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REVIEW

EMMPRIN Plays a Vital Role in Cancer Metastasis by Regulating MMPs and VEGF

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ABSTRACT

The interplay between cancer cells and fibroblasts, facilitated by the extracellular matrix metalloproteinase inducer (EMMPRIN), plays a pivotal role in the invasion of cancer cells. The interaction between CD73 on fibroblasts and EMMPRIN on cancer cells is critical for the production of matrix metalloproteinases (MMPs). EMMPRIN is an essential protein that activates the vascular endothelial growth factor receptor (VEGFR), which subsequently governs signaling pathways related to cancer cell invasion, migration, angiogenesis, and metastasis, thereby contributing to the advancement of various cancers. EMMPRIN affects MMP production through direct cell-to-cell interactions and its influence on fibroblasts due to their close contact. It is proposed that disrupting the EMMPRIN-CD73 interaction and utilizing an antagonist for both EMMPRIN and VEGFR-2 may significantly impede cancer metastasis. This review aims to investigate how EMMPRIN regulates MMPs and VEGF in the context of cancer metastasis.

Keywords: EMMPRIN, Metastasis, MMP, VEGF.

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1. Introduction

Metastasis refers to the process through which cancer cells detach from the primary tumor and migrate to other areas of the body, forming secondary tumors. This complex process encompasses several stages, including separation, movement, encroachment, and attachment. Cancer cells escape their initial site, navigate through the bloodstream and lymphatic system, endure the pressures within blood vessels, and acclimate to new environments across the body. Timely detection and prompt treatment can significantly reduce the likelihood of solid tumors spreading, thereby improving their manageability. Metastasis represents a major contributor to mortality in patients with advanced cancer and plays a significant role in increasing illness and death rates [1]–[3].

EMMPRIN, commonly referred to as CD147, is a transmembrane glycoprotein extensively found in human cells and plays an essential part in various physiological functions [4], [5]. Studies conducted by Stenzinger *et al*. [6] and Chu *et al*. [7] have recognized EMMPRIN as a critical element in the advancement and spread of cancer. It is known to be overexpressed in multiple tumor types [8], with increased levels detected in metastatic cells [9]–[11] and in the serum of breast cancer patients with lymph node involvement [12]. EMMPRIN is primarily recognized for its angiogenic function, as it promotes the induction of VEGF and MMPs through homophilic interactions between tumor cells and the surrounding stromal cells, particularly fibroblasts. Recent studies have pinpointed a specific short epitope within EMMPRIN crucial for the activation of both VEGF and MMP-9 [13], highlighting its significance in mediating interactions between tumor cells and fibroblasts, with increased expression noted in cultured cells [14]. Acting as a central hub protein, EMMPRIN interacts with various protein partners to form complexes [15] and plays a role in several biological functions, including: enhancing the secretion MMP-1, MMP-2, MMP-3, MMP-9 and membrane-type 1-MMP from cancer cells, fibroblasts, and endometrial cells, leading to degradation of the basement membrane and ECM, thus facilitating tumor growth, invasion, and metastasis [16], [17]; stimulating tumor angiogenesis by increasing MMP and VEGF levels in cancer cells and adjacent mesenchymal tissues [18]; contributing to chemoresistance in diverse cancers, potentially through activation of the PI3K and MAPK pathways [19], [20]. In addition, EMMPRIN has been linked to epithelial-mesenchymal transition (EMT) due to its role in TGFβ1 signaling [21], [22].

MMPs, a family of metal-dependent endopeptidases, are predominantly produced by stromal cells in solid tumors rather than by the cancer cells themselves. The interaction between tumor cells and stromal cells, mediated by EMMPRIN on tumor cells, partially governs this expression. Fibroblasts in the stroma serve as the primary source of MMP production, playing a central role in remodeling the extracellular matrix (ECM) vital for cancer cell behavior. MMPs significantly contribute to essential processes including angiogenesis, invasion, and metastasis [23], [24]. The regulation of MMP production by fibroblasts is influenced by EMMPRIN [25], [26]. Endothelial cells use MMPs to degrade the basement membrane of the original blood vessel and remodel the ECM around newly formed blood vessels. EMMPRIN has been shown to stimulate neighboring stromal cells, both fibroblasts and endothelial cells, to increase their MMP synthesis.

