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Extracellular matrix proteases - cytokine regulation role in cancer and pregnancy

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1. ABSTRACT

The extracellular matrix proteases act in diverse physiological and pathological processes involving tumor growth, angiogenesis, and pregnancy through the cleavage of extracellular matrix (ECM) and non-matrix proteinaceous substrates. Matrix metalloproteinases (MMPs) constitute a main family among the ECM proteases. Endogenous tissue inhibitors of metalloproteinases (TIMPs), as one kind of MMPs inhibitors (MMPIs), reduce the excessive proteolytic ECM degradation by MMPs. The balance between MMPs and TIMPs plays a major role in cancer tumorigenesis, angiogenesis, as well as embryo implantation and trophoblastic invasion during pregnancy. A variety of literature concerns the correlated changes in MMPs and MMPIs during the formation of cancer and pregnancy-related complications. Importantly, MMPs and TIMPs may act as regulators of signaling pathways through the cleavage of non-matrix substrates, including cytokines, chemokines, and growth factors. In this review, we concentrate on mutual interactions between ECM proteases and cytokines during cancer development and pregnancy. The current knowledge in the field of identified ECM proteases will be contributive to the innovative therapeutic intervention in both cancer and pregnancy-related processes.

2. INTRODUCTION

The extracellular matrix (ECM) provides a structural framework to support cells and maintains cellular functions by mediating the cell-cell or cell-ECM interactions. Matrix metalloproteinases (MMPs) are a family of structurally related, zinc-containing enzymes that degrade the ECM and connective tissue proteins. The MMPs play an important role in vascular remodeling, cellular migration, and the processing of ECM proteins and adhesion molecules (1). Under normal physiological conditions, the activities of MMPs are regulated at the level of transcription, followed by activation of the precursor zymogens, and then interaction with specific ECM components. Also, endogenous TIMPs provide a balancing mechanism to prevent excessive degradation of ECM. MMPs play a key role not only in normal processes of ECM degradation, but also in pathological processes such as tissue remodeling during inflammatory diseases, cancer invasion, and metastasis. Classical MMPs play an important role at all stages of tumorigenesis. There are substantial evidences that overexpression of MMPs correlates with more aggressive phenotypes of tumor cells and poorer prognosis (1-4). Furthermore, MMPs are stressed to have expanded roles for the creation and

maintenance of a microenvironment that facilitates growth and angiogenesis of tumors at both primary and metastatic sites (2).

Previously, we have demonstrated a novel role of metalloproteinase in cancer-mediated immunosuppression and the possible functional role of MMPs in cervical cancer progression (3, 4). Our data show that the function of certain cytokines and/or their receptors can be modified by these ECM immuno-regulatory mediators. Growing evidences in the literature have shown that these ECM proteases can modify many non-matrix substrates, including selected cytokines, chemokines, and growth factors. Essentially, the ECM proteases can either activate or inactivate these substrates, or further generate other products that have biological consequences.

Recent evidences show that MMPs are also essential for embryonic development, pregnancy and labor. Furthermore, extensive tissue remodeling occurs during pregnancy. MMPs and TIMPs play important roles throughout various stages of pregnancy, including embryo implantation, trophoblastic invasion, placentation in early gestation, cervical dilatation in later gestation, and feto-maternal membrane lyses. Meanwhile, maintenance of a normal pregnancy depends on the delicate interaction between cytokine and MMPs. Once these interactions loss its control, it may result in some complications, such as preterm delivery and abortion (5). A better understanding of the correlations between the ECM proteases and the cytokine regulation, either under physiological or pathological conditions, can shed new lights on the novel therapeutic interventions in both cancer- and pregnancy-related disease entities.

3. ECM PROTEASES & INHIBITORS IN CANCER

3.1. MMPs functions in promoting cancer development

Up to now, a growing number of 26 correlated enzymes of the MMP family have been identified in the vertebrates. Among them, 23 have been found in humans (6). Globally, MMPs are divided into six groups as the follows: 1). Collagenases, including MMP-1, -8, -13, and -18 (Xenopus); 2). Gelatinases, including gelatinase-A (MMP-2) and gelatinase-B (MMP-9); 3). Stromelysins, including stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10); 4). Matrilysins, including matrilysin-1 (MMP-7) and matrilysin-2 (MMP-26, endometase); 5). Membrane-type MMPs (MT-MMPs), including the type-I transmembrane proteins MT1-, MT2-, MT3-, and MT4-MMP (MMP-14, -15, -16, and -24), and the glycosyl-phosphatidylinositol (GPI)-anchored proteins MT5-, and MT6-MMP (MMP-17 and -25); and 6). Other MMPs, including MMP-11, -12, -19, -20, -22, -23, and -28 (Figure 1).

The regulations of MMPs in cancer are complicated with the final functional entities. Diverse regulatory signals initiate a cascade of events that lead to the generation of functional MMPs. Active MMPs are involved in a number of processes that promote cancer development, including promoting genetic instability, cell growth, angiogenesis and invasion. MMPs can also interfere with the induction of apoptosis and the host anti-tumor immune response (Figure 2). Clinically, several studies on different human cancer models have found that increased expression of MMPs correlates with poor prognosis, short survival time, and even the presence of local invasion or distant metastases. MT1-MMP, which selectively cleaves both collagen and fibrin, is proposed to be essential for tumor cell invasion (7). As a consequence, suppressing the expression of MT1-MMP in fibroblasts or tumor cells can block the observed invasiveness of cancer cells (8-10). In human salivary gland carcinomas, an enhanced activation of pro-MMP-2, which is also mediated by MT1-MMP, is proposed to be correlated with the invasion and metastasis of these tumors (11).

Based on research of different human cancer models, increased expressions of different ECM proteases have been found to correlate with cancer malignant potentials. In human prostate carcinomas, elevated expression of MMP-26 has been proposed to be necessary for the activation of pro-MMP-9 (12). This results in the degradation of fibronectin and type IV collagen, which promotes cancer cell invasion (12). In squamous cell carcinomas (SCCs), a mitogen-activated protein kinase kinase ½ (MEK½) inhibitor or a p38 inhibitor abolishes the induction of MMP-1 and MMP-10 by ultra-violet radiation (13). MMP-11 is expressed by breast tumor-associated fibroblasts and its expression is increased during breast carcinogenesis (14). Importantly, MMP-21 has dual functions in both the fetal development and in the cancer biology, which links the plausibility of relatively immune-compromised condition of pregnancy and cancer. MMP- 21 is regulated in keratinocytes by transforming growth factor beta1 (TGF-β1) and presented at the invasive front of cutaneous and esophageal SCCs (15). Moreover, human basal cell carcinoma (BCC) epithelium can express multiple MMPs including MMP-3, MMP-7, MMP-10, MMP-12 and MMP-13 (16). Of these MMPs, MMP-13 has been found to play a key role in the ECM degradation associated with tumor progression and malignant epithelial growth of skin carcinogenesis (16, 17).

MMPs also contribute to the modulation of epithelial-mesenchymal transformation (EMT). Several MMPs, including MMP-3, MMP-7 and MT1-MMP can cleave E-cadherin and thus release a soluble 80 kDa peptide with the motility stimulatory activity, which indicates the essential role of MMPs in EMT. Interestingly, the degradation of E-cadherin by MMPs reciprocally enhances the expression of MMPs, which signifies the existence of a MMP-dependent positive feedback mechanism (18). Through this positive feedback mechanism, several MMPs, like MMP-7 and MT1-MMP, are transcriptionally upregulated by *β*-catenin lymphoid enhancer factor/T cell factor (LEF/TCF) complexes (18). During the invasion process of human pancreatic cancer, Tumor-associated trypsinogen, urokinase-type plasminogen activator, MMP-2 and MMP-9 each play a dominant role in the degradation of the ECM (19). MMPs also contribute to the so-called vicious cycle linking bone matrix turnover and tumor expansion in bone metastasis formation. Of

