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Matrix Metalloproteinases in Head and Neck Cancer

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Abstract

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, which degrade all kinds of extracellular matrix proteins. MMPs play an important role in cell behaviors such as proliferation, migration, differentiation, apoptosis, and host defense. Polymorphisms in the promoter regions of multiple MMPs and overexpression of MMPs and tissue inhibitors of metalloproteinases (TIMPs) are associated with head and neck cancer risk and a worse prognosis. Serum and plasma levels of MMP and TIMP might be useful in diagnostics and follow-up. However, their use as therapeutic target should be further investigated, since the antitumor activity of matrix metalloproteinase inhibitors has been disappointing thus far.

Key words: Head and neck cancer, HNSCC, Matrix metalloproteinases, MMP, Prognostic marker, Matrix metalloproteinase inhibitor

Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, which degrade most extracellular matrix proteins [1-4]. Dissolution of the extracellular matrix is a key event of invasion and metastasis of malignant lesions of the head and neck [1; 5]. Matrix metalloproteinase substrates also include cytokines, chemokines, growth factors, receptors, and factors associated with angiogenesis, cell adhesion, cell motility, blood clothing cascade, and complement cascade [6]. Therefore, MMPs play an important role in cell behaviors such as proliferation, migration, differentiation, apoptosis, and host defense [7]. Matrix metalloproteinases facilitate tissue remodeling associated with various physiological and pathological processes such as morphogenesis, angiogenesis, tissue repair, and metastasis [3]. Currently, more than 20 different types of MMPs have been identified among vertebrates, and most of them are conserved in humans [2; 8]. Based on their substrate specificity, MMPs have been divided into distinct subclasses: collagenases (MMP-1, MMP-8, MMP-13, and MMP-18), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10 and MMP-11) and matrilysins (MMP-7, MMP-26) and other MMPs [2; 9]. Most of the MMPs are inhibited by specific endogenous tissue inhibitors which are known as tissue inhibitors of matrix metalloproteinases (TIMPs).

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Head and neck squamous cell carcinoma (HNSCC) is characterized by the upregulation of a large number of proteolytic enzymes, including urokinase plasminogen activator (uPA) and also multiple MMPs [10].

The incidence of head and neck cancer is approximately 14/100,000, accounting for 16 % to 40 % of all malignancies [11]. In several countries, the incidence is increasing probably due to the increased use of tobacco and alcohol, which are well documented risk factors for HNSCC [12].

Matrix metalloproteinase expression and head and neck cancer risk

Polymorphisms in the promoter regions of multiple MMPs are associated with an increased HNSCC risk [13-17]. According to meta-analyses, MMP-2-1306 C>T polymorphism is associated with head and neck cancer risk, as is the MMP-1-1607 1G>2G polymorphism, and the MMP-3-1171 5A>6A polymorphism in some subgroups of patients [16; 17]. The single nucleotide +7096 and +6767 polymorphic genotypes and haplotypes +6727 C: +6767 G: +7096 T: +8153 G of the MMP-14 gene are associated with oral cancer risk [18]. Matrix metalloproteinase-2, MMP-7, and MMP-9 expression is upregulated in supraglottic carcinoma tissues as compared with the adjacent non-neoplastic tissues [19], and MMP-2, MMP-9, MMP-20, and tissue inhibitor of metalloproteinase-1 (TIMP-1) are overexpresssed in laryngeal squamous cell carcinoma (SCC) as compared with the adjacent normal laryngeal epithelium [20; 21].

Furthermore, overexpression of MMP-1 and MMP-9 mRNA is associated with progression of oral dysplasia to cancer [22]. Peschos *et al.,* demonstrated that the tissue expression of MMP-9 is upregulated in a stepwise fashion, with two main steps. The first one, when a dysplastic lesion evolves and the next one, when the dysplasia progresses to invasive carcinoma of the larynx [23].

According to a cohort study by Vairaktaris *et al.,* MMP-7 gene expression is associated with increased risk only for early stages of oral cancer [24].

Cytotoxicity of natural killer (NK) cells against an oral (O) SCC cell line is significantly reduced after pretreatment with either MMP-2 or MMP-9, suggesting a potential role of MMP-2 and MMP-9 in an immune escape mechanism of OSCC [25].

