LAMPs: Shedding Light on Cancer Biology

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Abbreviations:

LAMP	Lysosomal Associated Membrane Protein
DCs	Dendritic cells
TAMs	Tumor Associated Macrophages
ECM	Extra Cellular Matrix

Keywords:

LAMPs, lysosomes, cancer, metastasis

ABSTRACT

Lysosomes are important cytoplasmic organelles whose critical functions in cells are increasingly being understood. In particular, despite the long-standing accepted concept about the role of lysosomes as cellular machineries solely assigned to degradation, it has been demonstrated that they play active roles in homeostasis and even in cancer biology. Indeed, it is now well documented that during the process of cellular transformation and cancer progression lysosomes are changing localization, composition and volume and, through the release of their enzymes, lysosomes can also enhance cancer aggressiveness. LAMPs, Lysosome Associated Membrane Proteins, represent a family of glycosylated proteins present predominantly on the membrane of lysosomes whose expression can vary among different tissues, suggesting a separation of functions. In this review we focus on the functions and roles of the different LAMP family members with a particular emphasis on cancer progression and metastatic spread. LAMP proteins are involved in many different aspects of cell biology and can influence cellular processes such as phagocytosis, autophagy, lipid transport and aging. Interestingly, for all the five members identified so far, LAMP1, LAMP2, LAMP3, CD68/Macrosialin/LAMP4 and BAD-LAMP/LAMP5, a role in cancer has been suggested. While this is well documented for LAMP1 and LAMP2, the involvement of the other three proteins in cancer progression and aggressiveness has recently been proposed and remains to be elucidated. Here we present different examples about how LAMP proteins can influence and support tumor growth and metastatic spread, emphasizing the impact of each single member of the family.

CHARACTERISTICS AND FUNCTIONS OF LYSOSOMES

Lysosomes are eukaryotic acidic organelles originally thought to be exclusively involved in the degradation of intracellular and extracellular macromolecules into building blocks available for the cells. Lysosomes have only recently been recognized as crucial regulators of cell homeostasis and there is accumulating evidence of their involvement in different diseases such as neurodegenerative disorders, cardiovascular diseases and cancer (1, 2). Lysosomes are single membrane cytoplasmic organelles present in almost all eukaryotic cells. They exert several functions in the regulation of cell homeostasis including lysosomal exocytosis, cholesterol homeostasis and, possibly more importantly, the degradation of macromolecules, such as lipids, nucleic acids and proteins. This is achieved through the action of several hydrolases (more than 50 different lysosomal hydrolases have been described so far), among which cathepsins (proteases targeting either cysteine or aspartic acid residues) occupy a prominent place (3, 4). In particular, degradation of intracellular material is generally obtained via different forms of autophagy, whereas degradation of exogenous material occurs via endocytosis (1).

In the mid-twentieth century, de Duve referred to lysosomes as “suicide bags” because of the important role of these organelles in cell death signaling (5). Indeed, lysosomes are implicated in three main distinct pathways of cell death: apoptosis, necrosis and autophagy (6). However, the recognition of autophagy as a cell death mechanism is still controversial, being a process aimed at survival during stress conditions that can also result is cell death (7). Specifically, the autophagic process (sometimes reported as type II programmed cell death) represents an evolutionarily well-conserved pathway where entire organelles or part of the cytoplasm are recycled as a response to starvation or to remove damaged organelles. This multi-step process is mediated through the formation of the so-called autophagosome, a double-membrane vesicle that subsequently will fuse with the lysosomes forming the autolysosome for the final degradation step (8). Lysosomes are the most critical components for a proper clearance of mature autophagosomes, which for instance can cause neurodegenerative disorders when they accumulate as a result of not being properly digested. Alternatively, the phenomenon of lysosomal permeabilization and the consequent release of proteolytic enzymes into the cytosol have been recognized as a “lysosomal pathway for apoptosis”. In this process lysosomes are not just passive bystanders, but rather play an active role that is tightly regulated. The factor considered a key determinant in the kind of cell death triggered by lysosomal enzymes, especially as regards apoptosis vs. necrosis, is believed to be represented by the magnitude of lysosomal permeabilization, namely the amount of proteolytic enzymes released into the cytosol (9). A complete collapse of the organelle itself with the release of high levels of

lysosomal enzymes triggers unregulated necrosis, while selective lysosomes permeabilization results in the induction of apoptosis (10, 11). As soon as lysosomal hydrolases are released into the cytosol, they can take part in the execution of the apoptotic cascade by acting either in concert with the canonical caspase pathway or directly to actively cleave key cellular substrates (12, 13). However, the precise mechanisms by which lysosomes are involved in apoptosis are still poorly understood and currently under intense investigation.

The lysosomal surface has been identified as the subcellular site where mTORC1 (mammalian Target Of Rapamycin Complex 1) activation in response to amino acids occurs (14). mTOR, the main catalytic component of mTORC1, is an atypical serine/threonine kinase reported as master regulator of cell growth, energy production and protein synthesis (15); its functions are often deregulated in different diseases and in particular in cancer (16). These studies have demonstrated that amino acids trigger the translocation of the mTORC1 complex to the lysosomes where it gets activated by interacting with Rag GTPases, and Ragulator and Rheb, two proteins that are anchored to the lysosomes' membrane (14). Active mTORC1 is responsible for the phosphorylation and the subsequent accumulation in the cytosol of TFEB, a nuclear transcription factor responsible for lysosomal biogenesis, thereby integrating signals from the lysosomes to the nucleus (17).

ROLE OF LYSOSOMES IN CANCER

During transformation and cancer progression lysosomes are changing localization, volume and composition and by releasing their enzymes they can increase cancer aggressiveness (4, 18). For instance, several lysosomal enzymes, including cathepsins, are over-expressed in different cancer types, such as breast, prostate and colon cancers (19, 20), and there is data that their expression levels can be clinically significant (11). Different reports have suggested that an increased production and subsequent secretion of these proteases via exocytosis can foster proliferation and invasion of cancer cells (19, 21, 22). Therefore, this can enhance cancer progression and metastasis formation by promoting the degradation of the extracellular matrix and increasing the potential for angiogenesis (23). Indeed, inhibition of cathepsin B by synthetic cysteine protease inhibitors has been shown to effectively reduce the invasiveness of glioblastoma (24) and breast cancer cells (25). At the same time cancer cells are strongly dependent on lysosome function and are very sensitive to lysosome mediated cell death (1, 26). Lastly, it has been demonstrated that lysosomal dysfunction can promote the inclusion of lysosomal materials (e.g. proteins) to exosome cargo in order to simplify their elimination from cells (i.e. neurons affected by Alzheimer Disease) (27). Exosomes are small vesicles (30-100 nm in diameter) derived from the

endosomal system that can be released from cells and represent critical structures for different types of cellular communication including the immune response (28). Initially it was thought that the fusion of exosomes with lysosomes would serve exclusively for the removal of unnecessary exosomal materials (29), however, since exosome materials can be shuttled to neighboring or even distant cells, secretion of unwanted material to the extracellular environment within exosomes may have either positive or negative effects on surrounding cells. Therefore, the interplay between exosomes and lysosomes may represent a novel layer of exploration for different pathologies including cancer.

This review focuses on the role of a specific family of highly glycosylated membrane proteins usually found within lysosomal membranes known as lysosomal associated membrane proteins (LAMPs) and their involvement in cancer.

LAMP FAMILY OF LYSOSOMAL PROTEINS

The LAMP family is characterized by an evolutionary conserved membrane-proximal LAMP domain, composed of around 200 amino acids and containing several conserved cysteine residues, that allow for the formation of two critical disulfide bonds (30). Other common features in the family are represented by i) a specific proline and two glycine residues in their single transmembrane region (30), ii) the presence of several N-linked glycosylation sites within their luminal domain (31) and iii) a short cytoplasmic tail harboring an endosomal and lysosomal sorting signal (32) (**Figure 1**).

The LAMP family is composed of 5 known members: LAMP1/CD107a, LAMP2/CD107b, LAMP3/DC-LAMP, LAMP4/Macrosialin/CD68 and LAMP5/BAD-LAMP. LAMP1 and LAMP2 are ubiquitously expressed in human tissues and cell lines, whereas LAMP3, LAMP4/Macrosialin/CD68 and LAMP5/BAD-LAMP are cell-type specific proteins. LAMPs are involved in a variety of cellular processes including phagocytosis, autophagy, lipid transport and aging (30); moreover, growing evidence suggests an important role for LAMP family members in cancer (Tables 1-5 and Figures 5 and 6).

LAMP1 AND LAMP2

LAMP1 and LAMP2 represent the major constituents of the lysosomal membrane, are classified as type I transmembrane proteins and share similar length and 37% amino acid sequence homology (30, 33). Their structure is characterized by a highly glycosylated luminal region forming a glycoprotein layer in the lysosomal lumen, a transmembrane region and a short C-terminal cytosolic domain (Figure 1). LAMP1 has only one transcript, whereas LAMP2 has three different

splicing isoforms: LAMP2A, LAMP2B and LAMP2C (30, 33). LAMP2 isoforms are expressed in a tissue specific manner and can exert opposing functions (34, 35). Specifically, the LAMP-2A isoform is recognized to be responsible for chaperone-mediated autophagy (CMA), a process that targets specific proteins to degradation by lysosomes via recognition of a specific motif within their amino acids sequence, and loss of the LAMP-2A isoform is associated with the formation of α-synuclein-positive aggregates in Parkinson's disease (36). The LAMP-2B isoform is not involved in CMA, but mutations in exon 9 have been found in patients bearing a defective fusion process between lysosomes and autophagosomes, suggesting a function for this isoform in macroautophagy (37). Finally, LAMP-2C has been demonstrated to act as an inhibitor of CMA particularly in B cells and to be capable of mediating the autophagy of nucleic acids by binding to RNA and DNA (38, 39). Many different mutations have been found in the LAMP2 gene and these are causative of Danon disease, a severe condition characterized by skeletal and cardiac myopathy and cognitive impairment (40-42). Additionally, the loss of the LAMP-2B isoform could represent the phenotypic leading cause of Danon disease, probably given its putative role in macroautophagy (43). A similar phenotype to Danon disease is observed in LAMP2 knockout mice, whereas LAMP1 single knockout mice are viable and fertile while LAMP1/LAMP2 double knockout mice show embryonic lethality, suggesting these two proteins play key and partially overlapping functions in cellular homeostasis (30). LAMP2 deficiency has also been associated with pancreatitis, strengthening the importance of a correct lysosomal/autophagic compartment and its associated proteins for cell homeostasis (44).

