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REVIEW

# EMMPRIN in gynecologic cancers: pathologic and therapeutic aspects

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**Abstract** The highly glycosylated transmembrane protein extracellular matrix metalloproteinase inducer (EMMPRIN) is associated with several pathological conditions, including various types of cancers. In different gynecological malignancies, such as ovarian, cervical, and endometrial cancers, EMMPRIN plays significant roles in cell adhesion modulation, tumor growth, invasion, angiogenesis, and metastasis by inducing the production of various molecules, including matrix metalloproteinases and vascular endothelial growth factor. Because of its high level of expression, EMMPRIN can possibly be used as a diagnostic marker of gynecological cancers. Recent studies have showed that targeting EMMPRIN, especially by RNA interference (RNAi) technology, has promising therapeutic potential in basic research on gynecological cancer treatments, which make a platform for the future clinical success. This review study focused on the association of EMMP RIN in gynecological cancers in the perspectives of pathogenesis, diagnosis, and therapeutics.

**Keywords** Extracellular matrix metalloproteinase inducer · Matrix metalloproteinases · Ovarian cancer · Cervical cancer · Endometrial cancer · Cancer therapeutics

## Introduction

Extracellular matrix metalloproteinase inducer (EMMPRIN) is a highly glycosylated transmembrane protein of the immunoglobulin superfamily. This protein is also known as cluster of differentiation 147 (CD147) or basignin that in human is encoded by the *BSG* (*basigin)* gene [1–3]. In humans, EMMPRIN contains 269 amino acids and has two heavily glycosylated C2-type, immunoglobulin-like domains, a short cytoplasmic tail, and a single transmembrane domain [4–6]. There are four different EMMPRIN protein isoforms (EMMPRIN-1 to EMMPRIN-4) that have been identified as a result of the alternative splicing [7]. Among these four isoforms, EMMPRIN-1 is the larger retina-specific isoform which can be distinguished by an additional extracellular membrane-distal, Ig-like domain in the extracellular part [6, 8]. EMMPRIN-2 is the prototypical isoform expressed most abundantly in tumor cells [9]. EMMPRIN-3 is the shortest isoform, which consists of only one Ig-like domain in its extracellular part and interacts with the internalized EMMPRIN receptor–Cyp ligand complex. EMMPRIN-3 was first identified in human endometrial stromal cells whereas EMMPRIN-4 isoform in cervical carcinoma cell lines. EMMPRIN-3 and EMMPRIN-4 isoforms are thought to be involved in additional protein–protein interactions within the cell [7, 9]. EMMP RIN was named based on its function as it induces the production of extracellular matrix metalloproteinases (MMPs) [10]. It is a widely expressed multifunctional protein and is involved in several physiological processes, such as embryonic development, retinal function, thymic T cell development, and neural functions, such as vision, behavior, memory, and olfaction [2, 11]. EMMPRIN is also involved in several pathological conditions, including various types of cancers. It plays significant roles in cell adhesion modulation, tumor growth, invasion, angiogenesis, and metastasis by inducing the production of various MMPs (such as, MMP-1, MMP-2, and MMP-9), vascular endothelial growth factor (VEGF), caveolin-1 (Cav-1), urokinase-type plasminogen activator (uPA), monocarboxylate transporters (MCTs), and

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cyclophilins (Cyp) through the activation of different cell signaling pathways [1, 4].