Matrix metalloproteinases as tumor markers

Serum and plasma levels of both MMP and TIMP might be useful markers in diagnostics and follow-up after treatment. Multiple MMPs, including MMP-3 [26], MMP-8 [27], and MMP-9 [28] can be elevated in the serum of patients with HNSCC as compared to healthy controls and therefore might be useful as tumor markers for clinical monitoring. Tumor and salivary MMPs are robust diagnostic biomarkers of OSCC. Particularly, salivary concentrations of MMP-1 and MMP-3 were significantly higher in OSCC patients compared to healthy controls [29].

MMP-9, TIMP-1, and TIMP-2 are significantly elevated in plasma of patients with oral cancer. Matrix metalloproteinase-9 emerged as the best statistically significant, single marker in plasma for oral cancer detection and it showed an increase in diagnostic performance when tested in combination with MMP-2 and TIMP-2 [30]. Tsiropoulos *et al*., collected pre-and post-treatment serum from 49 patients with laryngeal cancer and identified the latent forms of MMP-2 and MMP-9. Both gelatinases were increased in the serum of these patients as compared to healthy individuals. In addition, both patients with supraglottic tumors and active smokers had significantly higher pre-treatment levels of proMMP-2 than patients with glottic tumors or ex-smokers [31]. During the follow-up period the proMMP-2 serum levels increased significantly in the first ten to

fifteen days after treatment, gradually decreasing over the following months. The proMMP-9 serum levels showed a gradual decrease after treatment [31].

Matrix metalloproteinase expression and stage and prognosis

Prognosis of HNSCC and MMP expression is correlated for MMP-2 and MMP-9. The first was found to be associated with a worse overall and disease-free survival in laryngeal cancer [32]. Increased MMP-9 expression is a predictor of worse prognosis in laryngeal cancer [33-35], hypopharyngeal cancer [33], OSCC [36-38], nasopharyngeal cancer, and oropharyngeal cancer [39;40]. Matrix metalloproteinase-9 expression is also correlated with invasion depth in head and neck cancer lesions [41], and at histologically-negative surgical margins, MMP-9 expression is a predictor for recurrence in OSCC [42]. Moreover, MMP-9 is correlated with blood vessel density in laryngeal SCC [43]. Expression of MMP-2 and MMP-9 is associated with the presence of lymph node metastases in HNSCC [35; 40; 44-47]. Matrix metalloproteinase-7 expression is also significantly correlated with lymph node metastasis in OSCC [48]. Görögh *et al*., found MMP-2 expression to be positively correlated, and TIMP-1 and TIMP-2 expression to be negatively correlated with lymph node metastases in laryngeal SCC [49]. TIMP-2 expression and tumor size were also negatively correlated [50]. Moreover, plasma TIMP-1 levels predict survival in HNSCC [49] and high TIMP-2 expression is an independent factor for worse prognosis in early-stage OSCC [51].

Burduk *et al*., [52] searched for 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 found both in cancer cells and tumor stroma. The expression of analyzed antigens was higher in patients with lymph node metastases comparing patients without lymph node involvement, suggesting that microenvironment changes are one of key factors in tumor progression. Divergent expression of MMPs and their inhibitors might be used as prognostic factor of oropharyngeal carcinoma progression [52].

High expression of MMP-10 is frequently observed and is significantly correlated with invasiveness and metastasis in patients with HNSCC. Knockdown of MMP-10 suppressed the invasion of HNSCC cells in vitro [53]. Some polymorphisms in MMP-13 are associated with tumor stage and prognosis [54], and high nuclear MMP-13 expression is predictive of poor outcome in tongue cancer [55].

High level of MMP-14 expression is closely related to the invasion and metastasis of laryngeal carcinoma, and indicates poorer prognosis [56]. Moreover, patients with supraglottic cancer with high MMP-14 protein expression have a poorer prognosis than patients with weak or negative expression of MMP-14 protein [57].

MiR-34a is an important tumor suppressor gene in various cancer types. miR-34a expression in primary tumor tissues from patients with tongue (T) SCC with lymph node metastases is significantly lower than the expression level in patients with negative lymph nodes. Overexpression of miR-34a significantly 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 correlated with protein expression of MMP-9 and MMP-14 in the TSCC samples [58].