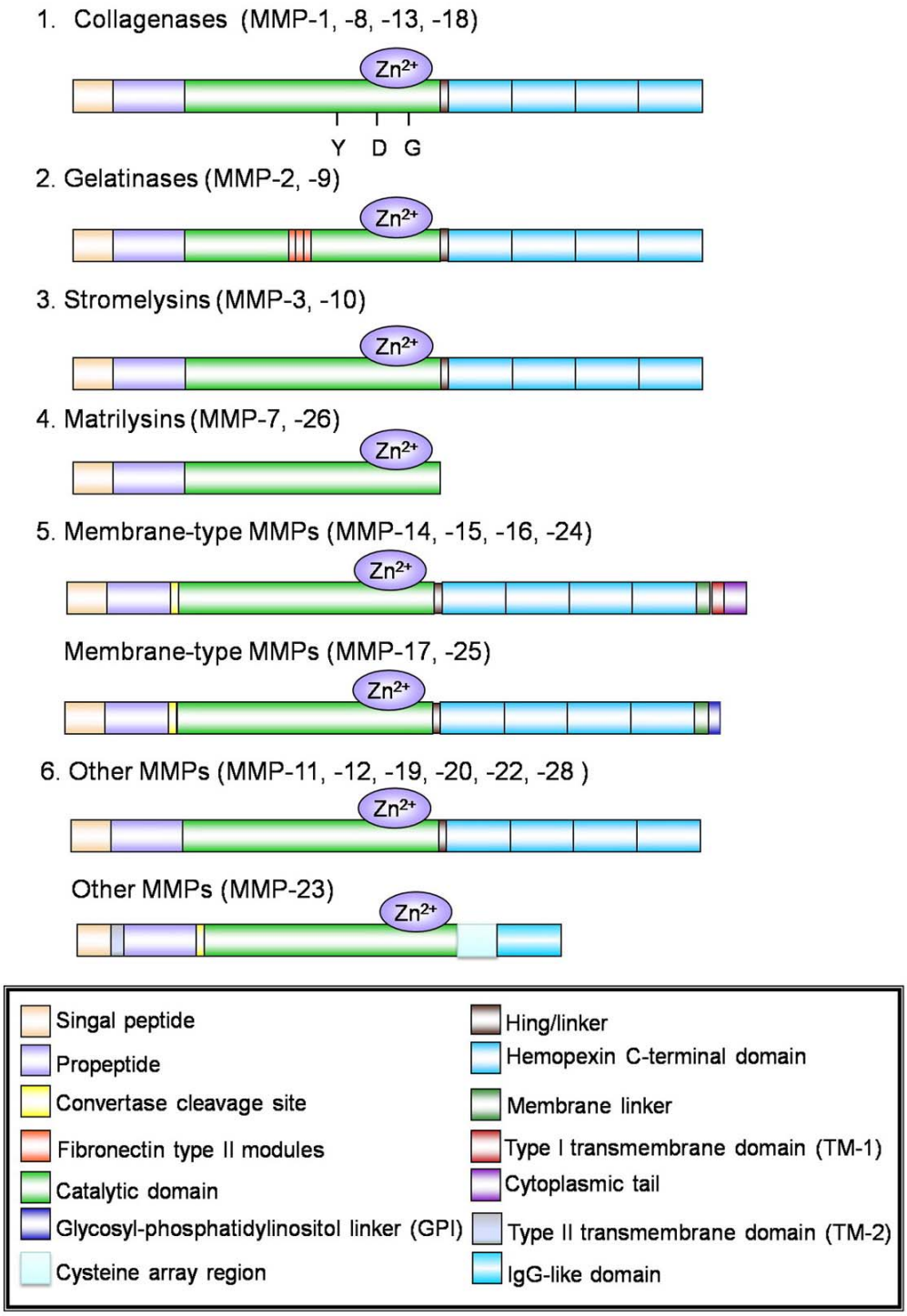

Figure 1. Classification and domain structure of the MMPs. Most MMPs contain a signal peptide (necessary for secretion), propeptide, a catalytic domain that binds zinc (Zn^{2+}), hinge region and a hemopexin carboxy (C)-terminal domain. Y, D, and G represent tyrosine, aspartic acid and glycine amino acids that are present in the catalytic domain of all collagenases. In the catalytic domain, MMP has a Zn^{2+} binding site, and a binding site for the specific substrate. Gelatinases contain fibronectin type II modules that improve collagen and gelatin degradation efficiency. Matrilysins lack a hemopexin domain. MT-MMP has an additional transmembrane binding domain. Most MMPs are secreted, but six membrane-type MMPs (MT-MMPs) have been identified, which are anchored by either a transmembrane domain or a GPI link. TM, transmembrane domain; GPI, glycosyl-phosphatidylinositol linker.

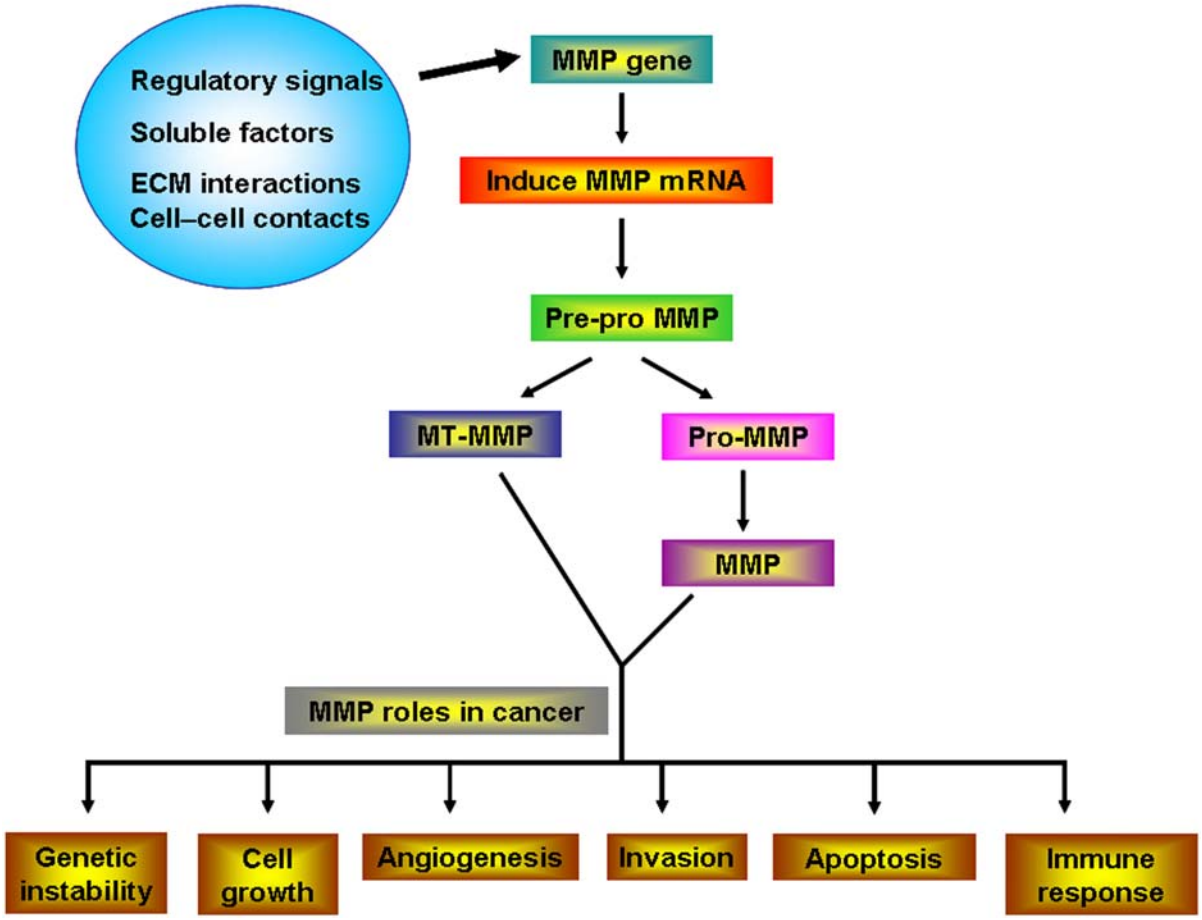

Figure 2. The role of MMPs in cancer. Diverse regulatory signals initiate a cascade of events that lead to the generation of functional MMPs, which are MT-MMPs or proMMP. Active MMPs are involved in a number of processes that promote cancer development, including promoting genetic instability, cell growth, angiogenesis and invasion. They also interfere with apoptosis induction and the host antitumour immune response.

particular importance, MMP-2 and MMP-9 are expressed in both human cervical and prostate cancer tissues and correlated with human cancer invasion and metastasis (3, 4, 20). Furthermore, MMPs are important mediators involved in the establishment and growth of metastatic prostate cancer in bone (20).

