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MMP- Matrix Metalloproteinase

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ABSTRACT

Matrix metalloproteinase arecalcium dependant zinc containing endopeptidase which play important role in the degradation of extra cellular matrix . MMP play major role in cell proliferation , migration , differentiation , apoptosis.Role of MMP in vascular remodeling is also significant. MMP are involved in various diseases such as matastsis of cancer,athroma , arthritis, and tissue ulceration MMP inhibitors have potential therapeutic value in various diseases.

Keywords: MMP, Matrix metalloproteinase arecalcium.

INTRODUCTION

Matrix metalloproteinases (MMPs) are calcium-dependent zinc-containing endopeptidases[1]; Also know as matrixins,which are synthesized as proMMP The MMPs belong to a larger family of proteases known as the metzincin superfamily.[2]

MMPs were first described by Jerome Gross and Charles Lapiere (1962)[3] who obsrerved the enzymatic activity during tadpoletail metamorphosis, Later, it was purified from human skin (1968)[4], and was recognized to be synthesized as a zymogen

MMP play important role in degradation of extra cellular matrix which act as barrier to microorganism, MMPs are capable cleaving and rebuilding collagen, gelatin, elastin and casein .They are known to be involved in the cleavage of cell surface receptors, apoptotic ligands release (FAS ligand), and chemokine/cytokine inactivation.[5] MMPs are also belived to play a important role in cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, apoptosis, angiogenesis, and host defense. Selectivity of MMP depend on zinc binding group, which play the important role in pathopysiology

The MMP are distinguished from other endopeptidases by their dependence on metal ions as cofactors, their capability to degrade extracellular matrix, and their specific evolutionary DNA sequence.

Structure and Classification

In common MMPs family members have roughly 40% of their primary structures. Based on their substrate recognition and cleavage mechanism MMP aredivided into 6 groups: Gelatinase , Collagenase, stromelysins, membrane

type MMP s (MT-MMPs) and other MMPs. Approximately 20 different types of MMPs have been discovered and classifiedon on the basis of their pre-synthetic region on chromosomes and their various substrate specificities[6]. Number designations MMP-1 to MMP-28 are used for classification, but some have still not been identified through this system MMP-4,MMP-5,MMP-6, MMP-18 are not found in xenopus enzyme.

The enzyme is divided into three domains: N-terminal propeptide, catalytic domain and C-terminal domain[7].The MMPs have a common domain structure. The three common domains are the pro-peptide, the catalytic domain, and the haemopexin-like C-terminaldomain, which is attached to the catalytic domain by a flexible hinge region.[2]

The pro-peptide

Initially the MMPs are synthesized as inactive zymogens with a pro-peptide domain. Before the activity of enzyme the pro- peptide domain should be removed . The pro-peptide domain is part of the “cysteine switch.” The pro peptide domain have a conserved cysteine residue

MMP	kDa	Substrate
MMP-1	43	Collagens (I,II,III,VIII and X); gelatin; aggrecan;Lselectin;IL-1ÀÛ˜?proteoglycanes; entactin; ovostatin; MMP-2; MMP-9
MMP-2	66	Collagens (I,IV,V,VII,X,XI and XIV); gelatin;elastin; fibronectin;aggrecan; MBP; osteonectin;laminin-1; MMP-1; MMP-9; MMP-13
MMP-3	46	Collagens (III,IV,V, and IX); gelatin; aggrecan;perlecan; decorin; laminin; elastin; casein; osteonectin;ovostatin; antactin; plasminogen; MBP;IL-1ÀÛ˜; MMP-2/TIMP-2; MMP-7; MMP-8; MMP-9;MMP-13
MMP-7	20	Collagens (IV and X); gelatin; aggrecan; decorin;fibronectin; laminin; entactin; elastin; casein; transferrin;plasminogen; MBP; ÀÛ˜4-integrin; MMP-1;MMP-2; MMP-9; MMP9/TIMP-1
MMP-8	58	Collagens (I,II,III,V,VII,VIII and X); gelatin; aggrecan;fibronectin
MMP-9	92	Collagens (IV,V,VII,X and XIV); gelatin; entactin;aggrecan; elastin; fibronectin; osteonectin; plasminogen; MBP; IL-1b
MMP-10	46	Collagens (III-V); gelatin; casein; aggrecan; elastin; MMP-1; MMP-8
MMP-11	44	Unknown (the most likely casein)
MMP-12	45	Collagen IV; gelatin; elastin; casein; fibronectin;vitronectin; laminin; entactin; MBP; fibrinogen; fibrin; plasminogen
MMP-13	55	Collagens (I,II,III,IV,IX,X and XIV); gelatin; plasminogen;aggrecan; perlecan; fibronectin; osteonectin; MMP-9
MMP-14	54	Collagens (I-III); gelatin; casein; fibronectin;laminin; vitronectin; entactin; proteoglycans; MMP-2; MMP-13
MMP-15	61	Fibronectin; entactin; laminin; perlekan; MMP-2
MMP-16	55	Collagen III; gelatin; casein; fibronectin; MMP-2
MMP-17	54	Unknown
MMP-18		Collagens (I,II,III,VIII a X); gelatin; aggrecan
MMP-19		Gelatin; aggrecan; fibronectin
MMP-20		Amelogrenein; aggrecan
MMP-21		Unknown
MMP-22		Unknown
MMP-23		Unknown
MMP-24		Unknown
MMP-25		Pro-gelatinase A; fibrin; fibronectin; collagen IV;gelatin
MMP-26		Gelatin IÀÛÜ; P1; fibrinogen; fibronectin; vitronectin
MMP-28		Casein