In numerous cancers, there is excessive VEGF production, a potent factor that enhances vascular permeability by binding to tyrosine kinase receptors [27]. EMMPRIN upregulation in tumor cells may enhance VEGF expression, underscoring its potential role in angiogenesis. Research has shown that EMMPRIN is crucial in the metastasis of osteosarcoma, as it regulates the production of MMP-1 and VEGF in both cancer cells and the surrounding stromal cells [28]. EMMPRIN promotes VEGF secretion in fibroblasts and cancer cells via the PI3K-Akt signaling pathway and enhances the expression of VEGFR2 through the transcription factor HIF2α [29], [30]. Additionally, EMMPRIN has been identified as a co-receptor for VEGFR2, with interaction through its extracellular domain near the cell membrane being critical for the VEGF-induced activation of VEGFR2. This suggests that overexpression of EMMPRIN in cancer may intensify VEGFR2 activation. Furthermore, EMMPRIN facilitates the release of VEGF by directly prompting the secretion of MMP-2, MMP-9, and MT1-MMP and has demonstrated the ability to enhance VEGF expression via the Src pathway [31].

Study states that EMMPRIN functions as a scaffold protein, facilitating the organization of various proteins into one or more signaling complexes. These complexes play a critical role in driving cell proliferation, angiogenesis, invasiveness, epithelial-mesenchymal transition (EMT), and cell survival-all essential processes for tumor metastasis. As a result, EMMPRIN is gaining attention as a potential target for therapeutic intervention. Therefore, this review seeks to clarify the role of EMMPRIN in the regulation of important factors involved in cancer metastasis, specifically MMPs and VEGF.

2. EMMPRIN Regulates MMPs in Cancer Cells

MMPs, a group of proteolytic enzymes, are crucial for the remodeling of the ECM in cancer cells, a process vital for metastasis [32]. MMPs become activated through intricate mechanisms involving interactions between cells and the ECM, as well as interactions among different cell types. A soluble and cell-associated factor known as EMMPRIN stimulates MMP production and features two distinct domain structures: extracellular domains I and II [33], [34]. Domain I is particularly important for MMP regulation [35], and EMMPRIN forms homodimers via extracellular domain I on cell surfaces, which promotes MMPs expression [36]. EMMPRIN fulfils its biological roles by inducing the synthesis of several MMPs while not affecting the tissue inhibitors of metalloproteinases [37]–[39]. Study on cancer metastasis has shown that EMMPRIN influences MMPs through cell-to-cell interactions [40] or a paracrine mechanism [41], impacting fibroblast cells via close contact. Thus, the induction of MMPs production is, at least in part, mediated by the interactions between tumor cells and stromal cells through EMMPRIN [42], [43]. Peritumor stromal cells play a crucial role in the production of tumor-associated interstitial collagenase (MMP-1), stromelysin-1 (MMP-3), and stromelysin-3 (MMP-11), gelatinase A (MMP-2), and gelatinase B (MMP-9) across various cancer types, including breast, colon, lung, skin, and neck cancers [44]–[46]. Investigation has showed that EMMPRIN prompts fibroblasts to produce MMP-2, MMP-3, and membrane type MMPs (MT-1 MMP, MT-2 MMP), with MT-2 MMP serving as an endogenous activator of MMP-2 [47], [48]. Consequently, EMMPRIN regulates the upstream production of MMPs within the local tumor microenvironment, thereby facilitating tumor invasion and metastasis.

