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Review Article

Matrix Metalloproteinases (MMPs) in Oral Squamous Cell Carcinoma

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Abstract: Tumor growth and development involves interaction between tumor cells and extracellular matrix components characterized by cell proliferation, survival, migration into other tissues by invasion or metastasis. Migration of these tumor cells involve degradation of ECM which is facilitated by matrix metalloproteinases (MMPs). Thus MMPs serve useful tool for early diagnosis, prognosis and survival of the disease. Active role of various MMPs in oral squamous cell carcinoma have been evaluated by previous researchers. In this review we depicted various details regarding MMPs as well as their role in oral cancer regarding different aspects and its importance as marker have been highlighted.
Keywords: tumor cells, Tumor growth, matrix metalloproteinases (MMPs)

INTRODUCTION

Globally, oral squamous cell carcinoma (OSCC) is a chief health hazard with 270,000 new cases and 145,000 deaths annually out of which two-thirds occur in developing nations. The peak incidence of oral squamous cell carcinoma has been observed in the Indian subcontinent. Oral cancer is characterized by a high degree of local invasiveness and a high rate of metastasis to cervical lymph nodes. Death due to cancer is frequently the result of local recurrence or regional and/or systemic metastasis [1].

The prognostic evaluation for oral squamous cell carcinoma is mostly based on clinical TNM staging system which comprises four different stages based on the progression of cancer. The TNM classification system was conceived and modified to assist planning, aid evaluation, facilitate exchange of information and indicate prognosis. It was designed to be simple, reproducible and prognostically suitable [2, 3].

Matrix Metalloproteinases (MMPs) are a family of structurally connected but genetically different enzymes that destroy extracellular matrix and basement membrane components [4]. MMPs are significantly important in tissue remodeling, repair, and destruction. The up and down regulated expression of MMPs considerably differ when applied to predicting tumor cell invasion and transfer. The over expression of some MMPs were linked with oral cancer occurrence, proliferation, lymph node metastasis, and prognosis in current studies [5].

Several studies have shown the contribution of different MMPs in OSCC, which accounts for 95% of the malignant neoplasms of the oral cavity. However, the diversity of the results concerning their participation in these processes has not been clarified. This might be due to different strategies implemented in the study design, the type of analysed samples, and the different number or combination of explored enzymes and different methods used. One of the frequent method used is IHC expression of MMPs but it can be misleading because most antibodies do not differentiate between the pro and active forms of these protein [6].

In this review we would like to highlight the various roles of MMps in oral squamous cell carcinoma.

ORAL CANCER PATHOGENESIS

Oral cancer arises through a sequence of histopathologic stages beginning from benign hyperplasia to dysplasia to carcinoma in situ followed by invasive squamous cell carcinoma. The malignancy

is frequently preceded by potentially malignant disorders like leukoplakia, erythroplakia and oral submucous fibrosis with a transformation rate ranging from 0 to 20% in 1–30 years, according to the type of lesion [7].

Various molecular changes characterized by the sequential stimulation of additional genetic defects, followed by clonal expansion. The genetic alterations are mainly due to oncogene activation and tumor suppressor gene supression, leading to de-regulation of cell proliferation and death. These genetic alterations, include gene amplification and overexpression of oncogenes such as myc, erbB-2, Epidermal Growth Factor Receptor (EGFR), cyclin D1 and mutations, deletions and hypermethylation leading to *p16* and *p53* tumor suppressor gene inactivation [8-10].

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are zinc dependent endopeptidases, which degrade mainly extracellular matrix proteins. Based on their substrate specificity, MMPs have been categorized into distinct subclasses [11]:

Table 1:

Collagenases	Gelatinases	Stromelysins	Matrilysins	Membrane type	Metallo-elastase	Other
MMP-1	MMP-2	MMP-3	MMP-7	MMP-14	MMP-12	MMP-19
MMP-8	MMP-9	MMP-10	MMP-26	MMP-15		MMP-21
MMP-13		MMP-11		MMP-16		MMP-23A
MMP-18				MMP-17		MMP-23B
				MMP-24		MMP-27
				MMP-25		MMP-28

