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EMMPRIN is an emerging protein capable of regulating cancer hallmarks

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Abstract. – EMMPRIN, also known as Basigin or CD147, is a transmembrane glycoprotein member of the immunoglobulin superfamily. It is expressed basally in cells that regulate physiological processes of the cardiovascular, nervous, and immune systems. However, EMMPRIN is also capable of interacting with different proteins, like VEGFR, SMAD4, Integrin, MCT, CyPA, GLUT1, CAIV, Annexin II, Cav-1, CAML, etc., and regulating signaling pathways that stimulate the cell processes of proliferation, apoptosis, metabolism, adhesion, invasion, migration, metastasis, tumor immune response, and angiogenesis processes, which favors the development of different types of cancer. EMMPRIN is the first protein reported that favors cancer development due to its ability to interact with extracellular, intracellular, and membrane proteins. In conclusion, EMMPRIN regulates several proteins associated with the development of tumor processes. Therefore, blocking the expression of EMMPRIN can be a therapeutic target, and the analysis of its expression can be used as an important biomarker in cancer.

Key Words:
EMMPRIN, Cancer, Proliferation, Metabolism, Metastasis.

Introduction

Cancer is the second leading cause of death globally; in 2020 it caused approximately one in six deaths. The most common types of cancer are breast (2.26 million cases), pulmonary (2.21 million cases), colorectal (1.93 million cases), prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases), and gastric (1.09 million cases). The cancers that caused the highest number of deaths were lung cancer (1.8 million deaths), colorectal cancer (935,000 deaths), liver (830,000 deaths), gastric (769,000 deaths), and breast (685,000 deaths). Cancer is produced by transforming normal into tumor cells[1,2]. Any normal cell type can transform into a malignant tumor, and the main feature is uncontrolled division. However, alterations are also observed in the processes of apoptosis, metabolism, migration, adhesion, metastasis, angiogenesis, etc[3,4]. The tumor cells present alteration in the expression of several proteins, among them the inducer of extracellular matrix metalloproteinases (EMMPRIN), known as Basigin or CD147, type I transmembrane glycoprotein of the immunoglobulin superfamily, is expressed in a basal manner in epithelial cells, fibroblasts, peripheral blood mononuclear cells, trophoblasts, hepatocytes[5-10]. It plays an essential role in cardiovascular, nervous, and immune[5,8,11-13]. In addition to its participation in physiological processes, EMMPRIN can interact with different proteins such as integrins, cyclophilins, caveolins, E-cadherin, MCT4, etc., and regulate signaling pathways that participate in the stimulation of the development of tumor processes[14-18]. In different types of cancer, such as pancreatic cancer[19], bladder[20], hepatocellular[14], ovary[21,22], lung[23], breast[24,25], cervical[26,27], prostate[17], oral[28], melanomas[29] EMMPRIN overexpression has been observed. In these cancers, it modulates cell metabolism, adhesion, and facilitating proliferation[15], invasion[14,30], migration[28], metastasis[29,31], angiogenesis[18,32], and regulation of the

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immune system[8,33]. Therefore, this literature review aimed to analyze the role that EMMPRIN plays in the regulation of cancer hallmarks.

EMMPRIN

EMMPRIN, also called Basigin (BSG) or CD147, is a transmembranal glycoprotein belonging to the immunoglobulin superfamily and functions as an inducer of matrix metalloproteinases (MMP)[34]. It is encoded by the BSG gene located on chromosome 19.13.3 and consists of ten exons that span ~ 12 kb 8404035[35]. In 1982, EMMPRIN was initially purified from the LX-1 human lung cancer in the membrane[36]. The EMMPRIN receptor has 269 amino acids and comprises a short intracellular region, an extracellular region, and a transmembrane region[37]. It is a highly glycosylated protein that recognizes various molecules in a *cis* or *trans* form; trans binding to a soluble protein or a protein from adjacent cells and cis to membrane proteins from the same cell[35] (Figure 1a).

Non-glycosylated EMMPRIN has a molecular weight of 27 kDa, while the glycosylated form has a molecular weight between 43 and 66 kDa. Glycosylated EMMPRIN exists in two forms: highly glycosylated EMMPRIN (HG-EMMPRIN) weighing ~ 40-60 kDa and low glycosylated EMMPRIN (LG-EMMPRIN) weighing ~ 32 kDa. HG-EMMPRIN contains complex-type carbohydrates sensitive to peptide N glycosidase F (PNGase F). In contrast, LG-EMMPRIN contains carbohydrates with a high content of mannose that is sensitive to endoglycosidase H (Endo H). Therefore, LG-EMMPRIN is the precursor of HG-EMMPRIN in ER, which requires further modification in the Golgi before being expressed on the cell surface[38]. EMMPRIN can dimerize in a *cis* manner; dimer formation occurs when EMMPRIN is highly glycosylated. Three glycosylation sites are observed in the crystal structure of EMMPRIN: Asn44 at the end of the B chain and Asn152/ Asn186 in the middle of the C´D loop and F chain, respectively[39].

Basigin Isoforms

The BSG gene encodes EMMPRIN; it has ten exons, presents four isoforms called Basigin 1 (BSG 1), Basigin 2 (BSG 2), Basigin 3 (BSG 3), and Basigin 4 (BSG 4). These isoforms are generated from alternative splicing and the use of alternate promoters. The first promoter for Basigin is upstream of exon 1 (alternative promoter), and the second is upstream of exon 2[40]. The extracellular region of CD147 can be variable, depending on the isoform[35].

The BSG 1 and BSG 2 isoforms are generated from the promoter upstream of exon 2; BSG 1 is the longest isoform; its translation begins from exon 2, presenting three immunoglobulin domains. BSG 2, unlike BSG 1, does not express exon 3, showing two immunoglobulin domains[35]. BSG 3 and 4 begin transcribing from the alternative promoter upstream of exon 1. BSG 3 is translated from exon 5 to 9, presenting a single immunoglobulin domain. BSG 4 is similar to BSG 3 but has a signal peptide in exon 1 and one single immunoglobulin domain[41] (Figure 1b).

Role of EMMPRIN in the Development of Cancer

Several studies show that EMMPRIN and its isoforms regulate cellular processes that favor cancer development, such as adhesion, metabolism, apoptosis, proliferation, invasion, migration, metastasis, angiogenesis, and immune response, from the interaction with various proteins[8,14-18,29,33] (Figure 2). Therefore, the participation of EMMPRIN in cellular processes related to tumor development is described below; the order of appearance of cellular processes is about the progression of cancer development.

EMMPRIN Promotes the Cell Proliferation

Cell proliferation is a process of cell division that increases the number of cells; it is a complex process and strictly controlled[42]. EMMPRIN is a critical protein in regulating proliferation; it is carried out from the union with molecules such as SMAD4, Cyclophilin A (CyPA), integrins, CD98hc, and MCT[15,16,43,44].

EMMPRIN interacts with SMAD4 or DCP4 by the MH2 domain of Smad4 with serine 252 phosphorylated in EMMPRIN. SMAD4 belongs to a family of signal transduction proteins[45], is a tumor suppressor, and inhibits epithelial cell proliferation[46]. The EMMPRIN-SMAD4 interaction leads to the inhibition of the SMAD4/p21 signal since the nuclear translocation of SMAD4 is avoided to regulate the transcription of p21, inducing an increase in proliferation[15].

CyPA is a natural ligand of EMMPRIN; CyPA is a protein with highly conserved peptidylprolyl

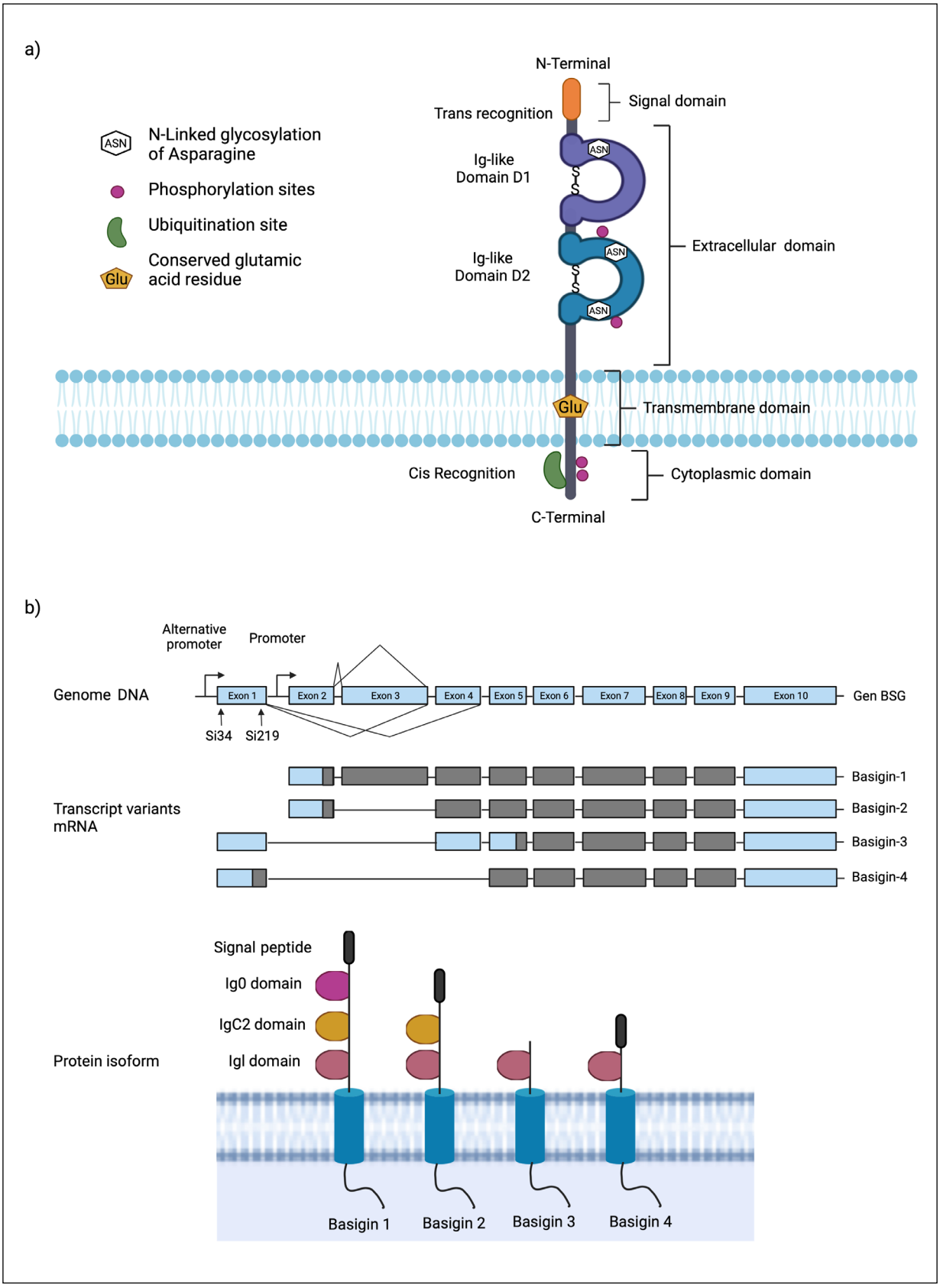

Figure 1. EMMPRIN structure scheme. **a)** Domains of the EMMPRIN structure essential to its function, **b)** EMMPRIN isoforms.

