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Role of Matrix Metalloproteinase in Different Types of Cancer and Other Pathological Conditions

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ABSTRACT
The matrix metalloproteinase family of enzymes is comprised of critically important extracellular matrix remodeling proteases whose activity has been implicated in a number of key normal and pathological processes. These are Calcium and Zinc dependent endopeptidases that are active at neutral P^H. Currently, at least 25 members of this family are known to exist. Based on substrate specificity and domain organization, the MMPs can be loosely divided into four main groups: the interstitial collagenases, gelatinazes, stromelysins and membrane type MMPs. The later include MMPs plays major role in tumor growth, progression and metastasis as well as the dysregulated angiogenesis in different types of cancer. As a result, these proteases have come to represent important therapeutic and diagnostic targets for the treatment and detection of human cancer.

Keywords: Matrix metalloproteinase, cancer, angiogenesis, metastasis.

INTRODUCTION

The MMPs, which are also known as matrixins, are a family of structurally and functionally related endoproteinases that are involved in the degradation of the ECM. Physiologically, these enzymes play a role in normal tissue remodeling events such as embryonic development, angiogenesis, ovulation, mammary gland involution and wound healing. Abnormal expression appears to contribute to various pathological processes including rheumatoid arthritis and osteoarthritis, pulmonary emphysema, and tumor growth, invasion and metastasis [(1)]. Uncontrolled ECM remodeling of the myocardium and vasculature are features of cardiovascular disorders such as atherosclerosis, stenosis, left ventricular hypertrophy, heart failure, and aneurysm. Humans have 24 matrixin genes including duplicated MMP-25 genes; thus there are 25 MMPs in humans [(2)]. Catalytic activity depends on the presence of zinc ions at the catalytic active site. Most MMPs are synthesized and secreted in a zymogen form. Activation is usually accompanied by loss of a 10-kDa amino-terminal domain. Finally, proteolytic activity is inhibited by tissue inhibitors known as TIMPs. Thus, the balance between MMPs and TIMPs are critical for the eventual ECM remodeling in the tissue [(1)].

Types and functions of MMPs:

Based on in-vitro substrate specificity and domain structure, MMPs have traditionally been divided into four main subgroups: interstitial collagenases, gelatinizes, stromelysins and membrane MMPs. The collagenases comprise interstitial collagenase (MMP-1), neutrophil collagenase (MMP-8) and collagenase 3 (MMP-13) [(3)]. These MMPs catalyze degradation of fibrillar forms of collagen (i.e. types I, II and III). MMP-1 shows a preference for the type III form,

MMP-8 preferentially degrades type I collagen, and MMP-13 has highest affinity for type II collagen.
The gelatinazes, which are also known as type IV collagenases, degrade gelatin (denatured collagen), and type IV, V, VII, IX and X collagen. Type IV collagen is particularly abundant in basement membranes, which are the membranes that separate organ parenchyma from the underlying stroma.

The third subgroup of MMPs are the stromelysins (ie stromelysin-1 [MMP-3], stromelysin-2 [MMP-10], stromelysin-3 [MMP-11] and matrilysin [MMP-7]). The stromelysins have relatively broad substrate specificity, catalyzing degradation of many different substrates in the ECM. The substrates include proteoglycans (core protein), noncollagenous proteins such as laminin, fibronectin and the nonhelical regions of collagen IV [(4)].

The fourth subgroup consists of the membrane-type MMPs, which possess a trans membrane domain. Five members of this group have been described, the best characterized species being membrane-type 1 MMP. This MMP has been shown to catalyze activation of progelatinase A, to degrade a variety of ECM substrates and to function as a fibrinolytic enzyme in the absence of plasmin. As with stromelysin-3, the membrane-type MMPs possess a consensus domain that is recognized by a furin-like enzyme [(1)].

Angiogenesis and Metastasis

New growth in the vascular network is important since the proliferation, as well as metastatic spread of cancer cells depends on an adequate supply of oxygen and nutrients and the removal of waste products. New blood and lymphatic vessels form through processes called angiogenesis and lymph angiogenesis, respectively. Angiogenesis is regulated by both activator and inhibitor molecules [(5)]. More than a dozen different proteins have been identified as angiogenic activators, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growth factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor, interleukin-8, hepatocyte growth factor, and epidermal growth factor.

Neovascularization, including tumor angiogenesis, is basically a four-step process [(5)].

- First, the basement membrane in tissues is injured locally. There is immediate destruction and hypoxia.
- Second, endothelial cells activated by angiogenic factors migrate.
- Third, endothelial cells proliferate and stabilize.
- Fourth, angiogenic factors continue to influence the angiogenic process.

Metastasis is the general term used to describe the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs and is the primary cause of cancer morbidity and mortality.

