CHAPTER 23

MATRIX METALLOPROTEINASES AND MATRIX METALLOPROTENASE INHIBITORS IN DERMATOLOGIC DISORDERS

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INTRODUCTION

Extra cellular matrix (ECM) includes interstitial matrix and basement membrane where interstitial matrix is composed of the fibrous proteins and glycosaminoglycans filling the interstitial space and basement membrane witha sheet like deposition of ECM. Although their major role is supporting structurally surrounding cells they are no longer considered solely as a passive blanket. Rather they are active players of multicellular integrity of tissues. The most common cells synthesizing ECM components are fibroblasts but their degradation and remodelling maintained by various kind of cells including connective tissue and pro-inflammatory cells, including fibroblasts, keratinocytes, osteoblasts, endothelial cells, macrophages, neutrophils and lymphocytes. ECM degrading enzymes matrix metalloproteinases (MMP) collectively called matrixins comprise a large family of zinc-dependent endoproteinases. They also catalyse activation of latent growth factors, cell surface receptors, and adhesion molecules. Additionally matrikines arise from ECM degradation products or motifs found in these ECM components have the ability to control biological processed via binding to growth factor, cytokine and ion channel receptors which make these processes achieved by MMPs more complex. Many normal biological processes, such as reproduction, fetal development and wound healing, are critically dependent on controlled degradation of extracellular matrix (ECM) macromolecules. Tissue inhibitors of matrix metalloproteinases (TIMP) which inhibits MMP activity and α2-macrobgobulin which causes MMP endocytosis and breakdown, are endogenous inhibitors of MMPs. The balance in protease/anti-protease activity is a contributing factor in a number of disease such as cutaneous cancer, psoriasis, rhomatoid arthritis. After the discovery of MMPs role in cancer interest on MMPs increased. Their role in tumor angiogenesis, metastasis and various tumorogenic conditions such as cell migration, proliferation attracted scientist to develop exogenous MMP inhibitors. Couple MMPs were identified and their roles in disease state were not understood well enough to carry out successive trials of MMP inhibitors. Also these MMP inhibitors functions on chelating Zn^{+2} ion which lacks specifity. Recent trial targeting other domains in order to increase specifity are ongoing and promise better results. In this chapter you will find brief presentation of MMPs structure, function, regulation, their role in skin and pathological dermal conditions such as melanoma, psoriasis and eczema. Therapeutic approaches using MMP inhibitors will be covered in this chapter.

Matrix Metalloproteinases

The first Matrix metalloproteinases (MMP) discovered was a collagenase in 1962 by Gross in the tail of a tadpole undergoing metamorphosis.[1] To date 25 different vertebrate MMPs have been identified, 24 of which are present in humans including human specific dublication of MMP-23.[2] MMPs collectively called matrixins comprise a large family of zinc-dependent endoproteinases. They are found in all kingdoms of life and belong to the metzincin superfamily of metalloproteinases, which is characterized by the presence of a catalytic zinc atom in their active center followed by a conserved methionine residue.[3] Matrix metalloproteinases have likely evolved from a single-domain protein which underwent successive rounds of duplication, gene fusion and exon shuffling events to generate the multidomain architecture and functional diversity currently exhibited by MMPs.[2]

Structure of MMPs

They are synthesized as zymogens with a signal peptide which directs them to a secretory pathway. ~80 aa propeptide with a cycstein switch motif and a ~180 aa catalytic metalloproteinase domain are common in all MMPs with the exception MMP-23 which lacks cysteine switch motif. Cysteine switch motif is the cysteine residue targeted by extracellular proteins for activation of MMPs.[4] Alternatively MMPs with a furin recognition site between pro and catalytic domains may be activated by protein convertases or furin/paired basic amino-acid-cleaving enzymes.[5] Except matrilysins (MMP-7, -26) and MMP-23 all MMPs have a hemopexin domain linked to the catalytic domain via a linker or hinge domain and mediates collagen binding for subsequent peptide cleavage and is required for homodimerization of MMP-14 and activation of MMP-2.[6,7] Another function of PEX domain is binding MMPs to

in perivascular space, which is frequently abundant with fibrin.[54] MMPs MMP-19 expression in melanoma cell lines was correlated to their migratory abilities.