Growing evidence of a role for lysosomes in different diseases has raised interest in deciphering the role of LAMP1 and LAMP2 in cancer progression. Examples of the roles of LAMP1 and LAMP2 in cancer are summarized in **Tables 1 and 2** and depicted in **Figures 2 and 6**. Reported roles for LAMP1 and LAMP2 as pro-invasive and pro-metastatic factors refer to their abnormal localization on the plasma membrane of cancer cells, as shown in human melanoma A2058 cells, human colon carcinoma CaCo-2 cells and human fibrosarcoma HT1080 cells (45). There is still no clear explanation on the way LAMP1 and LAMP2 translocate to plasma membrane but, possibly, this could be the result of plasma membrane damage leading to lysosome fusion and exocytosis as a membrane repair mechanism (46). It has been proposed that a Rab3a-dependent complex or the tumor protein D52 could possibly mediate LAMP1 and LAMP2 trafficking to the plasma membrane (47, 48). *In vitro* studies have shown that the translocation of LAMP2 could be driven by an acidic microenvironment, which could support the thesis that plasma membrane damage recruits lysosomes and lysosomal associated membrane proteins to the plasma membrane (49). Specifically, in the early phases of *in situ* breast carcinoma, progression, glycolytic

metabolism and the absence of vascularization generate an acidic microenvironment, that results in increased localization of LAMP2 on the plasma membrane serving as a protective shield as shown in Figure 2 (49). In addition to protection, LAMP1 and LAMP2 expression on the plasma membrane provide binding to E-selectin through sialyl-Le^X residues and binding to galectin-3 through poly-N-acetyl-lactosamine (polyLacNAc)-substituted β1, 6 branched N-glycans. Thereby, LAMP1 and LAMP2 can promote both the adhesion of cancer cells to extracellular matrix, basement membrane and endothelium and the migratory potential of cells during metastasis (45, 50). Both LAMP1 and LAMP2 can also be modified by the alpha1, 2-fucosyltransferases enzyme, FUT1, that works by adding a fucose molecule to N-acetylglucosamine via α1, 3-linkage and generates Lewis Y (LeY) antigens. The presence of these modified LeY termini on LAMP1 is increased in breast cancer cells relative to their normal mammary counterpart and it has been associated with breast cancer cell migration (51, 52). The presence of this modification on both LAMP1 and LAMP2 is able to influence the localization of lysosomes and the autophagic flux, since FUT1 down-regulation has been demonstrated to lead to an accumulation of lysosomes to perinuclear regions and to correlate with increased autophagy and decreased mTORC1 activity (52).

Despite the high expression of both LAMP1 and LAMP2 on the surface of some types of invasive cancer cells, only the surface translocation of LAMP1, but not LAMP2, has been shown to correlate with the metastatic potential of melanoma, non-small cell lung cancer (NSCLC) and laryngeal squamous cell carcinoma (LSCC) (50, 53). One well described mechanism responsible for the LAMP1-mediated invasion in melanoma cells is the high expression of polyLacNAc bound to LAMP1 which activates the ERK and p38 pathways, thus leading to the secretion of matrix-metallo-protease-9 (MMP-9) and consequent ECM remodeling (54). In other types of cancer, specifically glioblastoma, pancreatic and ovarian cancer, LAMP1 expression on the cell surface plays a role during early phases of cancer progression rather than in the metastatic process, thus suggesting different LAMP1 functions depend on the cancer type (55-57). In these cases, the exact mechanism for LAMP1 tumor promoting role is still poorly studied, but there are data reporting a regulation of the EGF pathway in some serous ovarian malignancies (56). One possibility is that localization of LAMP1 to the plasma membrane could shape growth factor signaling, thereby modulating cancer development at various stages.

LAMP1 expression on the cell surface is commonly found also in some types of immune cells, such as natural killer cells (NK cells) and T cells, and is commonly used as a marker for degranulation and active cytotoxicity (Figure 3) (58-63). In particular, in NK cells LAMP1 is necessary for an efficient expression of perforin in lytic granules, and at the same time to protect NK cells from damage during exocytosis of cytotoxic granules (60, 61). LAMP1 expression on

cancer cells could possibly recapitulate the role carried out in immune cells, thus protecting cancer cells from lytic granules and immune mediated destruction. Similarly, both LAMP1 and LAMP2 expression has been associated with the ability of leukocytes to adhere to the endothelium and to migrate, and in this way favoring the migration of cancer cells (64).

LAMP1 over-expression can also influence cancer progression from its normal localization inside the lysosomal membrane. In particular, increased expression of LAMP1 can influence lysosomal biogenesis and cancer cell viability: its knockdown in acute myeloid leukemia (AML) cells leads to diminished cancer cell viability through lysosome disruption (65). In the lysosomal membrane, LAMP1 can also promote drug resistance by increasing lysosomal size and lysosomal exocytosis as it has been shown in rhabdomyosarcoma, soft tissue sarcomas, renal and colorectal cancers. This ultimately leads to drug sequestration in lysosomes and drug release via exocytosis, thereby causing drug resistance (66, 67). Increased lysosomal exocytosis is also responsible for increased invasiveness of aggressive soft tissue sarcomas (68). However, reduced expression of LAMP1 and LAMP2 have been reported in ovarian carcinoma cells resistant to cisplatin, suggesting their role in drug resistance could either be drug specific or cancer cell type specific (69). Tissue and type specificity effect of LAMP1, could also explain some conflicting evidence regarding a tumor-suppressing role of LAMP1 reported in pancreatic carcinoma and ovarian carcinoma cells exposed to ascites. Indeed, LAMP1 expression correlates with prolonged survival in pancreatic carcinoma, whereas ascites-mediated up-regulation of LAMP1 expression in ovarian carcinoma cells is responsible for a decreased cancer cell migration (70, 71).

Increased expression of LAMP1 could be driven by the activation of specific cancer signaling pathways (such as STAT3, ETS1 and p65) or could be a result of a gene amplification as seen in chronic lymphocytic leukemia (CLL) and in a number of p53 null and basal-like breast cancers (ENCODE database (72, 73)). In the latter case, LAMP1 was seen to be over-expressed compared to normal mammary epithelium as a result of gene amplification, although this phenomenon alone did not correlate with survival (72, 73); while, a homozygous deletion of the LAMP1 gene has been found in some cases of gastric carcinoma, demonstrating again the opposing roles of LAMP1 in cancer progression (74). Finally, LAMP1 is also commonly found expressed on the membrane of exosomes secreted by different types of tumors (28, 75). The exact role for LAMP1 expression on secreted exosomes is still unknown, however it could be involved in the different effects of exosomes on the immune system by either promoting recognition of cancer antigens or inducing immune tolerance to cancer cells (75, 76).

LAMP2 has fewer reports on its involvement in cancer progression than LAMP1, but similarly to it, some contradictory functions are also reported. LAMP2 may regulate migration of

ovarian clear cell adenocarcinoma possibly through ANXA4 (Annexin A4), whose knockout in the OVISE cell line resulted in a reduced expression of LAMP2 and was associated with a loss of migration and invasion capability (77). Compared to normal tissues, LAMP2 is also highly expressed in poorly differentiated human gastric adenocarcinoma, hepatocellular carcinoma, salivary adenoid cystic carcinoma and in the broncho-alveolar lavage fluid of patients with lung adenocarcinoma, representing one novel molecular marker for these cancer types (78, 79). It may be involved in the pathogenesis of patients whose multiple myeloma harbor a specific BCL1/JH t(11;14)(q13;q32) translocation and could be used as a prognostic marker or therapeutic target (80). The LAMP2A isoform has shown increased expression in breast tumor tissues and prognostic value in non-small cell lung cancer. Indeed, LAMP2A inhibition or genetic knockdown resulted in the sensitization of tumor cells to doxorubicin and radiation therapy (81-83). Another important role reported for the LAMP2A isoform in cancer refers to its involvement in immunogenic cell death, a type of apoptosis that stimulates anti-cancer immune response (84). In particular, the LAMP2A isoform can induce the expression of calreticulin and the secretion of ATP upon mitoxantrone and hypericin-based photodynamic therapy, thus leading to immunogenic cell death, thereby suggesting opposing roles for this isoform in cancer (84).

Another reported tumor suppressor role for LAMP2 stands on its ability to induce cell death upon depletion of the VEGF-NRP2 axis in prostate cancer cells. The up-regulation of LAMP2 and WDFY1 resulting from autophagy blockade caused by VEGF-NRP2 axis inhibition leads to increased cell death (85). Similar oncosuppressive effects have been observed in neuroblastoma cells cultured under hyperoxia, which causes up-regulation of LAMP2 and LC3-II, macro-autophagy and ultimately induces apoptosis (86). A protective role of LAMP2 in drug resistance has been reported in lung cancer, where it is directly targeted by miR-487b-5p, a microRNA often found over-expressed in temozolomide resistant lung cancer cells(87). Finally, LAMP2 is often found expressed on the membrane of exosomes secreted from immune cells but its role is still largely unknown; however, there could be a possible role for both LAMP1 and LAMP2 exosomal expression in shaping the immune system response (**Figure 3**) (28).

LAMP3/DC-LAMP

Lysosomal-associated membrane protein 3 (LAMP3) is a 44-kDa protein and, unlike LAMP1 and LAMP2, which are ubiquitously expressed, LAMP3 is expressed only in specific conditions and tissues. To avoid ambiguity, it is worth noting that the LAMP3 gene/protein name can be also wrongly referred to CD63, which, despite being a protein enriched in late endosomal

and lysosomal compartment, belongs to the tetraspanin family (88). In this review, we always refer to LAMP3 as a member of the LAMP family.