Metastasis involves a series of sequential and interrelated steps. In order to complete the metastatic cascade, cancer cells must detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, and invade and proliferate in distant organs[(6)].

Role of Matrix Metalloproteinase in different types of cancer:

a) Breast cancer:

Tumor initiation and growth: It is generally believed that the key genes involved in breast carcinogenesis are c-oncogenes such as c-erbB-2, c-myc, ras, some members of the ets family, and tumor suppressor genes such as p53 and Rb. MMPs may also play a role in breast cancer initiation and growth. Indeed some of the c-oncogenes may contribute to tumor genesis by regulating the expression of MMPs [(1)]. Overexpression of stromelysin-1 in transgenic mice gave rise to preneoplastic and malignant mammary gland tumours.

Stimulation of angiogenesis: MMPs may promote angiogenesis by at least two different mechanisms: by degrading barriers and thereby allowing endothelial cell invasion; and by liberating factors that promote or maintain the angiogenic phenotype. An example of the latter is the degradation of the ECM protein laminin-5 by MMP-2, which results in enhanced mammary epithelial cell growth. Similarly, both MMP-1 and MMP-3 have been shown to

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breakdown endothelial-derived perlecan, releasing basic FGF, a potent endothelial mitogen [1].

It is important to point out that, although clear evidence exists that MMPs potentiate angiogenesis, these proteases also have the potential to inhibit this process. For example, a number of MMPs, such as MMP-3, -7, -9 and -12, can degrade plasminogen, generating the angiogenesis inhibitor angiostatin. Another potent inhibitor of angiogenesis is endostatin, which is a breakdown product of collagen XV111. It is presently unknown whether MMPs play a role in generating endostatin.

Invasion and metastasis: It is generally assumed that the primary mechanism by which MMPs promote cancer spread is by degradation of the ECM, which consists of two main components: basement membranes and interstitial connective tissue. Although collagen IV is the main component of basement membranes, other proteins such as laminin, proteoglycans, entactin and osteonectin are also present in this structure. The collagen IV component of basement membranes is thought to be degraded mostly by MMP-2 and MMP-9. These MMPs may therefore play a critical role in the conversion of in situ breast cancers to invasive lesions.

A frequent site of breast cancer metastasis is to bone, where the presence of cancer cells upset the balance between bone resorption and bone formation, resulting in net bone loss. Thus, the main effect of breast cancer metastasis in bone is degradation, which appears to be primarily mediated by osteoclasts [7].

b) Gastric cancer:

Gastrointestinal cancer is a variety of cancer types, including the cancers of gastrointestinal tract and organs, i.e., esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus.

The process of carcinogenesis is tightly regulated by antioxidant enzymes and matrix degrading enzymes, namely, matrix metalloproteinase (MMPs). Degradation of ECM proteins like collagen, proteoglycan, laminin, elastin and fibronectin is considered to be the prerequisite for tumor invasion and metastasis. MMPs can degrade essentially all of the ECM components and, most MMPs also substantially contribute to angiogenesis, differentiation, proliferation and apoptosis in gastric cancers [8].

In addition, RECK (REversion including Cysteine-rich protein with Kazal motifs) is a membrane bound glycoprotein that inhibits MMP-2, -9 and -14. Moreover, α2-macroglobulin mediates the uptake of several MMPs thereby inhibit their activity.

Cancerous conditions increase intrinsic Reactive Oxygen Species (ROS) through mitochondrial dysfunction leading to altered protease/anti-protease balance. ROS, an index of oxidative stress is also involved in tumor genesis by activation of different MAP kinase pathways including MMP induction. Oxidative stress is involved in cancer by changing the activity and expression of regulatory proteins especially MMPs. One of the important features of the malignant phenotype in both colorectal and gastric cancer is the overexpression of MMP-2 and -9 as well as activation of proMMP-2 to active MMP-2.The basement membrane which prevents an invading epithelial tumor is mainly made up of type IV collagen, which is substrate of MMP-2 and -9. The event of basement membrane degradation promotes epithelial tumor invasion [9].

c) Ovarian cancer:

There are 3 main types of ovarian cancer including epithelial ovarian cancer, sex cord stromal tumors, and germ cell tumors. Of these, epithelial tumors account for about 90 % of ovarian cancers. Overexpression of the MMPs may transduce the signals for tumor cell migration and invasion through a cell surface receptor coupled to G proteins, PAR1 (Protease-Activated Receptor-1). PAR1 is cleaved by MMP1 which promotes breast cancer migration and invasion. PAR1 has also been identified in ovarian cancer. A metalloprotease cascade where pro-MMP1 was activated to MMP1 which in turn directly activate PAR1. This activation of MMP1-PAR1 induces the secretion of several angiogenic factors from ovarian carcinoma cells which cause endothelial cell proliferation, endothelial tube formation, and migration as well as epithelial ovarian cancer cell invasion [10].

