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RESEARCH ARTICLE

THE INTERPLAY OF MATRIX METALLOPROTEASES IN ORAL CANCER AND THEIR ASSOCIATED CLINICAL OUTCOMES

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ABSTRACT

Cancer is one of the most common reasons behind mortality among people, and oral cancer occupies the sixth position in the incidence of cancer cases throughout the world. It is among the top three cancers prevalent in India due to heavy alcohol, smoking, and cigarette use and chewing betel nuts. In the present review, the authors have underlined the roles of different recurrent matrix Metalloproteases (MMPs) in OSMF (oral sub mucous fibrosis) and OSCC (oral squamous cell carcinoma). OSCC has a higher degree of invasiveness and propagates to lymph of the neck, and the invasiveness of OSCC is due to the disintegration of the basement membrane which is fulfilled by the release of proteases by tumor cells. Additionally, survival rates of patients diagnosed with oral cancer decrease along with clinical stages and advancing age.

Key words: Matrixins, Xenobiotics, Collagenases, Gelatinases, Stromelysins and Matrilysins

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INTRODUCTION

Cellular metastasis is a key contributor and a leading causal of death incidents induced by cancer as an inevitable step in the progression of cancer and the dissolution of tissue barriers throughout the body of patients and spread to distant wild-type sites. Carcinogenesis is considered a multistep process and it requires producing alterations in the internal flora to convert healthy cells into malignant ones. MMPs are one such carcinogen that is a significant player in tumor infiltration and angiogenesis. Cells possess membrane protection in the form of the extracellular and basement membranes, which protects their internal components from the impact of Xenobiotics. Metalloproteases in the matrix are enzymes produced as inactive zymogens and are further induced by other MMPs that possess the immense capacity to disintegrate the ECM membrane components and matrix proteins in order to invade normal cells (1). Several mutations in the normal as well as the tumor suppressor genes results in the ability of escaping immune surveillance, suppressing apoptotic genes and over-activating cell signalling pathways to cause uncontrolled cell division.

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In the present review the authors have provided an overview of different MMPs in OSCC and OSMF. OSCC forms about 94% of the total oral cancers prevalent throughout the world (2,3) and Oral Verrucous Carcinoma (OVC) is one of the acute grade variants of OSCC which forms about 1-10% of OSCC. OVC is considered to be a localized form of OSCC, and it rarely metastasizes (3-5). Several array studies had revealed over expression of MMP1 (6), MMP7, MMP9, MMP12 (7) and MMP11 (8) in oral cancer progression.

Oral Cancer: A Global Burden

When it comes to oral cancer is perhaps the most widespread, and it is perhaps one of the most destructive and destructive. Approximately 40–50% of those diagnosed with oral carcinoma would survive most probably for 5 years after diagnosis, despite the fact that it accounts for more than 450000 annual mortality globally. Nearly 3.5 billion populations across the world suffer from ailments, according to the WHO Global Oral Health Status Report (2022), with three-quarters of those individuals living in low- and middle-income nations. In India, oral cancer accounts for about 20% of the total types of cancer present and its statistics are increasing every hour every day. States like Bihar and Uttar Pradesh are prone to higher risk of oral cancer.

The major reason behind such frequent incident cases in India is because of the outrageous consumption of tobacco, alcohol and betel nuts. However, oral cancer in India is also related with low income, nutrition, living conditions and health care. Since, diagnosis of any type of cancer can lead to high health expenditure and may threaten social stability.

Structure of MMPs: First MMP was discovered for the very first time in a tadpole causing tail resorption (9-11). The MMP group had expanded since then to include at least 24 MMPs out of which 23 are found in humans (9, 12). They resemble zinc-dependent endopeptidases structurally. On their foundational component specificity and homology, they can be classified as Membrane-type MMPs, stromelysins, matrilysins, collagenases, gelatinases, and additional MMPs (13). MMP contains several distinct domains as shown in Figure 1 *i.e.* (i) Pre-domain (absent in MT-MMPs), (ii) Pro-peptide with a highly conserved sequence PRCXXPD present in all MMPs are essential for enzymatic activation, (iii) The catalytic region contains conserved sequence containing three histidine which for zinc chelation to occur and (iv) Hemopexin portion present in all except MMP-7 engaged in the interaction of other MMPs and tissue inhibitors (14).