LAMP3 is also called DC-LAMP, because it was firstly shown to be induced progressively upon maturation of human dendritic cells (DCs), where it transiently co-localizes with MHC class II molecules at the limiting membrane of specific intracellular compartments (i.e. MHC class II compartment, MIIC), and is thus considered as a marker of mature DCs in humans (89). In the same year of this observation, LAMP3 was independently characterized as a gene specifically expressed in lung tissue, and designated as TSC403 transcript (90). Indeed, LAMP3 is highly expressed in a specific cell-type in mammals, normal and transformed type II pneumocytes (PnIIs) (91), which are specialized pulmonary cells important for the repopulation of lung tissue during normal homeostasis and injury, and responsible for surfactant synthesis, secretion and recycling (92, 93). However, the expression of LAMP3 in time and space is significantly different between human DCs and type II pneumocytes. LAMP3 is transiently expressed in the MIIC compartment (responsible for the exposure of MHC class II/peptide complexes on the plasma membrane) during the maturation of DCs and it then accumulates in perinuclear lysosomes without localizing to the plasma membrane (89). Conversely, LAMP3 is constitutively expressed at the limiting membrane of PnII lamellar bodies (responsible for secretion of surfactant proteins, and also containing MHC class II molecules), and low levels of the protein can also be detected at the cell surface membrane in these cells (91). Functional similarity between MIIC in DCs and lamellar bodies in PnIIs suggests a possible role for LAMP3 in the regulation of the exocytosis of these lysosomes, and particularly in MHC class II-restricted antigen presentation, which is a characteristic of both mature DCs and PnIIs (94).

LAMP3 expression is induced by the unfolded protein response (UPR) activated by hypoxic condition (95) and this induction is mediated by the PERK/eIF2α arm of UPR (96). Further, proteasome inhibition induces LAMP3 expression in an ATF4 (a UPR transcription factor)-dependent manner. Increased expression of LAMP3 is able to trigger autophagy, whereas preventing LAMP3 induction enhanced apoptotic cell death, thereby demonstrating that LAMP3 regulation is important for proteasomal degradation and cell survival during proteasome dysfunction (97). Furthermore, a recent meta-analysis of genome-wide association studies in Parkinson disease has identified the MCCC1/LAMP3 genetic locus associated with Parkinson disease risk (98, 99). LAMP3 expression is also driven by IFN-α during dendritic cell maturation (100), and it has been shown to regulate the expression of antiviral genes in cervical cancer (101). LAMP3 expression is also induced in an interferon-dependent manner upon influenza A and

hepatitis C virus infection and may play a role in the regulation of virus replication and infection at the post-entry stages (102, 103).

Growing evidence has shown that LAMP3 is over-expressed in various human tumors, where it correlates with poor prognosis (LAMP3 functions in cancer are summarized in **Table 3** and **Figures 4 and 6**) (104, 105). Studies have revealed that LAMP3 might be important in tumor metastasis and resistance to therapies, suggesting LAMP3 could become a molecular marker for the prognosis of various cancers (106, 107). Indeed, LAMP3 expression has been shown to be higher in several primary cancers compared to normal tissues, including cancers of the esophagus, colon, fallopian tube, ovary, uterus, breast, and liver (90, 108). Moreover, the 3q27 region where the LAMP3 gene is located is often amplified in various types of cancers, in particular squamous cell carcinomas and penile carcinomas (109).

LAMP3 over-expression in uterine cervical cancer cell lines is able to promote metastasis *in vitro* and *in vivo* (106), and its expression has been associated with lymph node metastasis (104), (110) and increased migration in breast cancer cells (95), suggesting a role for LAMP3 in the metastatic process (106). However, the mechanism whereby it might promote metastases has not been completely elucidated; however, similarly to LAMP1 and LAMP2, its exposure on the plasma membrane could allow cancer cells to interact with endothelial cells. Nevertheless, LAMP3 expression on the cellular plasma membrane could be detected only in specific circumstances on cancer cells, such as upon Influenza A virus infections in HeLa cells (102), whereas it could not be detected on the plasma membrane of other cancer cell lines, for example MDA-MB-231 (95). Another possible mechanism by which LAMP3 expression can increase the metastatic potential of cancer cells is through the modulation of the autophagic flux, which is known to play key roles in cancer metastasis (111). Particularly, the cytoplasmic tail of LAMP3 seems to be required for the fusion of the autophagosome with the lysosome (i.e. maturation step), a process inhibited in cancer cells when LAMP3 is knocked down (112).

LAMP3 expression has also been correlated with poor overall survival in head and neck squamous cell carcinomas (107, 108), uterine cervical cancer (106), gastric and colorectal cancers (105), whereas its expression levels, together with the expression of other pneumocyte-specific genes has been associated with increased survival in the adenocarcinoma subgroup of non-small cell lung cancer (NSCLC) (113). These conflicting data could be due to the high levels of LAMP3 expression in lung normal tissue, where LAMP3 could play a specific role that could be compromised during cancer development.

LAMP3 has also been implicated in drug resistance with up-regulation of LAMP3 associated with resistance to chemotherapy and radiotherapy in breast cancer (112, 114), and its

down-regulation possibly increasing cisplatin sensitivity in prostate cancer cells (115). LAMP3 expression could decrease the sensitivity of cancer cells to chemotherapy by modulating autophagy, a process whose ability to influence drug resistance has been extensively studied (116). LAMP3-mediated radiotherapy resistance has conversely been attributed to its ability to positively regulate the response to DNA damage (114). Finally, induction of LAMP3 among a subset of genes, following combined treatment with the chemotherapeutic drug doxorubicin and the inflammatory cytokine TNF-α in breast cancer cells, suggests a possible involvement of LAMP3 in cancer related inflammation (117).

Given that LAMP3 is highly expressed in DCs, it is essential to distinguish between its contribution to cancer when expressed by cancer cells or by dendritic cells infiltrating the tumor. For example, it has been observed that infiltration of $LAMP3^+$ DCs in the sentinel lymph nodes of melanoma patients was correlated with the absence of metastasis in downstream lymph nodes (118).

CD68/Macrosialin/LAMP4

CD68, the human homologue to murine Macrosialin, is a heavily glycosylated transmembrane glycoprotein mainly localized in the endosomal/lysosomal compartment of macrophages showing a distinctive structure corresponding to the LAMP signature, with highest homology to LAMP3 (119, 120). Similarly to LAMP3, CD68 contains only a single LAMP-like domain and a mucin-like domain (**Figure 1**) (119); but, unlike LAMP3, which is mainly located within lysosomes, CD68 is found in endosomes and can rapidly shuttle to the plasma membrane (121).

CD68/Macrosialin/LAMP4 has been extensively used as a histological marker of macrophage lineage cells, since it is preferentially expressed by resident macrophages of multiple tissues, including macroglia in the brain, Kupffer cells in the liver and bone marrow macrophages (122-124). Although initially classified as a group D scavenger receptor due to its ability to bind oxidized low-density lipoproteins (OxLDL) (125), CD68 silencing and knockout experiments failed to affect OxLDL binding and uptake to macrophages (126, 127). Beyond the use of CD68/Macrosialin/LAMP4 as a histological marker to identify macrophages, the apparent specificity of the expression of CD68/Macrosialin/LAMP4 has led some to propose the use of CD68 transcriptional regulatory sequences to specifically drive *in vitro* and *in vivo* transgene expression, as well as for gene therapy approaches (89, 128, 129). However, recent studies show that a high expression of CD68/Macrosialin/LAMP4 is not limited to cells of macrophage lineage, but is observed also in other hematopoietic and non-hematopoietic cells (130, 131); therefore,

CD68/Macrosialin/LAMP4 should be considered a non-specific marker of macrophages.

Although a role for CD68/Macrosialin/LAMP4 in antigen processing is unknown, studies have shown enhanced capacity of antigen presentation to $CD4^+$ T cells by $CD68^{-/-}$ mononuclear phagocytes, suggesting CD68/Macrosialin/LAMP4 may have negative regulatory functions in MHC class II trafficking or antigen uptake and loading (127). Interestingly, CD68 is expressed also in immature DCs, and its expression progressively disappears during maturation at the same time as LAMP3 accumulates in the lysosomes (89) suggesting a putative competing role in the antigen presentation process.

Immunohistochemical staining of bone specimens has identified CD68/Macrosialin/LAMP4 expression in osteoclasts (124), multi-nucleated cells responsible for bone reabsorption during normal bone remodeling or pathological conditions (132), and genetic ablation of CD68/Macrosialin/LAMP4 resulted in morphological alteration and functional defects in osteoclasts and increased bone in mice (133). Importantly, infiltration of CD68/Macrosialin/$LAMP4^+$ cells is a marker for both inflammation and tumor progression (see **Table 4** and **Figures 5 and 6)** (134, 135). A population-based cohort study of malignant uveal melanoma observed diffuse infiltration of CD68/Macrosialin/$LAMP4^+$ macrophages in 83% of analyzed tumors and the number of macrophages has been associated with the largest basal tumor diameter (LBD), presence of epithelioid cells and high microvessel density (MVD) in areas of high vascularization (135), which represent independent high-risk indicators for metastasis in uveal melanoma (135, 136 1996).

Tumor-associated macrophages (TAMs), for which CD68 represents one of the most recognized marker (137), are one of the most abundant population of normal cells in the tumor microenvironment and there is accumulating evidence for TAMs' pivotal role in driving pro-tumorigenic phenotype. Indeed, density of $CD68^+$ TAMs is increased in poorly differentiated thyroid cancers (PDTCs), and a high density of these cells correlates with invasion and decreased cancer-related survival in these advanced thyroid cancers (138). Furthermore, increased expression of $CD68^+$ macrophages in the tumor stroma of patients with a diagnosis of triple-negative breast cancer (TNBC) and of patients with classic Hodgkin's lymphoma correlates with a poor prognosis (139, 140). In contrast, a high density of CD68/Macrosialin/$LAMP4^+$ macrophages correlates with increased overall survival in non-small cell lung cancer and esophageal squamous cell carcinoma (141, 142). This discrepancy in the predictive power of CD68/Macrosialin/LAMP4 for tumor prognosis could be due to several factors, including technical variability, specificity of the antibodies, and differences in the case series (143). We have reported here some evidence of the role of CD68/Macrosialin/$LAMP4^+$ macrophages in the tumorigenic processes and we refer to other

recent reviews for a comprehensive description of the role of TAMs in cancer (144-147).

