# MATRIX METALLOPROTEINASE: AN OVERVIEW

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**ABSTRACT**

*Matrix metalloproteinases (MMPs) has collagenase and gelatinase activities. They play important role in cancer invasion and metastasis. There are many MMP inhibitors have been discovered. However, the present inhibitors show adverse effects. Therefore, inhibition of specific types of MMPs has become an attractive target for therapeutic intervention.*

***Key words***: **matrix metalloproteinases, collagenase and gelatinase, metastasis, inhibitors, therapeutic intervention**

## OVERVIEW

Nowadays, cancer develops rapidly in people of all ages. The diagnosis and treatment are too late for local therapeutic strategies and most patients already harbour occult or overt metastasis. Unfortunately for the cancer patient, the existence of metastasis greatly reduces the success of current surgical, chemotheraphy and radiotherapy strategies.

During the course of the disease most patients suffer from metastases at multiple sites, not all of which may be occurring at the same time. Furthermore, metastases have the potential to metastasize further: the presence of large identifiable metastases in a given organ is frequently accompanied by a greater number of micrometastases. And lastly, formation of metastatic colonies is a continuous process that commences early in the growth of the tumour and increases with time.

Cancer metastasis is a highly complex process that involves the deregulation of interacting proteins and genes that are responsible for invasion, angiogenesis, circulation of tumour cells in blood vessels, colonization at secondary organ sites, and finally evasion of host defense systems. (Liotta and Paweletz, 2001)

Matrix metalloproteinase (MMPs) are a family of zinc endopeptidases that are structurally and functionally related. MMPs are capable of degrading many extracellular matrix proteins. To date, at least 25 different MMPs have been identified that share significant sequence homology and common multi-domain organization. According to structure and function, MMPs are classified into five groups:

collagenase, gelatinase, stromelysins, matrisyl and membrane-type MMPs (Johanne et. al. 2001). In general, MMP enzymes are composed of a signal peptide, a propeptide, a catalytic domain, a hinge region and a hemopexin domain.

The N-terminal signal peptide directs the newly synthesized preproenzyme for secretion and is subsequently removed from the latent enzyme. The propeptide contains a conserved cysteine residue, which forms a covalent bond with the catalytic zinc ion in the catalytic site, called cysteine switch, which maintains the proenzyme in latent state (Springman et al., 1990). The catalytic domain contains a highly conserved zinc binding sequence HEXXHXXGXXH, which is essential for the proteolytic activity of MMPs. Glutamate and aspartic acid rich sequences at the N- and C- terminal ends of the catalytic domain are thought to represent calcium binding motifs. MMPs have a hemopexin domain linked to a catalytic domain via a praline-rich hinge region. The hemopexin domain shows sequence similarity to a heme-binding protein hemopexin, and it is highly conserved among MMPs. Two cysteine residues flanking the hemopexin domain form a disulfide bridge folding the domain into a four bladed structure (Overall and López-Otín, 2002; Egeblad et al., 2002).

The synthesis, activation, and inhibition of MMPs are tightly regulated at several levels in order to maintain proper balance between anabolism and catabolism of the articular tissue. Regulatory pathways are found at the transcriptional (stimulation or inhibition of gene expression) and post-transcriptional levels (activation of the secreted latent enzymes and inhibition of active MMPs). The mechanisms governing regulation of the transcription of MMPs are complex. The promoter regions of the MMP genes have been cloned and sequenced and analyses have revealed the presence of several *cis*-acting DNA sequences. These elements have been implicated in both basal and modulatory transcriptional activities. Many of the proteins binding to these regulatory sequences have also been identified, and an understanding of their role as either stimulators or inhibitors of transcription has emerged (Johanne et al., 2001). In normal intact tissues, MMP genes are usually expressed at low levels, but their production rapidly induced when active tissue modeling is needed. The expression of MMPs is induced in response to exogenous signals, such as growth factors, cytokines, chemical agents like phorbol esters, physical stress, oncogenic transformation, cell-cell and cell-matrix interactions. This results in activation of transcriptional factors that bind to specific DNA sequences on 5’-regulatory regions of genes. The transcriptional response to different stimuli then

