controversial and can vary, depending on the subsets of patients (138). TNF-α is well observed in NZB/W F1 hybrid mice, MRL/lpr and C3H.SW lupus-prone mouse models. The NZB/W F1 lupus model denotes an F1 cross between the NZB and NZW strains (139). In 1988, Jacob and McDevitt (25) demonstrated that, unlike NZW mice (healthy mouse strains), NZB/W mice were defective in TNF-α production and developed severe lupus-like phenotypes. They also noted that the early application of recombinant TNF-α to NZB/W mice attenuated the progression of lupus nephritis (25). In 1989, Gordon *et al* (27) continued research on NZB/W mice, demonstrating that the use of TNF-α, even following the onset of renal symptoms, increased survival, reduced the progression of kidney damage and delayed the emergence of lupus in these mice. In 2000, the study by Kontoyiannis and Kollias (26) demonstrated that NZB mice with an engineered heterozygous TNF deficit developed lupus nephritis and autoimmunity due to a lower production of TNF. Contrary to these findings, Brennan *et al* (140) found high steady-state levels of TNF-α and IL-1 β in the renal cortices of NZB/W mice with lupus nephritis. They also noted that the administration of a lower dose of TNF-α increased kidney injury (140). Furthermore, in MRL/lpr mice, an elevation in TNF-α expression was previously detected, which was linked to the degree of inflammation and organ dysfunction (141-143). The upregulation of TNF mRNA was discovered in the lungs of MRL/lpr mice in the study by Deguchi and Kishimoto (144). Overall these findings suggest that TNF-α may have both beneficial and harmful effects in experimental lupus models, based on its concentration and ability to play both immune-regulatory and pro-inflammatory functions (116). Thus, this cytokine can be considered as a therapeutic target in SLE. Rabbit anti-mouse TNF-α immunoglobulin (Ig)G antibody therapy has been shown to reduce autoimmune pulmonary inflammation in lupus-prone mice (144). It has been demonstrated that therapies directed at blocking TNF/TNFR interactions, such as soluble, dimericTNFR I (sTNFRI), which binds to TNF-α with high affinity, thus neutralizing it, reduce the infiltration of mononuclear cells into joints, lungs and skin in NZB/W mice, improving the symptoms of the disease and extending the lifespan (145). Bethunaickan *et al* (146) used a NZB/W murine model of IFN-induced lupus nephritis and treated mice with recombinant fusion proteins, such as TNFR2-Ig. They revealed that TNFR2-Ig treatment reduced the renal inflammatory response to immune complex deposition, stabilizing nephritis, thus prolonging survival (146).

Given the promising results of TNF blockade in SLE mouse models, the inhibition of this cytokine was previously investigated in patients with SLE. Clinically authorized TNF-α suppressors have been revealed to be effective in several autoimmune disorders, and novel TNF-α signaling blockers are currently being investigated in clinical trials. Infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi) and etanercept (Enbrel) are the five anti-TNF drugs approved by the US Food and Drug Administration (FDA) for the treatment of rheumatic inflammatory diseases, such as RA, psoriasis, psoriatic

arthritis and Crohn's disease (Table I) are currently being studied in patients with SLE (44,147).

However, these agents may induce autoimmunity, leading to the production of antinuclear antibodies and/or anti-double-stranded DNA antibodies, and may occasionally trigger the anti-TNF-α-induced lupus-like syndrome (ATIL) defined by clinical features suggestive of SLE (148). The majority of cases occur in patients with RA, inflammatory bowel disease and ankylosing spondylitis (29,149-152). Previous studies have demonstrated that nephritis may occur following the administration of anti-TNF-α drugs (153,154).

Infliximab is a chimeric genetically modified monoclonal antibody that includes a murine variable region and a human IgG1 constant region. It is particular for all types of TNF in humans and effectively prevents TNF from attaching to both transmembrane and soluble receptors (147). Due to its chimeric structure, infliximab is the anti-TNF-α molecule with a larger degree of immunogenicity (152). Nevertheless, open-label studies and case reports have reported the effectiveness, acceptable safety and tolerability profile of infliximab in patients with SLE. Aringer *et al* (155-157) observed that short-term induction therapy with infliximab along with azathioprine or methotrexate elicited long-term improvement in individuals with lupus nephritis. The majority of patients with SLE exhibited a transient elevation in autoantibodies against phospholipids and nuclear antigens, which was not associated with disease flares (NCT00368264) (155-157). Other studies have confirmed the safety and efficiency of infliximab in patients with difficult-to-treat lupus nephritis (158,159). Hayat and Uppal (159) also demonstrated the efficacy of infliximab in a patient with difficult-to-treat active non-renal SLE. In a pilot study, Uppal *et al* (160) demonstrated that infliximab significantly decreased the SLE disease activity index (SLEDAI) without raising any safety concerns.