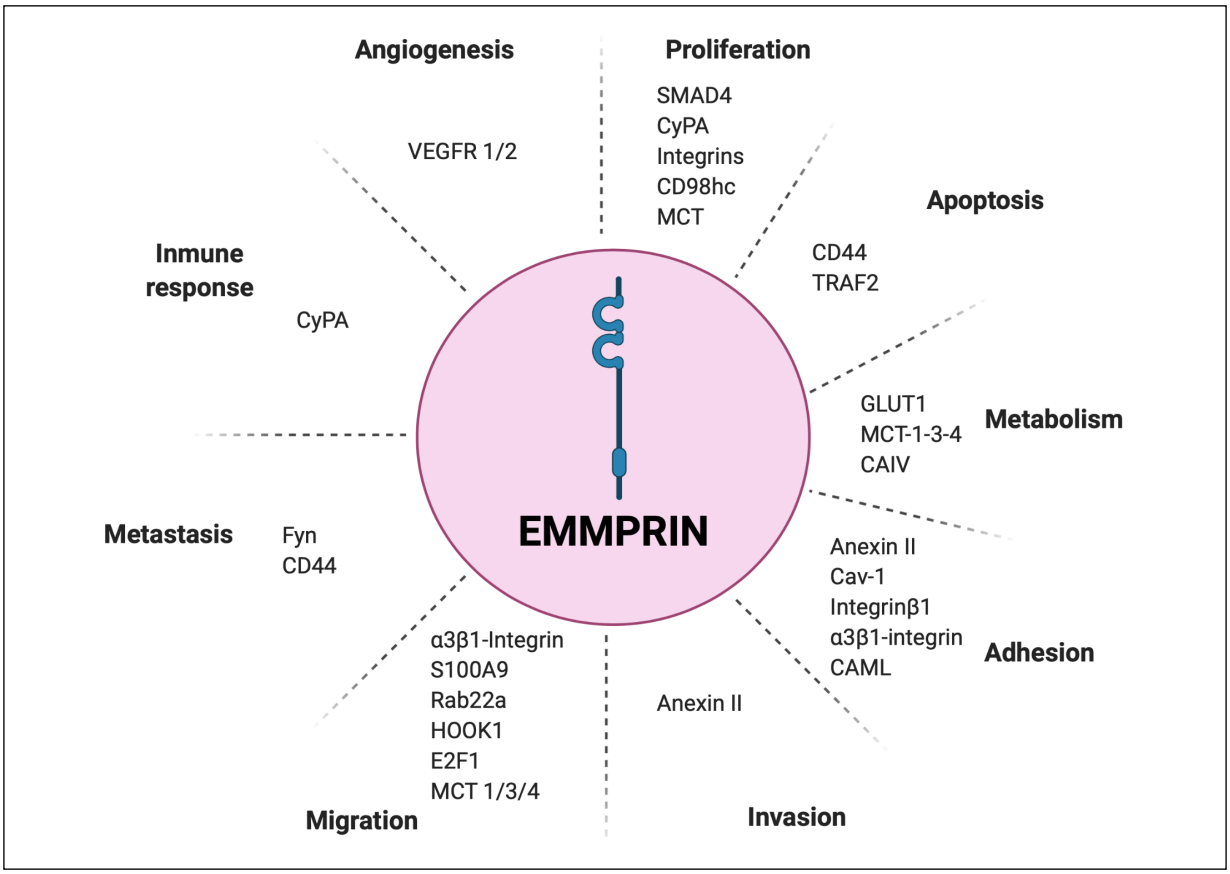

Figure 2. Direct interaction of EMMPRIN with proteins that participate in cancer development. VEGFR: Vascular Endothelial Growth Factor Receptor, MCT: Monocarboxylate transporter, CyPA: Cyclophilin A, TRAF: Tumor receptor-associated factor, GLUT: Glucose transporter, CAIV: Carbonic Anhydrase IV, CAML: calcium modulating cyclophilin, Cav-1: caveolins, HOOK1: Hook Microtubule Tethering Protein 1, E2F1: E2F Transcription Factor 1. This figure was created on BioRender.com.

isomerase activity and functions as an autocrine/paracrine chaperone molecule that facilitates the expression and activation of EMMPRIN in the cell membrane[12,47]. Binding between CyPA and EMMPRIN activates the ERK1/2, p38, and NF-kB signaling cascade downstream, promoting proliferation[48].

EMMPRIN also interacts with integrins, a family of transmembrane receptors composed of 18 α subunits and 8 β subunits[49]. Integrins activate various signaling pathways, which contribute to the regulation of cell proliferation[44]. By interacting with EMMPRIN, β1 integrins induce activation of the downstream FAK/cortactin pathway, inducing the proliferation of tumor cells linked to extracellular matrix (ECM)[44,49].

EMMPRIN and CD98hc (CD98 cell surface heterodimer heavy chain) form a complex in the cell plasma membrane of normal and tumor cells. Co-expression and binding of EMMPRIN to CD98hc promotes cell proliferation through the PI3K/Akt pathway[23]. However, EMMPRIN also binds directly with MCT, forming a super-complex in which more molecules are involved: MCT-EMMPRIN-CD98hc-LAT1, which also includes ASCT2 and EpCAM. There is also a direct association between EpCAM and 4F2hc in the complex and between LAT1 and 4F2hc. However, there is no direct crosstalk between EMMPRIN and LAT1 and between EMMPRIN and ASCT2. EMMPRIN favors the biosynthetic assembly of the MCT-EMMPRIN-4F2hc-LAT1 complex or exerts a stabilizing effect on each molecule once they are present on the cell surface. It favors the activation of the mTOR signaling pathway and increases the proliferation of tumor cells[19,50].

In addition to interacting directly with proteins to promote cell proliferation, EMMPRIN also increases proliferation by alternative pathways, in some cases unknown. A correlation between the expression of GSDMD and EMMPRIN has been demonstrated; inhibition of EMMPRIN expression decreases GSDMD expression. GSDMD overex-

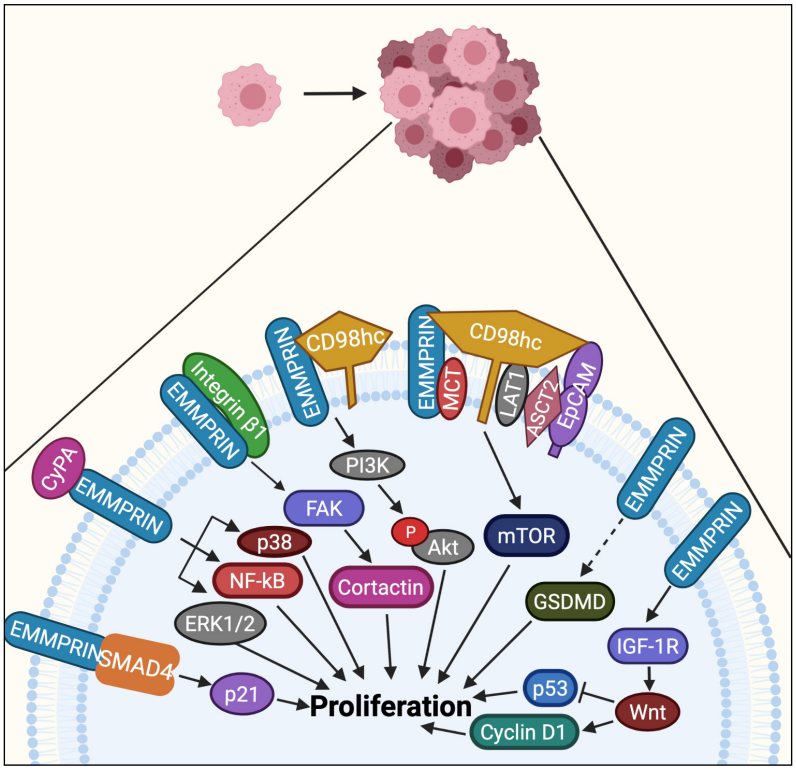

Figure 3. Regulation of proliferation by EMMPRIN. Black arrow: direct activation; T bar: inhibition of processes and dotted black arrow: activation through unknown/not displayed other molecules. ERK: extracellular signal-regulated kinases, NF-kB: Nuclear factor-kB, PI3K: Phosphoinositide 3-kinase, CD98hc: CD98 cell surface heterodimer heavy chain, mTOR: Mechanistic target of rapamycin, IGF-1R: insulin-like growth factor 1 receptor, FAK: Focal adhesion kinas, GSDMD: Gasdermin D, MCT: Monocarboxylate transporter, LAT: linker for activation of T cell, ASCT: Alanine, Serine, Cysteine Transporter, CyPA**:** Cyclophilin A**.** This figure was created using BioRender software.

pression is associated with larger tumor size[20,51,52]. EMMPRIN is related to activities of the cell cycle, cyclin D1, and cyclin E. It activates IGF-1R, a ubiquitous tyrosine kinase that regulates cell growth[53]. Activation of IGF-1R activates the Wnt pathway, inducing overexpression of cyclin D1 and reducing the expression levels of the tumor suppressor p53, thus promoting proliferation in tumor cells [24,54] (Figure 3).