Gynecologic cancer is a particular type of cancer that occurs in the female reproductive system. The most common gynecologic cancers are ovarian cancer, cervical cancer, and endometrial cancer that cause cancer-related death in women [12, 13]. Ovarian cancer is the leading cause of death from gynecologic cancers and the fifth leading cause of cancer-related death in women [14, 15]. It is a multifactorial disease and occurs more commonly in developed countries (approximately 9.4 per 100,000) compared to developing countries (5.0 per 100,000), as reported in 2014 [16–18]. Most symptoms of ovarian cancer are nonspecific at its early stages and difficult to diagnose until it spreads to advanced stages [19]. Although standard therapy of surgery combined with chemotherapy and radiation therapy results in complete remission in most patients, relapse and onset of chemoresistant disease are very common and leading to a fatal outcome [20, 21]. Cervical cancer is the second most common cause of cancer-related death in women worldwide [22]. Infection with some types of human papillomavirus (HPV) and several other risk factors have been implicated in the development of cervical cancer [23, 24]. In 2010, it was estimated that there were 454,000 cases of cervical cancer and 200,000 deaths in women [25]. The early stage of cervical cancer is often asymptomatic. Symptoms of locally advanced stage may include abnormal vaginal bleeding, pelvic pain, loss of appetite, weight loss, fatigue, and dyspareunia [26]. Many women with locally advanced cervical cancer receive various combinations of surgery and radiotherapy, although long-term morbidity from treatment is common. Treatment of recurrent cervical cancer remains mostly ineffective [27]. Endometrial cancer is the sixth most common cancer in women worldwide [28]. The incidence of global endometrial cancer death increased from 45,000 women per year in 1990 to 58,000 women per year in 2010 [29]. Multiple risk factors such as age, obesity, genetic mutation, and hormone therapy have been identified in the development of endometrial cancer. Abnormal vaginal bleeding is the most common symptom of endometrial cancer [28, 30]. Surgery is the primary treatment of endometrial cancer, but local and distant recurrences remain the major problems after surgical treatment of primary endometrial cancer [31, 32]. Adjuvant therapy is necessary for patients at high risk of recurrence but it remains unsatisfactory due to the association with adverse side effects [33, 34].

Usually, gynecologic cancers have high mortality rates, because it is difficult to detect the cancer in early stage. Therefore, convenient diagnostic strategies for early detection of gynecologic cancers are needed. As EMMPRIN is overexpressed in a variety of human cancers, including gynecologic cancers, EMMPRIN can serve as a promising diagnostic biomarker for the prognosis and treatment of gynecologic cancers. In this review, I have discussed the role of EMMPRIN in the progression of gynecologic cancers and the recent developments of its usage in diagnostic and therapeutic research and applications.

## Expression patterns of EMMPRIN in gynecologic cancers

EMMPRIN plays a critical role in a variety of tumor-promoting molecular events such as tumor progression, invasion, tumor cell-induced angiogenesis, metastasis, and multidrug resistance [35, 36]. It is overexpressed in numerous types of cancers, including gynecologic cancers, and the increased expression of EMMPRIN is associated with clinicopathological characteristics as well as poor patient survival [37–39].

Jin et al. [40] performed an immunohistochemical analysis of EMMPRIN in tissue microarrays of ovary neoplasms and found that EMMPRIN is overexpressed in all malignant ovary tumors. Zhao et al. [41] detected the upregulated expression of EMMPRIN protein and messenger RNA (mRNA) in ovarian cancer and suggested that the upregulated expression of EMMPRIN might be involved in the pathogenesis and progression of ovarian cancer possibly by modulating the cellular events such as proliferation, migration, invasion, and apoptosis. Szubert et al. [42] detected the expression of EMMPRIN in patients with ovarian cancer and found the upregulated expression of EMMPRIN and VEGF at an advanced stage compared to early stage ovarian cancer which may play a role in angiogenesis and cancer aggressiveness.