3.2. ADAMs share similar functions with MMPs in cancer development

The subcategory of A Disintegrin and Metalloproteinase (ADAMs) may be considered as an extended family of the MMPs. ADAMs are integral membrane glycoproteins containing a disintegrin domain, which is related to snake-venom integrin-binding ligands that disrupt integrin/ligand interactions; a metalloprotease catalytic domain, which may or may not exhibit the MMP-like activity, a cysteine-rich domain, a EGF-like domain, a transmembrane region and a cytoplasmic tail. Many ADAMs regulate cellular behavior through their cell-surface convertase and sheddase activities and by mediating cell-signal transduction activities of certain receptors (21).

The family of ADAMs has diverse functions including the cleavage of proteoglycans, ECM degradation, angiogenesis inhibition, tissue development, and organogenesis (22-25). The association of ADAMs has been shown in multiple human cancers. In a human pancreatic cancer study, the presence of ADAM-9 distinguishes the pancreatic cancerous tumors from solid benign tissues (22). ADAM-10 degrades the ECM in prostate cancers resulting in cancer cell proliferation and tissue invasion. In human liver cancers, the upregulation of both ADAM-9 and -12 is correlated with an increase of MMP 2 expression, tumor aggressiveness, and progression (23). ADAM-12 is also shown to be elevated in the urine of breast cancer patients and correlated with breast cancer progression (24). Above all, ADAM-12 is highly expressed in human glioglastomas and plays a role in cancer cell proliferation by the shedding of heparin-binding epidermal growth factor (HB-EGF) (25).

3.3. TIMPs functions in suppressing cancer development

In the blood and lymphatic system, MMPs are inhibited by α2-macroglobulin. However, the MMP inhibitions within vital tissues are mainly accomplished by four mammalian TIMPs (1–4). In biological tissues, MMP-2 and MMP-9 are usually found as zymogens bound by TIMP-2 and TIMP-1, respectively. In addition to their inhibitory functions, TIMPs have also been shown to have a paradoxical role in MMP activation. For example, TIMP-2 binds to pro-MMP-2 and plays a key role in the surface activation of MMP-2, and TIMP-1 plays a similar role in MMP-9 activation. TIMPs can inhibit almost all kinds of MMPs as tested so far, except that TIMP-1 does not inhibit MT1-MMP. The inhibitory properties of TIMP-3 are different from the rest, because it inhibits the extended MMP category of ADAMs (26). Discretely, TIMP-4 is localized mostly in vascular tissue.

TIMP-1 has a dual role in cancer promotion and suppression. TIMP-1 has been illustrated to stimulate the cancer cell growth while inhibit the gelatinolytic activity within the tumor stroma, thus stabilize the ECM collagen fibrils (27). In a human pancreatic cancer model, over-expression of TIMP-1 can reduce the cell growth, metastasis, and angiogenesis, and by the way increase the tumor apoptosis without altering the production of MMP-2 (28). In primary human breast cancers, the expression of TIMP-1 and plasminogen activator inhibitor (PAI) genes have been shown to be elevated and related to cancer development (29). The stromal-cancer cell interactions are important for the cancer progression. TIMP-1 in these human cancers is highly expressed by myofibroblasts, which is further shown to be associated with the invasiveness of colon cancer cells (30).

The upregulation of mitogen-activated protein kinase (MAPK) phosphatase in tumors that overexpress TIMP-2 leads to dephosphorylation of p38 MAPK, inhibition of tumor growth, and angiogenesis (31). TIMP-2 and TIMP-4 are potent inhibitors for MMP-26-mediated pro-MMP-9 activation in breast cancer invasion (32). TIMP-3 can increase the apoptosis of melanoma cells by the stabilization of their death receptors and the activation of their apoptotic signaling cascade through caspase-8 (33). TIMP-4 can inhibit a broad spectrum of MMPs, including MMP-1, -2, -3, -7, -9, -14, -26, as well as tumor necrosis factor α (TNF-α)-converting enzyme (TACE). In a variety of human cancers, TIMP-4 is shown to be upregulated in cervical cancer, ovarian cancer, invasive endometrial cancer, and ductal *in situ* breast cancer (34, 35). The upregulation of TIMP-4 often co-localizes with the expression of MMP-26 (34, 35). TIMP-4 expression is also upregulated in dysplastic changes in prostatic tissue but downregulated in invasive cancer.

3.4. Other MMP inhibitors antagonize MMPs functions

In addition to the regulation of TIMPs, a variety of protease inhibitors can also mediate the inhibitory functions of certain MMPs. Plasma α2-macroglobulins are general endopeptidase inhibitors that inhibit most proteinases by trapping them within the macroglobulin after proteolysis of the bait region of the inhibitor. It has been shown that MMP-1 reacts with α2-macroglobulin more readily than with TIMP-1 *in vitro*. Furthermore, tissue factor pathway inhibitor-2, formally as a serine protease inhibitor, can also inhibit a broad spectrum of MMPs. Specially, a C-terminal fragment of the procollagen C-terminal proteinase enhancer protein and the secreted form, membrane-bound β-amyloid precursor protein, can inhibit the function of MMP-2. It has been reported that the reversion-inducing cysteine-rich protein with Kazal motifs (RECK), a GPI-anchored glycoprotein, can down-regulate the expressions of both MMP-9 and active MMP-2 within cancer milieu, thus suppress the angiogenic sprouting and lead to tumor cell-death (6).

4. EFFECTS OF MMPS AND CYTOKINES MUTUAL REGULATION IN CANCER DEVELOPMENT

4.1. MMPs regulate cytokine induction in cancer development

Physiologically, growth factors and cytokines are stored in their inactive forms in the cellular microenvironment and immobilized within the ECM through the bindings of glycosaminoglycans. It has been shown that the ECM proteases can regulate the functions of certain growth factors and/or cytokines. MMP-7 generates bioactive insulin-like growth factor-II (IGF-II) by the degradation of the insulin-like growth factor-II /insulin-Like growth factor binding protein 2 (IGF-II/IGFBP-2) complex, which binds the heparin sulfate proteoglycan in the ECM, and results in IGF-II-induced signal transduction (36). In human colon cancer model, the membrane-bound plasmin generated by plasminogen and urokinase-type plasminogen activator (uPA) derived from stromal cells can induce selective proteolysis of IGFBP-4 in the ECM, and thus promote the autocrine IGF-II bioavailability of cancer cells (37). MMP-9 derived from cancer cells can trigger an IGF-I autocrine response by degrading the membrane-bound IGF-I/IGFBP-3 complex in human androgen-independent prostate cancer cells (38). These clinical evidences indicate that the ECM-associated proteases can regulate the function of certain growth factors and cytokines through modulating their receptor-binding abilities in the tumor microenvironment (Figure 3).

In human cancer tissues, MMP-7 is frequently over-expressed and associated with cancer progression. MMP-7 has been shown to play important roles not only in degradation of ECM proteins, but also in the regulation of several biochemical processes, including activation, degradation, and shedding of non-ECM proteins. Proteolysis of the IGF binding protein by matrilysin results in increased bioavailability of IGFs and enhanced cellular proliferation. Besides, MMP-7 has also been proposed to be crucial in the ecto-domain shedding of several cell surface molecules. MMP-7 is shown to cleave the HB-EGF precursor (proHB-EGF) into mature HB-EGF, which further promotes the cellular proliferation. The ECM protease can also mediate the regulations of a variety of vital cellular ligands. The membrane-bound Fas ligand (FasL) is cleaved by MMPs into the soluble FasL, which