EMMPRIN Inhibits the Apoptosis

Apoptosis is a highly regulated physiological process that maintains the balance between cell survival and death. Controlled apoptosis contributes to maintaining genomic integrity, while inhibition apoptosis promotes carcinogenesis[55]. Dysregulation of apoptotic pathways promotes tumorigenesis and makes the cancer cell resistant to treatments, including chemotherapy, radiotherapy and immunotherapies, they primarily act by activating cell death pathways including apoptosis in cancer cells, facilitating tumor development and metastasis[56]. EMMPRIN interacts with TRAF2, a factor known to regulate NFκB and extrinsic apoptotic signaling, but being bound to EMMPRIN, TRAF2 cannot activate apoptotic signaling[10].

EMMPRIN interacts directly with CD44, activating the JAK/STAT3 signaling pathway, generating an increase of Bcl-2, and inhibiting apoptosis[57]. It has been observed that EMMPRIN also forms a tetrameric complex with Xkr8 (two molecules of Xkr8 and two molecules of EMMPRIN). Xkr8 is essential to expose phospholipids during apoptosis. When the cell undergoes apoptosis, caspases cleave Xkr8, mixing phospholipids between the inner and outer shells of the plasma membranes, thereby exposing phosphatidylserine (PtdSer), which is exposed on the cell surface and is recognized by macrophages for phagocytosis of dead cells. By binding EMMPRIN to Xkr8, it inhibits the function of the Xkr8 and blocks PtdSer exposure during apoptosis, inhibiting apoptosis[58].

EMMPRIN is associated with the expression of insulin-like growth factor-binding protein 2 (IG-

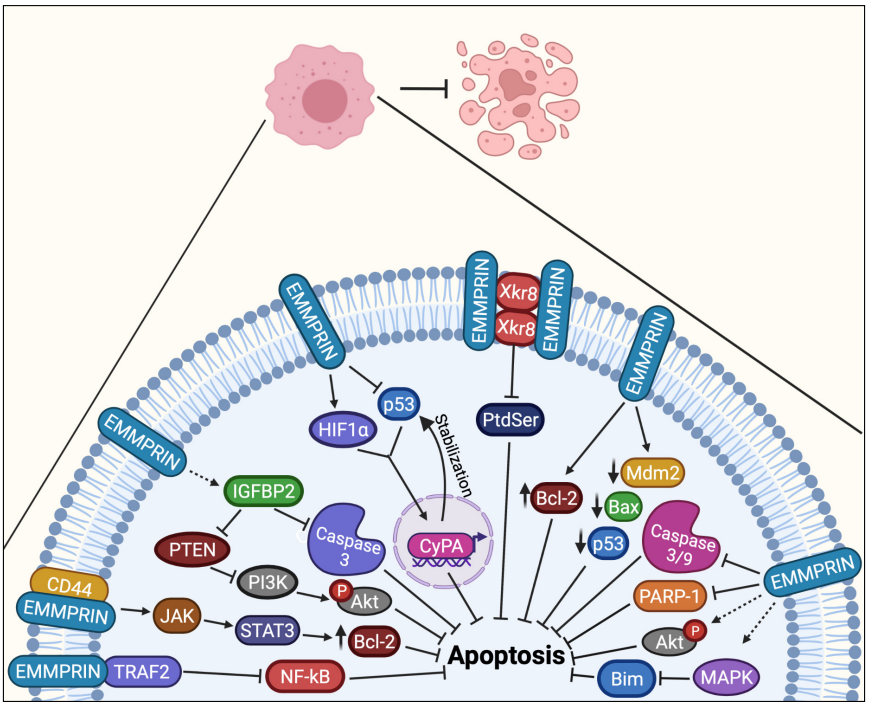

Figure 4. Regulation of apoptosis by EMMPRIN. Black arrow: direct activation; T bar: inhibition of processes and Dotted black arrow: activation through unknown/not displayed other molecules. TRAF2: tumor necrosis factor type 2 receptor-associated protein, STAT3: Signal transducers and activators of transcription 3, JAK: Janus kinases, Bcl: B-cell lymphoma, IGFBP: insulin-like growth factor binding proteins, HIF1α: hypoxia-inducible factor-1alpha, PtdSer: Phosphatidylserine, Mdm: Mouse double minute 2, Bax: BCL2 Associated X, PARP: Poly (ADP-ribose) Polymerases, MAPK: mitogen-activated protein kinases, Bim: Bcl-2-like protein. This figure was created on BioRender.com.

FBP2), which belongs to the IGF-binding protein family; it inhibits apoptosis by regulating caspase activation -3 and the PTEN/PI3K/Akt pathway[59,60]. Also, inhibition of CyPA and EMMPRIN expression active apoptosis[16]. EMMPRIN overexpression has also been associated with hypoxia. In this sense, EMMPRIN, being overexpressed, inhibits apoptosis through p53 and HIF1α, stabilizing p53 protein[61,62].

EMMPRIN increases Bcl-2 levels and reduces p53, Bax, and Mdm2 levels, inhibiting apoptosis[63] because Bcl-2 (B2 cell lymphoma gene family) is an anti-apoptotic protein. In contrast, Bax (Bcl-2-associated protein X) is a proapoptotic protein[64], p53 is a protein that promotes apoptosis, and MDM2 ubiquitin ligase E3, a negative regulator of p53 activity[65].

EMMPRIN reduces the expression of Caspases 3/9 and poly (ADP-ribose) polymerase (PARP-1). Caspases -3/9 are proteolytic enzymes that induce apoptosis, and PARP-1 releases the mitochondrial apoptosis-inducing factor and its translocation to the nucleus[66-68]. EMMPRIN also correlates with increased mitogen-activated protein kinase (MAPK) expression and Akt phosphorylation in HER2-positive breast cancer cells[66]. MAPK activation is related to apoptosis; in some cell lines, it promotes apoptosis, but in other cell lines, it inhibits apoptosis, while Akt is a serine-threonine kinase that inhibits apoptosis[69,70].

The expression of EMMPRIN is related to the reduction of Bim, a pro-apoptotic BH3 protein, through a MAPK-dependent pathway, which triggers resistance to anoikis, a form of apoptosis triggered by the lack of inappropriate interactions between the cell and the matrix[71] (Figure 4).

EMMPRIN Involvement in Energy Metabolism

Cellular energy metabolism is the bioprocess responsible for converting nutrients such as carbohydrates, lipids, and proteins into energy and biomass to maintain cell survival and proliferation[72]. EMMPRIN can improve the adaptation of tumor cells by positively regulating their metabolic pathways, which gives them a selective advantage during tumorigenesis and helps the cell to survive under stress conditions and proliferate to pathological levels. EMMPRIN regulates cell metabolism through its direct or indirect interaction with pro-

teins related to hypoxia, glycolysis, oxidative phosphorylation, and lipolysis[33,73].

EMMPRIN plays a crucial role in the metabolic adaptation of tumors to hypoxia. HIF-1α and Sp1 mediate the expression of EMMPRIN during hypoxia[74]. HIF-1 is a heterodimer consisting of a constitutively expressed HIF-1β subunit and an oxygen-sensitive HIF-1α subunit[75]. Under hypoxic conditions, HIF-1α binds to a conserved DNA consensus, termed the hypoxia-sensitive element (HRE), in the promoters of numerous hypoxia-sensitive genes. There are two binding sites for HIF-1 and three for Specificity protein 1 (Sp1) in the 3 'and 5' flanking regions of the EMMPRIN gene, respectively[21,76]. EMMPRIN also participates in the adaptation of the tumor to hypoxia, favoring other metabolic processes such as glycolysis through the interaction with GLUT1[77].

The direct interaction between EMMPRIN and GLUT1 has been demonstrated[78]. GLUT1 is a highly hydrophobic transmembrane protein that participates in the internalization of glucose, the interaction and overexpression of EMMPRIN with GLUT1 facilitates the entry of glucose into tumor cells to promote glycolysis, which leads to an increase in ATP synthesis, energy molecules necessary to perform the general functions of tumor cells[73,78,79]. GLUT1 overexpression has been related to increased glucose uptake and an adverse prognosis in various tumor types since it leads to progression, invasion, and metastasis[80]. The high glycolytic rate during hypoxia produces an increased lactate concentration and can alter cell homeostasis in non-tumorigenic cells; however, in tumor cells, the increased lactate production is regulated due to the participation of EMMPRIN[81].

EMMPRIN can bind directly to transporter monocarboxylate 1 (MCT1), monocarboxylate 3 (MCT3), and monocarboxylate 4 (MCT4)[78], which catalyze the export of lactate from cells[81-83]. EMMPRIN regulates the expression of MCT1, MCT3, and MCT4 and their presence on the cell surface, where they remain tightly bound to each other[84]. EMMPRIN overexpression is directly related to MCT1 overexpression; EMMPRIN bound to MCT1 initiates activation of the PI3K/Akt/mTOR pathway, enhancing lactate export, thereby regulating glycolysis in tumor models[33,78]. On the other hand, MCT1, MCT3, and MCT4 require association with glycosylated EMMPRIN for their correct translocation to the plasma membrane. EMMPRIN must remain tightly bound with MCTs to maintain transporter activity[81]. MCT1-4 alone, still overexpressed, cannot translocate to the plasma membrane and accumulate in the perinuclear region and the Golgi apparatus. In another way, when their co-expression is associated with EMMPRIN, this induces MCTs to target the plasma membrane and acts as a chaperone for them[85]. Therefore, the co-expression of MCT and EMMPRIN can support glycolysis, inhibit mitochondrial biogenesis and oxidative phosphorylation, regulating the pH balance within the tumor[84].

Carbonic anhydrase (CA) is a ubiquitous enzyme that catalyzes carbon dioxide, protons, and bicarbonate balance. Its isoform II (CAII) (intracellular) and isoform IV (CAIV) (extracellular) can be attached to the MCT-EMMPRIN complex[86] and can work together to secure the rapid transport of metabolites across the cell membrane. They increase the transport activity of MCT1[87] and MCT4 by a non-catalytic mechanism, facilitating the transport of lactate coupled to protons through the cell membrane since EMMPRIN functions as a proton attractant for the transporter[88]. CAIV is anchored to the extracellular side of the plasma membrane through a GPI (glycosylphosphatidylinositol) anchor. CAIV also binds to MCTs through the Ig1 domain of EMMPRIN, bringing CAIV close enough to the membrane pore to transport protons[89].