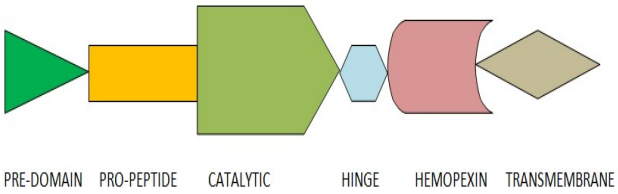

Figure 1. Structure of MMP

Levels of tumour invasion by MMPs: Alterations in the structural genomic material causing genetic instability can initiate the secretion of pro-oncogenes and inactivation of TSGs (tumour suppressor genes). MMPs have been found to have role in proteolytic degradation of ECM and cell-cell interaction, furthermore mediates release of cytokines, growth factors and anti-apoptotic genes (15).

The pathological process called angiogenesis resulting in angiogenesis. The various MMPs cause the induction of vascular endothelial growth factors, which furthermore alter the ratio of signals that encourage growth to ones that prevent it (16). The overexpression of MMPs causes a breakdown generating tumour cells from the ECM and basement membrane potent to invade and become malignant. Cancer spread to three phases to generating healthy tissue: to attach to the matrix become localized, secretes proteases for the dissolution of the membrane and then metastasizes to become malignant (16-18).

Role of different MMPs in Oral cancer

Collagenase-1(Interstitial Collagenase)/MMP-1: Encoded by MMP-1 gene is an interstitial collagenase and fibroblast collagenase. A comparison between OSCC and normal buccal mucosa (NBM) took us to the conclusion that MMP-1 is expressed more significantly in OSCC as those in NBM cells. Therefore, inhibition of its activity can be used as a strong biological marker to keep a check on metastatic activity in OSCC summarized in Figure 2 (19).

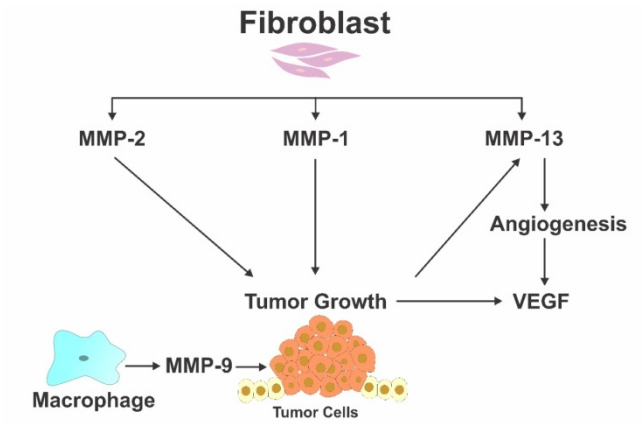

Figure 2. Showing role of MMPs in growth of tumor

Gelatinase-A (type IV collagenases)/MMP-2: Encoded by the MMP-2 gene plays role in endomenstrual breakdown, regulation of vascularisation and inflammatory responses. A study conducted by Mehran and his colleagues in which they utilized OSCC model in rats to see the effect of doxorubicin-methotrexate-loaded nanoparticles (DOX-MTX NPs). It displayed a decline in the mRNA expressions of MMP-2 in the cancer models used. Therefore, the findings prove that DOX-MTX NPs can be used as a potent chemotherapeutic agent (20). *Dioscorea nipponica* extract (DNE) was found to potentially downregulate the MMP-2 activity by promoting tissue inhibitor of expression MMP-2 also known as TIMP-2, inhibiting the DNA binding activity of CREB (cAMP response element-binding) and AP-1 (activating protein-1) are found on the MMP-2 gene promoter. (21).The antimetastatic effect of kaempferol on SCC4 cells was found out to be due to the suppression of c-Jun and inhibition of ERK1/2 is phosphorylated and associated with repression protein and mRNA levels for MMP-2 and TIMP-2 (22). Dehydroandrographolide is also used as a treatment for oral cancer that modifies the NF-B, AP-1, and SP-1 factors that encourage the suppression of MMP-2 (23). Similar findings were observed when cellosaurus SCC-9 cells were treated with Sariolic acid (SAA), a Chinese herbal compound potentiating anti-thrombotic, anti-inflammatory, anti-platelet, and anticancer effects decreases MMP-2 expression *via* c-Raf/MEK/ERK pathway inhibition (24).

Stromelysin-1/MMP-3: Encoded by MMP-3 gene is an extracellular endopeptidase present in vertebrate tissues. In the past years. The expression had been influenced by a variety of polymorphisms of various immunological suppressors, anti-angiogenic factors or tumor suppressing genes and therefore is now being correlated with increasing risks of developing cancers. In a clinical test conducted, polymorphism was found in the MMP-3 gene's 5A allele in the promoter region of oral submucous fibrosis patients (OSF) lead to causal of overexpression of MMP-3 genes. When compared to controls, OSF patients' expression was shown to be greater to OSCC in Indian population (25, 26). Cyr61 (Cysteine-rich 61), a protein that is released and connected to the matrix having role in growth and differentiation of cells promotes the mobility of oral cancer cells by enhancing the production of MMP-3 through the NF-kB signalling pathway, a6b1 or avb3 integrin receptor, MEK, FAK, and ERK(27).