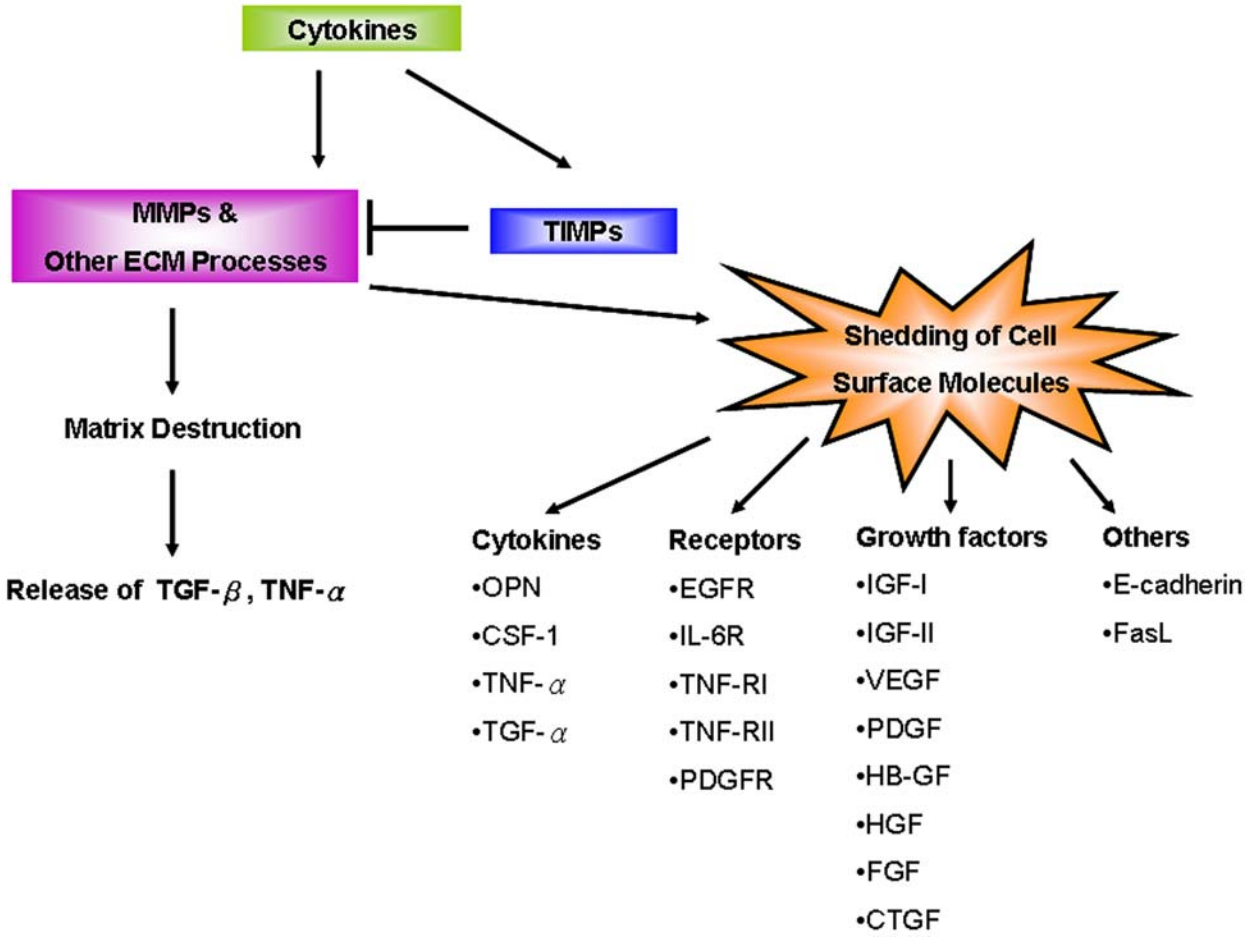

Figure 3. Cytokine-MMP associations. Cytokine activation of cells can lead to increased processing of MMPs from inactive zymogens to the active enzymes and induce TIMPs expression to inhibit MMPs activity. Cytokines and their receptors can also be substrates for MMP action. Many of the membrane-bound cytokines, receptors, growth factors and adhesion molecules can be released from the cell surface by the action of a subset of metalloproteinases.

increases the apoptosis of cells adjacent to tumor cells. The E-cadherin can be converted into soluble E-cadherin and promote the cancer invasion. Moreover, MMPs can cleave the TNF-α precursor into soluble TNF-α and thus induce the cell apoptosis (39).

Death receptor 6 (DR6) is an orphan member of the tumor necrosis factor receptor superfamily (TNFRSF21). By negatively affecting the generation of anti-tumor activity, DR6 is proposed to play a facilitating role in the tumorigenesis. DR6 is uniquely cleaved from the cell surface of tumor cell lines by the membrane-associated MMP-14. The cleaved DR6 extracellular domain can alter the normal differentiation of monocytes into immature dendritic cells (iDC) upon the stimulation of lipopolysaccharide (LPS) and/or interferon-γ (IFN-γ). The effects of DR6 are mostly amended when these iDC are matured by the administration of interleukin-1β (IL-1β) and/or TNF-α. Thus, as a mechanism that tumor cells can employ to actively escape the immune-surveillance, MMP-14 and DR6 jointly affect and modify the generation of antigen presenting cells upon their recognition of tumor antigens (40).

Increased expression of osteopontin (OPN, SPP1), a ligand for αvβ3 integrin and CD44 receptors, is associated with the metastases in several types of human malignancies. OPN can transactivate the epidermal growth factor receptor (EGFR) signaling and thus enhance the production of MMPs *in vitro* (41). In human cancer models, OPN is proposed to regulate the MMP-2 expression and mediate the hepatic metastasis of colorectal adenocarcinoma by enhancing tumor cell invasion and migration through the ECM (42). In addition, MMP-3 and MMP-7 are reported to cleave OPN *in vitro (*43). The MMP-generated OPN fragments can increase the tumor cell adhesion via cell-surface integrin receptors and peritoneal macrophage migration (43). In a human hepatocellular carcinoma (HCC) study, an alternative splicing event (OPN-c) promotes the extracellular cleavage of OPN by MMP-9, and further releases a distinct region of OPN (OPN-5 kDa) that is critical for the cellular invasive and metastatic potentials (44). In human rhabdomyosarcoma, a common soft tissue sarcoma of childhood, OPN in conjunction with MMPs (MMP-2 and MMP-14) and nuclear factor-kappa B (NF-κB) activations

are proposed to construct a putative signaling pathway involved in the tumor growth (45).

ECM proteases also intervene the process of angiogenesis in both the pregnant and cancerous conditions. Angiogenesis involves the tissue revascularization in the pathogenesis and progression of cancer (26, 39). Certain angiogenic growth factors, including acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), TGF-α, TGF-β, TNF-α, vascular endothelial growth factor (VEGF), and angiogenin, are secreted by endothelial cells to accelerate the process of angiogenesis. These factors act as autocrine or paracrine growth factors to induce angiogenesis. Reciprocally, these angiogenic factors can induce the expressions of MMPs in endothelial and stromal cells, and further enhance their own availability and bioactivity. Degradation of the ECM can release certain ECM/basement membrane-sequestered angiogenic factors, such as VEGF, bFGF, and TGF-β (46). It has been shown that both MMP-1 and -3 can degrade the perlecan in the endothelial cell basement membranes and thus release bFGF. Furthermore, MMP-1, -3, -7, or -13 can release the active VEGF165 by cleaving the inactive complex of connective tissue growth factor (CTGF) and VEGF165 (46). MMP-2, -3, and -7 are shown to degrade the ECM proteoglycan decorin and release the latent TGF-β1. The latent TGF-β1 is further activated through the cleavage of latency-associated peptide by MMP-2 and -9. Up-regulation of MMP-9 expression in the angiogenic islets enhance the release of VEGF from the ECM and then promote the generation of the angiogenic phenotype.

4.2. The impact of cytokine induction on MMPs expression in cancers

Several soluble growth factors and cytokines produced by tumor cells are potent inducers for the expression of MMPs by stromal cells (Figure 3). VEGF is shown to induce the expression of several MMPs in endothelial cells. IL-6 and its soluble agonist receptor (sIL-6R) stimulate the expression of MMP-1 and MMP-2 in bone marrow mesenchymal cells, as a plausible mechanism involved in promoting the myeloma progression. The expression of MMP-9 in fibroblasts can be induced by tumor cell-derived TNF-α and TGF-β, and this stimulatory effect is dependent on the "Small Mothers against Decapentaplegic" (Smad)-, Ras-, and phosphatidylinositol 3-kinase (PI3K) signaling pathway. The stimulatory effect of MMP-9 expression is also modulated by the hepatocyte growth factor (HGF)- and EGF-mediated signaling. In the bone, stromal cell-derived factor-1 (SDF-1) can increase the expression of MMP-9 and thus enhance the MMP-9-mediated transcollagen migration of the osteoclast precursor cells (47). Although primarily expressed by stromal bone marrow cells, SDF-1 is also expressed by the human prostate cancer cells and adjudicates the prostate cancer bone metastasis by stimulating the expression of MMP-9 in osteoclasts (48).