Importantly, the association of CD68/Macrosialin/LAMP4 with cancer is not only related to its expression in TAMs, but also in tumor cells (131). For example, CD68/Macrosialin/LAMP4 was found to be highly expressed in human gliomas by both microglia and tumor cells; its expression was associated with malignancy in these tumors, and was suggested as a prognostic marker of reduced survival in human gliomas (148). This observation is in agreement with the fact that tumor cells often express immune cells-markers to evade the immune system during the metastatic process, most frequently expression of macrophage antigens, such as CD68, CD47, CD163 and DAP12 (149-151). The mechanism explaining the expression of macrophage antigens by tumor cells is still debated, and it seems to be mediated by genetic exchange as a result of either direct macrophage-cancer cell fusion (152), or by exosome-mediated transfer (149). CD68 was found to be expressed in mouse macrophages-derived exosomes (153), thereby supporting the hypothesis that exosomes can mediate a genetic exchange between macrophages and cancer cells and, ultimately, it could also explain the expression of CD68/Macrosialin/LAMP4 in cancer cells.

Although CD68/Macrosialin/LAMP4 is widely used as diagnostic and prognostic marker for several malignancies, the role of this protein in cancer is still to be explained and further studies investigating its mechanism of actions are needed.

BAD-LAMP/LAMP5

BAD-LAMP (Brain and Dendritic Cell associated LAMP-like molecule), also known as LAMP5 or C20orf103 is the *C. elegans* ortholog of UNC-46 and the latest characterized LAMP protein, Unlike other LAMP family members, BAD-LAMP/LAMP5 does not localize to late endosomes or lysosomes and, similarly to LAMP3 and CD68/Macrosialin/LAMP4, its expression is limited to specific tissues. BAD-LAMP/LAMP5 is a 280 amino acid protein with a transmembrane domain and a cytoplasmic tail containing a YKHM sequence, corresponding to a classic YXXΦ internalization and endosomal-targeting signal. It also contains several N-glycosylation sites, as well as four cysteine residues separated by a fixed number of amino acids, allowing for the formation of the disulfide bonds required for the “LAMP-fold” (Figure 1) (32).

BAD-LAMP was first identified as a new LAMP family member in mice, where it is mainly expressed in specific subtypes of cortical projecting neurons. In these cells, BAD-LAMP expression considerably increased after birth, suggesting its involvement in the late steps of neuronal differentiation. BAD-LAMP/LAMP5 can be endocytosed and directed to uncharacterized vesicles clustered in the growth cone of developing axons or in defined dendritic domains, identified as a specific class of early neuronal endosomes(32). In *C. elegans* mutations in the BAD-LAMP

ortholog, UNC-46, cause defects in most GABA-mediated behaviors, and it has been proposed as a sorting factor able to address the GABA transporter (UNC-47) to the synaptic vesicles (154). In humans, like in mice, BAD-LAMP/LAMP5 is expressed at higher levels in the brain, but, among blood cells, it is also specifically expressed in the type I IFN-producing primary plasmacytoid dendritic cells (pDCs) and transformed pDCs (blastic plasmacytoid dendritic cell neoplasms or BPDCNs), for which it represents a relevant biomarker (155). In these cells, BAD-LAMP/LAMP5 is principally localized in the ER-Golgi intermediate compartment (ERGIC) and its expression is lost upon pDC activation by Toll-like Receptor (TLR) ligands (155).

A second observation for an association between this poorly studied protein and cancer comes from the analysis of the expression of a set of genes, including BAD-LAMP/LAMP5, which has been shown to be correlated with a poor prognosis in stage II gastric cancer patients treated with chemo-radiotherapy (**Table 5** and **Figure 6**) (156); however, it is not clear whether BAD-LAMP/LAMP5 expression observed in the analyzed tissues is determined by pDCs infiltration within the tumor or by a higher expression of the protein in cancer cells. Further studies are required to establish the putative role of BAD-LAMP/LAMP5 in cancer.

CONCLUSIONS

Correct functioning of the lysosomal compartment represents a guarantor for an efficient cell homeostasis and a critical protection against various diseases, among them cancer. Differential expression of proteins associated with the lysosomal membrane, categorized as LAMP family members, can substantially influence various processes of cancer progression. This review inspected the various LAMP proteins and their reported roles in oncogenic processes, with conflicting evidence for some of the members.

LAMP1 represents the most studied member of the family and together with LAMP2 is involved in various oncogenic processes, such as local cancer progression, ECM adhesion and remodeling, migration, drug resistance and metastasis. The strong potential of LAMP1 in cancer therapy encouraged the Sanofi S.A. pharmaceutical company to patent anti-LAMP1 antibodies and immunoconjugates for detection and treatment (patent number: WO2014102299). Furthermore, LAMP1 and LAMP2 expression on the plasma membrane of cancer cell renders them optimal targets for immunotherapy approaches. Nevertheless, LAMP1 has important reported roles in the immune system, thus when planning its targeting by immunotherapies, it is crucial to bear in mind the importance of specifically targeting LAMP1 and LAMP2 expressed on cancer cells. A decreased expression of LAMP1 in NK cells would reduce their perforin-mediated cytotoxicity, which represents the most efficacious NK-mediated cell death (157), thereby potently decreasing

any anti-cancer immune response. Furthermore, a better understanding of the role of LAMP1 in cancer-derived exosomes and its effects on the immune system is of paramount importance, also for future applications of exosomes in cancer immunotherapy.

The other members of LAMP family are not extensively studied yet, but there is growing evidence supporting their pro-tumorigenic potential. For instance, LAMP3 and CD68/Macrosialin/LAMP4, which are activated by various stimuli often present during cancer development and therapy, and are closely connected with inflammation, represent additional promising targets for cancer therapy. The mechanisms by which LAMP3 expression can affect tumor progression is still to be elucidated, however, a possible explanation could be inferred from its role in the trafficking of MHC class II/peptide complexes (158), which is critical for antitumor immune response (159).

Interestingly, LAMP3, CD68/Macrosialin/LAMP4 and BAD-LAMP/LAMP5 are highly expressed in immune cells and have been shown to be associated with various types of tumors, when expressed on immune cells or cancer cells. Therefore, it would be intriguing to investigate their role at the interplay between cancer and the immune system and to elucidate whether they could play a direct role in the immune response to cancer.

In conclusion, a better knowledge of LAMP family and the role of the lysosomal in cancer progression could represent a fruitful approach in cancer research.

ACKNOWLEDGEMENT

We thank Prof. Alberto Inga, Dott. Alessandra Bisio, Dott. Sara Zaccara and Francesca Precazzini for helpful discussions. This work was partially supported by CIBIO Start up funds, University of Trento (Y.C.).

FIGURE LEGENDS

Figure 1. Structural organization of the LAMP family members. Sequential boxes stand for domains, small flags indicates glycosylation residues and protein length is also provided for each depicted member. SP: signal peptide; LAMP: LAMP domain; H: hinge region; TM: transmembrane domain; C: cytoplasmic domain.

Figure 2. LAMP1-LAMP2 subcellular localization and their roles in cancer. LAMP1 and LAMP2 can influence cancer biology in different ways depending on their localization. On the plasma membrane they promote adhesion to the endothelium and the extracellular membrane (ECM), migration and metastasis; whereas on the lysosomal membrane they promote drug resistance by increasing lysosomal drug sequestration and lysosomal exocytosis. LAMP1 expression on the plasma membrane can also play a role in ECM remodeling and invasion, whereas LAMP2 can act as a protective shield. LAMP1 is often found expressed in tumor-derived exosomes but its role in exosome biology it is still unknown.

Figure 3. LAMP1-LAMP2 subcellular localization and their roles in immune cells. LAMP1 and LAMP2 in immune cells can act as activation markers when expressed on the plasma membrane and they can promote adhesion to endothelium and migration. LAMP1 specifically has a crucial role in the degranulation process, whereas LAMP2 is expressed in immune cancer cells-derived exosomes.

Figure 4. LAMP3 subcellular localization and its roles in cancer and immune cells. LAMP3 can localize to different cellular compartments and can therefore exert different functions. LAMP3 can be bound to the lysosomal membrane or to the plasma membrane and regulate migration, metastasis, and drug resistance in cancer cells. Moreover, its cytoplasmic tail plays a role in the process of fusion of the lysosome with the autophagosome, thereby modulating the autophagic process, which can also mediate its pro-tumorigenic functions. LAMP3 is also a marker for mature dendritic cells, in which it is progressively expressed during maturation. During this process LAMP3 co-localizes with MHC class II molecules (MHCII) within the MHC class II compartment (MIIC), suggesting a possible role for LAMP3 in the antigen presentation process.

Figure 5. CD68/Macrosialin/LAMP4 **subcellular localization and its roles in cancer and immune cells.** CD68/Macrosialin/LAMP4 represents a marker for tumor-associated macrophages,

where it can rapidly shuttle between the endosomal compartment and the plasma membrane. Recent observations suggest that CD68/Macrosialin/LAMP4 may also have a negative role in the antigen presentation process. CD68/Macrosialin/LAMP4 has recently been found to also be expressed by some cancer cells, where it is associated with increased malignancy, possibly caused by immune evasion mechanisms. Expression of this immune-cell marker by cancer cells could be explained by genetic exchange between macrophages and cancer cells, which is supported by the recent detection of CD68/Macrosialin/LAMP4 in macrophages-derived exosomes.

Figure 6. Roles of LAMP family members in cancer progression. All the LAMP proteins are involved in cancer progression; LAMP1, LAMP2 and LAMP3 are also implicated in migration and stress or drug resistance. LAMP1 and LAMP2 also promote adhesion to the extracellular matrix (ECM) or remodeling whereas LAMP1 and LAMP3 can induce metastasis formation. CD68/Macrosialin/LAMP4 is often expressed on tumor-associated macrophages (TAMs).