Sato et al. [43] detected the enhanced expression of EMMP RIN in human uterine cervical carcinoma SKG-II cells and suggested that the increased expression of EMMPRIN might be responsible for tumor progression and invasiveness along with the increased expression of MMPs. Feng et al. [39] found elevated expression of EMMPRIN in cervical cancer tissues which might be correlated with the degree of tumor differentiation, depth of invasion, and lymph node metastasis. Yu et al. [44] detected the upregulated expression of EMMPRIN and MMP9 correlated with invasion and metastasis in squamous cell carcinoma (SCC) of the uterine cervix. Wu et al. [45] reported that overexpression of EMMPRIN isoform-4 is involved in the progression of cervical cancer. They transfected EMMPRIN isoform-4 (CD147-4) in the cervical cancer cell line SiHa and found that overexpression of EMMPRIN isoform-4 stimulated the proliferation of SiHa cells with a substantial amount of cells in the S phase which might be involved in cervical cancer progression.

Meng et al. [46] monitored the expression profile changes of EMMPRIN between normal endometrial tissue and endometrial cancer tissue by complementary DNA microarray technology and found higher expression of EMMPRIN in endometrial cancer tissue which might be useful in evaluating the progression and infiltration of endometrial cancer.

Nakamura et al. [47] found that the expression levels of EMMPRIN were significantly increased in the endometrial cancer specimens than the normal endometrium and endometrial hyperplasia specimens which is a significant predictor for a poor prognosis of endometrial cancer.

## Role of EMMPRIN in the pathogenesis of gynecologic cancers

Elevated level of EMMPRIN expression has been reported to promote cancer cell invasion and metastasis in several types of human cancers [36, 39]; however, the mechanism of action is not fully clear. A simple diagram presenting the currently understood mechanism of EMMPRIN action in cancer metastasis is shown in Fig. 1. In cancer development, EMMPRIN acts via cell–cell interactions with surrounding cells to stimulate the production of proteolytic enzymes such as MMPs (MMP-1, MMP-2, and MMP-9) through the potential regulators and facilitates the synthesis of MT1-MMP and MT2-MMP, which leads to the destruction of the extracellular matrix (ECM) [48, 49]. In addition to mediating the degradation of the ECM, EMMPRIN also stimulates the secretion of hypoxia-inducible factor-2α, VEGFR-2, and soluble forms of VEGF in both tumor cells and endothelial cells, thus directly regulating the angiogenic process, which is a critical event for progression, invasion, and cancer metastasis [50–52].

EMMPRIN is expressed in micro-vesicles derived from ovarian cancer cells, and the upregulated expression of

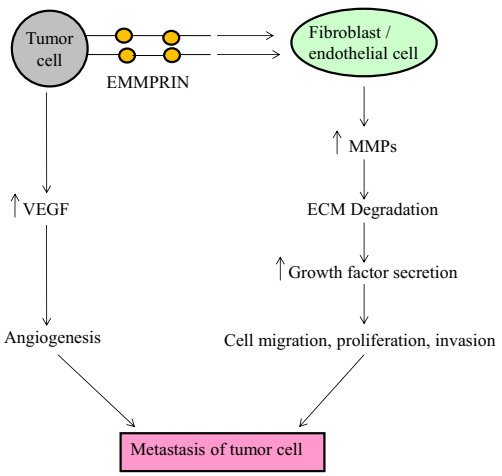


**Fig. 1** EMMPRIN action in cancer metastasis. Tumor cells produce EMMPRIN that interacts with surrounding cells (fibroblast or endothelial cells) through direct cell interactions and induces the production of MMPs leading to the destruction of the extracellular matrix (*ECM*) [48, 49]. MMP-mediated degradation of ECM increases the secretion of growth factors that can lead to cell migration, proliferation, and invasion. EMMPRIN also induces tumor cells to stimulate VEGF secretion that can contribute to initiate angiogenesis during cancer metastasis [50]

EMMPRIN stimulates pro-angiogenic activities of human umbilical vein endothelial cells (HUVECs). The stimulation of HUVECs by EMMPRIN expressed in micro-vesicles mediates ovarian cancer cell proliferation, migration, and invasion via activating VEGF and MMP-9 secretion [53]. EMMPRIN expression is often concurrent with other factors involved in the progression of ovarian cancer such as MCTs. Under a hypoxic microenvironment, EMMPRIN is overexpressed and induces the expression of MCT1 and MCT4 resulting in enhanced lactate efflux into the hypoxic ovarian cancer cells which is responsible for cell proliferation and drug resistance during ovarian cancer metastasis [54–56].