EMMPRIN is mostly expressed in tumor cells and plays a key role in regulating the expression of MMPs, particularly MMP-2 and MMP-9, recognized as the primary inducers of MMPs through both homotypic and heterotypic cell interactions. EMMPRIN activates various signaling pathways, including nuclear factor κB (NF-κB), mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinase (ERK) 1/2, Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), and c-Jun N-terminal kinase (JNK) [49], [50]. These pathways ultimately promote MMPs production by initiating transcriptional processes in the cell nucleus. The NF-κB pathway is vital for controlling the transcription of various molecules, including adhesion proteins, cytokines, and MMPs [51], [52]. Typically, NF-κB is found in the cytoplasm bound to the inhibitory protein I-κB. Cellular stresses can lead to the ubiquitination, phosphorylation, and degradation of I-κB, allowing NF-κB to move to the nucleus, where it binds to specific sites to enhance gene transcription [53]. The MAPK signaling pathway specifically regulates EMMPRIN and MMPs, with EMMPRIN also activating the ERK1/2 pathway, which supports cellular proliferation and invasion [54], [55]. MAPK and ERK1/2 signaling activate the AP-1 transcription factor through nuclear translocation, inducing gene transcription of MMPs. Meanwhile, the JAK-STAT signaling pathway is critical for regulating cell proliferation, survival, differentiation, and maintaining tissue homeostasis [56]. In this pathway, JAK phosphorylates STAT proteins, which then dimerize and move to the nucleus to activate gene transcription. Additionally, both the PI3K/AKT and JNK pathways can stimulate MMPs production [49].

EMMPRIN is involved in ECM breakdown and fibrosis, facilitating ECM degradation by regulating MMP synthesis and promoting myofibroblast differentiation

[57]. Angiogenesis relies on ECM degradation, which allows tissue invasion and endothelial cell migration. EMMPRIN significantly contributes to angiogenic processes through MMPs and VEGF [58]. Studies suggest that MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, and MT1-MMP play crucial roles in modulating the activities of vascular cells and stem/progenitor cells during angiogenesis [59], [60]. The ECM is critical for tumor growth, with MMPs recognized as central drivers of various tumor phenotypes. The expression patterns of MMPs are primarily regulated by interactions between tumor cells and the surrounding stroma via EMMPRIN. Within the tumor microenvironment, increased MMP activity leads to the proteolytic cleavage of membrane-bound EMMPRIN, resulting in the release of soluble EMMPRIN. This soluble form exerts paracrine effects on neighboring and distant stromal cells, further stimulating the production of MMPs and EMMPRIN, thereby promoting tumor growth, angiogenesis, and metastasis [61].

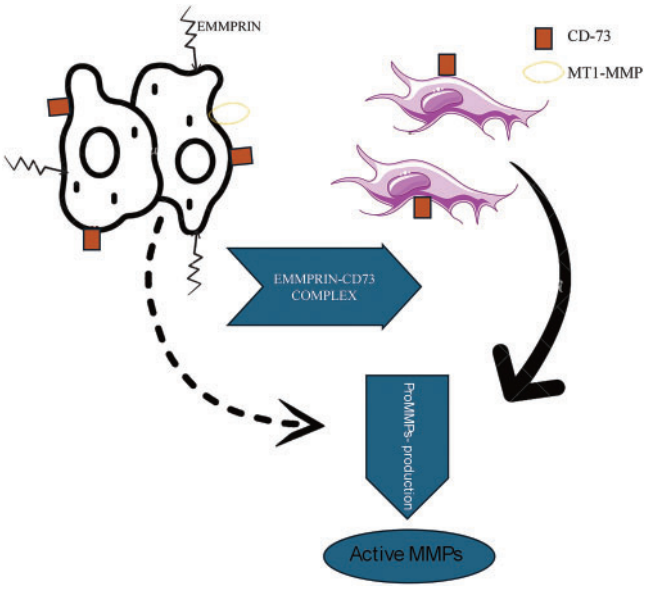

Fig. 1. The interaction between EMMPRIN found on tumor cells and CD73 located on fibroblasts.

3. EMMPRIN Interacts with CD73 to Regulate MMPs

CD73 is a cell surface protein anchored by glycosylphosphatidylinositol, which is highly expressed in various human solid tumors, including colorectal, prostate, gastric, breast, ovarian, and squamous cell carcinomas [62]–[69]. Its presence in cancer cells has been validated using multiple tumor models that lack CD73 [70]–[74], and its activity has been linked to cancer cell invasion and metastasis [75]. CD73 also plays a role in cancer cell proliferation by influencing the cell cycle, and key signaling pathways such as EGFR, β-catenin/cyclin-D1, and AKT/ERK [76]–[79]. Furthermore, recent studies suggest that CD73 intrinsic to cancer cells accelerates metastasis by promoting EMT through the PI3K/AKT and RICS/Rho GTPase signaling pathways [80], [81].