In human breast cancer, the metastatic role of activated TGF-β type I receptor, ALK5, in conjunction with three MAPKs have been investigated. The TGF-β-ALK5-MAPK signaling is shown to promote angiogenesis by upregulating the expression of MMP-9 in tumor cells (46). Pleural malignant mesothelioma is a locally aggressive tumor of mesothelial cell origin. The progression of mesothelioma depends on an interaction with mesothelial cells that provide MT1-MMP necessary to activate pro-MMP-2, which facilitates the migration of tumor cells through ECM under the existence of TGF-β1 and a platelet derived growth factor (PDGF-BB, a chemo-attractant for mesothelial cells) (49).

HGF and its receptor MET are proposed to be crucial for cancer invasion and metastasis. Activation of MET elicit multiple cellular responses regulating cell survival, morphogenesis, adhesion, migration, breakdown of ECM and angiogenesis. Tumor cells can adhere to the ECM via the integrin receptors and form the so-called "focal adhesion complexes". Following the adhesion to ECM components, tumor cells must degrade and invade through this structure to establish the cancer invasion and/or metastasis. Furthermore, HGF can induce the production of various proteases, including the uPA-dependent proteolytic network, MMPs and TIMPs (50). Recently, both the EGF and HGF have been shown to cooperatively induce the ovarian cancer cell migration, invasion, and MMP-9 production through the coordinate activation of unique and overlapping signaling pathways (51). TNF-α enhances the invasiveness of T98G glioma cells through MMP-3 induction, and such enhancement of cell migration can be inhibited by. The inhibitory effect of IFN-γ is based on the binding of TNF-α-activated Ets-1 and NF-κB to their respective enhancer elements found in MMP-3 promoter (52). In human pancreatic cancer, MMP-21 can be upregulated by EGF and act as a marker of differentiation rather than invasiveness (53).

4.3. The impact of chemokine induction on MMPs expression in cancers

Chemokines like monocyte chemo-attractant protein-1/chemokine C-C motif ligand 2 (MCP-1/CCL2), macrophage inflammatory protein-1α/chemokine ligand 3 (MIP-1α/CCL3), and regulated upon activation, normal T cell expressed and secreted/chemokine ligand 5 (RANTES/CCL5) can stimulate the release of monocyte-derived MMP-9 in a TNF-α-dependent manner (46). Besides, SMAD4-deficient tumor cells have been shown to produce chemokine CCL9 and recruit the receptor-expressing cells that further promote the tumor invasion. Increased expression of CCL9 can recruit the immature myeloid cells that carry the CCL9 receptor CCR1 from the blood to the tumor invasion front. These immature myeloid cells then produce both MMP9 and MMP2 and facilitate the tumor epithelium to migrate and invade into the stroma (54).

Malignant plasma cells in multiple myeloma originally reside in the bone marrow (BM), accumulate in different niches and, in late disease, migrate from the BM into blood. The BM is proposed to express the chemokine C-X-C motif ligand 12 (CXCL12) and contribute to the trafficking of myeloma cells within the BM, which is attribute to the MMP-9 and MT1-MMP activities (55). In a

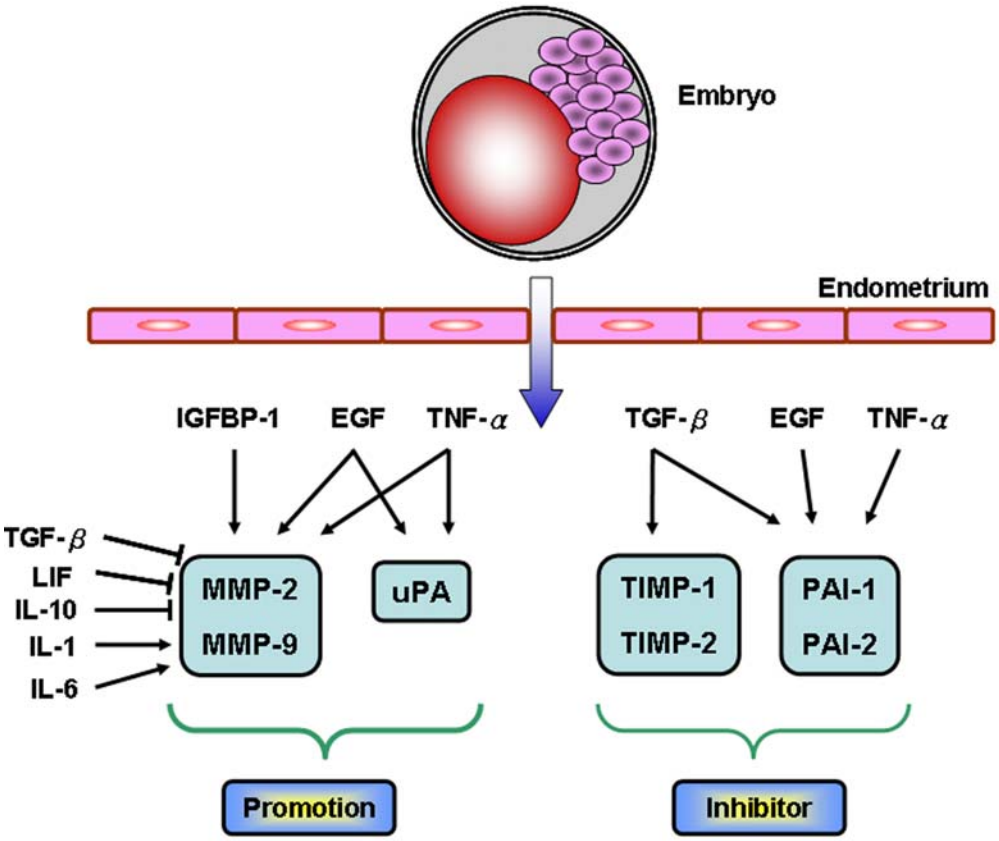

Figure 4. Factors regulating the expression of MMP-cascades from maternal and fetal origin also play important roles during embryo implantation. Embryo implantation and cancer invasion share certain common ECM biochemical mediators for invasion. Both MMPs and TIMPs are equally important for the embryo implantation and the trophoblast penetration. The balanced expressions of MMPs/TIMPs are regulated by several cytokines, including IL-1, IL-6, IL-10, TGF-β, EGF, LIF, IGFBP and TNF-α.

study of human basal cell carcinoma (BCC), up-regulation of MMP-13 mRNA expression and gelatinase activity is proposed to mediate the SDF-1α/ C-X-C motif receptor 4 (CXCR4) expressions and direct the BCC invasion (56).

Within the tumor milieu, cancer cells can recruit the MMP-expressing stromal cells and, in particular, the CD45-positive inflammatory cells that express a variety of MMPs, including MMP-2 and MMP-9. Among the factors that mediate the recruitment of these cells to the tumor microenvironment, colony stimulating factor-1 (CSF-1) is a major regulator of the mononuclear phagocyte lineage. CSF-1 may promote the metastatic potential of cancer cells by regulating the infiltration and function of tumor-associated macrophages at the tumor site, where these cells produce abundant stromal-derived MMPs that further contribute to the tumor progression (57). Chemokines like SDF-1/CXCL12 and MCP-1/CCL2 not only can stimulate the release of MMPs, but also attract the CD45-positive bone marrow-derived inflammatory cells. Particularly, the stromal-derived MMP-9 has a dual-site of action: it promotes the mobilization of bone marrow cells in the bone marrow yet promotes angiogenesis at the tumor site. It has been shown that MMPs is critical for the successful recruitment of inflammatory cells into the tumor microenvironment (54-57).