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Table 1: Summary of cancer-associated functions for CD107a/LAMP1 [Lysosome Associated Membrane Protein-1]

Pro-tumorigenic roles	Evidence	Strength / Weakness of the Evidence
Early cancer progression (56)	• In OVCAR3 cells, LAMP1 was up-regulated 1.84-fold 24 h post-EGF treatment and down-regulated 48 h post-EGF exposure • Tissue microarray for LAMP1 positive in 35% of ovarian serous adenocarcinomas	• Although confirmatory studies not reported, observations are supported by GESA analysis using the TCGA database that revealed LAMP1 positively associated with EGFR-modulated molecular pathways ($p < 0.0060$)
Cancer cell survival (65)	• Screening identified anti-malarial agent mefloquine as compound selectively killing AML cells and stem cells • Genome-wide functional screen for mefloquine sensitizers in yeast, identified genes associated with yeast vacuole, the homolog of mammalian lysosome, and demonstrated mefloquine disrupts lysosomes, by permeabilizing membranes, and releasing cathepsins into cytosol	• Knockdown of LAMP1 and LAMP2 reduced AML cell viability, as did treatment with a lysosome disruptor, suggesting lysosomal disruption preferentially targets AML cells and progenitor cells, providing rationale for therapy. In support of this observation, artemisinins, artesunate, and dihydroartemisinin, have been shown to be toxic to AML cells
Local tumor progression (55)	• LAMP1 detected in cytoplasm of tumor cells, and in blood vessels in glioblastoma • Percentage of LAMP1+ tumor cells and staining intensities increased with tumor grade • LAMP1 and CD133, a putative marker of stemness, were co-expressed suggesting “cancer stem cells” contain LAMP1 positive lysosomes	• Data do not fully support higher number of lysosomes in glioblastoma “cancer stem cells” • Despite increase in LAMP1+ tumor cells with tumor grade, association between LAMP1 expression and OS could not be found
Cancer development (57)	• LAMP1 was identified as a sialylated glycoprotein from metabolically oligosaccharide engineered pancreatic cells • Immunohistochemistry, showed preferential expression of LAMP1 in tumor cells but not in paired non-tumor pancreatic ductal cells	• At odds with previous studies showing longer survival after resection for patients whose pancreatic tumors expressed high levels of LAMP1 mRNA • Transfection of CAPAN-1 cells with LAMP1 decreased cell growth compared with non-transfected cells • Role for LAMP1 in cancer development remains uncertain
Adhesion of cancer cells to ECM, basement membrane and endothelium (45); ECM remodeling (54)	• Flow cytometry showed LAMP1 expression on cell surface of A2058, HT1080 and CaCo-2 cells, increasing with 2 mM sodium butyrate treatment for 24-48 hr • FACS analysis proved interaction between LAMP1 expressing A2052 cells and Galectin-3 (45) • LAMP1 down-regulation using shRNA in B16F10 murine melanoma cells, decreases induction of	• Data supported by studies showing increased LAMP1 expression on plasma membrane of highly metastatic compared to poorly metastatic cells • Associated with increased expression of carriers for polyLacNAc that can represent ligand structures to cell-adhesion molecules • However, role of LAMP1 in adhesion to the ECM and in ECM remodeling is indirect, since it uses

	MMP9 expression by p38 MAPK signaling, activated by Galectin-3 binding to the polyLacNAc present on LAMP1 (54)	Galectin-3 as mediator, giving more importance to the role of LAMP1 as carrier of polyLacNAc rather than protein itself. Other proteins can also be carriers of these modifications rendering role of LAMP1 in ECM regulation not exclusive (45; 54)
Metastasis (50; 53)	• Anti-LAMP1 antibodies proved to reduce lung metastasis of murine melanoma B16F10 cells in 4 mice	• Data supported by previous studies showing increased LAMP1 expression correlating with metastatic potential of human colon carcinoma and melanoma cells, and by silencing experiments linking LAMP1 expression with the metastatic potential • Absence of direct involvement diminishes possible therapeutic potential of LAMP1 targeting
Cancer cell migration (51; 52)	• LAMP1 found as a BR96 antigen expressed on the cell surface domains responsible for locomotion (51) • FUT1 reported to be able to fucosylate LAMP1, thereby influencing lysosomes localization and promoting cell migration (52)	• The link between LAMP1 expression and migration is not direct, but controlled by LAMP1 polylactosamine modifications and fucosylation, responsible for the binding to key antigens for migration such as BR96 (51-52)
Drug resistance (66; 67; 68)	• Increased LAMP1 protein expression shown in RMS cells resistant to AS-DACA (66) and in renal and colorectal cancer cells resistant to TKIs (67) • Higher LAMP1 expression found in human sarcomas associated with relapse, and its direct role in increasing lysosomal exocytosis was found to be responsible for promoting invasion and doxorubicin-resistance in human sarcomas	• Increased LAMP1 protein expression used as a proxy for increased lysosomal capacity, without clearly stating the molecular mechanism involved in this process (66-67) • In contrast, detailed analysis of the role played by LAMP1 in lysosomal exocytosis is clearly stated (68)

Abbreviations: AML, acute myeloid leukemia; AS-DACA, N- [2-(Dimethylamino) ethyl] Acridine-4-CarboxAmide; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; GESA, gene-set enrichment analysis; OS, overall survival; polyLacNAc, poly-N-AcetylLactosamines; RMS, rhabdomyosarcoma; TCGA, The Cancer Genome Atlas; TKIs, tyrosine kinase Inhibitors

Table 2: Summary of cancer-associated functions for CD107b/LAMP2 [Lysosome Associated Membrane Protein-2]

Pro-tumorigenic roles	Evidence	Strength / Weakness of the Evidence
Cancer pathogenesis (78; 80)	• Increased LAMP2 protein expression reported in poorly differentiated human gastric adenocarcinoma relative to adjacent gastric mucosal tissues (78) • *LAMP2* gene is located in a region involved in BCL1/JH t(11;14) (q13;q32) translocation found in multiple myeloma patients (80)	• LAMP2 protein expression increase used as a proxy for autophagy-lysosome signaling with no clear indications on its specific role in the signaling • Conflicting data regarding role of autophagy-lysosome circuitry in cancer pathogenesis (78) • Functional studies supporting pathogenic significance of LAMP2 in multiple myeloma still missing (80)
Cancer cell migration (52; 77)	• LAMP2 modification by FUT1 reported able to control localization of lysosomes, which often shift from perinuclear to peripheral compartment in invasive cancer (52) • LAMP2 protein highly expressed in invasive OVISE human ovarian clear cell adenocarcinoma cells, and ANXA4 knock-out decreased LAMP2 protein expression and migration (77)	• LAMP2 is not directly involved in the regulation of migration, but rather its modification by FUT1 plays a more important role (52). • A direct LAMP2 knock-out experiment is needed to confirm its possible direct involvement in ovarian cancer cells migration (77)
Support early cancer growth (49)	• LAMP2 expression on plasma membrane supported early breast cancer progression by acting as protective shield against acidic extracellular microenvironment	• Relevance for a LAMP2 role in survival within acidic microenvironment supported by strong data from both breast cancer cell lines and patients • Exact molecular mechanisms involved in LAMP2 protective action not addressed in the reported study and are not yet discovered
Adhesion of cancer cells to ECM, basement membrane and endothelium (45)	• LAMP2 observed by flow cytometry on cell surface of A2058, HT1080 (human fibrosarcoma) and CaCo-2 (human colon adenocarcinoma) cells and interaction with Galectin-3 reported	• Data supported by previous studies but the fact modifications of LAMP2 rather than their expression are reported as causal link with ECM adhesion diminishes the therapeutic potential of their targeting
Drug resistance (67)	• Increased protein expression of LAMP2 reported in renal and colorectal cancer cells resistant to TKIs (67)	• Study didn't a provide data regarding mechanisms involved in lysosomal control exerted by LAMP2 and how this could lead to increased drug secretion
CMA activation (81; 82)	• Ectopic expression of LAMP2A isoform, through its key action on CMA able to support cell survival upon oxidative stress; conversely, its inhibition promoted apoptosis and doxorubicin-resistance in breast cancer cells (81) • Inhibition of LAMP2A blocked constitutive activation of CMA and led to the reduction of cell proliferation, the growth of preexisting tumors and promoted metastatic potential of lung cancer cells (82)	• LAMP2A key role in cancer supported by high expression in patient-derived invasive carcinoma compared with adjacent tissues and in several cancer cell lines • Given its direct control on CMA, LAMP2A inhibition could represent a very promising strategy for sensitizing cancer cells to chemotherapy (81; 82)

Abbreviations: CMA, chaperone-mediated autophagy; ECM, extracellular matrix; TKIs, tyrosine kinase inhibitors.

Table 3: Summary of cancer-associated function for DC-LAMP/LAMP3 [Lysosome Associated Membrane Protein-3]

Pro-tumorigenic roles	Evidence	Strength / Weakness of the Evidence
Metastasis induction (106; 95; 112)	• Ectopic over-expression of LAMP3 in a uterine cervical cancer cell line (TCS), led to a higher migratory potential (106) • In SCID mice 82% (9/11) of injected LAMP3 over-expressing TSC cells efficiently generated metastases (primarily to liver and lung) compared to 9% (1/11) of controls (106) • LAMP3 detection by RT-qPCR and IHC in lymph node metastases from cervical carcinoma patients revealed distant metastasis formation associated with higher expression levels of LAMP3 (106) • Increased migration potential of breast cancer-derived cells correlated with higher basal LAMP3 expression levels. LAMP3 knockdown resulted in decreased migration potential of MDA-MB-231 cells after exposure to 1% O_2. Moreover, MDA-MB-231-derived spheroids depleted of LAMP3 showed reduced migratory properties and lower invasion into collagen (95). • Patients with breast cancer with soft tissue metastases showed higher LAMP3 mRNA expression compared with ones with non-soft tissue or bone metastases (p=0.034) (112)	• Results obtained *in vitro* also supported by *in vivo* experiments. However, these results were based on over-expression experiments and therefore rely on excessive expression levels and need to be further validated. However, data were also confirmed by analyses on human patient samples (106) • A stronger migration potential of LAMP3 expressing cells also found in breast cancer-derived cell lines and spheroids, structures that represent a more physiologic model of the disease (95)
Lymph node metastasis (104; 110)	• Despite variability among samples, high level of LAMP3 mRNA found in lymph node-positive breast cancer patients (n=183; p=0.019) and ER/PR-negative tumors (p<0.001) (104) • Loco-regional recurrences in patients with breast cancer who underwent lumpectomy and radiotherapy found more frequently in those whose tumors had higher LAMP3 mRNA levels (104) • IHC staining in biopsies from patients with HNSCC found high expression of LAMP3 restricted to normoxic regions of tumors and correlated with occurrence of lymph node metastasis (110). Moreover, worse metastasis-free survival observed in patients whose tumors showed higher levels of LAMP3 (110)	• Data underline relevant role of LAMP3 in tumor progression and metastatic spread including patient-derived samples both from breast cancers (104) and HNSCC (110) • Surprisingly, same investigators reported controversial observation that while LAMP3 expression is associated with hypoxic regions in breast cancer tumors (104), it is limited to normoxic regions in HNSCC (110)
Poor overall survival of patients (105; 106; 107; 108)	• TMA of gastric (n=750) and colorectal (n=479) tumors, found LAMP3 expression significantly higher in tumors compared to normal or benign tissues. In both cancer types, significant association between high LAMP3 levels, tumor stage and poorer OS with HR of 2.8 and 2.9, also confirmed with multivariate analysis (HR=2.8 and 2.6). • Study conducted on tumors from 24 patients with stage I or stage II cervical cancer who underwent radical hysterectomy reported high LAMP3 mRNA levels associated with poorer prognosis and	• Remarkable association between high LAMP3 levels in tumors, clinical features and OS in patients with diagnosis of gastric as well as colorectal cancer • Relevance of results from patients with cervical cancer limited by smaller number of patients • Significant correlation between LAMP3 and TP53 expression was shown in