The exact mechanism of action of EMMPRIN in the progression and metastasis of cervical cancer has not been studied well. EMMPRIN expression is reported to be correlated with MCT1 and MCT4 and enhances growth and drug resistance activity in human cervical cancer cells through the production of MMPs and VEGF [57–59].

EMMPRIN is overexpressed in endometrial cancer cells and induces proliferation, migration, and invasion through the upregulated expression of TGF-β, EGF, NF-κB, VEGF, MMP-2, and MMP-9 which in turn promotes epithelial–mesenchymal transition (EMT) by reducing E-cadherin level and enhancing vimentin and snail level in endometrial cancer [47].

## Targeting EMMPRIN in therapeutic approach of gynecologic cancers

The current treatment strategies for gynecologic cancers are mainly surgery, chemotherapy, and radiation therapy. The conventional treatment of gynecologic cancers is still unsatisfactory due to the association of these therapies with severe side effects [12, 60]. The greater understanding of the pathogenic mechanism of gynecologic cancers is essential to develop innovative therapeutic strategies. Identification of appropriate mediator of tumor-promoting molecular events might be an effective therapeutic approach for the treatment of gynecologic cancers. As EMMPRIN is reported to be upregulated in various types of cancers including gynecologic cancers, it could be considered as a promising marker to predict the tumorigenesis and aggressiveness of gynecologic cancers. Targeting this protein may develop safe and effective treatments for the patients with gynecologic cancers (Fig. 2).

Zou et al. [61] suggested that EMMPRIN might be a potential target for therapeutic anti-cancer drugs for ovarian cancer. They induced short hairpin RNA (shRNA)-triggered RNA interference (RNAi) to block the expression of *EMMPRIN* in the human ovarian cancer cell line HO-8910pm and found that knockdown of *EMMPRIN* by shRNA reduced the invasion activity and increased

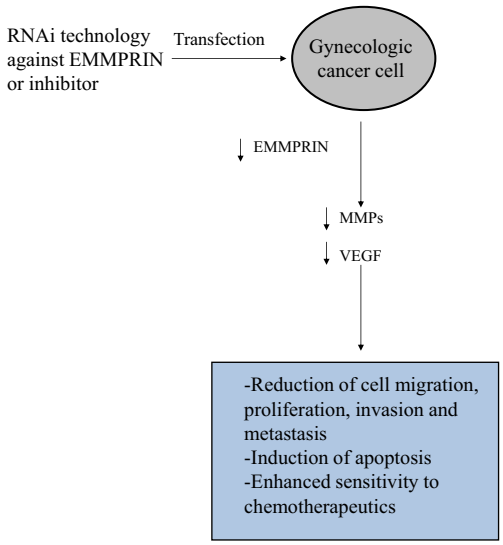


**Fig. 2** Targeting EMMPRIN for the treatment of gynecologic cancers. The blockade of EMMPRIN expression by using RNAi technology or specific inhibitors reduces the production of MMPs and VEGF in gynecologic cancer cells, which, in turn, reduces cell proliferation, migration, invasion, and metastasis; induces apoptosis; and enhances sensitivity to chemotherapeutics [47, 59, 62, 63]