MMP Inhibitors

The early hypothesis was that tumor cells expressed MMPs to make holes in the ECM, thereby initiating the development of metastasis. This hypothesis was the powerhouse of MMP inhibition trials with synthetic inhibitors. Initial MMP inhibitors designed were focusing on the active site Zn^{2+} ion binding hydroxamate-based inhibitors. Hydroxamate chelates Zn^{2+} and other divalent metal ions with a backbone mimicking natural peptide substrates in these types of first generation inhibitors.[55] Although animal studies show some good results, clinical trials were all disappointing. Lack of specifity of these inhibitors seems like the most important cause of Worsening prognosis and side effects such as musculoskeletal syndrome.[56,57] At that time only three of the 24 human MMPs were discovered and their known role repertoire was restricted to degradation of ECM.

Non-hydroxamate inhibitors such as carboxylates, hydrocarboxylates, sulphydryls, phosphoric acid derivatives and hydantoin were which targets Zn^{2+} ion, developed in order to overcome major limitations of the first generation inhibitors such as metabolic inactivation and non-selective chelation of metal ions. With the thriving crystallography studies of MMP structure, researchers were no longer limited to substrate-like compounds and new inhibitors designed with various peptidomimetic and non-peptidomimetic backbone structures targeting less conserved sites of the enzyme MMP.[58] Therefore inhibitors selectivity increased with this strategy. The thiol-based inhibitor SB−3CT contains a diphenylether deep-pocket-binding scaffold and is a competitive, mechanism-based inhibitor that is specific for MMP-2 and MMP-9.[59]

One of the earliest non-hydroxamate MMP inhibitor developed was Rebimastat (BMS-275291) which contains a thiol zinc-binding group with a deep-pocket binding backbone is a broad spectrum MMP inhibitor.[60]

Tetracycline antibiotics such as minocycline and deoxycycline have innate MMP inhibitory capacity. Doxycycline hyclate is indicated for periodontal disease and is the only collagenase inhibitor approved by US Food and Drug Administration for any human disease.[61] Its topical application to the skinmay also be beneficial against dermonecrosis induced by Loxosceles spider venom.[62]

Mechanism-based MMP inhibitors bind to the active site of MMPs, resulting in a covalent enzyme modification. This strategy was also used to develop a mechanism-based inhibitor exclusively for MMP-2.[63]

Recent research has also focused on the use of functional blocking antibodies, which have high selectivity and potency. Combining a human antibody phage display library with automated selection and screening strategies97 resulted in the identification of a highly selective antibody-based MMP14 inhibitor called DX−2400. DX−2400 displayed anti-invasive, anti-tumour and anti-angiogenic properties and blocked MMP14−dependent pro−MMP2 processing.[64]

Antibody strategy using TIMP mimics have good results in case of selectivity. A neutralizing antibody designed for MMP-13 targeted active MMP-13 but not latent form or other MMPs.

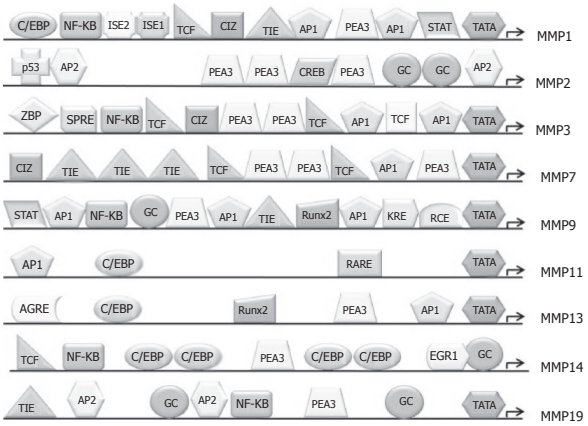


Figure 2. Cis-elements regulating MMP transcription (ref:13).

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