Matrilysin/MMP-7: Encoded by MMP-7 gene are mainly expressed in mucosal tissues (28). Their expression relatively

increases in tumor cells including oral, colon and breast carcinomas. The proteolytic activity possessed by MMP-7 (Matrilysin-1) proves their expression in numerous malignant tumours, such as those of the mouth, stomach, breast, lungs, colorectal, and liver and pancreatic cancers. Their activity can be detected in various tissue remodelling processes and activation of other MMPs. Additionally, a study revealed that the role of MMP-7 in OSCC and non-neoplastic buccal epithelium as well as in tumor cells, but confirmed that Only tumour cells contained active MMP-7. MMP-7 functions by boosting the death of cells nearby the tumour by enhancing tumour cell invasion and progression, therefore inhibiting the cell death of cancerous cells (29-32). Researchers conducted experiments proving BRD4 is a chromatin adapter with which SIPA1 binds directly.(33) in OSCC which might directly controlMMP-7 expression but not MMP-2 or MMP-9 (32).

Collagenase-2/MMP-8: Encoded by MMP-8 gene which is mainly expressed in polymorphonuclear (PMN) leukocytes. When secreted, it degrades collagen type I and therefore MMP-8 null mice developed a greater risk of OTSCC (oral tongue squamous cell carcinoma) (35). OTSCC is regarded as to have a higher metastatic rate and considered as the most severe kind of oral cancer (36). In OTSCC, high VEGF and low MMP-8 have a very substantial predictive importance (37). As reported by Balbin et al, MMP-8 was found out to be the first onco-suppressive MMP's produced by several cells including OTSCC (38-40). In a recent study, we demonstrated that MMP-8 expression in mice induced with carcinogen induced OTSCC improved the survival rate of the mice (41). To support their role, they function by induction of interleukins 6 and 8 (42), regulation of cell adhesion (43), De corin cleavage reduces TGF-b1 activity (44) and inactivation of b1-integrins (45). Moreover, the increased MMP-8 expression in mouse tongue carcinoma completely fades tumour in the periphery. Interestingly, the overexpression of MMP-8 leads to decreased expression of proangiogenic protease called MMP-1 (46-50).

Gelatinase-B/MMP-9: Encoded by MMP-9 gene is mainly found in PMN and have role in tumor invasiveness. Gelatinase-B, sometimes referred to as MMP-9, is a 92kDa type IV collagenase have been shown to contribute in OSCC. In a recent study, the use of PMA, or phorbol 12-myristate-13-acetate in order to promote the expression of protein kinase C (51-53) and eventually the activation of MMP-9 to induce tumor invasion at specified location. Moreover, examination of oleananetriterpenesaponin derived from *Kalopanax pictus* also known as Kalopanaxsaponin A (KPS-A) was also performed. KPS-A is considered to be a potent blocking, anti-invasive agent the PMA-induced activation of signaling molecules including HuR and RaB 1A which eventually inhibits MMP-9 expression and secretion (54). Similar findings were observed when oral cancer SAS cells were introduced with quercetin, which caused a regulation in MMP-9 and MMP-12 expression leading to the reduction in the tumor invasion and progression of cells (55). Tricetin, a flavonoid derivative was also reported to have a substantial impact on the suppression of 12-O-tetradecanoylphorbol-13-acetate-induced oral cancer cell growth in SCC-9, HSC-3, and OECM-1 *via* inducting a reduction in MMP-9 expression (56). However, very few studies reports that MMP-9 was discovered to be more accurate and superior marker to detect the prognosis of TSCC (57). The level of expression of Lymph node metastases and mouth cancer are related via MMP-9 and prevalence was found to be higher in Asians (58). An essential scaffold protein in the basement membrane, type IV collagen (ColIV) controls tumour invasion and angiogenesis. A clinical trial conducted by Fan and his colleages on OTSCC patients concluded that degradation of ColIV increases the expression of MMP-9 and MMP-2 in cancer growth (59). Melatonin is considered to be antimetastatic and was fud to weaken the activation of MMP-9 by affecting expression of E1A binding protein p300 and CREB binding protein (CREBBP) (EP300). Therefore, an increased expression of MMP-9, Oral cancer cells include CREBBP and EP300 were observed (60). The above mentioned studies provide us a brief knowledge about the biological markers used and further can be utilized in the inhibition of metastasis. The phenolic substance resveratrol (3,40,5-trihydroxystilbene) is present in grapes which when subjected to SCC-9 cells *in vitro* decreased phosphorylation and activation indirectly influencing the transcription of MMP-9 are extracellular signal-regulated kinase (ERK) 1/2 and c-Jun N-terminal kinase (JNK) 1/2. (61).