	higher mortality • TMA from 117 LSCC tumors found stronger LAMP3 signal associated with worse tumor stage (p=0.029), bigger size (p=0.012) and poorer prognosis (HR=5.706) • mRNA levels in 157 ESCC patients and 50 uninvolved normal tissues and protein level by IHC in 46 paired normal and cancerous tissues reported elevated LAMP3 levels correlated with OS (HR = 1.90) and DFS (HR = 1.80) • Increased expression of LAMP3 in cancer tissues correlated well with DNA Copy Number Amplification (observed in 35/50 cases).	LSCC, even if authors considered LAMP3 and TP53 as independent prognostic markers for LSCC • Taken collectively these studies, while relevant, reported retrospective analyses on human samples and the conclusions drawn might not apply to the general population. Moreover, there was not a direct impact on the therapeutic strategy used and the OS
Resistance to hormonal therapy (112)	• In MCF7 cells silencing of LAMP3 increased sensitivity to tamoxifen. Observation linked to activation of autophagy, a process associated with tamoxifen resistance. Indeed, tamoxifen induced LAMP3 mRNA levels, leading to resistance • LAMP3 mRNA levels 7-fold higher in tamoxifen-resistant MCF7 cells relative to tamoxifen-sensitive counterparts • In tumors of patients with advanced breast cancer treated with tamoxifen, higher LAMP3 expression associated with shorter PFS (p=0.003) and post-relapse OS (p=0.040)	• Inhibition of autophagy by silencing of associated genes such as MAP1LC3B, ATG5, and BECN1 resulted in enhanced sensitivity to tamoxifen, suggesting impact of LAMP3 on autophagy is crucial step in tamoxifen resistance. • LAMP3 inhibition may be clinically relevant to hinder tamoxifen resistance in breast cancer
Resistance to radiation therapy (114)	• Silencing of LAMP3 (along with PERK and ATF4, two other members of UPR during hypoxia) sensitized MDA-MB-231 breast cancer cells to radiation therapy. This result seemed related to an attenuated DNA damage response during radiation when LAMP3 was down regulated by siRNA as measured by the quantification of □-H2AX foci. Therefore, resistance to radiotherapy can be driven by up-regulation of LAMP3 (and PERK and ATF4) through UPR pathway and relies on an increase of DNA repair process • Effect more evident with MDA-MB-231 cells compared to MCF7 breast cancer cells with wild-type p53 - suggesting presence of functional p53 may reduce effect of LAMP3 knock-down	• The specific mechanism underlying the LAMP3-dependent radio-resistance not completely elucidated and can rely on autophagy, as shown for resistance to hormonal therapy • Other evidence indicates MDA-MB-231 cells (but not HCT116) can be sensitized by treatment with the autophagy inhibitor chloroquine. Thus, these effects may be cancer type-dependent
Resistance to chemotherapy (115)	• Research suggests LAMP3 may be a direct target of miR-205, a miRNA down-regulated during EMT in prostate cancer • miR-205 impaired autophagy through reduction of lysosome-associated proteins LAMP3 and RAB27A, thus enhancing the cytotoxic effects of cisplatin in prostate cancer cells • Similar effects seen with silencing of LAMP3 with synthetic oligonucleotides, confirming putative role of LAMP3 expression in the resistance to cisplatin	• Effects on LAMP3 based on *in silico* predictions and indirect measurements, but did not provide direct evidence of miR-205 binding to LAMP3 mRNA • While miR-205 repression or loss in prostate cancer patients is well established expression of LAMP3 in the same patients has not been evaluated

Abbreviations: DFS, disease-free survival; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; LSCC, laryngeal squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor; TMA, tissue microarray; UPR, unfolded protein response

Table 4: Summary of cancer-associated functions for CD68/Macrosialin/LAMP4 [Lysosome Associated Membrane Protein-4]

Pro-tumorigenic roles	Evidence	Strength / Weakness of the Evidence
Marker for pro-tumorigenic TAMs in malignant uveal melanoma (135)	• CD68/Macrosialin/LAMP4+ tumor infiltrating macrophages identified in 83% of 167 malignant uveal melanomas • Abundance of CD68/Macrosialin/LAMP4+ TAMs associated with parameters of known poorer prognosis, such as largest basal diameter (LBD) heavy pigmentation and high microvascular density • Melanoma-specific mortality rate 10 years from diagnosis higher in patients with larger number of CD68/Macrosialin/LAMP4+ macrophages	• Evidence regarding enrichment of CD68/Macrosialin/LAMP4 macrophages in uveal melanoma and its association with aggressiveness is strong. However, as expected from functions identified thus far for CD68/Macrosialin/LAMP4 protein, there is not a direct role in cancer cells for CD68/Macrosialin/LAMP4, rather it is only relevant its impact on TAMs, where it represents one of the most used markers
Associated with TAMs in Hodgkin's lymphoma (137; 140)	• CD68/Macrosialin/LAMP4 expression in TAMs analyzed by IHC on TMAs from lymph nodes of 166 patients with classical Hodgkin's lymphoma (cHL) including 79 for whom treatment failed. Patients whose tumors were "enriched" with CD68/Macrosialin/LAMP4+ TAMs had at least 8-times lower progression-free survival compared to patients whose tumors had very low levels of CD68/Macrosialin/LAMP4+ TAMs (<5%) (137). Moreover, CD68/Macrosialin/LAMP4 expression revealed to be more effective with respect to the conventional International Prognostic Score (IPS) value used for cHL samples (137) • In two series of advanced cHL patients (n=266 and n=103) CD68/Macrosialin/LAMP4 expression used as macrophage marker in IHC along with CD163, LYZ and STAT1 • CD68/Macrosialin/LAMP4 the only marker associated with clinical features (140)	• At least two different studies from three independent patients' cohorts proved the prognostic value of CD68/Macrosialin/LAMP4 positivity within tumor tissues of cHL patients, suggesting effectiveness and value of this measurement. Weakness of the first observation is the reduced number of cHL cases with very low levels of CD68/Macrosialin/LAMP4+ TAMs and low risk patients (137) • Interestingly, the fact that only CD68/Macrosialin/LAMP4 staining (among TAM markers) was significantly associated with clinical parameters underlies possibility CD68/Macrosialin/LAMP4 could be also expressed by cancer cells (see below).
Marker for TAMs in advanced thyroid cancer (138)	• CD68/Macrosialin/LAMP4 used as a marker for TAMs in thyroid cancers. Using TMAs observed that TAMs density increased with aggressiveness of thyroid cancer; specifically, from 27% in WDTC (n=33), to 54% in PDTC (n=37) and 95% in ATC (n=20)	• Remarkable correlation between LAM CD68/Macrosialin/LAMP4+ status and tumor progression (increased grade, invasion property and decreased survival) in thyroid cancers
Marker for TAMs in TNBCs (139)	• CD68/Macrosialin/LAMP4+ TAMs found in 71.5% of TNBCs • Increased presence of TAMs correlated with poorer prognosis and was associated with enhanced expression of IL-6 and CCL-5 diffusible factors	• Another report supporting association of high infiltration of TAMs (measured as CD68/Macrosialin/LAMP4+ cells) with cancer progression and poorer prognosis in TNBCs

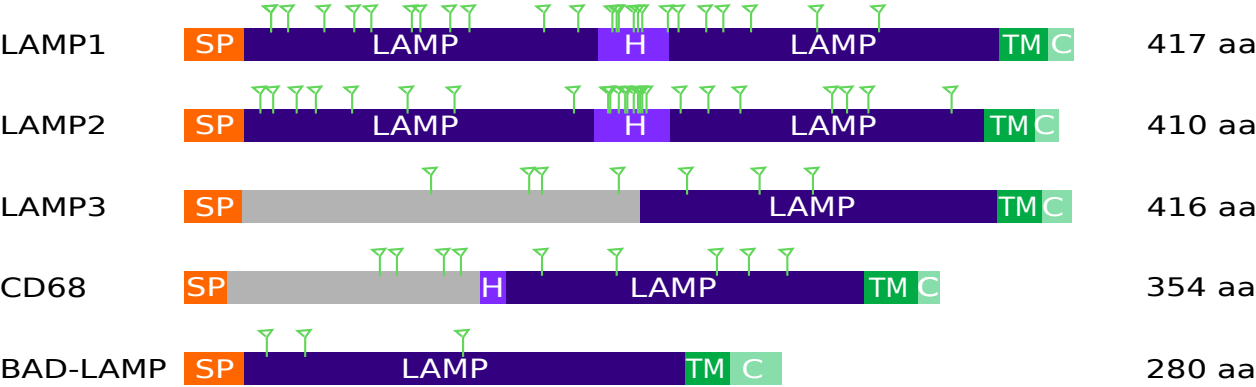
Associated to poor prognosis (148)	• CD68/Macrosialin/LAMP4 immunostaining detected in histological sections of 51 primary astrocytic tumors (11 benign astrocytomas, 40 malignant tumors) and 8 relapses • LA CD68/Macrosialin/LAMP4 signal significantly higher in malignant tumors compared to benign ones (p=0.036) • Higher staining score for CD68/Macrosialin/LAMP4 associated with a poorer OS for all the tumors analyzed (p<0.01), with remarkable enrichment for anaplastic astrocytomas (p=0.021)	• CD68/Macrosialin/LAMP4 can also be considered a marker for microglia and in gliomas the infiltration of macrophages and microglia has been established. This is in line with the characteristics mentioned above • Notably, authors showed presence of CD68/Macrosialin/LAMP4+ also on the surface of cancer cells as well as in U87 glioblastoma-derived cell line