Serum, plasma, and salivary levels of MMP and TIMP might be also be useful prognostic markers. Concomitantly elevated MMP-3 and MMP-9 serum levels can predict survival of SCC of the upper aero-digestive tract and

might even serve as a better predictor of prognosis than TNM staging, in case of synchronous esophageal SCC and HNSCC [59]. Pre-treatment serum levels of MMP-9 might also serve as a prognostic factor in HNSCC [60; 61]. In patients with oral cancer, post-treatment plasma levels of MMP-9 were significantly lower in responders as compared to their pre-treatment levels [62]. Furthermore, MMP-7 and MMP-13 expression is associated with resistance to cisplatin in HNSCC cell lines [63]. Salivary concentrations of MMP-1 and MMP-3 in OSCC patients displayed an increasing trend with higher stage disease [29].

Matrix metalloproteinases as targets for treatment

A number of MMP inhibitors (MMPIs) have been developed for cancer treatment. The most extensively studied classes of MMPIs include Batimastat, Marimastat, Salimatat, Prinomastat and Tanomastat. However, the despite the strong rational for the use of MMPIs, their clinical efficacy has been disappointing thus far [1; 64-66]

Marimastat (BB-2516) is an orally active broad-spectrum MMPI with collagenase- and angiogenesis-inhibiting properties [67], which reduces the growth of some HNSCC cell lines in vitro. The combination of chemoradiation and Marimastat delayed tumor growth as compared to chemoradiation alone in athymic nude mice bearing SCC-1 xenografts [68]. However, clinical development of Marimastat was halted after disappointing results in phase III trials [69].

Carboxyamidotriazole, a calcium influx inhibitor, also blocks MMP production, cellular proliferation, migration, and chemo-invasion of HNSCC cells in vitro [70].

Although various synthetic broad-spectrum MMPIs had little success in cancer treatment thus far, preclinical data strongly support the use of MMPIs. Nafamostat mesilate (FUT-175), a synthetic serine protease inhibitor, which down-regulates expression of both MMP-2 and MMP-9, has shown anti-tumor activity towards adenocarcinoma and reduces the production of VEGF and transforming growth factor β1 (TGF-β1) by HNSCC cell lines [71]. Treatment with alpha-mangostin also decreased MMP-2 and MMP-9 expression, and reduced cell proliferation in various human HNSCC cell lines [72].

MMPs can be targeted via inhibition of their processing molecule furin. Transfection of HNSCC cell lines with the selective furin inhibitor, alpha 1-PDX, resulted in a significant decrease or absence of tumorigenicity, invasion, and penetration after subcutaneous inoculation of mice. Furthermore, these HNSCC cells showed a remarkable decrease in MMP-2 processing and activity [73]. Schafer *et al.,* explored the use of an intercomplementing anthrax toxin that requires combined cell surface uPA and MMP activities for cellular intoxication and specifically targets the ERK/MAPK pathway for the treatment of HNSCC [10]. They found that this toxin displayed strong systemic anti-tumor activity towards a variety of xenografted human HNSCC cell lines by inducing apoptotic and necrotic tumor cell death, and by impairing tumor cell proliferation and angiogenesis [10].

Overexpression of epidermal growth factor receptor (EGFR) in human HNSCC cell lines is correlated with MMP-9 expression and invasion *in vitro* [74]. Ligands for EGFR differentially upregulate MMP-9 in these cells [75]. Besides inhibition of invasion, MMPIs could also prevent tumor progression by their ability to inhibit HNSCC proliferation via interferance with EGFR autocrine loops [76].

GACFSIAHECGA is a selective MMP-14 peptide-inhibitor, which prevents the migration and invasion both *in vitro*, and in xenograft models of tongue carcinoma, and prolonged the survival of tumor bearing mice [77]. Also the orally active MMP-2 and MMP-9

specific inhibitor MMI-166 has shown activity in HNSCC xenografs in mice [78].