depends on the function of tissue specific regulatory elements on the MMP genes (Risto and Kahari, 2005). A variety of growth factors stimulate the expression of MMP genes via signal transduction pathways that converge to activate protein-1 (AP-1) complex transcription factors. Mitogen activated protein kinase (MAPK) pathways ERK1, 2; JNK and p38 induce the expression of AP-1 transcription factors. AP-1 transcription factors regulate the expression of a variety of genes involved in proliferation, development, differentiation, inflammation, stress response and tumor progression (Karin et al., 1997).

Most MMPs are secreted as latent, inactive proenzymes or zymogens, and their activity is controlled in extracellular space by zymogen activation and inhibition of the catalytic activity of the enzyme. A cysteine switch formed by the interaction between the conserved cysteine residue near the C-terminal end of the propeptide and the zinc ion in the catalytic site maintains the latency of proMMPs (Van Wart and Birkedal-Hansen, 1990). Activation of proMMPs requires disruption of the cystein-zinc bond by cleavage of the propeptide by proteinase such as plasmin, trypsin, kallikrein, chymase, and mast cell tryptase. Many MMPs can also activate other latent MMPs. In addition, disruption of the cystein switch by various organic and inorganic components, like organomecurials, SH-reactive agent, reactive oxygen and detergents results in autocatalytic cleavage of the propeptide in the conformational change into catalytically active form (Springman et al., 1990; Van Wart and Birkedal-Hansen, 1990).

Once activated, the MMPs are further regulated by several naturally occurring inhibitors, such as the tissue inhibitors of metalloproteinases (TIMPs) and $\alpha_2$-macroglobulin. There are four mammalian TIMPs, TIMP-1 to -4. The TIMPs have molecular weights of 21-28 kDa and are variably glycosylated. They have a two-domain structure, which is formed of 12 separated cysteine residues with six disulphide bonds. The inhibitory activity of the TIMPs resides almost exclusively in the N-terminal domain. However, both domains take part in enzyme-inhibitor binding. The C-terminal domain usually binds to the hemopexin domain of MMPs and the N-terminal to the catalytic domain of MMPs. Like MMPs, TIMPs can also associate with cell membrane proteins or extracellular matrix (ECM) proteins, with exception of TIMP-1, which is only found in an unbound form. TIMPs have other functions apart from MMP inhibition. They can affect cell proliferation, apoptosis and angiogenesis and stimulate tumour metastasis formation (Baker et al., 2002; Sternlicht

and Werb, 2001). $\alpha_2$-macroglobulin is an abundant plasma protein and the major inhibitor of MMPs in tissue fluids. It is mainly synthesized in the liver by hepatocytes. $\alpha_2$-macroglobulin forms complexes with MMPs, and these complexes are removed by scavenger receptor-mediated endocytosis.

Under tightly regulated mechanism of gene expression and enzyme activation, MMPs degrade extracellular matrix proteins and play a major role in modeling and remodeling the extracellular in normal physiology and disease pathology (Benbow and Brinckerhoff, 1997). In excess, MMPs play role in arthritic diseases (Johanne et al., 2001); cancer (Mook et al., 2004; Klein et al., 2004, Risto and Kahari, 2005, Zhang et al., 2004) and tumor invasion and metastasis (Mook et al., 2004). Direct evidence for the involvement of distinct MMPs in tumor growth and invasion has been revealed by studies with either MMP-9 knockout mice having reduced melanoma tumor progression and angiogenesis (Itoh et al., 1998).

At present, several MMP inhibitors are under clinical trials and most of these MMP inhibitors are synthetic peptides, chemically modified tetracycline, bisphosphonates or compounds isolated from natural sources. However, most of these drugs are reported to exert side effects such as, musculoskeletal pain in tendons and joints (Nelson et al., 2000). Therefore, it is urgent to find new MMP inhibitors. New effective MMP inhibitors will be potential in cancer treatment.

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