chemosensitivity to chemotherapeutic drug, paclitaxel, in HO-8910pm cells. Zhao et al. [41] transfected EMMP RIN siRNA into ovarian cancer cell lines OVCAR3, SKOV3/DDP, and HO-8910pm and found reduced expression of EMMPRIN which resulted in a lower tumor growth; G1 arrest; apoptotic induction; and reduced migration and invasion in OVCAR3, SKOV3/DDP, and HO-8910pm cells than the control and mock cells. EMMPRIN is a target protein of STAT3, and activation of STAT3 has been reported as a key factor for ovarian cancer metastasis and chemoresistance. Zhang et al. [62] transfected SKOV3 and OVCAR3 cells with STAT3 decoy oligodeoxynucleotide (ODN) and showed that STAT3 decoy ODN inhibited the expression of EMMP RIN which, in turn, inhibited cancer cell-invasive activity and enhanced sensitivity to paclitaxel for SKOV3 and OVCAR3 cells. Zhao et al. [63] transfected *EMMPRIN-2* siRNA into HO-8910pm cells and reported that knockdown of *EMMPRIN-2* reduced production of active MMP-2/9, migration, invasion, and metastasis of HO-8910pm cells. Gao et al. reported that overexpression of EMMPRIN is a risk factor for the resistance to chemotherapeutic drugs in ovarian cancer and suppression of the expression of EMMPRIN increased chemosensitivity to chemotherapeutic drug, which might be a potential target for the prevention of ovarian cancer [64].

Sato et al. [65] transfected human uterine cervical carcinoma SKG-II cells with *EMMPRIN* siRNA which suppressed the production of EMMPRIN and enhanced SKG-II cell migration. In this study, they administered *EMMPRIN* siRNA with two extracellular loop domains (eEMP-I/II) to the cell surface of SKG-II cells, which transcriptionally and competitively suppressed the native EMMPRIN-mediated augmentation of proMMP-1/procollagenase-1 production on the cell surface of SKG-II cells. Fan et al. [66] investigated the anti-invasive effect of siRNA against EMMPRIN on human cervical squamous carcinoma cell line SiHa. They found that the downregulation of EMMPRIN by transfection with siRNA inhibited the invasiveness of SiHa cells which may have anti-tumor effects by downregulating MMP-9. Zhang et al. [59] transfected human cervical cancer cells with EMMPRIN siRNA and found the reduced expression of EMMPRIN at both mRNA and protein level which resulted in G1/S phase transition, inhibited tumor growth, and increased chemosensitivity in human cervical cancer cells. Recently, Huang et al. reported that co-expression of EMMPRIN and glucose transporter (GLUT-1) enhanced resistance to radiotherapy at a clinically relevant level in patients with locally advanced cervical squamous cell carcinoma (LACSCC). In this study, they found that reduced expression of EMMPRIN by transfection with siRNA suppressed the glycolytic rate and the glucose transport which might be regarded as both a therapeutic target and a prognostic factor for LACSCC [67].

There is a lack of sufficient evidences which can support EMMPRIN as a successful target to treat endometrial cancer. In a study, Nakamura et al. [47] transfected endometrial cancer cell lines HEC-50B and KLE with *EMMPRIN* siRNA and reported that *EMMPRIN* knockdown by siRNA inhibited proliferation, migration, and invasion in endometrial cancer cell lines. Their study suggested that EMMPRIN might be a molecular marker for predicting the progression and prognosis in endometrial cancer which may represent a potential therapeutic target for endometrial cancer prevention in the future.

## Conclusions

Gynecologic cancers are the major threat to modern life that causes cancer-related death in women due to the late onset of symptoms. The conventional treatments of gynecologic cancers still remain unsatisfactory because these treatments are mainly based on symptoms and are largely associated with adverse side effects. Early diagnosis and administration of effective treatment are necessary for the treatment of gynecologic cancers. Recently, EMMPRIN has been demonstrated as a potential diagnostic marker to detect the disease at early stage and recognized as an effective therapeutic target for various types of cancers, including gynecologic cancers. More investigations are necessary for the better understanding of the physiological and pathological mechanisms of EMMPRIN

involved in cancer progression which may provide a basis for the efficacy to diagnose and to the selection of appropriate therapeutic approaches for the treatment of gynecologic cancers.

**Conflicts of interest** None

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