d) Prostate cancer:

In prostate cancer tissue, there is an imbalanced expression of MMPs and TIMPs, manifested as a general loss of TIMPs and an up regulation of

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MMPs. Elevated MMP activity promotes prostate cancer progression not only by facilitating metastasis, but also by profoundly impacting multiple steps of cell proliferation, apoptosis, angiogenesis and epithelial to mesenchymal transition (EMT). As such, it is generally thought that MMPs are more active in advanced stages of prostate cancer. Especially MMP-2,-7,-9 and MT1 - MMP plays major role in tumor invasion and metastasis in prostate cancer [(11)].

Role of MMPs in different pathological conditions:

a) Wound healing:

The loss of ECM during wound healing triggers the rapid expression of MMP-1 in basal keratinocytes at the migrating epithelial front in wounds. MMP-1 expression is controlled by the binding of type I collagen to α2β1 integrin. The MMP-1 expression is induced when cells are in contact with type I collagen promoting migration. For sustained MMP-1 expression, cross talk between α2β1 integrin and the EGF receptor is required. The MMP-1 expression peaks at day 1 after wounding in migrating basal keratinocytes at the wound edge followed by a gradual decrease until re-epithelialization is complete. Laminin isoforms expressed during the final stage of tissue remodeling in keratinocytes act as a signal for the down regulation of MMP-1. Down regulation of MMP-1 seems to be important for normal tissue remodeling as there are high levels of MMP-1 in chronic nonhealing wounds. MMP-8 is another interstitial collagenase that is secreted by wound fibroblasts, neutrophils, and macrophages. An increased expression of MMP-8 in chronic wounds is detrimental to wound repair causing breakdown of type I collagen. Another collagenase, MMP-13, which is expressed by fibroblasts deep in the chronic wound bed, plays an important role in the maturation of granulation tissue, including modulating myofibroblast function, inflammation, angiogenesis, and degradation of matrix.

The MMP-2 expression at the edge of acute wounds is linked with the expression of laminin-332 and increased keratinocyte migration. Metalloproteinase-9 is expressed in several injured epithelia, including the eye, skin, gut, and lung, playing a role in wound healing and cell signaling. It plays an important role in keratinocyte migration; it is expressed at the leading edges of migrating keratinocytes during wound closure.

Both MMP-2 and MMP-9 play a role in regulating angiogenesis during wound healing through the activation of proangiogenic cytokines, including TNF-α and VEGF, and by generating antiangiogenic peptides (e.g., endostatin from type XVII collagen, expressed in the basement membrane) [(12)].

b) Acute Coronary Syndrome:

MMPs and atherosclerosis: MMP activity may contribute to the pathogenesis of atherosclerosis by facilitating migration of vascular smooth muscle cells through the internal elastic lamina into the intimal space, where they proliferate and contribute to plaque formation. On the other hand, MMP activity may diminish plaque volume by degrading extracellular matrix in the intima. MMPs may also facilitate positive remodeling of the artery wall through digestion of the external elastic lamina, thereby minimizing luminal encroachment of accumulating plaque [(13)].

MMP activity with plaque rupture: Acute coronary syndromes may also be influenced by MMPs through degradation of the fibrous cap of vulnerable atherosclerotic lesions. The tensile strength of the fibrous cap protecting the plaque from disruption is mainly derived from collagen types I and III; however, the fibrous cap also contains elastin and proteoglycans. The accumulation of macrophage-derived foam cells in atherosclerotic lesions correlates with increased local release of MMPs and a thin fibrous cap [(14)].

MMPs and platelet aggregation: Some MMPs have been demonstrated to be involved in platelet aggregation. MMP-1 is located at the plasma membrane of platelets where it modifies αIIbβ3 integrin, thereby inducing intracellular tyrosine phosphorylation events and priming platelets for aggregation. MMP-1 also redistributes β3 integrins to discrete areas on the cell periphery and co-localizes in cell contact sites. MMP-2 has been localized to the cytosolic compartment of human platelets and is translocated to the platelet surface and released during platelet aggregation. MMP-2 also potentiates vWF-induced GPIb expression and platelet adhesion. In contrast, some MMPs have been shown to have inhibitory effects on platelet aggregation. Very high

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concentrations of MMP-2 as well as MMP-9 have been shown to inhibit platelet aggregation [15].

c) MMPs in inflammation in response to tissue injury and innate immunity:

Injury initiates a programmed, coordinated series of responses to both repair the damaged tissue and to defend against infection. Almost all resident cells, particularly epithelial cells, endothelial cells and fibroblasts, participate in these processes and contribute to the regulation of inflammation. This occurs partly through the specific activity of a variety of matrix metalloproteinase (MMPs) that are produced by these cells.