Abbreviations: ATC, anaplastic thyroid cancer; IHC, Immunohistochemistry; OS, overall survival; PDTC, poorly differentiated thyroid cancer; TAMs, tumor-associated macrophages; TMAs, tissue micro-arrays; TNBCs, triple negative breast cancers; WDTC, well-differentiated thyroid cancer

Table 5: Summary of cancer-associated functions for BAD-LAMP/LAMP5 [Lysosome Associated Membrane Protein-5], C20orf103

Pro-tumorigenic roles	Evidence	Strength / Weakness of the Evidence
Associated with poor prognosis (156)	• BAD-LAMP/LAMP5 identified through gene expression profiling with microarrays on FFPE samples along with 7 other genes as part of the GCPS as a high-risk gene for recurrence in three different cohorts of stage II gastric cancer patients who underwent adjuvant chemo-radiotherapy • Higher expression of BAD-LAMP/LAMP5 associated with poorer prognosis	• The GCPS was validated in more than 700 stage II GC patients and proposed for the routine usage in the clinic. The increased BAD-LAMP/LAMP5 expression was however significantly higher in stromal cells rather than in cancer cells, highlighting a more important role for BAD-LAMP/LAMP5 in the tumor microenvironment

Abbreviations: FFPE, formalin-fixed paraffin-embedded; GC, gastric cancer; GCPS, ”Gastric Cancer Prognostic Score”


LAMP1
SP
LAMP
H
LAMP
TM
C
417 aa
LAMP2
SP
LAMP
H
LAMP
TM
C
410 aa
LAMP3
SP
LAMP
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C
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CD68
SP
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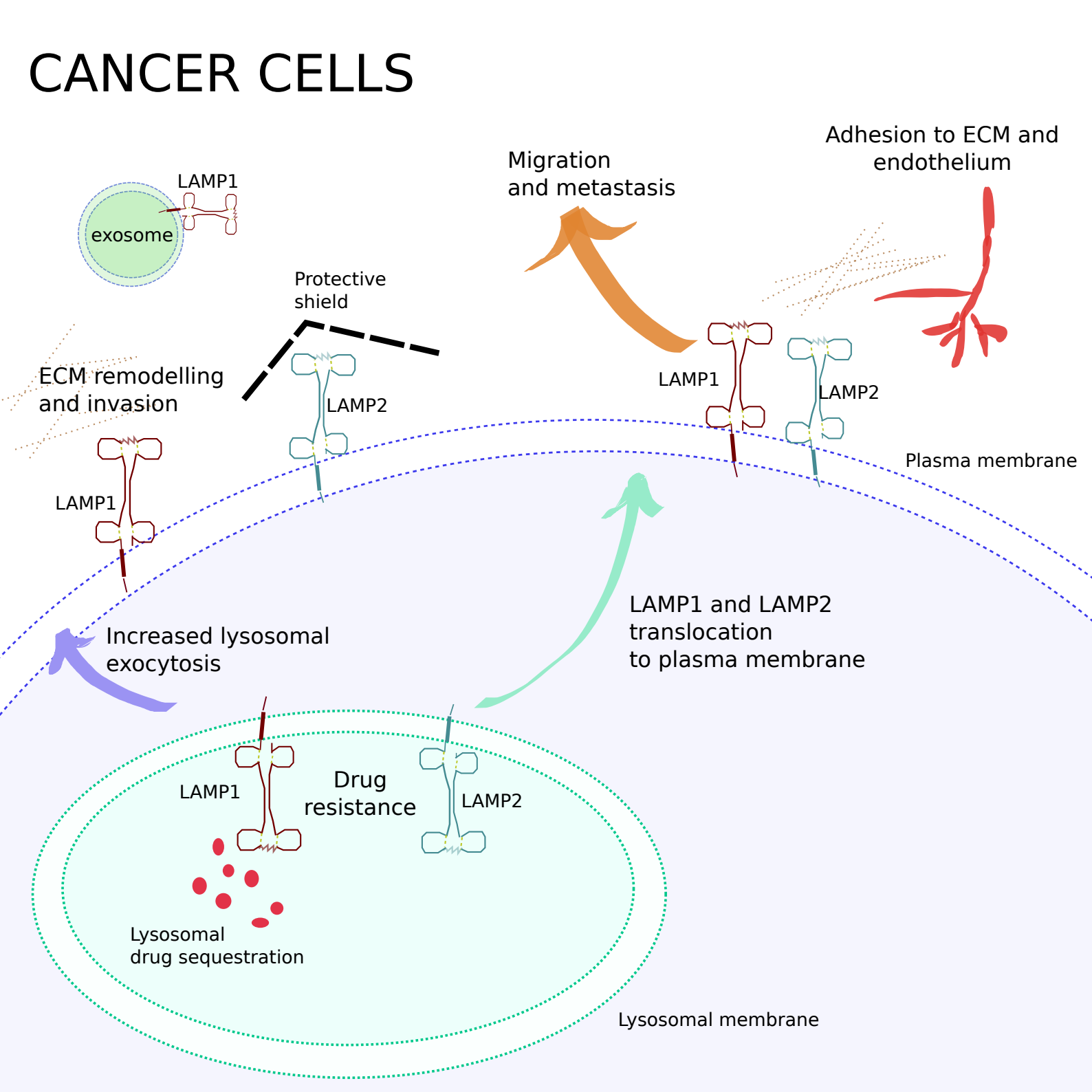
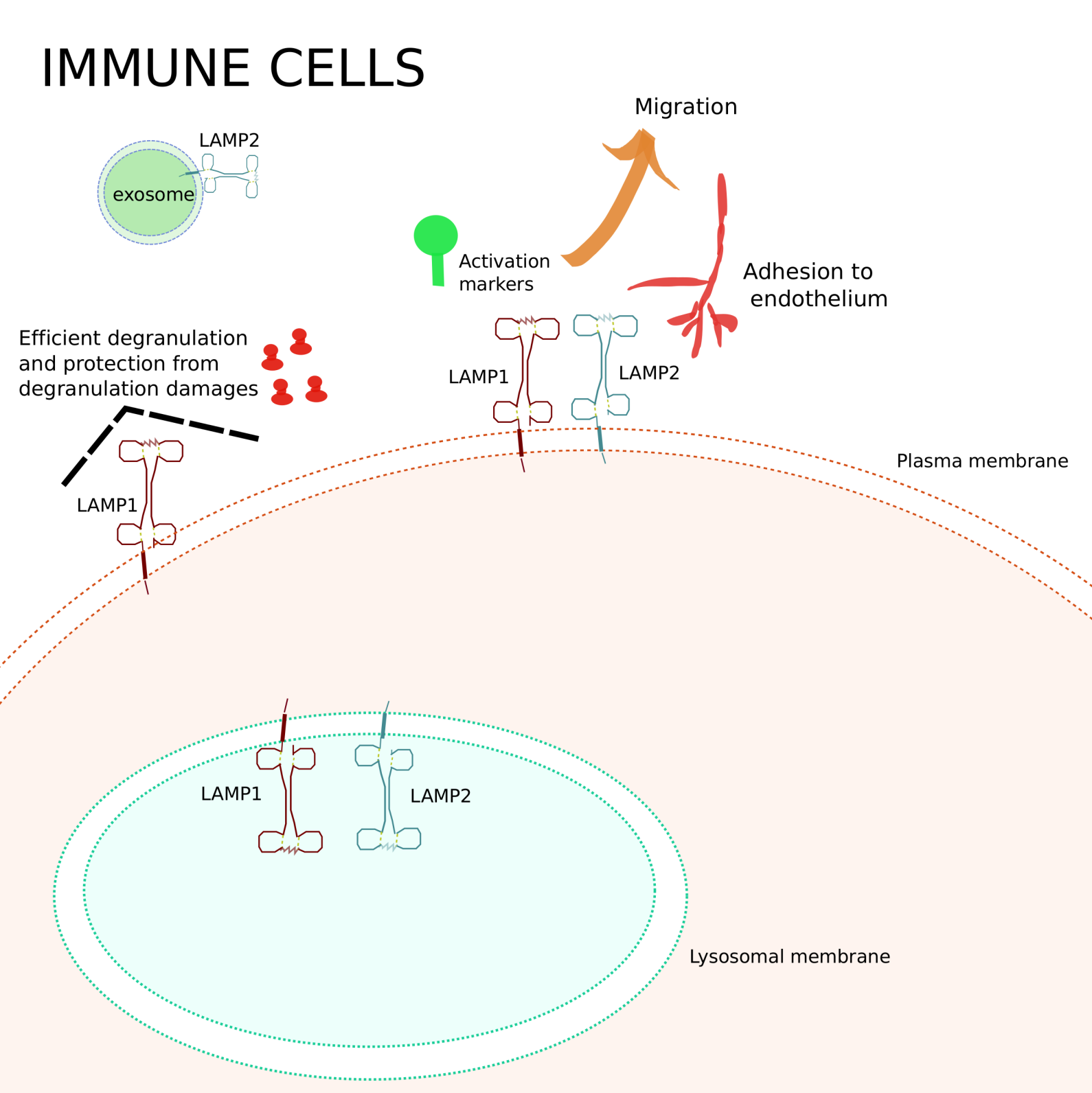
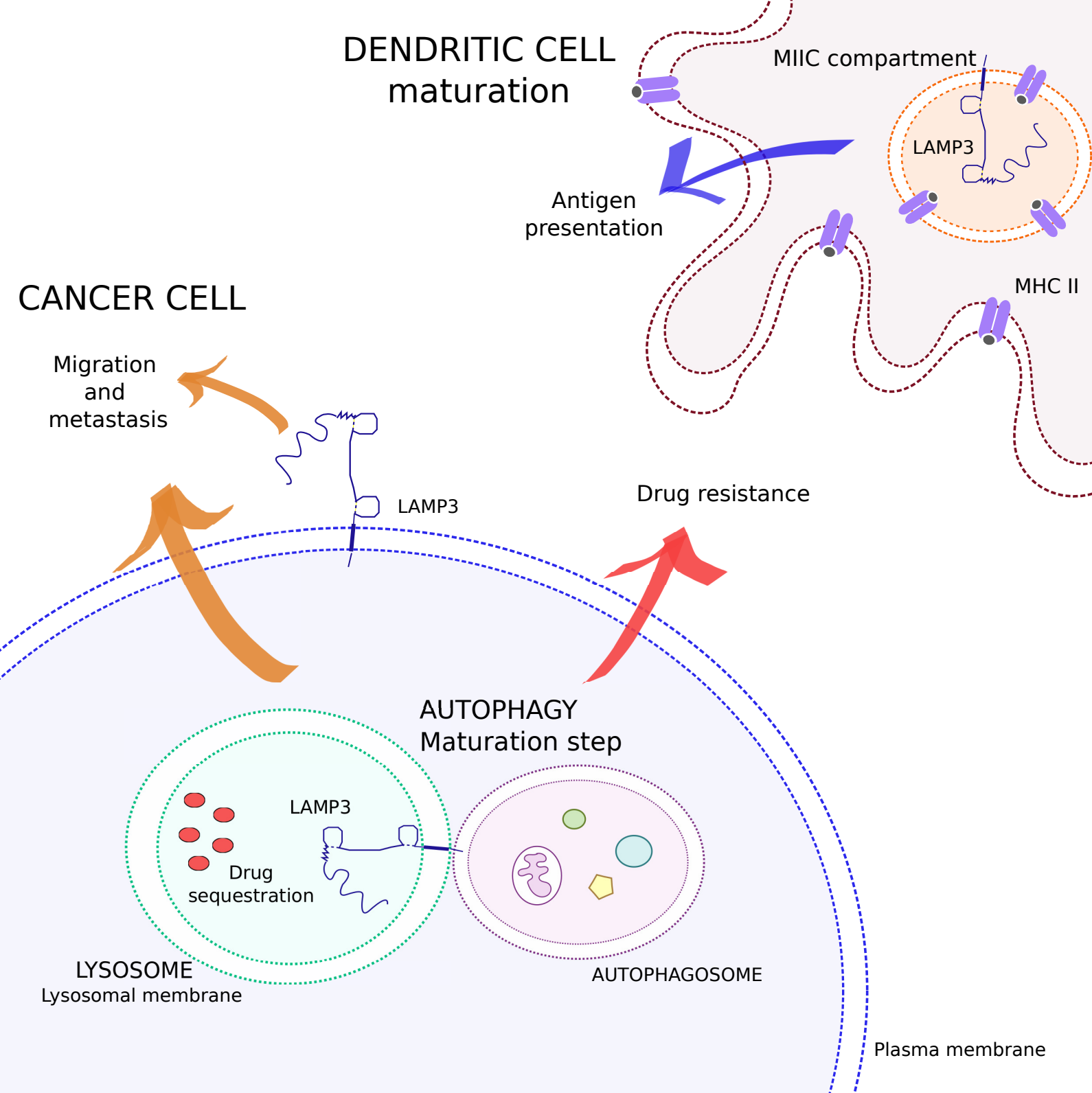
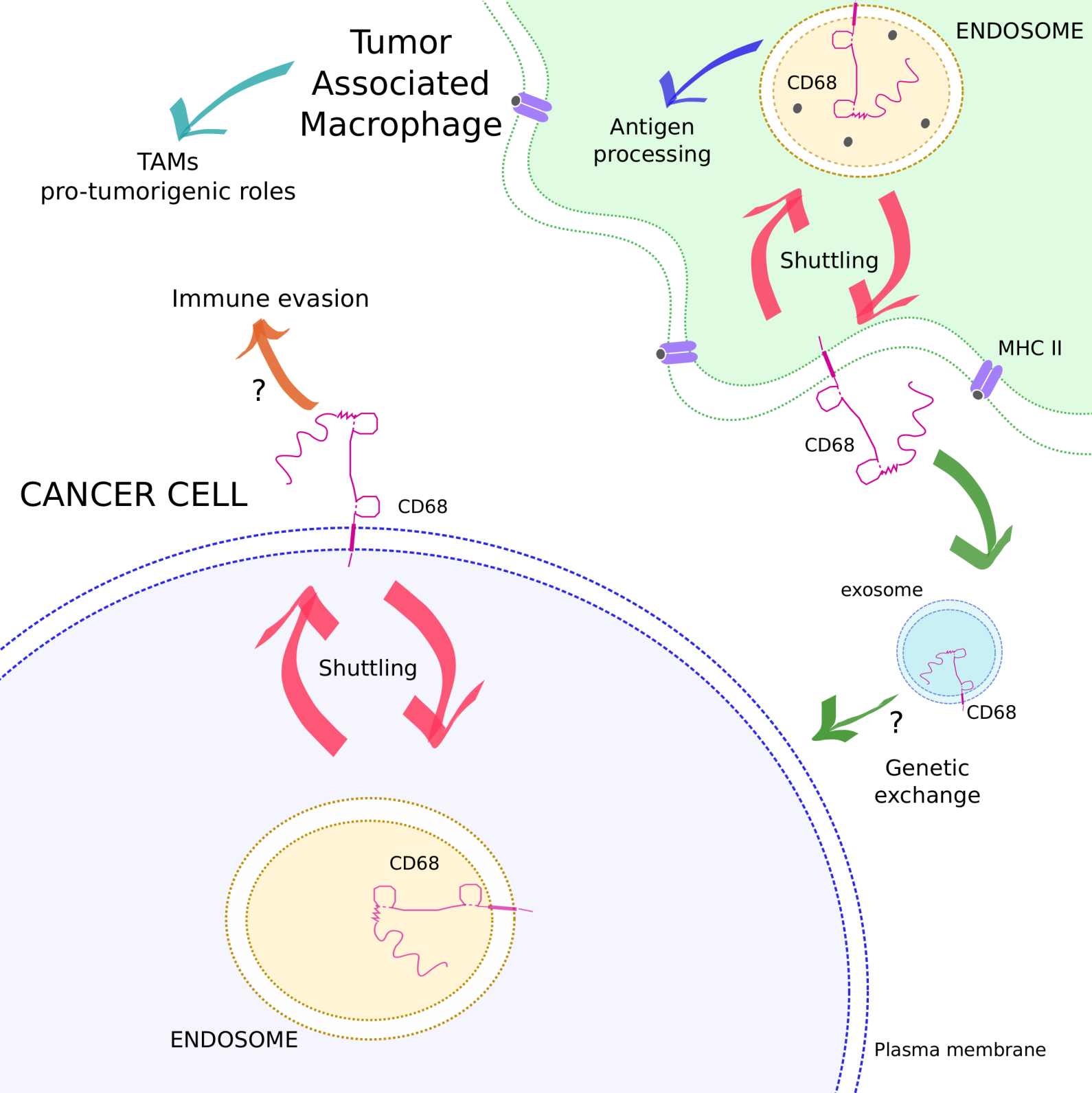
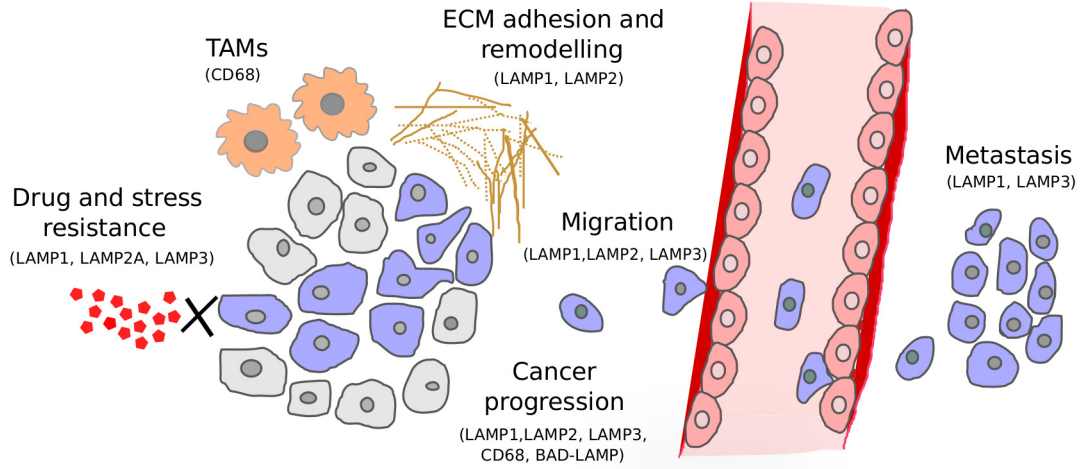
C
354 aa
BAD-LAMP
SP
LAMP
TM
C
280 aa