which interacts with the zinc in the active site and hence they prevents binding and cleavage of the substrate, keeping the enzyme in an inactive form. The cysteine residue is in the conserved sequence PRCGxPD in most of the MMP. Some MMPs activation of enzyme take place by cleavage of prohormone convertase in that site as a part of domain.. MMP-23A and MMP-23B include a transmembrane segment in this domain[8].

The catalytic domain

The structure of MMP catalytic domain X-ray crystallographic structures shown that this domain is an oblate sphere measuring 35 x 30 x 30 Å (3.5 x 3 x 3 nm). The active site is a 20 Å (2 nm) groove that runs across the domain. catalytic domain forming the active site there is a catalytically important Zn^{2+} ion, which is bound by 3histidine residues found in the conserved sequence. Hence, this sequence is a zinc-binding element.

MMP-2 (the gelatinase), integrateFibronectin type II modules inserted immediately before in the zinc-binding site in the catalytic domain.[9]

The hinge region

The catalytic domain is attached to the C-terminal domain by a flexible hinge. This is up to 75 amino acids long, and has no definable structure.

The hemopexin-like C-terminal domain

The C-terminal domain has similarities in structure to the serumproteinhemopexin. It has a 4-bladed â-propeller structure. â-Propeller structures support a large flat surface involved in protein-protein interactions. substrate specificity and site of interaction with TIMP's (tissue inhibitor of metalloproteinases)are determined. The hemopexin-like domain is absent in MMP-7, MMP-23, MMP-26. The membrane-bound MMPs (MT-MMPs) are connected to the plasma membrane through a transmembrane or a GPI-anchoring domain.

Function

The MMPs play an significant role in tissue remodeling associated with various physiological / pathological processes such as morphogenesis, , tissue repair,angiogenesis, cirrhosis, arthritis, and metastasis. MMP-2 and MMP-9 are thought to be involved in metastasis. MMP-1 play an important role in rheumatoid arthritis and osteoarthritis.. Acute and chronic cardiovascular diseases is characterized by the imbalance of MMPs and MMPs inhibitors.[10]

MMP-Inhibitors

MMPs inhibitors are endogenous tissue inhibitor of metalloproteinase for specific MMPs.There are four MMPs Inhibitors are present TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Synthetic MMPs inhibitors have chelating group which bind to the catalytic Zinc atom in MMP active site tightly. There are four common chelating group are present Hydroxamate,Carboxylate,Thiols and Phosphinyls. In which Hydroxamate is a potent inhibitors on MMPs It also inhibit the zinc depentant enzyme because of their bidentate chelation of zinc atom.

Doxycycline inhibits MMP activity at submicrobial does . It is used for the treatment of periodontal diseaseclinically. Tetracycline antibiotic also shown to inhibit MMP activity.

CONCLUSION

MMPs are involved in both turn over and degradation of extra cellular matrix protein. MMPs shows major role in certain diseases also believed to be involved in embryogenesis , morphogenesis, reproduction , tissue remodeling tumor growth and metastasis . Regulation between MMPs and MMPs inhibitors is essential for extra cellular matrix remodeling.

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