5. EFFECTS OF MMPS AND CYTOKINES MUTUAL REGULATION IN PREGNANCY

5.1. MMPs and cytokines mutual regulation during embryo implantation

In mammalian pregnancy, embryo implantation is an essential step involving sophisticated communications between maternal decidual and fetal trophoblast cells. Embryo implantation and trophoblast invasion are tightly regulated processes, consisting of three consecutive phases as apposition, adhesion and invasion (58). In the same way, embryo implantation and cancer invasion share certain common ECM biochemical mediators for invasion. However, contrary to the cancer invasion, the trophoblast invasion is limited both in time and space: it occurs during the first trimester of pregnancy and does not invade beyond the decidualized endometrium. Increasing evidences suggest that certain growth factors and cytokines regulate the maternal-fetal interaction during embryonic implantation. In addition, factors regulating the expression of MMP-cascades from maternal and fetal origin also play important roles during embryo implantation (Figure 4).

Essentially, both MMPs and TIMPs are equally important for the embryo implantation and the trophoblast

penetration. The balanced expression of MMPs/TIMPs are regulated by several cytokines, including IL-1, IL-6, IL-10, TGF-β, EGF, HB-EGF, Leukemia inhibitory factor (LIF), IGFBP and TNF-α (59,60). In embryo implantation and placentation, both MMP-2 and MMP-9 are positively linked to the invasive ability of trophoblast cells (61). Contrarily, TIMPs of decidual and/or trophoblast cell origin have a negative physiological role in controlling the trophoblast invasion. The expression of TIMPs in mouse uterine wall and hatching blastocysts can lead to an attenuation of trophoblast penetration *in vitro (*62). Certain MMPs are proposed to be involved in the placental remodeling during pregnancy. In first trimester human placental tissue, the expression and activity of MMP-2 are observed mainly in the extravillous trophoblasts (EVT), whilst MMP-9 mainly in the villous cytotrophoblasts (CTB). The expression of MMP-9 is minimal as compared with MMP-2, suggesting that MMP-2, rather than MMP-9, can be in charge of the first trimester human embryo implantation (63). After the eighth week, the MMP-9 secretion increases gradually, while the MMP-2 production reciprocally declines. Expression of MMP-9 coincides with the maximal invasive potential of CTB, which stresses the major role of MMP-9 in the invasiveness of these cells (63).

At the feto-maternal interphase, IL-1 is present in trophoblastic cells and decidualized stromal cells. The IL-1 receptor is present in endometrial epithelial cells as well as in trophoblasts (64). It is shown that IL-1 can stimulate the expression and activity of MMP-9 in both the trophoblasts and endometrial stroma cells, thereby induce the trophoblast invasion (64). Moreover, certain cytokines are also present at the feto-maternal interface and play quite diverse functions. IL-6 is proposed to enhance the MMP-2 and MMP-9 activity, whereas IL-10 is allied to down-regulate the MMP-9 and trophoblast invasion (65, 66). TGF-β is expressed both in endometrial and trophoblastic cells and shown to inhibit the trophoblast proliferation and invasion. TGF-β1 can mediate the up-regulated expression of E-cadherin and β-catenin in addition to the down-regulated MMP-9 production in early pregnancy (67). It is proposed that TGF-β1 up-regulates the expression of TIMP-1 and -2 as well as PAI-1 and -2 during the trophoblast invasion (68).

Further, certain epithelial growth factors exist in both the decidual and trophoblastic cells and affect the embryo implantation in several ways. EGF is regarded as a major regulator of the implantation process because it can induce the trophoblast invasion, differentiation, and proliferation. EGF has been shown to increase both the MMP-2 and MMP-9 as well as uPA and PAI-1 activities in the trophoblastic cells (69, 70). HB-EGF is expressed in the stromal and epithelial cells of uterus and is linked to the regulation of endometrial proliferation, secretion and decidualization (71). Besides, LIF secreted from the uterus is also regarded as an essential factor in early embryo implantation. LIF and its receptor are present in the pre-implantation embryos and in the CTB. It is proposed that LIF can inhibit the gelatinase activity of MMPs in CTB, thereby abrogate the cell invasiveness (71). Additionally, IGFBP-1 is the main secretory product of the decidualized endometrium. IGFBP-1 can modulate the metabolic effect of IGF-I and IGF-II and intensify the gelatinolytic activity of trophopblasts, thus increase the trophoblast invasiveness and cell migration (72).

The pleiotropic cytokine TNF-α and its two receptors are also present in the endometrium and in the placental trophoblasts. TNF-α can modulate the up-regulation of uPA from CTB and enhance the activation of MMP-9 through the plasminogen activation system, thereby augment the trophoblast invasiveness (73). Elevated expression of TNF-α is observed in certain pathologic processes including pregnancy loss, preterm delivery and preeclampsia, which implicates the abnormal trophoblast endocrine function (74). On the other hand, despite the increased MMP-9 expression, TNF-α is shown to inhibit the *in vitro* trophoblast migration and invasion. Conversely, the PAI-1 that blocks the plasminogen activator system is found to be increased (75). Thus, TNF-α seems to exert diverse effects in mediating the cytokine and ECM protease network during early pregnancy.

5.2. MMPs and cytokines mutual regulation during parturition

The mechanisms by which human parturition occurs are exceedingly complex. The widely recognized events of parturition include increased myometrial contractility, cervical ripening and decidual/membrane activation. Parturition processes comprise organized formation of the cytokine mediators, the uterotonic phospholipid metabolites (e.g. prostaglandins (PG)), and the induction of ECM remodeling.

In the course of parturition, the cervix, mainly composed of fibrous connective tissue, is remodeled in a two-step process. During the first 36 weeks of gestation, a hormone-driven effect directs the decrease of cervical collagen and proteoglycans, thus shapes the cervix to be a soft and elastic organ for the passage of the fetus. This is attained by a breakdown and reconstitution of the ECM, which is achieved via the recruitment of neutrophils, increase in MMPs, and ultimately changed ECM constructions. During this final cervical-ripening step, certain cytokines, including IL-6, IL-8 and granulocyte-colony stimulating factor (G-CSF), increase and mediate the ECM remodeling. IL-8 promotes recruitment and activation of neutrophils, which in turn stimulate IL-6 and IL-8 production from fibroblasts. The activated neutrophils secrete a variety of proteolytic enzymes, such as MMP-1, MMP-3 and MMP-8 and leukocyte elastase, necessary for the final breakdown of the cervical ECM collagen network (76). Thus, the ECM remodeling of the human cervix is orchestrated by neutrophils, fibroblasts and cytokines, either activated or recruited during the ripening cascade. In human myometrium at term pregnancy, NF-κB activation is shown to mediate the induction of the cyclooxygenase (COX-2) and MMP-9 genes, follow-by the increased production of PG and ECM degradation. The signaling pathway of IL-1β-induced COX-2 and MMP-9 production in human myometrium is also mediated by NF-κB activation (77).

5.3. MMPs and cytokines mutual dysregulation during abortion

In preterm premature rupture of the membranes, elevated fetal plasma MMP-9 concentrations are observed and correlated to facilitated placental separation from maternal mucosa (78). Since abundant expression of MMP-9 is related to embryo excessive invasion, an increased concentration of MMP-9 is shown in patients with recurrent spontaneous abortions (RSA) (79). TGF-β is a credible signal that shuts down the maternal immune system and exerts immunosuppressive effect in normal pregnancy (80). The expression of TGF-β mRNA of decidual cells in abortion-prone mice is significantly lower than that in normal pregnant mice, suggesting the related abnormal expression of TGF-β in decidual cells and the subsequent abortion (81). In the local decidual microenvironment, reduced expression of TGF-β may impair the inherent immunosuppressive activity of pregnancy and relatively enhance the maternal immunologic rejection to the fetal antigens, thus result in the occurrence of abortion. Moreover, PAI-1 is a major inhibitor of PAs, including t-PA and u-PA. The Binding of u-PA with its receptor (uPAR) can elicit various physiological and pathological events, including the conversion of plasminogen to plasmin, which is unfavorable to normal pregnancy (82).

In gestational diabetes, the placenta at term of gestation is characterized by various structural and functional changes. Alterations of serum levels of certain chemokines (MCP-1, RANTES and MMP-9) in diabetic patients can even give rise to abortion during the first trimester of diabetic pregnancy (83). A dys-regulation of placental MT1-MMP in the first trimester of type 1 diabetic pregnancies is shown to be correlated to elevated maternal insulin and TNF-α serum levels (84).

