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REVIEW ARTICLE

Matrix metalloproteinases in oral squamous cell carcinoma - A review

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Abstract

The matrix metalloproteinases (MMPs) belong to a group of proteolytic enzymes. They are synthesized as inactive zymogens and ultimately get activated and degrade extracellular matrix which, in turn, leads to tumor progression and metastasis. Numerous studies suggest that individual MMPs have crucial role in tumor invasion and metastasis. As the understanding of the MMPs has advanced, the therapeutic approach on blocking these enzymes by matrix metalloproteinases inhibitors has rapidly developed. At present, clinical assessment of broad spectrum and low-molecular-weight MMP inhibitors is made. In this review, we provide an overview of MMP activities and mentioned briefly on previous studies conducted on appearance of MMPs in oral squamous cell carcinoma. Finally, we have discussed the role of MMPs as potential biomarkers and therapeutic targets.

Introduction

Oral squamous cell carcinoma (OSCC) is the malignancy mainly seen in oral cavity. It is aggressive because it invades and metastasizes very efficiently, thus the prognosis of OSCC patients is poor.[1]

Matrix metalloproteinases (MMPs) are structurally similar and associated to group of zinc-dependent proteolytic enzymes but differ genetically, which play a key role in tumorigenesis by degrading almost all extracellular matrix (ECM) components. In tumor biology, the role of MMPs is wider than has formerly been assumed. They not only play role in breakdown of ECM but also participate in release of growth-promoting signals, apoptosis, modulation of immune responses, and angiogenesis.[2]

In addition, some MMPs degrade basement membrane which, in turn, contributes to cancer cell migration.[3]

In several cancers as compared to normal tissues, there is increased production and activity of various MMPs is seen. However, in OSCC, the exact role and regulation mechanisms of each MMP are not understood.

Classification of MMPs

MMPs are largely divided into interstitial collagenases, matrilysins, metalloelastase, stromelysins, gelatinases, membrane-type MMPs (MTMMP), and remaining on the sources of their substrate specificity.[4,5] Interstitial collagenases (MMP1, -8, and -13) are synthesized by MMPs which mainly degrades Types I, II, and III fibrillar collagens. Degradation of gelatin, collagens, elastin, proteoglycan, and fibrillin takes by gelatinases.[6] Gelatinases are secreted by chondrocytes, osteoblasts, and malignant cells. MMP12 known to degrade Type I gelatin, elastin, Type IV collagen, antitrypsin, and myelin basic protein. They are expressed mainly by macrophages and related with different pathologic as well as inflammatory conditions.[7] Of late MTMMP, their domain structure, substrate activities, and biologic behavior were described. MTMMPs include MMP14 (MT1-MMP), -15 (MT2-MMP), -16 (MT3-MMP), -17 (MT4-MMP), -24 (MT5-MMP), and -26 (MT6-MMP). The pro-MMP2 present on the surface of the cell is activated by MT1-, MT2-, MT3-, and MT5-MMPs and also degrades laminin and fibronectin.[8] The fibrin degradation and cellular invasion shown by MT1-, MT2-, and MT3-MMPs into matrices.[9-11]

The expression of MMP20 (enamelysin) was seen in OSCCs and salivary glands, especially in metabolically active duct epithelial systems.[12]

Structure of MMPs

MMPs encoded by 26 distinct genes and are zinc-dependent endopeptidases. Among the members of MMP family, they have

structural similarity with slight, but considerable differences have been recognized. All MMPs have propeptide (prodomain) region specific for maintaining the latency of the inactive enzyme. This is followed by a catalytic domain having the zinc (Zn^{2+}) active site that attaches to a conserved methionine and three histidine residues and the hemopexin-like C-terminal domain related to the catalytic domain by a hinge region. The C-terminal domain decides the interactions with inhibitors and substrate specificity. The extracellular activation of MMPs takes place in the presence of integrins (e.g., pro-MMP2) or inside the cell with furin-like proprotein convertases (e.g., MT-MMPs), which cleaves the prodomain from the catalytic domain, thus activating MMPs.[13]

Regulation of MMPs

Expression of MMP gene level is low in normal condition. However, during physiological and pathological events, their production is increased, such as embryogenesis, arthritis, tooth eruption, and malignancy. Expression of MMP regulation is a complex event, and it is controlled at many intervals including transcription, activation, and inhibition of the active enzyme.[3]