A growing body of evidence suggests that components of the tumor micro-environment, including cancer-associated fibroblasts (CAF), may modulate the treatment sensitivity of tumor cells. Johansson *et al.,* investigated the possible influence of CAFs on the sensitivity of HNSCC cell lines to cetuximab [79]. Cetuximab treatment caused a reduction in the proliferation rate of these cells, whereas the growth of HNSCC-derived CAF cultures was unaffected. When tumor cells were co-cultured with CAFs, the cetuximab-induced growth inhibition was reduced, and a complete protection from growth inhibition was observed in one of the tumor cell lines investigated. This co-culture resulted in an elevated expression of MMP-1 in both the tumor cells and CAFs. Moreover, the CAF-induced resistance was partly abolished by the presence of an MMPI. However, CAFs treated with siRNA targeting MMP-1 still protected tumor cells from cetuximab treatment, suggesting that several MMPs may cooperate to facilitate resistance or that the protective effect is mediated by another member of the MMP family. These results suggest that inhibiting MMPs may improve the effects of EGFR-targeted therapy [79]. Extracellular matrix metalloproteinase inducer (EMMPRIN) expression in HNSCC is upregulated by the EGF [80]. Epidermal growth factor receptor stimulation induces HNSCC cell invasion and MMP-9 expression which can be abrogated by down-modulation of EMMPRIN. Treatment of HNSCC cells with a combination of an EMMPRIN function-blocking antibody and the EGFR inhibitor AG1478, results in a stronger inhibition of cell proliferation and migration than with either one of the individual agents alone [80]. McNally *et al*., evaluated treatment of a replicating adenovirus armed with TIMP-2, radiation, and cisplatin in several combinations in vitro and in vivo in HNSCC xenografts [81]. Treatment with the Ad-TIMP-2 virus and radiation decreased cell viability in vitro and resulted in an additional anti-angiogenic response in vivo. The combination of Ad-TIMP-2 virus, radiation, and cisplatin in the SCC1 nude mice demonstrated the greatest response rates on tumor growth and angiogenesis, underscoring the potential benefits of combining chemoradiation and MMPIs.

Multiple anti-cancer agents, who are currently developed or already used, act at least partially through interaction with MMPs. The metastatic ability of CAL-27 cells was suppressed by epigallocatechin gallate (EGCG) and gefitinib via attenuation of the enzymatic activity and protein expression of MMP-2 by mediation through MAPK signaling [82]. Imatinib is a tyrosine-kinase inhibitor (TKI) used in the treatment of several forms of cancers. Via blockage of the signal transduction of protein-tyrosine kinases receptors, MMP-2 and MMP-14 expression was suppressed and an inhibitory effect on malignant cell growth in HNSCC cell lines was observed [83; 84]. Schulz *et al.,* incubated different HNSCC cell lines with rising concentrations of imatinib and/or carboplatin [85]. The combination of carboplatin with imatinib resulted in a significant decrease in MMP-2 expression and an increase in apoptosis in all cell lines. The EFGR TKI gefitinib decreased both MMP-2 and MMP-9 enzyme activity by approximately 25-30% in the highly invasive human OSCC YD-10B cell line in vitro [86]. Icotinib is also an EGFR TKI, which has been shown to inhibit proliferation in tumour cells. Icotinib reduces cell invasion, suppresses the protein levels of MMP-2 and MMP-9, and increases the expression of TIMP-1 in Tca8113 TSCC cells *in vitro* [87]. Inhibition of cyclooxygenase-2 suppresses the invasiveness of OSCC cell lines via down-regulation of MMP-2 production and activation [88]. Docetaxel exposure significantly decreased MMP-14 expression in the HPV-negative 11A and 14C HNSCC cell lines but not in the HPV-positive CERV196 HNSCC cell line [89; 90]. 5-FU had no significant effect on MMP-14 expression

independent of the HPV-status. Significant alterations of MMP-2 could be detected in 11A only [89; 90].

Conclusions

Matrix metalloproteinases play an important role in cell behaviors such as proliferation, migration, differentiation, apoptosis, and host defense. Polymorphisms in the promoter regions of multiple MMPs and overexpression of MMPs and TIMPs are associated with head and neck cancer risk, stage and prognosis. Serum and plasma levels of both MMP and TIMP might be useful both as prognostic markers as well as predictive markers in diagnostics and follow-up. Matrix metalloproteinases are appealing targets for treatment but none of the tested MMPIs has shown meaningful clinical activity thus far.

Conflict of Interest

The authors declare that there is no conflict of interests

Authors' Contribution

PS: searching and preparing the draft manuscript, and editing the final manuscript.

AB: searching and preparing the draft manuscript, and editing the final manuscript.

Both authors read and approved the final manuscript for publication.

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