Structure of MMPs

The signal peptide directs emission of the proenzymes. The propeptide includes a conserved sequence (PRCGxPD), in which the cysteine forms a covalent bond (cysteine switch), with the catalytic zinc (Zn2+) to maintain the latency of proMMPs. The catalytic domain contains a highly preserved zinc binding site (HExGHxxGxxHS) in which Zn+2 in coordinated by 3 histidines. The proline rich hinge domain links the catalytic domain to the hemopexin domain, which determines the substrate specificity of specific MMPs. The hemopexin domain is not present in matrilysin (MMP-7) and matrilysin-2 (endometase, MMP-26). Gelatinase A and B (MMP-2 and -9, respectively) contain 3 repeats of the fibronectin –type 2 domain inserted in the catalytic domain.MT1-, MT2-, MT3- and MT5-MMPs contain a transmembrane domain, and MT 4- and MT 6-MMPs contain a glycosylphosphatidylinositol (GPI) anchor in the C-terminus of the molecule, which join these MMPs to the cell surface. MT-MMPs, MMP-11, MMP=23 and MMP-28 contain a furin cleavage to activation by intracellular furin convertases [12, 13].

MMP activation and inhibition

MMPs are mostly released in latent, non-active form, and activation through a so-called cysteine switch is required for the enzyme function. In many cases, activation involves elimination of the prodomain, resulting into lower molecular weight active forms [14]. Secreted MMPs are generally activated extracellularly or at the cell surface, the best-known example of cell surface activation being the activation of MMP-2 in a MMP-2/TIMP- 2/MT1-MMP complex. Several MMPs may also be activated within cell by furin or related proprotein convertases [15]. MMP activation and action can be controlled by inhibition in various ways: proteolytic destruction and inactivation, non-specific endogenous inhibitors such as *a*2-macroglobulin, and especially by definite tissue inhibitors of MMPs, TIMPs. At present, four TIMPs (TIMP 1–4) are known to be expressed in vertebrates. TIMPs restrain MMPs by forming 1:1 stoichiometric enzyme-inhibitor complexes. TIMP-1, -2 and -4 are secreted, while TIMP-3 is sequestred to the ECM. The substrate specificity of TIMPs differs [16].

Matrix metalloproteinase expression and cancer risk

Polymorphisms in the promoter regions of multiple MMPs are linked with an increased risk of HNSCC [17-18]. According to meta-analyses, head and neck cancer risk is linked with MMP-2-1306 C>T polymorphism, as is the MMP-1-1607 1G>2G polymorphism, and the MMP-3-1171 5A>6A polymorphism in several subgroups of patients [19-20]. The single nucleotide +7096 and +6767 polymorphic genotypes and haplotypes +6727 C: +6767 G: +7096 T: +8153 G of the MMP-14 gene are linked with oral

cancer risk [21]. Matrix metalloproteinase-2, MMP-7, and MMP-9 expression is observed high in carcinoma of supraglottic tissues as compared with the adjacent non-neoplastic tissues, and MMP-2, MMP-9, MMP-20, and tissue inhibitor of metalloproteinase-1 (TIMP-1) are highly expresssed in laryngeal squamous cell carcinoma (SCC) as compared with the adjacent normal laryngeal epithelium [22-23].

Furthermore, overexpression of MMP-1 and MMP-9 mRNA is linked with succession of oral dysplasia to cancer. Peschos *et al.*, observed that the tissue expression of MMP-9 is up regulated in a stepwise fashion, with two major steps. The first one, when a dysplastic disorder evolves and the next one, when the dysplasia advances to invasive carcinoma [24]. According to a cohort study by Vairaktaris *et al.*, MMP-7 gene expression is associated with increased risk for early stages of oral cancer [25].

Cytotoxicity of natural killer (NK) cells against an oral (O) SCC cell line is considerably reduced after pretreatment with either MMP-2 or MMP-9, suggesting an active role of MMP-2 and MMP-9 in an immune escape mechanism of OSCC [26].