Intracellular CAII binds to MCT1 or MCT4 through a group of three glutamic acid residues within the C-terminal tail of the transporter and a histidine residue at position 64 that is not involved in proton transfer between MCT and CAII[88,90]. Still, it mediates the enzyme's binding to the transporter, facilitating the exchange of protons between the transporter and intracellular protonable residues like CAIV. Through this non-catalytic mechanism, intracellular and extracellular carbonic anhydrases facilitate the flow of proton-coupled lactate across the cell membrane[91].

The increase in glucose metabolism may contribute to the proliferation of tumor cells by promoting the synthesis of fatty acids. In most tumor cells, fatty acids are derived from de novo synthesis, produced at a high rate, despite having a great supplement of extracellular lipids. The elevated synthesis rate of fatty acids in highly proliferative cells provides biogenesis of the membrane[92,93].

In vitro and *in vivo* tumor models, EMMPRIN overexpression has been shown to play a critical role in reprogramming fatty acid metabolism. Specifically, it has been reported that EMMPRIN overexpression increases lipogenesis and prevents fatty acid oxidation[94]. Overexpressed EMMPRIN increases lipogenesis by activating the Akt-mTOR signaling pathway, leading to increased expression of the sterol regulatory element-bind-

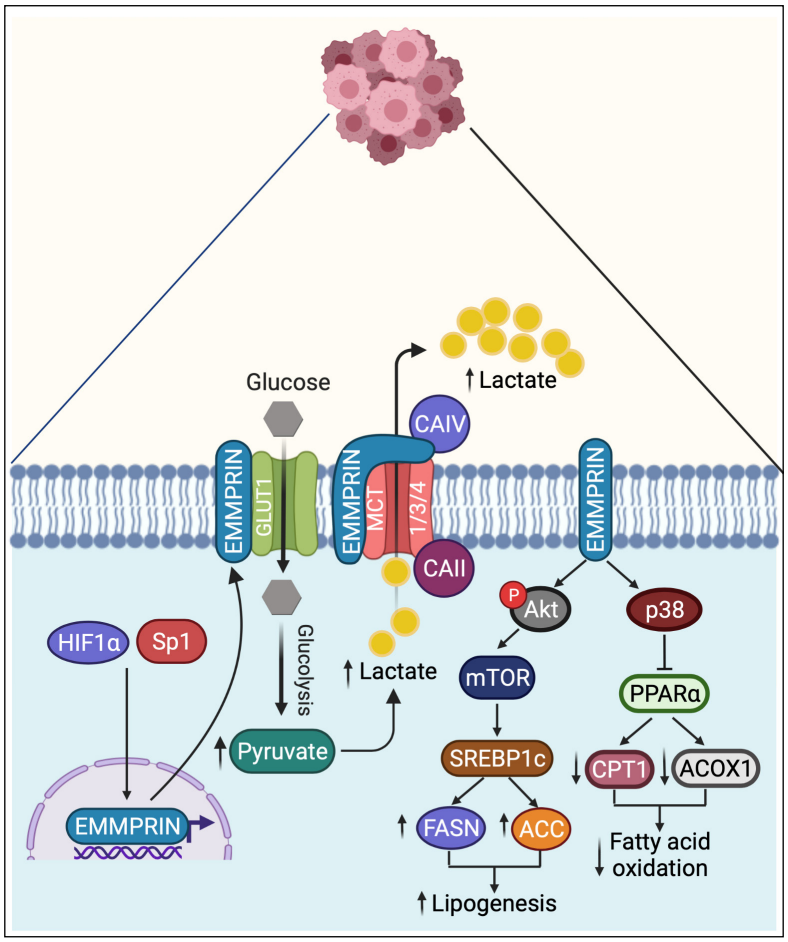

Figure 5. Regulation of metabolism by EMMPRIN. Black arrow: direct activation. HIF1α: Hypoxia-inducible factor 1α, Sp1: Specificity protein 1, MCT: Monocarboxylate transporter, CAIV: Carbonic Anhydrase, CAII: Carbonic Anhydrase II, mTOR: Mechanistic Target of Rapamycin Kinase, SREBP1c: Sterol Regulatory Element Binding Transcription Factor 1, FASN: Fatty Acid Synthase, ACC: acetyl-CoA carboxylase, PPARα: Poly (ADP-ribose) Polymerases, CPT1: Carnitine O-palmitoyltransferase, ACOX1: Acyl-CoA Oxidase 1. This figure was created using BioRender software.

ing protein 1c (SREBP1c), a transcription factor involved in the synthesis of lipids. Increased levels of SREBPlc activate transcription and increase the expression of fatty acid synthase (FASN) and acetyl CoA carboxylase (ACC), two of the main enzymes involved in lipogenesis, thus promoting de novo lipogenesis[35].

EMMPRIN decreases fatty acid oxidation (FAO) in cancer by reducing proliferator-activated peroxisome receptor alpha (PPARα) levels. PPARα promotes the expression of CPT1 and ACOX1. With the downregulation of PPARα, the expression of both enzymes is negatively regulated, which prevents the oxidation of fatty acids[94] (Figure 5).

EMMPRIN Inhibits the Immune Response

Tumor cells use a variety of mechanisms to evade the immune response, such as downregulation of membrane proteins, so cytotoxic T lymphocytes are not recognized by them[95].

EMMPRIN inhibits the T cell immune responses. EMMPRIN overexpression and its co-expression with Tim-3 and PD-1, two immune checkpoint molecules expressed on CD8 + tumor-infiltrating lymphocytes (TIL), significantly increased tumor growth *in vivo*; this same behavior has been observed in biopsies of metastatic tumors from patients. Additionally, a negative correlation was found between the expression of EMMPRIN and the decrease in CD8+TIL with the survival of patients[8].

TIL CD8 + is an indicator of antitumor immune response to tumor antigens; however, the successful elimination of tumor cells is locked by the coexistence of progressively growing tumors, which leads to the loss of the ability to proliferate in TIL,

produce cytotoxic cytokines, and lyse cancer cells. Down-regulation of antitumor immune responses facilitates tumor immune escape[96,97]. EMMPRIN inhibits CD8 + TILs due to upstream depletion of the cytotoxic transcription factors Runx3 and T-bet. They have been identified as crucial modulators in the transcriptional differentiation network and activation of cytotoxic functions in CD8 + T cells by promoting the expression of the cytotoxic effector molecules perforin and granzyme B[8]. EMMPRIN can also reduce the tumor immune response in CD8 + TIL by phosphorylating and activating the signaling molecule STAT3, which represses the expression of cytotoxic genes, including those encoding granzyme B, IFN-γ, and T-bet[8,98].

As another option, extracellular lactate derived from tumor cells blocks the differentiation of monocytes to dendritic cells (DC). It also inhibits the release of cytokines from differentiated DCs, reduces the cytotoxic activity of NK cells, suppresses the proliferation and production of cytokines of T lymphocytes in 95%, and inhibits their cytotoxic activity by 50%[99-101]. These alterations lead to cell survival, tumor growth, and metastasis[101,102]. Additionally, the percentage of T cells NK (CD3 - CD56 +), NT (CD3 + CD56 +) and TIL CD8 + negatively correlate with the expression of EMMPRIN in tumor tissues. While the prevalence of regulatory T lymphocytes (Tregs) expressing the forkhead box transcription factor P3 (FoxP3) positively correlates with the expression of EMMPRIN in tumor tissues[33]. FoxP3 is a key intracellular molecule for the development and function of Tregs; it has been shown that a high infiltration of Tregs FoxP3 + inhibits host immunity against cancer by suppressing antitumor cytotoxic T cells[103]. Tregs FoxP3 + have been reported in several *in situ* or metastatic human carcinomas[104-106].

EMMPRIN acts as an extracellular receptor for CyPA, which is released into the extracellular space by activated macrophages, smooth muscle cells, platelets, etc.; it has cytokine-like activities and is a potent chemoattractant of human monocytes, neutrophils, eosinophils, and T cells[107,108]. EMMPRIN expression increases tumor cells' viability when co-cultured with T cells and decreases the chemotaxis and infiltration of T cells induced by CyPA *in vitro,* and *in vivo*. Thus, EMMPRIN promotes the escape from tumor immune surveillance of T cells[108].

Another way, EMMPRIN has been related to antitumor immune escape is from the glycosylation of its structure, mediated by β-galactoside α2-6-sialyltransferase 1 (ST6Gal-I), the enzyme responsible for the addition of acid α2-6-sialic to terminal N-glycans on the cell surface[109]. ST6Gal-I overexpression promoted tumor immune escape by activating the EMMPRIN/MMP signaling pathway and its expression in tumor cells, causing inhibition in the proliferation of T cells and suppressing the intra-tumor penetration of CD8 + T cells[9] (Figure 6).

EMMPRIN Promotes the Angiogenesis

Angiogenesis is the growth of new blood vessels that tumors need to obtain nutrients to grow and perform their essential functions[110].

EMMPRIN overexpression has been associated with tumor cell angiogenesis by increasing vascular endothelial growth factor (VEGF) levels in the tumor and the stroma[111]. In several types of cancer, VEGF is overexpressed, it is a mitogenic and angiogenic mediator and a potent stimulator of vascular permeability, and it binds to three tyrosine kinase receptors VEGFR1 (Flt-1), VEGFR2 (KDR / Flk-1), and VEGFR3 (Flt-4)[112,113].

EMMPRIN induces VEGF secretion in fibroblasts and tumor cells through the PI3K-Akt signaling pathway and increases the expression of VEGFR-2 through the transcription factor HIF-2α[114,115]. VEGFR1 and VEGFR2 recognize VEGF[113]. Once VEGF is recognized by VEGFR, the activation of tumoral angiogenesis and the increase in the malignant characteristics of tumor cells begins[114]. It has been shown that EMMPRIN also acts as a coreceptor for VEGFR2. The interaction occurs through the extracellular domain of EMMPRIN located near the cell membrane, specifically at amino acids 195/199. Direct interaction is necessary for the VEGF-induced activation of VEGFR2. Therefore, overexpression of EMMPRIN in cancer can enhance the activation of VEGFR2[115].