CANCER CELLS
LAMP1
exosome
Migration
and metastasis
Adhesion to ECM and
endothelium
Protective
shield
ECM remodelling
and invasion
LAMP2
LAMP1
LAMP1
LAMP2
Plasma membrane
LAMP1 and LAMP2
translocation
to plasma membrane
Increased lysosomal
exocytosis
LAMP1
Drug
resistance
LAMP2
Lysosomal
drug sequestration
Lysosomal membrane


IMMUNE CELLS
LAMP2
exosome
Migration
Activation
markers
Adhesion to
endothelium
Efficient degranulation
and protection from
degranulation damages
LAMP1
LAMP2
LAMP1
Plasma membrane
LAMP1
LAMP2
Lysosomal membrane


DENDRITIC CELL
maturation
MIIC compartment
LAMP3
Antigen
presentation
MHC II
CANCER CELL
Migration
and
metastasis
LAMP3
Drug resistance
AUTOPHAGY
Maturation step
LAMP3
Drug
sequestration
LYSOSOME
Lysosomal membrane
AUTOPHAGOSOME
Plasma membrane


Tumor Associated Macrophage
TAMs pro-tumorigenic roles
ENDOSOME
CD68
Antigen processing
Shuttling
MHC II
Immune evasion
?
CD68
CANCER CELL
CD68
exosome
CD68
?
Genetic exchange
Shuttling
CD68
ENDOSOME
Plasma membrane


TAMs
(CD68)
ECM adhesion and
remodelling
(LAMP1, LAMP2)
Drug and stress
resistance
(LAMP1, LAMP2A, LAMP3)
Migration
(LAMP1,LAMP2, LAMP3)
Metastasis
(LAMP1, LAMP3)
Cancer
progression
(LAMP1,LAMP2, LAMP3,
CD68, BAD-LAMP)

CONFLICT OF INTEREST STATEMENT

There are not any conflicts of interest to disclosure.