Matrix metalloproteinase expression and stage and prognosis

Prognosis of SCC and MMP expression is associated for MMP-2 and MMP-9. The first was found to be related with a worse overall and disease-free survival in laryngeal cancer. Increased MMP-9 expression is a analyst of worse prognosis in laryngeal cancer, hypopharyngeal cancer, OSCC, nasopharyngeal cancer, and oropharyngeal cancer [27-29]. Matrix metalloproteinase-9 expression is also connected with invasion depth in head and neck cancer lesions and at histologically negative surgical margins, MMP-9 expression is a predictor for recurrence in OSCC [30]. Moreover, MMP-9 is linked with blood vessel density in laryngeal SCC. Expression of MMP-2 and MMP-9 is associated with the occurrence of lymph node metastases in HNSCC [31]. Matrix metalloproteinase-7 expression is also considerably connected with lymph node metastasis in OSCC [32]. Görögh *et al*., found positive expression of MMP-2, and negative expression of TIMP-1 and TIMP-2 with lymph node metastases in laryngeal SCC. There was no correlation noted between TIMP-2 expression and tumor size. Moreover, plasma TIMP-1 levels also helpful to predict survival in HNSCC and elevated TIMP-2 expression is an independent factor for worse prognosis in early-stage OSCC [33].

Burduk *et al*., investigated correlations between expressions of MMPs, such as MMP-2 and MMP-9 and their tissue inhibitors TIMP-1 and TIMP-2 and treatment outcome in 41 SCC of the oropharynx patients who underwent surgical treatment. Cytoplasmic expression of analyzed proteins was observed both in cancer cells and tumor stroma. The analyzed antigen expression was more in patients with lymph node metastases comparing patients without lymph node involvement, suggesting that microenvironment alterations are one of key factors in tumor progression. Different expression of MMPs and their inhibitors might be implemented as prognostic factor of oropharyngeal carcinoma progression [34].

The MMP-10 expression is highly observed and is considerably linked with invasiveness and metastasis in patients with HNSCC. Knockdown of MMP-10 suppressed the invasion of HNSCC cells in vitro [35]. Some MMP-13 polymorphisms are associated with tumor stage and prognosis, and high nuclear MMP-13 expression is predictive of poor outcome in tongue cancer [36].

High expression of MMP-14 is intimately related to the invasion and metastasis of laryngeal carcinoma, and indicates poorer prognosis. Moreover, high MMP-14 expression with supraglottic cancer patients have a worse prognosis than weak or negative expression of MMP-14 [37].

MiR-34a is a vital tumor suppressor gene in various types of cancer. The expression of miR-34a is considerably weak in primary tumor tissues from patients with tongue (T) SCC with lymph node metastases than the expression level in patients with negative lymph nodes metastasis. Overexpression of miR-34a considerably suppresses migration and invasion in TSCC cells in vitro and simultaneously inhibits the expression of MMP-9 and MMP-14. Moreover, miR-34a expression in TSCC is inversely associated with protein expression of MMP-9 and MMP-14 in the TSCC samples [38].

Serum, plasma, and salivary levels of MMPs and TIMPs might be also helpful prognostic markers. Concomitantly high serum levels of MMP-3 and MMP-9 can predict survival of SCC of the upper aero-digestive tract and might even serve as a superior predictor of prognosis than TNM staging, in case of synchronous esophageal SCC and HNSCC [39]. Pre-treatment serum levels of MMP-9 might also helpful as

a prognostic factor in HNSCC. In patients with oral cancer, post treatment plasma levels of MMP-9 were considerably lower in responders as compared to their pre-treatment levels. Furthermore, MMP-7 and MMP-13 expression is related with resistance to cisplatin in HNSCC cell lines [40]. Salivary concentrations of MMP-1 and MMP-3 in OSCC patients exhibited an increasing trend with higher stage disease [41].

Role of MMPs in oral squamous cell carcinoma

Kurahara et al. demonstarted that high expression of MMP-1 is related to the growth of oral cancer. Sutinen et al. indicated that MMP-1 expression is related to the incidence and prognosis of oral cancer. O-Charoenroenrat *et al*. found that MMP-1 expression is high in patients with oral cancer and is related to lymph node transfer. Overexpression of MMP-1 have been linked with progression of dysplasia to cancer [5].