Transcriptional regulation in OSCCs

Some genes in MMP (MMP-1, MMP-3, MMP-7, MMP-9, MMP-10, MMP-12, and MMP-13) are expressed and they preserve more quantity of regulatory elements inside the promoter regions of these genes. Two main binding sites in promoter regions are the polyoma enhancer activator 3 (PEA3) and activating protein-1 (AP-1) site.[3] The transcriptional response by the AP-1 site is essential to a variety of signals such as interleukin-1, tumor necrosis factor-a, and interferon-b. AP-1 transcription factors made up of proteins, consists of Fos and Jun subunits, and these are expressed as a result of mitogenic stimulus to the normal cells. PEA3 binds to Ets family of oncoproteins. There is a functional cooperation between AP-1 and PEA3 sites, and they have synergistic action between these sites.[3]

Activation of MMPs

The MMPs, for example, gelatinases, collagenases, and stromelysins, are "soluble" and synthesized as zymogens, which require activation. The loss of the amino-terminal prodomain is associated with proteolytic activity. The interaction of MMPs with each other and with other proteases is evident. The MT-MMPs differ in having hydrophobic transmembrane domain at the C-terminus from soluble MMPs. The activation of MT-MMPs involves interaction with tissue inhibitors of MMPs (TIMP).[14]

Studies conducted on expression of MMPs in OSCC samples

Giambernardi *et al.* showed that the overexpression of MMP-9 requires upregulation of H-ras oncoprotein and myc expression involved in upregulating MMP-7, MMP-11, and MMP-13. According to authors, alterations in MMP expression by transformed cells and its inappropriate expression are the main occurrence in the progression of cells to malignant phenotype.[15]

Kurahara *et al.* study suggests the progression of tumor dependents on the capacity of neoplastic cells to degrade ECMs. Different types of MMPs decide the tumor progression and metastasis and the metastasis also depends on excess production of MMPs which seems to be very essential.[16]

The prognostic value of tumor metastases and cause-specific survival depends on the expressions of MMP-9 and TIMP-2. Higher the expression of TIMP poor will be the prognosis in early-stage OSCC.[17]

A study conducted on role of MMP-28 by taking 92 OSCC cases showed that expression of MMP-28 was considerably high.[18]

De Vicente *et al.*, in this study, MMP-7 was expressed in cancer cells alone, whereas MT1-MMP expressed in both neoplastic tissue and stroma. MMP-7 and MT1-MMP, particularly in neck node-positive cases, displayed survival importance, and in multivariate study, they were independent predictive indicators.[19]

In this study, MMP1, MMP10, and MMP12 showed no significant difference in different stages and invasion. Therefore, MMP1 and MMP10, but not MMP12, are probable oral cancer markers.[20]

George *et al.* histopathologically evaluated the expression of MMP-1 in various grades of OSCC. They observed immune reactivity in whole of cytoplasm for MMP-1 in the epithelial as well as in connective tissue cells in OSCC.[21]

The biological behavior of OSCC is closely related to abnormal expression of COX-2 and MMP-7. The COX-2 induces MMP-7 and further lead to the invasion and metastasis of OSCC.[22]

The study conducted on MMPs and evaluated their prognostic value in OSCC and its association with angiogenesis. In each case of tumor examination, MMPs can be considered as prognostic indicators for the malignant potential in OSCC.[23]

Inhibition of MMPs in cancer treatment

In tumor spread and metastasis, MMPs have a crucial role and spread of tumor can be prevented or decreased by inhibiting the activity of MMPs. Several pharmaceutical companies have cum up with low-molecular-weight MMP inhibitors in clinical trials. Among this, batimastat (British Biotech) was first to be tested in patients which is water insoluble. The batimastat is a broad-spectrum inhibitor of MMP-1, MMP-2, MMP-3, and MMP-9. Second-generation synthetic MMP inhibitor is Marimastat (British Biotech), which resemble batimastat structurally, easily dissolved in water so readily given orally. Other MMP inhibitors at present in use are bryostatins, BAY 12-9566 (Bayer), and AG 3340 (Agouron). Bryostatins act by downregulating protein kinase C, which encodes MMP-1, MMP-3, MMP-9, and MMP-11.[14]

Conclusions

By considering many studies, it is proven that MMPs have vital role in tumor spread and metastasis. Different investigation methods are conducted on individual MMPs in different types of tumors.

Although several studies conducted on prognostic significance of individual MMPs, either their study group was relatively small or they studied individual or few numbers of MMPs. Thus, the MMP profiling methods with large sample size in defined series of patients for whom details of treatment intervention, pathological information, and clinical results are known. In regular diagnosis, there is a need for the assessment of MMP expression in histopathological reporting of tumor tissue so that appropriate inhibitor for tumor type can be selected.

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