In a study, a tumor cell co-culture model of tumor angiogenesis and HUVEC has created cells expressing EMMPRIN induced the formation of neovasculature-like network-like structures. This result was associated with increased VEGF secretion and insulin-like growth factor I (IGF-I) promoted by EMMPRIN. IGF-I was also found to positively regulate EMMPRIN expression in both tumor cells and HUVEC. These findings suggest positive feedback between EMMPRIN and IGF-I at the tumor-endothelial interface[116].

Another mechanism by which EMMPRIN promotes VEGF secretion is by direct stimulation of MMP-2 / -9 and MT1-MMP secretion; it has been reported to increase VEGF expression through the Src pathway [18,115,117]. MT1-MMP is a pro-MMP-2 activating transmembrane metalloproteinase; howev-

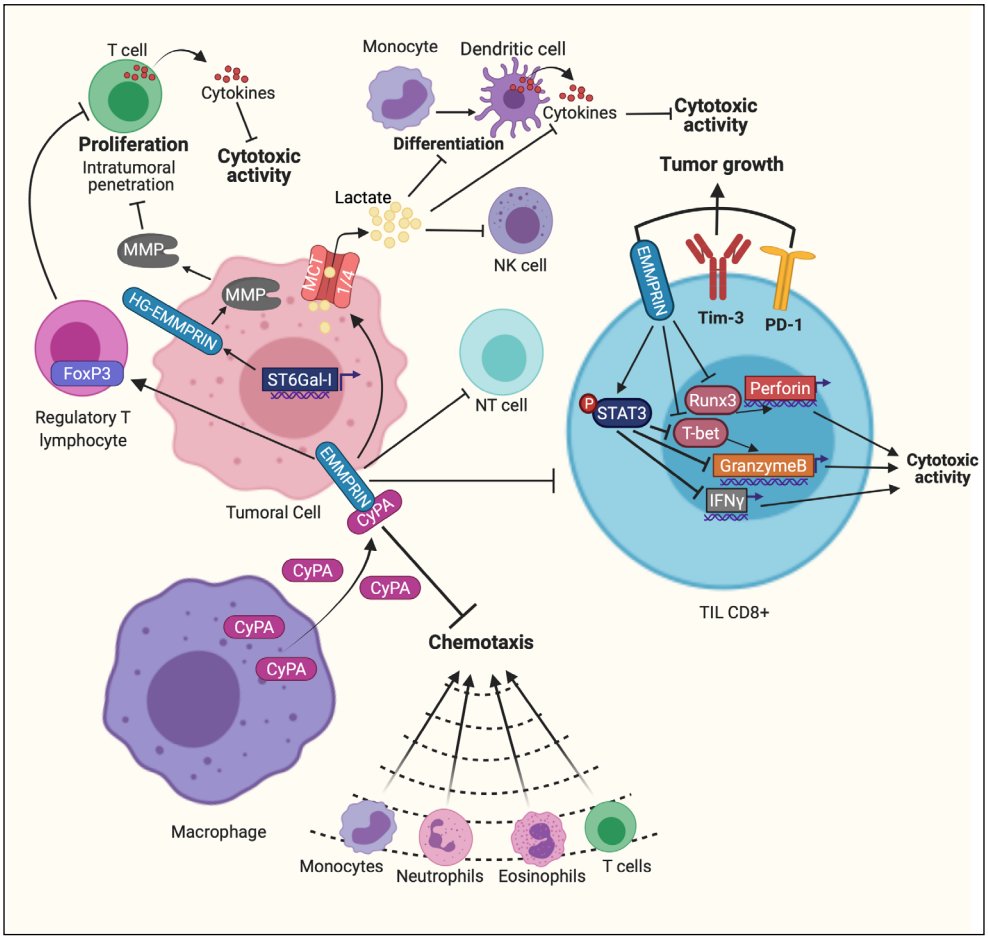

Figure 6. Regulation of immune response by EMMPRIN. Black arrow: direct activation, and T bar: inhibition of processes. MMP: Matrix metalloproteinases, FoxP3: Forkhead Box P3, STAT3: Signal Transducer and Activator of Transcription 3, T-bet: T-box expressed in T cells, Runx3: RUNX Family Transcription Factor 3, IFN: Interferon, Bim-3: Bcl-2-like protein, ST6Gal-I: ST6 Beta-Galactoside Alpha-2,6-Sialyltransferase 1, MCT: Monocarboxylate transporters, NT: neutrófilos, KN: natural killer. This figure was created on BioRender.com.

er, it also promotes VEGF expression independently of MMP-2[118]. MMPs also facilitate the cell migration of pericytes[119]. Pericytes are the primary vascular cells that control blood flow in tumor vessels[120]. MMPs also contribute to epidermal growth factor receptor (EGFR) activation *in vivo*[121]. The binding of EGFR to its ligand activates the PI3K-Akt signaling pathway that activates endothelial nitric oxide (NO) synthase, releasing NO in endothelial cells, which leads to vascular cell permeability and can trigger angiogenesis[122]. In addition to stimulating the expression of VEGF through the Src pathway, MMPs also promote its release and that of other angiogenic factors such as transforming growth factor β1 (TGFβ1)[123,124]. TGFβ1 can activate the Activin Receptor-Like Kinase (ALK1), and this, in turn, phosphorylates Smad1/5, increasing the expression of placental growth factor (PIGF) that positively regulates VEGF-A / VEGFR2 signaling, which that contributes to the development of endothelial angiogenesis[125] (Figure 7).

EMMPRIN Involvement in Adhesion

Cell adhesion is the ability to create extracellular cell-cell or cell-matrix junctions. Cells adhere through proteins present on the cell surface, called adhesion molecules (CAM), through homophilic or heterophilic interactions. During malignant transformation, cell-cell interactions are lost, and cell-extracellular matrix interactions formation[126,127].

EMMPRIN controls the adhesion process by regulating the expression and binding of various molecules. EMMPRIN generates homophilic binding, where the same molecule acts as a counter-receptor, mainly through its first Ig domain (D1).

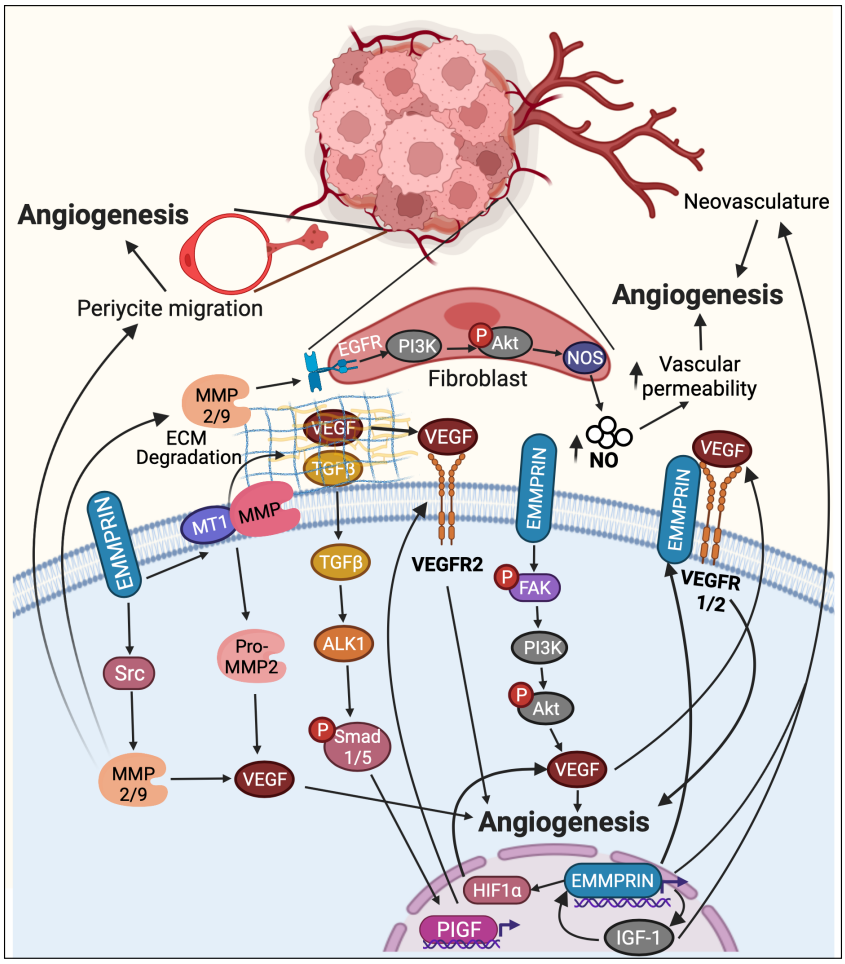

Figure 7. Regulation of angiogenesis by EMMPRIN. Black arrow: direct activation**.** MMP: Matrix metalloproteinases**,** MT1: Metallothionein 1, VEGF: Vascular Endothelial Growth Factor, Smad: Family Member, TGFβ: Transforming Growth Factor Beta 1, VEGFR2: Vascular Endothelial Growth Factor Receptor 2, PI3K: Phosphoinositide 3-kinases, HIF1: Hypoxia-inducible protein, PIGF: placental growth factor, IGF-1: insulin-like growth factor-1, NO: Nitric oxide, EGFR: Epidermal growth factor receptor. This figure was created using BioRender software.

This interaction involves the induction and oligomerization of matrix metalloproteinases (MMP) and can occur in tumor cells and stromal cells[128,129].

EMMPRIN interacts with Annexin II, which increases the adhesive potential of tumor cells[14]. Annexin II is an F-actin binding protein, so it has been suggested that acting with EMMPRIN increases adhesion potential[14,130]. On the other hand, EMMPRIN, through the Ig 2 domain in tumor lines, forms a complex with Cav-1, an essential structural protein of caveolae that induces adhesion of tumor cells to fibronectin by activating adhesion signaling mediated by focal adhesion kinase (FAK)[131,132]. Cav-1 bound to EMMPRIN positively regulates EMMPRIN glycosylation of tumor cells[128].