MMP-2 is considered responsible for the onset of degradation of the basal membrane and the extracellular matrix. Degradation of type-4 collegen is prerequisite for tumor invasion hence, the high levels of expression of these enzymes in neoplastic cells are related to a greater invasive capacity [1]. A part from that MMP-2 was also found higly expressed in lymph node metastatic tongue cancer which was suggestive its positive role in metastatis [19].

MMP-3 or stromelysin 1 is the enzyme noted in the progression of OSCC. Several authors report that its expression in neoplastic cells, aside from acting as a promoter, is associated with an increase incidence of metastases, while its expression in the peritumoural stroma is associated to less aggressive injuries, adversely affecting tumour progression. The consequence of inhibiting MMP-3 can contribute to one of these two opposite effects during the various phases of tumour progression [42].

The MMP-7 expression, mainly in neoplastic cells, has been observed in various tumours with different aggressive biological behavior. One of the characteristics is resistance of apoptotic signals in neoplastic cells.. Degradation of fibronectin, tenascin and b4 integrin by MMP-7 play a crucial role in the adhesion and migration of cells during tumourigenesis [43].

MMP-11 Expression in the peritumoural stromal cells of malignant tumours is considered a paracrine promoter, facilitating the invasion of neoplastic cells to the stroma. Also, an elevated expression of this enzyme is linked with the aggressiveness of the tumour [44].

MMP-9 are metalloproteases that have been shown to involve in cancer pathogenesis as they degrade type IV collagen, a chief constituent of basement membrane, as well as various other types of collagens (V, VII and X), elastin and fibronectin. They are highly expressed in stromal cells surrounding the invading front of metastasizing tumours and their levels are elevated in tumour endothelium and in urine of cancer patients [45]. Moreover, MMP-9 polymorphism was observed to have a strong relationship with high risk for developing OSCC whereas constitutive expression and secretion of MMP-9 in invasive OSCC cell lines were shown as well [46]. As for the demonstrated increase in MMP-9, it is worth noting that it was shown earlier to be increased in saliva and that strong stromal MMP-9-staining intensity was associated with poor tumour differentiation [47].

The MMPs mostly considered critical in the processes of lymph nodes metastases are MMP-1, -2, -3 and -9. in a metaanalysis, referred to the great discrepancy in methodology and evaluation of MMP expression between published studies, making it difficult to allow a comparison and validation of results [6].

MMPs in tumor invasion

Tumor invasion is complex and involves various procedures associated with tumor cell proliferation, interactions between proteolysis and the ECm etc. Before invasion of surrounding tissues, tumor cell lysates appear and the basement membrane is broken down. Tumor cell metastasis include various mechanisms such as cell and ECM interactive changes, intercellular adhesion damage and ECM degradation. Tumor cells enter the ECM, invade lymphatic and blood vessels, prevent immune system attack, adhere to endothelial cells in the circulatory system, overflow those vessels to proliferate, and finally provoke vessel outgrowth [48].

During tumor invasion, cancer cells break through the basement membrane and enter connective tissue, which is a crucial basic characteristics, and varies with changes in interactions of cells, the matrix and matrix-degrading enzymes, among which MMPs are some of the most important [49]. Among tumor cells, inflammatory cells are characterized by their potential for infiltrating tissues. Inflammatory cells not only secrete MMPs to the peripheral regions of a tumor

but also release cytokinase to activate MMps. It was further noticed that in malignant tumors, stromal fibroblasts are the chief source of MMPs. Therefore it would be useful to examine the regulation of MMPs in tumor cells in order to understand the mechanisms of invasion and metastasis of tumor cells. In tumor cells, interactions between the ECM and inflammatory cells are thought to provoke MMP expressions. For MMP genes, functional nucleotide polymorphism regulates the movement and metastasis of cancer cells [50].

CONCLUSION

The role of specific biomarkers play an immense role to improve the mortality and morbidity burden associated with OSCC. Thus identification of sensitive and specific biomarkers will be helpful for early detection and prognosis of the diseases. Various types of MMPs are involved in different stages of OSCC thus estimation of these markers can be useful in the prognosis of OSCC.

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