The expression of EMMPRIN in tumor cells, along with the expression of CD73 in both tumor cells and fibroblasts, is clearly evident. Notably, CD73 is more prominently expressed in the stromal fibroblasts located near the tumor cells, highlighting a significant tumor-stromal interaction related to CD73 in the stromal cells. CD73 and EMMPRIN form a complex at the adhesion points between tumor cells and neighboring fibroblasts, which plays a role in regulating the production of MMPs by the fibroblasts [82]. This interaction allows for the regulation of cancer cell invasion and metastasis by influencing how cancer cells interact with extracellular matrix (ECM) components. Particularly, the trans-interaction between fibroblast CD73 and tumor EMMPRIN has been identified as crucial, providing new insights into the role of CD73 in EMMPRIN-mediated cancer metastasis.

EMMPRIN is not necessarily found in every invasive tumor, and its presence alone does not account for the regulation of MMP-2 production. Moreover, the invasive mechanisms in tumors lacking EMMPRIN or in tumor tissues where CD73 is absent in the stroma remain unclear. However, tumors that exhibit high levels of EMMPRIN in the tumor cells and elevated CD73 expression in the stroma are generally associated with increased aggression and invasiveness [83]. Recent studies suggest that the interaction between CD73 on fibroblasts and EMMPRIN on tumor cells is crucial for modulating MMP-2 production. When CD73 is inhibited, MMP-2 production is suppressed at the transcriptional level, leading to a reduction in tumor invasion. This inhibition disrupts the complex formation between EMMPRIN and CD73, thereby decreasing MMP-2 production from fibroblasts and inhibiting tumor invasion. In this context, CD73 in fibroblasts acts as a receptor for EMMPRIN, facilitating a complex that boosts MMP-2 production and contributes to increased invasiveness. Nevertheless, this mechanism is not universally applicable; EMMPRIN is not present in all tumors, and tumors that lack CD73 in the stroma may utilize alternative pathways to regulate MMP-2 production and invasion [83].

EMMPRIN, which is present in cancer cells, creates a complex with CD73, which is found in both cancer cells and fibroblasts. This complex then modulates the production of pro-MMPs, leading to the generation of active MMPs from fibroblasts (Fig. 1).

4. EMMPRIN Regulates VEGF in Cancer Cells

Cancer cells enhance the proliferation and migration of endothelial cells to promote angiogenesis, a process driven by the VEGF and its receptor tyrosine kinase [84], [85]. Increased levels of VEGF have been identified in various human cancers and are closely linked to tumor progression [86]–[88]. Recently, Tang et al. demonstrated that higher expression of EMMPRIN in MDA-MB231 tumor cells can lead to elevated VEGF production, indicating EMMPRIN's potential role in tumor angiogenesis and EMMPRIN stimulates VEGF production via the PI3K-Akt pathway, which plays a significant role in neovascularization within cancerous tissues [89]. Additionally, EMMPRIN fosters tumor-stromal interactions and directly affects tumor angiogenesis by promoting

VEGF release. It has also been suggested that EMMPRIN expression on tumor cells can initiate the production of hyaluronan [90]. Both pathways may lead to VEGF overexpression, further facilitating angiogenesis and metastasis [91]. EMMPRIN has been shown to promote capillary formation, cell migration, and cell survival through its interaction with VEGF receptor-2 (VEGFR-2). Importantly, direct engagement with VEGFR-2 on the cell membrane is essential for the activation of VEGFR-2 by VEGF in melanoma cells, highlighting the intricate mechanism through which EMMPRIN functions [92].