EMMPRIN increases the activity and expression of FAK by overexpressing and forming a complex on the cell surface with α3β1-integrin, the interaction EMMPRIN-α3β1-integrin increases the activity of the integrin, and this forms an integrin-FAK signaling link, this interaction also activates FAK-paxillin-PI3K signaling pathways[133,134]. Activation of this pathway regulates IP3 levels, IP3 releases Ca^{2+} from intracellular deposits ($[Ca^{2+}]i$)[135]. Another way in which EMMPRIN increases $[Ca^{2+}]i$ is through the complex that it forms with calcium modulating cyclophilin (CAML), which is a ubiquitous protein located mainly in the endoplasmic reticulum (ER) and acts as intermediate signaling in numerous pathways that regulate $[Ca^{2+}]i$. EMMPRIN overexpression and its interaction with CAML regulate ER signaling and increase the concentrations of $[Ca^{2+}]I$; high concentrations of $[Ca^{2+}]i$ have been related to the regulation of cell

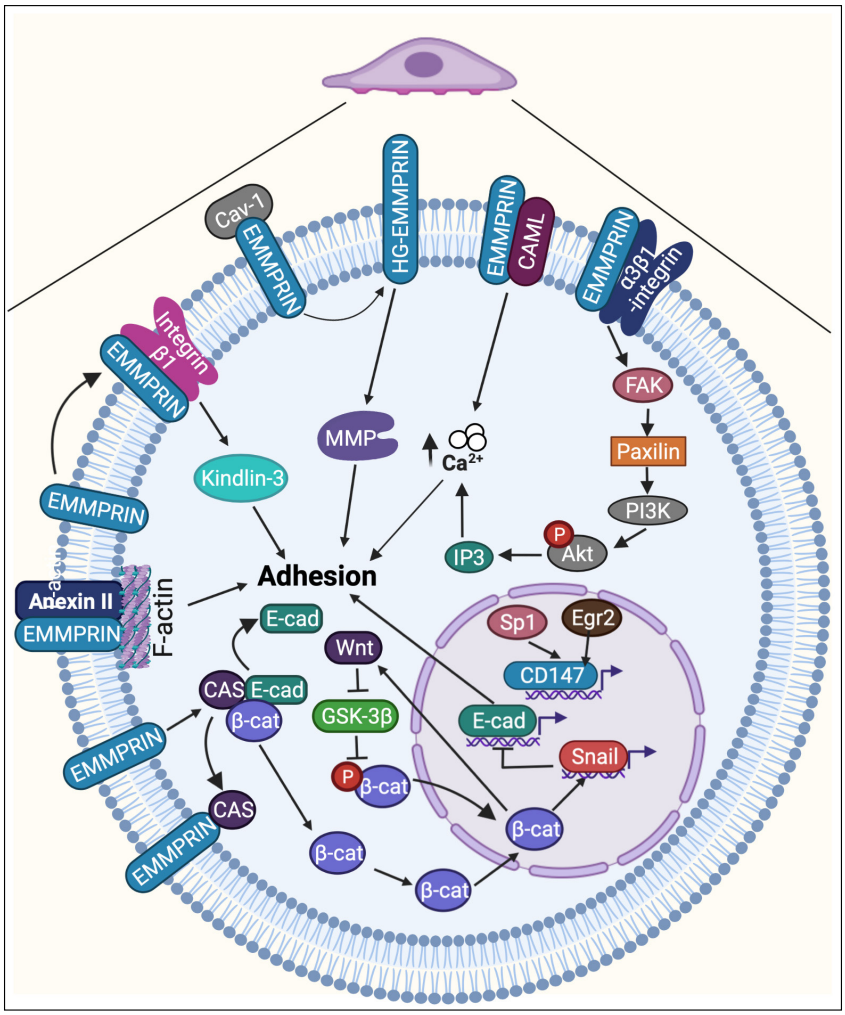

Figure 8. Regulation of adhesion by EMMPRIN. Black arrow: direct activation and T bar: inhibition of processes. CAS: CRISPR-associated proteins, E-Cad: E-cadherin, GSK-3β: Glycogen Synthase Kinase 3 Beta, MMP: matrix metalloproteinase, CA: Carbonic Anhydrase, Cav-1: Caveolin 1, CAML: Calcium Modulating Ligand, FAK: Focal adhesion kinase, PI3K: Phosphoinositide 3-kinase, Sp1: Sp1 Transcription Factor, Egr2: Early Growth Response 2. This figure was created using Biorender software.

adhesion mediated by dependent and independent signaling pathways of integrins[136-138].

EMMPRIN regulates adhesion with the ECM through the β1/Kindlin-3 integrin adhesion pathway[139]. Kindlin-3 belongs to the family of focal adhesion proteins; it is a crucial protein in the activation of β1 integrin, which regulates the interactions between the cell and the ECM, thus playing a pivotal role in regulating these junctions[140].

EMMPRIN overexpression causes loss of polarity in tumor cell lines by interacting with the cell apoptosis susceptibility protein (CAS) and inhibiting the complex formed by this protein with E-cadherin (E-cad) and β-catenin (β-cat), a complex known as CAS/E-cad/β-cat. Inhibition of the complex decreases the localization of β-cat and E-cad in the cell membrane, increasing the levels of β-cat in the nucleus and activating the β-cat pathway[28,141].

Activation of the β-cat pathway can enhance the expression of the Snail gene, which causes the transcriptional repression of E-cad, promoting the loss of membrane junctions in the cell[142,143]. EMMPRIN overexpression also causes activation of the Wnt/GSK-3β/β-cat pathway. In this pathway, GSK-3β is a factor upstream of β-cat, promoting its phosphorylation[144]. The phosphorylated form of β-cat is ubiquitin and degrades, thus maintaining low levels of β-cat. However, EMMPRIN inhibits the kinase activity of GSK-3β and decreases the levels of phosphorylated β-cat. Therefore, the levels of nuclear β-cat increase and consequently decrease the expression of E-cadherin, reducing cell-cell adhesion[17,144,145] (Figure 8).

EMMPRIN Promotes the Migration

Cell migration results from chemical and mechanical interactions between cells and their extracellular environment. The types of unicellular and collective migration, in addition to their interconversions, depend on the polarization, adhesion, deformability, contractility, and proteolytic capacity of the cells[146].

One of the tumor processes most related to cell migration is the epithelial-mesenchymal transition (EMT), a process in which stationary polarized epithelial cells become mobile mesenchymal cells, accompanied by activating an invasive phenotype and behaviors of neoplastic cells[147]. EMMPRIN plays an essential role in the collective migration of tumor cells. Collective migration is a type of cohesive and multicellular spread; it is different from the unicellular invasion that depends on the specific mechanisms of the cell type and contributes to carcinogenesis, progression, and distant spread of various types of cancers[148,149]. TGF-β1-induced overexpression of EMMPRIN is widely related to EMT. TGF-β1 is a tumor promoter that triggers EMT through the transcription factors Snail1 and Slug. Snail1 serves as an upstream factor of Slug in the TGF-β1-PI3K/Akt-GSK3β pathway in EMT, while Slug directly regulates the expression of EMMPRIN[150]. In addition, the overactivation of the β-cat pathway due to overexpression of EMMPRIN can also enhance the expression of genes associated with EMT, such as the mesenchymal markers N-cadherin, vimentin, and Snail, which causes transcriptional repression of E-cadherin. EMMPRIN also increases migration by enhancing F-actin rearrangement, decreasing adhesion by suppressing the adhesion molecule ICAM-1, and indicating the epithelial-mesenchymal transition by reducing the epithelial marker claudin-1[17,151]. In this way, the cell's loss of membrane junctions is promoted, and its transformation into mobile mesenchymal cells occurs[141].

EMMPRIN also promotes the mesenchymal phenotype by increasing hyaluronan synthesis[25,152,153]. EMMPRIN overexpression has been correlated with high nano-hyaluronan and CD44 levels in the cell membrane and has exhibited typical EMT properties, such as anchorage-independent growth and migration[153,154]. Hyaluronan is released in the pericellular medium; it interacts multivalently with CD44 to induce or stabilize signaling domains within the plasma membrane and activate signaling pathways such as RAF, PI3K-Akt, and FAK that cause, among some other tumor processes, cell migration. Hyaluronan-CD44 interactions also induce cytoskeletal changes that promote motility[155]. The result is that oncogenic cells acquire the ability to migrate to local and distant tissues. A higher expression of EMMPRIN has been reported in oncogenic cells near the border than in the nucleus of tumor samples[156].

EMMPRIN acts as a receptor for the S100A9 ligand, forming an S100A9-EMMPRIN complex. S100A9 is a chemoattractant derived from peripheral keratinocytes; its expression is induced by pro-inflammatory factors secreted by primary tumor cells, facilitating tumor cells to migrate to pre-metastatic sites[157]. Melanoma cells that overexpress EMMPRIN have been reported to migrate to skin expressing S100A9, whereas cells with low expression of EMMPRIN do not migrate or metastasize in response to S100A9. This effect is because the S100A9-EMMPRIN complex promotes MMP expression in neighboring cancer cells through EMMPRIN signal transduction. The disappearance of the basement membrane has been demonstrated just in the area where EMMPRIN and S100A9 are co-expressed[158]. In addition, the S100A9-EMMPRIN interaction induced the activation of cdc42, a member of the Rho GTPase family, which promotes filopodium formation, regulates polarity, and cell migration[159]. Thus, EMMPRIN is expressed in the invasive border and not in their densest mass[158].

EMMPRIN induces the expression of MCT1 and MCT-4 through the Akt-FoxO3-NF-κB pathway. The overexpression of EMMPRIN in tumor cells is related to the activation of PI3K, which phosphorylates and activates Akt (pAkt). Active Akt promotes the phosphorylation of FoxO3 and its proteasomal degradation. The suppression of FoxO3 promotes the phosphorylation of NFκB (p65), which causes its nuclear translocation and transcriptional activity on MCT-1/4. Consequently, the expression of MCT-1/4 is elevated, which has been related to the induction of tumor migration and invasion from lactic acid regulation[160-162]. MCT-1/4 export the lactic acid generated in large quantities in the tumoral process[84,133]. The accumulation of lactic acid in the extracellular medium induces the acidification of the tumor microenvironment. It influences the migration of tumor cells by promoting hyaluronan production, which acts on fibroblasts and the cytoskeleton of cancer cells through interaction with CD44[133,163].