i) Soon after injury, epithelial cells at the wound edge produce a chemokine that accumulates on the heparan sulphate chains of syndecan-1, a trans membrane proteoglycan. At the same time, these cells release MMP7, which sheds the ectodomains of syndecan-1, thereby establishing a local chemokine gradient that controls the influx and activation of neutrophils.

ii) Later on in the repair process, epithelial-derived MMP7 cleaves the ectodomains of epithelial (E)-cadherin, thereby disrupting adherens junctions and, in turn, facilitating cell migration. Re-epithelialization is also facilitated by the action of other MMPs, such as MMP1 in skin and MMP9 in lung cells.

iii) MMP7 also sheds and activates FAS ligand (FASL, also known as CD95L) that is produced by epithelial cells, thereby mediating apoptosis, which is a potential innate defence mechanism.

iv) After activation, neutrophils release several proteases. Among them, neutrophil elastase, a serine protease that is exclusively produced by neutrophils, which has direct antimicrobial activity. Activated neutrophils also release MMP9, which degrades and neutralizes the serine protease inhibitor α1-antiproteinase99, a potent inhibitor of neutrophil elastase. In this setting, MMP9 provides cover for the antimicrobial activity of neutrophil elastase, thereby assigning it an indirect role in innate immunity.

v) The activation of the latent form of Tumor-Necrosis Factor (TNF) on the surface of cells such as macrophages is due to metalloproteinase-mediated proteolysis. In addition to ADAM17, MMP7 and MMP12 can activate latent TNF.

vi) The influx of inflammatory cells is mainly directed by specific chemokines that are released by resident cells [16].

d) MMPs role in inflammatory bowel diseases [17]:

Inflammatory bowel disease (IBD) which includes both ulcerative colitis (UC) and Crohn's disease (CD) is a chronic and relapsing autoimmune disease characterized by inflammation of the gastrointestinal tract.

Matrix metalloproteinase (MMPs) and their endogenous inhibitors, tissue inhibitors of MMPs (TIMPs), are produced in the gastrointestinal tract by several structural cells. The balance between MMPs and TIMPs is essential for many physiological processes in the gut. However, imbalance between MMPs and TIMPs plays an important role in the pathophysiology of inflammatory bowel disease.

MMPs involves in the pathogenesis of IBD by 3 mechanisms:

1) Disruption of the epithelial barrier (direct effect on barrier or impaired healing in response to injury).

2) Access of luminal contents to the lamina propria, that is, immune cells.

3) An abnormal immune response [Increased inflammatory response].

Table 1: **MMPs as novel biomarkers of cancer [18]:**

Type of Cancer and MMPs/ADAMs and detected in tissue / body fluid	
Breast	
MMP-13	Tissue
MMP-9, TIMP-15	Serum, tissue

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MMP-9	Urine, serum, plasma, tissue
ADAM12	Urine
ADAM17	Tissue
MMP-15	Tissue
Pancreas	
MMP-9	Pancreatic juice, serum
MMP-2	Pancreatic juice, tissue
MMP-7	Tissue, plasma
Lung	
MMP-9, TIMP-1	Serum
MMP-7	Tissue
MMP-1	Tissue
Bladder	
MMP-9	Tissue
MMP-9, MMP-2	Urine
Colorectal	
MMP-2	Tissue, plasma
MMP-9	Tissue
MMP-2, MMP-9	Plasma
MMP-7	Serum
MMP-1	Tissue
Ovarian	
MMP-9	Tissue
MMP-9, MMP-14	Tissue
MMP-2	Tissue
MMP-2, MMP-9, MMP-1	Tissue
ADAM1	Tissue
Prostate	
MMP-2, MMP-9	Plasma, tissue
MMP-2	Tissue
MMP-9	Urine
ADAM8	Tissue
Brain	
MMP-2	Tissue
MMP-9	Tissue
MMP-2, MMP-9	Tissue, cerebrospinal fluid, urine

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Conclusion:

MMPs play a major role in different physiological and pathological conditions. Many evidences suggest that MMPs are involved in both tumor initiation and progression. MMPs remain a viable target for cancer therapy. Administration of MMP inhibitors can prevent the cancer growth as well as inhibit invasion and metastasis. Other strategies for the inhibition of individual MMPs are also under development including the use of ribozymes. Finally, these proteases have come to represent important therapeutic and diagnostic targets for the treatment and detection of human cancer.

Abbreviations:

MMPs: Matrix Metallo Proteinase

ADAM: A-Disintegrin-And- Metalloproteinase

TIMP: Tissue Inhibitor of MetalloProteinase

IBD: Inflammatory Bowel Disease

VEGF: Vascular Endothelial Growth Factor

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