Etanercept is a full human monoclonal antibody with reduced immunogenicity. It is a fusion protein consisting of two equal extracellular regions of TNFR2 linked to the Fc fragment of human IgG1 and strongly binds to sTNF-α or tmTNF-α (161,162). The FDA has approved the therapeutic application of this drug for the treatment of RA, polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis and plaque psoriasis (44). Although the FDA has not yet approved etanercept for the treatment of SLE, it has been used in several clinical studies, including a randomized, double-blind, phase II, multi-center study for the treatment of lupus nephritis (NCT00447265), and in two phase II open-label trials for the treatment of discoid lupus erythematosus (NCT02656082 and NCT00797784). In an observational study, long-term treatment with etanercept was revealed to be relatively safe and efficacious in refractory lupus arthritis (163). In a previous case report study, an enhancement of clinical symptoms and the quality of life were described in subacute cutaneous lupus erythematosus individuals by etanercept treatment (164). The efficacy and the acceptable safety profile of etanercept were also shown to treat rhupus, a disease with characteristics of both RA and SLE (165,166). Micheloud *et al* (167) described a pregnant woman with SLE with a severe diffuse proliferative nephritis who was successfully treated with etanercept, plasmapheresis and high-dose intravenous gammaglobulin.

Using molecular docking approach, a recent study investigated the potential of selected anti-inflammatory peptides from plant and animal sources as novel inhibitors for the treatment of SLE. Protein-ligand and peptide-protein docking of twenty anti-inflammatory peptides targeting IFN-γ, IL-3 and TNF-α were developed to reduce inflammatory events which lead to autoantibody production. The study represents an initial step for employment of these peptides in the treatment of autoimmune disorders (168).

8. Blocking of TNFRs: Therapeutic approaches in SLE; animal models and clinical trials

The present review article has noted the paradoxical involvement of TNF-α in lupus and explained the advantages and disadvantages of blocking this cytokine in preclinical and clinical studies. In addition to inducing ATIL, and autoantibodies to dsDNA and phospholipids, TNF-α inhibitors can increase the risk of infections, malignancies (169), central nervous system demyelinating disorders, and other autoimmune diseases, such as type I diabetes, psoriasis and multiple sclerosis (53,170-172). A probable cause of these side-effects is that prevailing TNF-α suppressors prevent the engagement between TNF-α and the receptors TNFR1 (with pro-inflammatory and pro-apoptotic role) and TNFR2 (with a regulatory function), leading to a loss of TNFR2 signaling regulatory function (173). Van Hauwermeiren *et al* (174) noted that $TNFR1^{+/-}$ mice, which express 50% of TNFR1 on cells, were highly resistant to lethal TNF-induced inflammation. Moreover, the decrease in p55TNFR mitigated TNF toxicity without compromising effectiveness (174), suggesting that TNFR can be considered as a therapeutic target (175). In SLE, the significance of TNF-α-TNFR1 interaction has been emphasized (176). Wu *et al* (177) demonstrated that the TNFR1 levels in the urine of mice and individuals with lupus nephritis increased; sTNFR1 and sTNFR2 levels have also been shown to be higher in patients with lupus nephritis (131). According to Deng *et al* (178) TNFR1 is abundantly expressed in skin lesions of MRL/lpr mice, unlike TNFR2, and the inhibition of TNFR1 signaling relieved skin lesions. On the other hand, thye acceleration of the disease course occurred in NZB/F1 mice defective in both TNFR1 and TNFR2 (179). However, the lack of the p55TNFR has been shown to lead to significantly increased lymphoproliferation and autoimmune disorder in the Fas deficient MRL-lpr/lpr mouse (180). Aderka *et al* (128) suggested that elevated serum sTNFR levels may be a valuable marker for assessing the progression of SLE. The effect of Brentuximab Vedotin targeting TNFR was investigated in adults with active SLE in a phase II, multi-center, randomized, double-blinded, multiple-ascending-dose study (NCT02533570) (Table II).

9. Conclusions and future perspectives

TNF-α is a potent pleiotropic cytokine with multiple cellular activities, also involved in developing autoimmune disorders. The impact of TNF-α on these diseases is not yet completely understood. On the one hand, TNF-α can play a pro-inflammatory and pro-apoptotic role, and on the other hand, it has a regulatory function. Currently, therapeutic strategies that target TNF-α are clinically utilized for the treatment of inflammatory

and autoimmune diseases, such as RA, inflammatory bowel disease and psoriasis. However, notwithstanding their clinical achievement, the application of anti-TNF drugs is restricted due to severe side-effects and ATIL development. Alternative therapeutic strategies that selectively target TNFRs have exhibited immense therapeutic potential. Thus, the majority of available evidence suggests that the usability of anti-TNF drugs could be broadened. Understanding the dual role of TNF-α in autoimmunity is difficult, particularly in a complex disease, such as SLE. The use of drugs targeting TNF-α and TNFRs in SLE remains controversial. Further investigations are thus required to establish the favorable therapeutics benefits/risk ratio associated with the use of anti-TNF-α drugs, as well as to determine the treatment's effectiveness and side-effects in patients with SLE.

Acknowledgements

The authors would like to thank Dr Afshin Derakhshani, Immunology Research Center, Tabriz University of Medical Sciences, Tabriz 5165665811, Iran, for critically reading and commenting on the manuscript.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

FG, PL, HA, BN, NSN, MP, EM, HS, NJT, VR and BB contributed to the conceptualization, methodology, data curation, investigation, visualization, and the drafting and editing of the manuscript. VR and BB critically reviewed the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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