EMMPRIN can recycle itself to the plasma membrane without undergoing proteasomal degradation through its interaction with Rab22a[164]. Rab22a is a Rab family member located at multiple levels in the endocytic pathway[165]. Endocyt-

ic recycling is coordinated with endocytic uptake to control the plasma membrane composition[166]. The cytoplasmic tail of EMMPRIN can be recognized by Hook1, which mediates its selection into Rab22a-dependent tubules associated with recycling[167]; therefore, after endocytosis, EMMPRIN enters the recycling tubules directly and relocates back to the plasma membrane, preventing ubiquitin-proteasome degradation[39]. Recycling EMMPRIN by Rab22a maintains EMMPRIN expression levels in the cell membrane and plays a critical role in transduction signals promoting tumor cell migration, favoring invasion[164].

The overexpression of EMMPRIN in the membrane of various types of tumor cells induces the transformation of normal fibroblasts into cancer-associated fibroblasts (CAF)[168]. The CAFs abundant in the tumor stroma contribute to the formation of the malignant micro-environment of cancers through the secretion of MMPs that degrade ECM, thus inducing EMT of tumor cells[169,170]. CAFs induce EMT depending on expression and favor the migration potential of tumor cells[168]. Another way that EMMPRIN has been associated with the migration process is through its interaction with the cell cycle-specific transcription factor and E2F1[171]. This transcription factor has been detected in various cancers, and oncogenic or tumor suppressor functions have been attributed to it depending on the type and subtype of cancer[172]. E2F1 regulates the expression of EMMPRIN, thus promoting EMT and migration in tumor cells; however, it has also been reported that E2F1 increases MMP expression, so this could be one of how EMMPRIN, overexpressed by E2F1, increases migration[171,172].

EMMPRIN is co-localized with the previous gradient 2 (AGR2) in tumor samples; its overexpression *in vitro* and *in vivo* increases cell migration[156]. Silencing AGR2 reduces the expression of EMMPRIN, the mesenchymal marker N-cadherin, Slug, Snail, and upregulates E-cadherin in tumor cells exposed to exogenous TGF-β1[173], so AGR2 could be a protein upstream of EMMPRIN, regulating its expression and favoring EMT[156].

Cells undergo dynamic actin cytoskeleton rearrangements during cell migration to form protrusive structures and generate the intracellular forces necessary for cell translocation. Src phosphorylation triggered by the EMMPRIN-α3β1 integrin complex blocks the activity of Rho and ROCK and thereby reduces MLC2 phosphorylation, promoting mesenchymal cell movement and suppressing amoeboid cell movement[174]. EMMPRIN inhibits the Rho/ROCK signaling pathway and amoeboid cell migration, inhibiting Annexin II phosphorylation[175]. Therefore, EMMPRIN leads to cell migration[174].

Activating the FAK pathway by the EMMPRIN-α3β1 integrin complex also plays an essential role in reorganizing the cytoskeleton. FAK, in turn, phosphorylates Src, recognized as a critical mediator in the organization of the cytoskeleton that in turn phosphorylates and promotes nuclear translocation of STAT3, promotes the expression of DOCK8, and activates Rac1. Rac1 activity increases the expression of WAVE2, which stimulates actin polymerization and membrane protrusions[174] (Figure 9).

EMMPRIN Promotes the Cell Invasion

Invasion is the ability of tumor cells to infiltrate neighboring tissues by rupturing the basement membrane. Cancer cells that become invasive can spread to secondary sites and metastasize[176].

EMMPRIN modulates invasion by negatively regulating GSK-3β and increasing the β-cat signaling pathway, positively regulating cathepsin B (CTSB) transcription[177]. CTSB is a cysteine proteolytic enzyme with a high expression level in tumor tissues, is released by tumor cells through exosomes, participates in the hydrolysis of ECM, and activates MMPs, thus increasing the invasion of cells tumorous[178].

The expression of BSG2 has been correlated with the induction of cell invasion by increasing the expression and secretion of MMP-2 and MMP-9; MMP is associated with epithelial-mesenchymal transition (EMT)[30]. EMMPRIN can stimulate MMP production, specifically MMP-1, -2, -3, -7, -9, -14 and -15[128,129,179,180]. The MMPs are an important family of enzymes that degrade the ECM; the degradation of the ECM is a crucial step in the local invasion. Therefore, the role of EMMPRIN in the induction of MMP is one of the most studied functions, hence the derivation of its other name: extracellular matrix metalloproteinase inducer (EMMPRIM)[13,181]. EMMPRIN stimulates MMP production in tumor cells and surrounding fibroblasts, which influences the balance of the tumor microenvironment, with the modulation of invasion by fibroblasts being greater, suggesting some interactions between cancer cells and fibroblasts can promote tumor invasion[179]. The overexpression of EMMPRIN, regulated by the transcription factors Sp1 and Egr2, promotes invasiveness in primary fibroblasts. It has been shown that EMMPRIN also increases MMP expression and tumor progression by interacting with other proteins, such

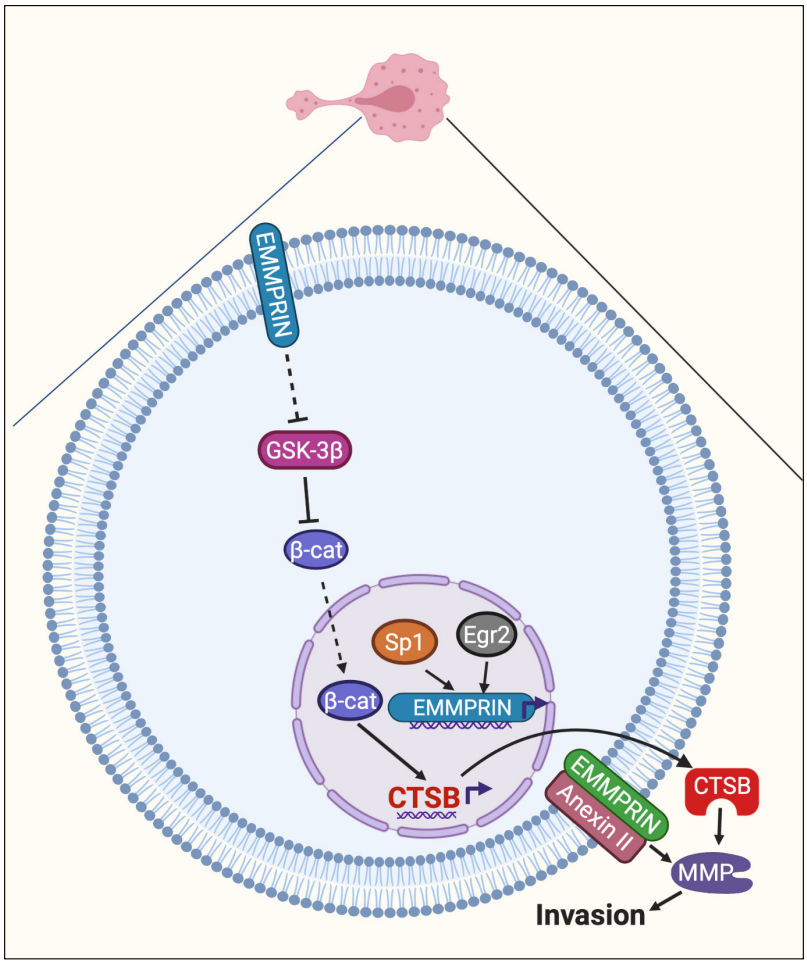

Figure 9. Regulation of invasion by EMMPRIN. Black arrow: direct activation; Red T bar: inhibition of processes, Dotted black arrow: activation through unknown displayed other molecules. GSK-3β: glycogen Synthase Kinase 3 Beta, Sp1: Sp1 Transcription Factor, Egr2: Early Growth Response 2, CTSB: Cathepsin B, MMP: matrix metalloproteinase. This figure was created with BioRender.com.

as complex formed by EMMPRIN and Annexin II that promotes MMP expression in tumor cells[7,14,182] (Figure 10).

EMMPRIN Promotes the Metastasis

Metastasis represents the end product of a multi-stage cellular biological process, called the invasion-metastasis cascade, which involves the spread of cancer cells to anatomically distant organ sites and their subsequent adaptation to foreign tissue microenvironments[183].

As already mentioned in the metabolism section, the overexpression of EMMPRIN deregulates the main enzymes involved in lipid metabolism, which increases lipogenesis and decreases the oxidation of fatty acids. In addition to being associated with growth, these processes are associated with tumor metastasis[35,184]. Meanwhile, *in vitro* and *in vivo* models, HG-EMMPRIN is correlated with highly metastatic potential in lymph nodes and high expression N-acetylglucosaminyltransferase (GnT) – IV, which is an enzyme that catalyzes the formation of the GlcNAC β1-4 branch in the central structure of N-Glycans and is responsible for inducing the glycosylation of EMMPRIN and increasing its β1-6 branches of N- Glycans[31,185]. Fyn is another enzyme that directly interacts and increases EMMPRIN glycosylation and metastasis using *in vivo* models[29]. Fyn is a tyrosine kinase associated with T cells and neuronal signaling in normal cell development and physiology and is overexpressed in clinical tissues of primary and metastatic tumors[186]. Fyn phosphorylates EMMPRIN at Y140 and Y183 and promotes their glycosylation and recruitment to the membrane; Fyn-mediated expression of EMMPRIN promotes MMP expression and a signifi-

cant increase in the size and number of metastatic nodules in mice[29].

In tumor biopsies, the co-expression of MCT1 and EMMPRIN is associated with the presence of lymph node metastases and distant metastases[187]. Additionally, the overexpression of MCT4 promoted by EMMPRIN and the EMMPRIN-CD44 complex favors metastasis and is associated with a poor prognosis in cancer patients[188]. The EMMPRIN-CD44 complex also promotes metastasis by regulating the PI3K/Akt and MAPK/ERK signaling pathways by reducing the levels of p-Akt and p-ERK in tumor cells[189].