5. Therapeutic Strategies for Targeting CD147

EMMPRIN involvement in tumor angiogenesis and metastasis has positioned it as a novel target for therapeutic advancements. Drug resistance presents a major challenge in cancer treatment, often leading to therapeutic failure. Developing more effective alternative strategies to combat this issue is crucial. Evidence indicates that CD147 plays a pivotal role in drug resistance. The CD147/CD98hc complex, characterized by a highly glycosylated chain linked to a low glycosylated chain, is overexpressed in human cancer cells [93]. The heightened expression of CD147 contributes to chemotherapeutic resistance against drugs such as BCNU, Doxorubicin, Vincristine, and Taxol via its interaction with hyaluronan [94] and CD44. Additionally, this interaction enhances receptor tyrosine kinase activity, ABC transporter functionality, and MCTs, facilitating drug efflux and contributing to resistance against cisplatin and methotrexate [95]. The collaboration between CD147 and LYVE1 (Endothelial hyaluronan receptor-1 of lymphatic vessels) may regulate chemoresistance in lymphoma by increase in the expression of the drug transporter ABCG2 (protein that resist breast cancer) [96]. Furthermore, CD147 is capable of forming a complex with ABCG2, thereby stabilizing it [97]. These insights suggest that therapies targeting CD147 could offer a viable means of circumventing drug resistance. Targeted therapy strategies focus on reducing EMMPRIN expression through RNA interference (RNAi) [98], small molecule inhibitors [99], monoclonal antibodies [100], and polyclonal antibodies aimed at blocking its function [101]. Licartin, a monoclonal antibody targeting CD147, has been developed and received approval for clinical use [102]. Additionally, the antibody MEM-M6/1, which focuses on the interactions between CD147 and MCT-1, has demonstrated the ability to induce necrosis in colon cancer and melanoma cells [100]. Inhibiting CD147 with a specific polyclonal antibody (161-Ab) can significantly suppress the release of VEGF and MMP-9 in accordance with the dosage, ultimately reducing tumor growth and metastasis [101]. The antibody 059-053, in combination with gemcitabine, decreased survival rates in pancreatic cancer cells [103], while an additional monoclonal antibody targeting CD147 (CNTO3899) was shown to promote apoptosis in head and neck cancer cells by increasing caspase-3 and caspase-8 activity [104]. Several variants of the HAb18 antibody targeting CD147 have been created to manipulate cytoskeletal rearrangement through the PI3K-AKT signaling pathway, thereby influencing metastatic spread in hepatocellular carcinoma [105]. In addition, the HcHAb18 antibody, conjugated with a maytansinoid derivative- a cytotoxic agent can effectively target lung cancer [106]. More recently, HAb18 has been demonstrated to sensitize pancreatic cancer cells in response to chemoradiotherapy (Gemcitabine and genfitinib) by inhibiting the STAT pathway [107]. Peptide vaccines targeting EMMPRIN have also been developed [108]. Researchers have identified AC-73, a compact molecule inhibitor of EMMPRIN dimerization, which suppresses MMP-2 synthesis in hepatocellular carcinoma through the CD147-ERK-STAT3-MMP-2 signaling cascade [99]. Furthermore, AC-73 treatment was found to stimulate leukemia cell proliferation by inactivating the ERK-STAT-3 pathway, and chimeric antigen receptor treatment utilizing CD147-CAR-modified immune cells represents a cutting-edge approach in cancer treatment [109]. There is also evidence that AC-73 enhances sensitivity to Chemotherapy with arsenic trioxide and Arabinosylcytosine, allowing for reduced dosages [110]. More recently, Acriflavine, a petite molecule, has been shown to inhibit CD147 and MCT-4 interactions, effectively blocking glioblastoma growth and angiogenesis [111]. The expression of EMMPRIN and MMP-9 correlates with EGFR expression, contributing to cancer progression. Combination therapies targeting EGFR and CD-147 have been found to decrease the proliferation and migration of squamous cell carcinoma cells [112].

6. Conclusion

EMMPRIN is an essential molecular element that significantly contributes to cancer progression. It is involved in the secretion of various MMPs and mediates the binding of fibroblasts. Importantly, the interaction between CD73 and EMMPRIN on cancer cells is essential for regulating the production of MMPs. The formation of a complex between EMMPRIN and CD73 enhances MMP production, leading to increased degradation of the ECM and promoting the invasion of cancer cells. Additionally, EMMPRIN stimulates the production of VEGF via the PI3K-Akt pathway, which supports tumor angiogenesis by regulating VEGF levels. The overexpression of EMMPRIN in cancer cells results in the activation of VEGFR-2, suggesting that inhibiting the interaction between EMMPRIN and CD73, as well as blocking the EMMPRIN/VEGFR-2 pathway, could have a crucial impact on reducing cancer angiogenesis and metastasis.

Author's Contributions

All authors contributed equally to the drafting of the manuscript and shared the responsibility for revising it.

Conflict of Interest

The authors affirm that there are no potential conflicts of interest related to the content of this manuscript.

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