5.4. MMPs and cytokines mutual dysregulation during preterm delivery

Abnormal uterine myometrial contractility causes preterm delivery with consequent perinatal morbidity and mortality (85). Disturbances in hormonal regulation and inflammation-related processes can attribute, at least in part, the pathophysiological mechanisms of uterine contractility. It is now becoming evident that infection and inflammation are involved in the pathogenesis of preterm labor and delivery. A link between TNF-α and IL-1β and premature childbirth has been proposed (85). In addition, increased evidences have shown that certain ECM proteases and mediators, including MMPs, are involved in precipitating the uterine premature contraction. Increased expressions of fetal membrane MMP-9 have been reported during active labor prior to delivery (86).

Chorioamnionitis (CAM)-elicited preterm delivery (PTD) is associated with elevated amniotic fluid levels of certain potent proinflammatory cytokines, including IL-6, IL-8, CSF, MIP-1α, IL-1β, and TNF-α (87). However, in a non-human primate model, preterm labor can only be induced by intra-amniotic infusions of IL-1β and TNF-α, but not IL-6 or IL-8, despite the uniformly inflammatory changes in fetal membranes and lungs (88). IL-1β and TNF-α may induce MMP-1 and MMP-3 activities and thus promote PTD. Augmented expressions of MMP-1 and MMP-3 by decidual cells in CAM-complicated pregnancies are linked to precipitating PTD through the decidual, fetal membrane, and cervical extracellular matrix degradation (89).

In patients with early-onset preeclampsia combined with intrauterine growth restriction (IUGR), adaptation of utero-placental circulation is compromised due to the insufficient invasion of ETV into the spiral artery wall. Markedly reduced expression of MMP-3 and MMP-7 by EVT, especially on the brink of spiral arteries, is shown in preeclamptic patients. Besides, LIF produced by uterine natural killer (uNK) cells that exist at the placental bed of preeclamptic patients and accumulate aside the spiral arteries can suppress MMP-expression (90). Thus, in pregnancy complicated with preeclampsia, altered maternal immune cell networks accumulating and interfering in the placental bed can lead to conversion of the local ECM and cytokine environments, and result in disturbed trophoblast cell function such as impaired MMP expression and reduced invasiveness (90).

5.5. Therapeutic approaches of MMPs in abnormal pregnancy and endometriosis

Recurrent abortions are mostly caused by immunologic rejection mediated by the activation of maternal antigen-specific T cells. Inhibition of the key costimulatory signals can lead to T cell anergy, which indicates the alloantigen-specific immunologic unresponsiveness. To this point, B7-2 (CD_{86}) is one of the representative costimulatory molecules. At the maternal-fetal interface, blockage of the costimulatory signal CD_{86} at early pregnancy with anti-CD86 monoclonal antibody (MoAb) in abortion-prone mice can increase the expression of TGF-β1 and PAI-1 but decline the expression of MMP-9 in decidual cells, indicating that blockage of CD86 can treat uncertain RSA and thus possibly reduce the embryo resorption rate (91).

The effect of heparin treatment during pregnancy is under investigation. Formally, heparin is used for the prevention of pregnancy loss in pregnant women with thrombophilia. Low-molecular weight heparin (LMWH) is proposed to regulate the *in vitro* trophoblast invasiveness and placental production of MMPs and TIMPs (92). Heparin can significantly enhance both pro- and active forms MMPs and decrease the TIMP-1 and TIMP-2 expressions, thus increase the invasiveness of the EVT and choriocarcinoma cells (92). These observations may help in understanding the effects of heparin treatment during thrombophilia-complicated pregnancy. Besides, vaginal application of indomethacin is effective for prolonging gestation by exerting its tocolytic actions via changes in cervical MMP activity. Indomethacin is shown to decrease the MMP-1, -8, and -9 activities and increased TIMP-1 levels in the pregnant cervix (93).

Additionally, certain *in vitro* investigations of natural nutrients are focused on the uterine tissue contractility. Collagen gel contraction driven by uterine

smooth muscle cells (SMC) can be notably counteracted by epigallocatechin gallate and green tea leaf extract. The addition of ascorbic acid and the amino acids lysine, arginine, cysteine and proline to green tea extract further increase its effectiveness through the decreased MMP expressions. For the possibility of therapeutic application for preterm delivery, a combination of naturally occurring nutrients is proposed to rectify the abnormal uterine myometrial contractility (94). Furthermore, recent research of chorioamnionitis-induced preterm delivery shows the plausibly alternative mechanisms to prevent CAM-induced PTD through inhibiting the effects of p38 MAPK signaling on cytokine-enhanced MMP-1 and MMP-3 expression in term decidual cells (89). Also, administration of an MMP inhibitor can result in a decreased rate of inflammation-mediated preterm delivery in an animal model (95).

Broadly, endometriosis is principally an estrogen-dependent disease with the growth of endometrial tissue outside the uterus. Recent research suggests that the presence of endometriosis can impair the capacity of the eutopic endometrium to respond to endogenous progesterone. In women with endometriosis, reduced progesterone responsiveness is shown to enhance the endometrial expression of MMPs during the secretory phase of the menstrual cycle, thus impair the nidation and promote the establishment of endometriosis (96). A newly developed progesterone receptor (PR) agonist is shown to down-regulate the endometrial expressions of MMPs (MMP-3, -7) *in vitro* and regress the experimental endometriosis *in vivo* (96). Further additional clinical trials of these MMP-inhibitory compounds for the possible treatment of abnormal pregnancy endometriosis are indicated.

6. THERAPEUTIC APPROACHES ABOUT MMPs IN CANCER

6.1. Synthetic MMP inhibitors

The expressions of MMP are up-regulated in a wide range of diseases, especially in cancer. The frequent expressions of these proteases may serve as plausibly therapeutic targets in these pathological conditions. In experimental models, several reagents targeting the protease activity have been employed and shown the preclinical efficacy in the inhibition of growth and progression of various cancers. However, results from clinical trials are disappointing mainly because of the lack of overall response and/or the dose-limiting toxicity (97). Even worse, some compounds show severe side effects, such as inflammation, musculoskeletal pain, and joint strictures (98). The initial attempts to inhibit MMPs for disease treatment go down because the MMPs cleave not only the ECM components, but also many other proteins including growth factor binding proteins, cytokine precursors, and chemokines. Therefore, it is not surprising that systemic and prolonged inhibition of MMP activities causes aberrant immune responses and other stromal reactions. The ineffectiveness of non-specific MMP inhibitions may be explained partly by the recent findings that cancer stromal cells have non-MMP proteinases that also degrade ECM, such as cathepsins and urokinase plasminogen activator receptor-associated protein (uPARAP) (50). Although clinical trials on systemic inhibition of MMPs have no major advance, local applications of selective synthetic MMP inhibitors on certain diseases, such as skin or cervical malignancies, are still under investigation.

6.2. TIMPs act as endogenous inhibitors

Localized TIMP gene transfer and over-expression might provide several advantages as compared to systemic drug administration. These advantages include: (i) an elevated local concentration of the therapeutic molecule through direct on-site administration, thus avoiding serious side effects at distant sites; (ii) sustained and prolonged expression of TIMP molecule by single gene administration if proper vector system is available. For example, TIMP-1 gene transfer delivered by an adenoassociated virus (AAV) vector is shown to inhibit the tumor growth and angiogenesis in a murine xenotransplant model (99). However, the paradoxical effects of TIMPs in cancer are still under investigation. The current limitations of gene therapy, including low transfer efficiency and poor specificity of response, also slow down the future clinical application of this approach.

6.3. Therapeutic approaches aim at MMPs expression rather than MMPs enzymatic activity

The induction of MMP expression is a result of the interplay of multiple transcription factors and chromatin-remodeling activities. Recently, screening systems of utility for small compounds that disrupt the interaction network of suppressed MMP expression have been developed (100-105). Carbon monoxide-releasing molecules (CO-RMs) are shown to exhibit potential anti-inflammatory properties. The tricarbonyl dichloro ruthenium (II) dimmer (CORM-2) can regulate the cytokine-associated MMP-7 expression by inhibiting the IL-6 gene expression (100). NRH:quinone oxidoreductase 2 (NQO2) is a cytosolic flavoprotein that catalyzes the two-electron reduction of quinones and quinoid compounds to hydroquinones. Deletion of NQO2 leads to a diverse role of the TNF signaling pathway by suppressing the cell survival signals and potentiating the TNF-induced apoptosis in tumors (101). Moreover, the NF-κB-regulated gene products, such as COX-2, and the MMP-9 can be down-regulated through the deletion of NQO2 (101).