Stromelysin-2/MMP-10: Is encoded by MMP-10 gene having role in degradation of proteoglycans and fibronectin. With consistent effects of other MMPs, MMP-10 levels in OSCC cells were found to be higher as compared to healthy cells and their over expression led to OVC and OSCC development from normal epithelial cells (62). N-cadherin is a cell adhesion protein found at the invading site of OSCC and is causal agent behind motility of oral cancer cells, increased invasiveness and production of MMP-9 (63). A critical assembly checkpoint called BubR1 budding uninhibited by benomyl (BUB) related 1 or We discovered that BubR1 expression was higher in normal human oral keratinocytes (HOK) and human gingival fibroblasts (HGF) cells compared to Ca9-22, HSC3, SCC9, and Cal-27 OSCC cell lines. This in turn was followed by over manifestation of MMP-2 and MMP-9 activity. The difference their actions is depicted in Figure 3 (64).

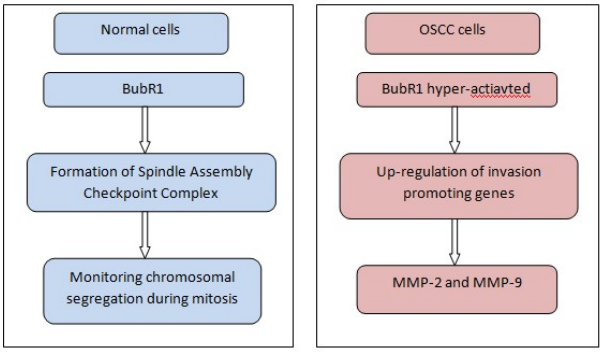

Figure 3. Normal cells VS OSCC cells

The bacteria that causes chronic periodontitis, P. gingivalis, causes YD10B oral cancer cells to aggressively divide through IL-8 dependent secretion MMP's. Whereas acetylshikonin, a flavonoid counteracts the activity of P. gingivalis by suppression of IL-8 and subsequent decrement in MMP secretion (65).

DISCUSSION

Identifying and determining Early detection and therapy are aided by emerging biomarkers for OSCC diagnosis and prognosis which in turn reduces mortality and morbidity rates among patients.

It is wise to investigate angiogenic factor and MMP expression patterns, as angiogenesis and MMPs play crucial roles in OSCC advancement and disease progression. It is unclear whether oral carcinomas prefer one infiltrative mechanism over another, but it is becoming clear that tumour cells have the ability to use MMPs produced by other cells while also creating their own MMPs. Numerous reports have shown that metalloproteinase mRNA and protein expression is elevated in OSCCs as well as SCCs, but the possible explanation and their role in the pathogenesis are still unclear. Studies revealed an elevated expression of growth factors Proteases (MMP-1, MMP-3, MMP-8, MMP-9, MMP-10, MMP-13, and TIMP-2) and growth factors (HGF, VEGF, PIGF, PDGF-BB) have been found in OSCC tissue and saliva of OSCC patients. There by indicating that these biomarkers may serve potentially future non-invasive diagnostic/prognostic markers for OSCC and potential treatment targets. Collectively, the understanding of MMPs has managed to grow; it can function as either a promoter of carcinoma according to the circumstances, which are associated with the patient's features, such as the tumor's stage, grade, and location. The authors hypothesize that detecting MMPs in patients with OSCC might contribute to targeted therapeutic applications and an improved outcome by elucidating the roles these proteases in oncogenesis.

CONCLUSION

Conclusively, there are an increasing number of shreds of evidence that suggest MMPs could be used to predict the outcome of OSCCs. However, there are still a lot of evidence that find it tough to figure out how much the findings are relevant. Additionally, the slow rate at which drugs are indeed being investigated that can be used to treat cancers with chemotherapy is especially delimiting. Previous attempts to develop anti-MMP pharmaceuticals centred just on catalytic function of proteases, which are believed to be in charge of matrix remodelling, tumor growth, and the advancement of cancer. Nevertheless, recent research revealed unrecognized hemopexin-like C-terminal region present in the structure of MMPs facilitates proteolysis-independent MMP activity in a number of critical cancer biology processes. Therefore, in support, MMPs and their structural components continue to be potent therapeutic markers and posses' immense potential for expanding the notion of personalized medicines.

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Conflict of Interest- None

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