EMMPRIN induces the release of Ca^{2+}, which regulates the expression or release of MMP, particularly MMP-2 and MMP-9, which improve the degradation of basal membranes, cell migration to distant organs, processes involved in cancer metastasis[134,136].

In vivo tumor models, EMMPRIN overexpression promotes liver and lung cell colonization. The enhancing effect of EMMPRIN on metastasis seems to be generalized for cancer cells since colonization in these cells has been reported in different types of cancer[150,151,190]. Tumor metastasis may be due to increased fibroblasts peripheral to the tumor tissue and increased MMP-2, MMP-11, and VEGF expression. Cancer-associated fibroblasts are the main effector population in the stroma that

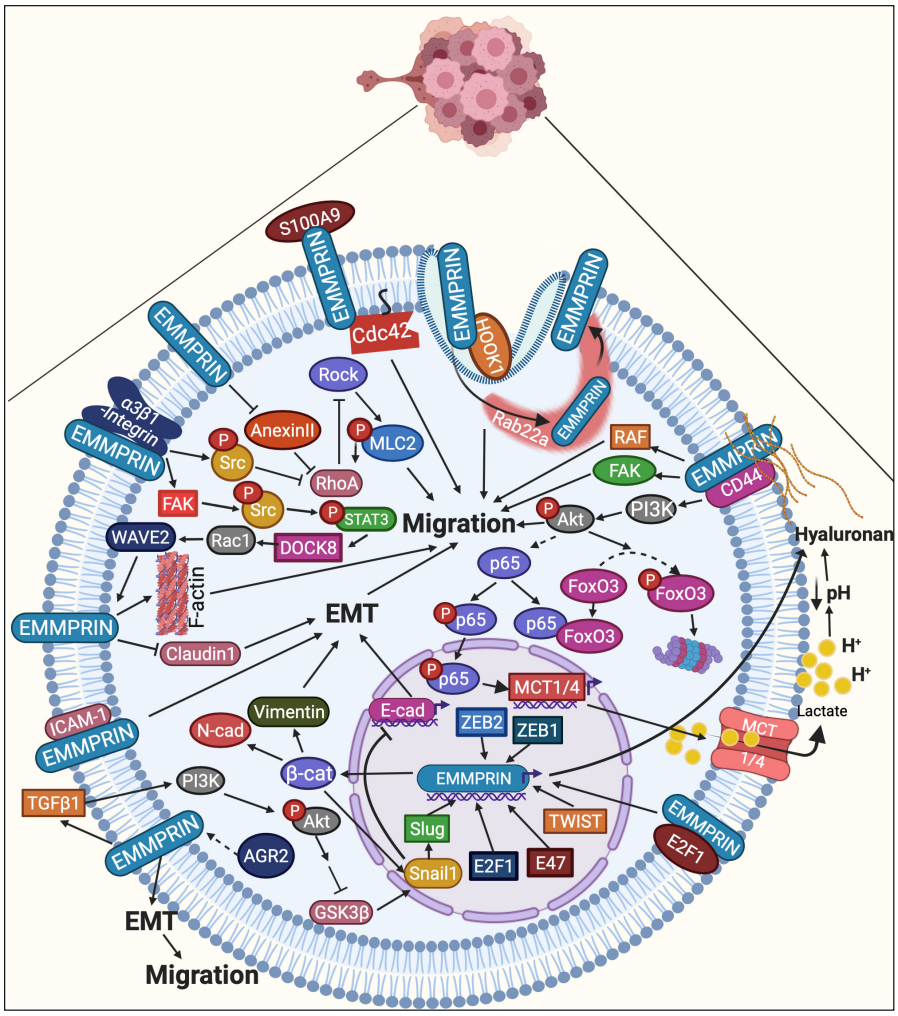

Figure 10. Regulation of migration by EMMPRIN. Black arrow: direct activation; Red T bar: inhibition of processes, Dotted black arrow: activation through unknown/not displayed other molecules, TGF-β1: Transforming Growth Factor Beta 1, AGR2: Anterior gradient protein 2 homolog, GSK3β: Glycogen Synthase Kinase 3 Beta, PI3K: phosphoinositide 3-kinase, N-cad: neural cadherin, ICAM-1: Intercellular adhesion molecule-1, FAK: Focal adhesion kinase, RhoA: Rhodopsin, ROCK: Rho-associated protein kinase, Cdc42: Cell Division Cycle 42, FAK: Focal adhesion kinase, PI3K: FoxO3: Forkhead Box O3, MCT: Monocarboxylate transporters, ZEB: Zinc Finger E-Box Binding Homeobox 2, TWUIS: Twist Family BHLH Transcription Factor 1, E2F1: E2F Transcription Factor 1. This figure was created on BioRender.com.

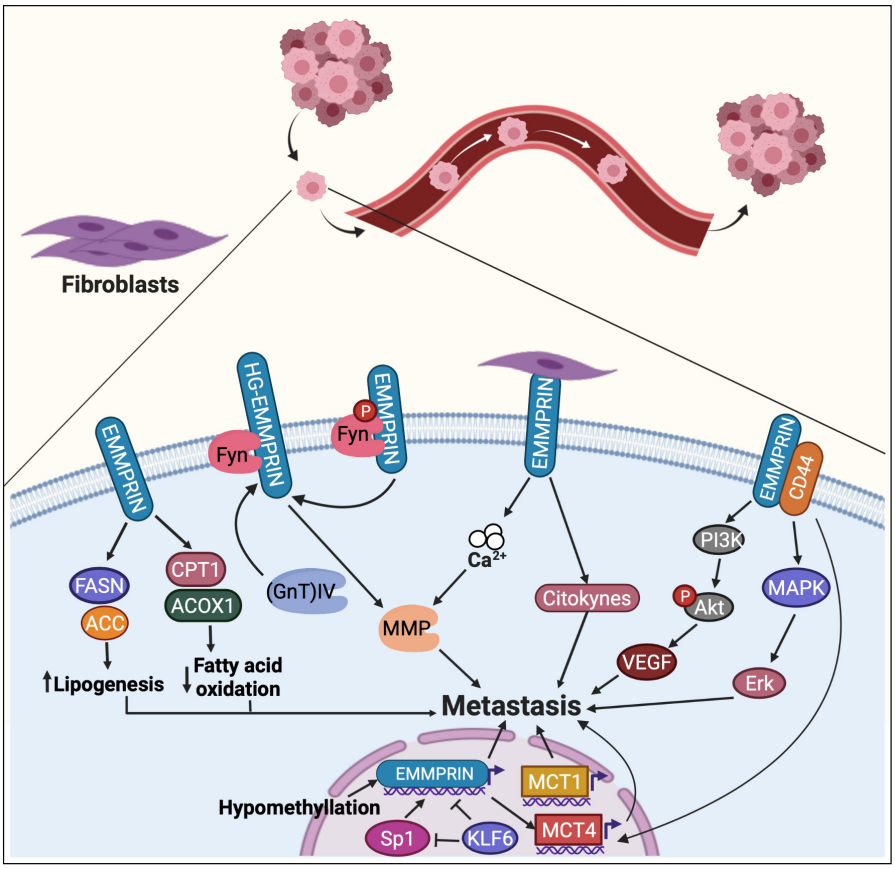

Figure 11. Regulation of metastasis by EMMPRIN. Black arrow: direct activation; Red T bar: inhibition of processes, Dotted black arrow: activation through unknown/not displayed other molecules. FASN: Fatty Acid Synthase, ACC: Acetyl-CoA carboxylase, CPT1: Carnitine Palmitoyltransferase 1A, ACOX1: Acyl-CoA Oxidase 1, (GnT)IV: N-Acetylglucosaminyltransferase-4, MMP: Matrix metalloproteinases, Ca: Carbonic Anhydrase, VEGF: Vascular Endothelial Growth Factor, PI3K: Phosphoinositide 3-kinase, MAPK: mitogen-activated protein kinase, Erk: extracellular signal-regulated kinases, MCT: Monocarboxylate transporters, Sp1: Sp1 Transcription Factor, KLF6: Kruppel Like Factor 6**.** This figure was created on BioRender.com.

interacts with EMMPRIN in tumor cells. Fibroblast-tumor cell interaction promotes secretion of MMP and some active cytokines, leading to tumor metastasis[32,179].

EMMPRIN has also been reported to promote metastasis independently of MMP by modulating only tumor angiogenesis. In *in vitro* and *in vivo* tumor models, the suppression of EMMPRIN did not affect the expression of MMP. Still, it did affect the expression of the angiogenic factor VEGF by regulating the PI3K-Akt signaling pathway[191,192]. Tumor cells, overexpress VEGF, induce increased blood vessel formation and metastasis *in vivo*[193].

Regarding the transcriptional regulation of EMMPRIN and its association with metastasis, antagonistic transcription factors Sp1 and KLF6 have been shown to regulate the expression of EMMPRIN. Sp1 binds to the promoter of EMMPRIN and activates its expression, while KLF6 represses the expression of Sp1. Therefore, KLF6 can suppress the expression of EMMPRIN directly or indirectly. The regulation mediated by these transcription factors on EMMPRIN is involved with metastasis in mice[194]. Also, hypomethylation is another critical factor that may be associated with the expression of EMMPRIN in human tumor cells and tissue; the demethylation of the EMMPRIN promoter leads to an increase in the binding affinity of Sp1 and the increased expression of EMMPRIN[195]. Therefore, the regulation in the expression of EMMPRIN from the hypomethylation of its promoter and the KLF6/EMMPRIN relationship could provide a new potential therapeutic target to treat metastasis[194] (Figure 11).

Conclusions

EMMPRIN is a transmembrane protein capable of interacting with multiple membrane cell, cytoplasmic, and extracellular proteins, regulating several signaling pathways, gene expression, and proteins related to cancer development. EMMPRIN regulates hallmarks in cancer, maintains proliferative signals, resistance to cell death, induction of angiogenesis, activation of invasion and metastasis, reprogramming of energy metabolism, and evasion of immune destruction. EMMPRIN may be a potential therapeutic target candidate or biomarker in various cancers. However, more studies on patients are necessary.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

None.

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