Additionally, Butein (3, 4, 2', 4'-tetrahydroxychalcone) (102), Celastrol (quinone methide triterpene derived from the medicinal plant *Tripterygium wilfordii*) (103), Gambogic acid (GA, xanthone derived from the resin of the *Garcinia hanburyi*) (104) and Salinosporamide A (also called NPI-0052, identified from the marine bacterium *Salinispora tropica,* potent inhibitor of 20S proteasome) (105) are shown to exhibit anti-inflammatory, anti-fibrogenic, and anti-cancer activities. These molecules have comparable capacity through the common inhibitory pathways of the NF-κB-regulated gene products (COX-2 and MMP-9) involved in invasion.

Furthermore, a CHM-1 (2'-fluoro-6, 7-methylenedioxy-2-phenyl-4-quinolone, a 2-phenyl-4-

quinolone derivative) is shown to potently inhibit the expression and proteolytic activity of MMP-9, thus abrogate the HGF-induced cancer cell invasion (106). Recently, hypericin mediated photodynamic therapy (PDT) is proposed to be a promising modality for the treatment of nasopharyngeal cancer (NPC). PDT can downregulate the MMP-9 expression via inhibition of granulocyte-macrophage colony stimulating factor (GM-CSF) production, which in turn modulates the AP1 (activating protein-1) and/or NF-κB transcriptional activities (107). Suppression of MMP-9 by hypericin-PDT is shown to have therapeutic implications.

6.4. Therapeutic approaches focus to the cancer microenvironment

The therapeutic strategy by the combination of selected MMP-targeting therapy within the cancer milieu and conventional cancer therapies may be advantageous. In a human prostate cancer model, adenovirus-mediated TIMP gene transfer targeting the bone microenvironment can efficiently inhibit the prostate cancer-induced osteolysis (108). Through this MMP-targeting pathway in the cancer microenvironment, we can protection the cancer-bordering normal tissue from the degradation and/or invasion of cancer cells. In addition, lack of CCR1 (chemokine (C-C motif) receptor 1) prevents the accumulation of MMP-expressing cells at the invasion front and suppressed tumor invasion, and provides a novel strategy for cancer therapy that targets the ‘‘assisting stromal cells’’ by using the chemokine receptor antagonists (50). Since chemokines are tissue-specific, the application of plausible chemokine antagonists as targeting therapy can diminish the systemic side effects for the localization of cancer cell migration.

6.5. Therapeutic approaches target to the MMP gene expression

In selected MMP-gene targeting researches, antisense oligonucleotides (ASONs) is shown to be effective for suppressing the inappropriately expressed MMP genes in cancer (109). ASONs are designed to specifically bind certain mRNAs, inhibiting the gene expression by interfering with protein translation and/or promoting mRNA degradation. In preclinical animal model studies, MMP-7 ASONs can suppress the MMP-7 expression and thus inhibit the metastasis of gastric and colon cancers (110). However, the instability, efficacy, and off-target effects of ASONs limit their potential as therapeutic drugs. In advance, selected engineered transcription factors can act as modulators of MMP gene expression (111). By employing the designer transcription factors (artificial zinc-finger transcription factors) that directly target transcription, we can fabricate a molecule fused to a robust repressor domain (such as Kruppel-associated box or Sin3 interacting domain) on the MMP promoter, and thus recruit transcription repression machinery for inhibiting the MMP gene expression (112).

7. PERSPECTIVES

An elevated expression of MMPs has been correlated with the growth and metastasis of preexisting cancers. The latest data suggest that MMPs are directly involved in the early stages of cell transformation from normalcy to malignancy and in incipient cancer. Due to the biological and clinical importance of cancer therapy, MMPs have long been targets for pharmaceutical intervention. Several synthetic MMP inhibitors have been developed and have shown successful anti-tumor activity in a variety of animal trials. However, in clinical studies of patients with advanced stages of cancer, the therapeutic strategy has not achieved as effective. The function of MMPs is also essentially engaged in human pregnancy and parturition, especially in preterm delivery, premature rupture of membranes, abortion, and intrauterine growth restriction. Exploration of the critical steps involving the MMPs and their inhibitors may shed light on the identification of MMP targets in tumors and pregnancy associated with cytokine regulation. As we gain better understanding of these mechanisms, adequate therapeutic approaches to reduce tumor cell invasion, cancer progression, and even pregnancy-related complications can be developed in the future.

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Abbreviations: A Disintegrin And Metalloproteinases (ADAMs); acidic fibroblast growth factor (aFGF); activated TGF-β type I receptor (ALK5); activating protein-1 (AP1); adenoassociated virus (AAV); Antisense oligonucleotides (ASONs); basal cell carcinoma (BCC); basic fibroblast growth factor (bFGF); bone marrow (BM); B7-2 (CD_{86}); carbon monoxide-releasing molecules (CO-RMs); chemokine C-C motif ligand (CCL); chemokine C-C motif receptor (CCR); chemokine C-X-C motif ligand (CXCL); chemokine C-X-C motif receptor (CXCR); chorioamnionitis (CAM); colony stimulating factor-1 (CSF-1); connective tissue growth factor (CTGF); cyclooxygenase-2 (COX-2); cytotrophoblast (CTB); death receptor 6 (DR6); epidermal growth factor receptor (EGFR); epithelial-mesenchymal transformation (EMT); extracellular matrix (ECM); extravillous trophoblasts (EVT); Fas ligand (FasL); gambogic acid (GA); glycosylphosphatidylinositol (GPI); granulocyte-colony stimulating factor (G-CSF); granulocyte-macrophage colony stimulating factor (GM-CSF); heparin-binding epidermal growth factor (HB-EGF); HB-EGF precursor (proHB-EGF); hepatocellular carcinoma (HCC); hepatocyte growth factor (HGF); HGF receptor (MET); immature dendritic cells (iDC); insulin-like growth factor (IGF); insulin-Like growth factor binding protein (IGFBP); interferon-γ (IFN-γ); interleukin (IL); intrauterine growth restriction (IUGR); leukemia inhibitory factor (LIF); lipopolysaccharide (LPS); low-molecular weight heparin (LMWH); Lymphoid enhancer factor/ T cell factor (LEF/TCF); macrophage inflammatory protein-1 alpha (MIP-1α); matrix metalloproteinases (MMPs); Membrane-

type MMPs (MT-MMPs); mitogen-activated protein kinase (MAPK); mitogen-activated protein kinase kinase (MEK); MMPs inhibitors (MMPIs); monoclonal antibody (MoAb); monocyte chemoattractant protein-1 (MCP-1); nasopharyngeal cancer (NPC); NRH:quinone oxidoreductase 2 (NQO2); nuclear factor-kappa B (NF-κB); osteopontin (OPN, SPP1); phosphatidylinositol 3-kinase (PI3K); photodynamic therapy (PDT); plasminogen activator inhibitor (PAI); platelet derived growth factor (PDGF); preterm delivery (PTD); progesterone receptor (PR); prostaglandins (PG); recurrent spontaneous abortions (RSA); regulated upon activation, normal T cell expressed and secreted (RANTES); reversion-inducing cysteine-rich protein with Kazal motifs (RECK); Sin3 interacting domain (SID); small mothers against decapentaplegic (Smad); smooth muscle cells (SMC); soluble IL-6 receptor (sIL-6R); squamous cell carcinoma (SCC); stromal cell-derived factor-1 (SDF-1); tissue inhibitors of metalloproteinases (TIMPs); TNF-α-converting enzyme (TACE); transforming growth factor-β (TGF-β); tricarbonyl dichloro ruthenium (II) dimmer (CORM-2); tumor necrosis factor-α (TNF-α); tumor necrosis factor receptor superfamily (TNFRSF); u-PA receptor (uPAR); urokinase plasminogen activator receptor-associated protein (uPARAP); urokinase-type plasminogen activator (uPA); uterine natural killer (uNK); vascular endothelial growth factor (VEGF).

Key Words: Extracellular matrix, Matrix metalloproteinases, Tissue inhibitors of metalloproteinases, Cytokine, Cancer, Pregnancy, Review

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