



Review Article

The Role of Stromelysin-3 (ST-3) in Progression of Oral Squamous Cell Carcinoma- A Narrative Review

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ABSTRACT

Matrix metallo proteinases (MMP) are zinc dependent endopeptidases. The role of MMP have been implicated in various physiological and pathological process including oraganogenesis, inflammation, vascular disease, wound healing, auto immune disease and cancer progression. Several MMPs was over expressed in head and neck squamous cell carcinoma (HNSCC) and the MMP found to have correlating with cell proliferation, angiogenesis, invasion, and metastasis. Epithelial–mesenchymal interactions involving cell–cell, cell–Extra cellular matrix (ECM), multistep process of carcinogenesis. ECM remodelling in tumor progression is mediated by MMPs. MMP 1,2,3,7,8,9,10,11,13,and 19 are most over expressed in HNSCC. The role of MMP 11(ST-3) in human breast carcinoma, ovarian cancer are well established whereas the expression of role of MMP 11 in oral squamous cell carcinoma (OSCC) gives varied observations. Hence the current review is aimed to various studies involved the immunohistochemical expression of MMP 11 in OSCC.

Key Words: Oral Sqaumous Cell Carcinoma, Matrix Metallo Proteinases(MMP), Stromelysin-3 (ST3), MMP-11.

Introduction

One of the major extracellular matrix-degrading enzyme implicated in cancer development is matrix metalloproteinases(MMPs), also called matrixins. A group of zinc and calcium-dependent endopeptidases, with a broad spectrum of proteolytic activity toward extracellular matrix components¹ The expression of MMP-11 is regulated by numerous growth factors, cytokines, stress, hormonal regulation, irreversible cellular changes etc. MMP's are set to have their own inhibitors that decide in the tissue (TIMPs), which in turn control the sustained expression of MMP. Matrix metallo proteinases (MMPs) regulate tumor invasion by remodeling the host tissue.² An imbalance between the various MMPs and their TIMPs attributes to pathological remodeling in cancer progression and metastasis. MMP-11 (Stromelysin-3) discovered in breast cancer, interacts with the stromal components and contributes to the early and late stages of tumor progression.³ These matrix degrading enzymes also hold apoptotic and anti- apoptotic roles. Expression of MMP-11 is noted in cancers that undergo metastasis. MMP-11 is a marker more profoundly used in therapy as well as assessing the prognosis.⁴ The role of MMP-11 in human breast carcinoma, ovarian cancer are well established whereas the expression of role of MMP-11 in HNSCC is not been studied to the fullest. Hence the current review is aimed at allude on varies studies involved the immunohistochemical expression of MMP 11 in oral sqaumous cell carcinoma.⁵

Materials and Methods

The period of 1995 to 2017 medical and dental articles were reviewed by using the search engines like Pubmed (PMC), Research gate, Elsevier, Google scholar etc.

Classification of Matrix Mettalo Proteinases:

MMPs are classified into collagenases, gelatinases, stromelysins, matrilysins, metalloelastase, membrane-type MMPs, and others on the basis of their substrate specificity. In the collagenases type includes MMP 1,8,13, in gelatinases 2,9, stromelysins comprises of 3,10,11, matrilysins is MMP 7 and membrane type MMPs were also included which are MT1,2,3,4,5, and other MMPs.

Commonly MMPs are degrades the extra cellular matrix and promotes the degradation this will led to progression of tumor and invaded to the adjacent structure as well as metastasis.⁶

Mechanism Action Of MMP 11:

Matrix metalloproteinase (MMP)-11or Stromelysin-3, are Zinc dependent endopeptidases. Which are widely expressed in both physiological and pathological conditions. Such as osteogenesis, spinal cord morphogenesis, embryonic implantation, interdigitation, placentation, epithelial growth and inflammation, wound healing.⁷ And pathologically involved in matrix

degradation and tissue remodeling and helps the tumor progression. Among the other MMPs, MMP-11 only secreted under active form, this characteristics have role in tumor progression and tissue remodeling processes.⁹ And it interacts with stromal component that contribute to cancer in the early and late stages of tumor progression in human. MMP-11 always expressed in the fibroblast around the invaded tumor islands.¹⁰

MMP-11 (Stromelysin-3) in OSCC

Polymorphism of numerous MMP genes are functional and they may contribute to tumorigenesis of OSCC. Studies have also shown that polymorphism of MMP-1 and MMP-2 is associated with head and neck carcinoma risk, whereas polymorphism of MMP-9 and MMP-13 are associated with increased risk of aggressive form of oral cancer. MMP-11 gene polymorphism found to exhibit synergistic effect of environment factors like betel nut and tobacco in OSCC formation.¹⁰

When there is a change in binding affinity between the promoter of Polymorphic MMP-11 gene and in betel nut or in tobacco constitutes, it can lead to alteration in expression or in activity of MMP-11. This in turn unregulated extra cellular proteases which promotes the development of OSCC. MMP-11 also found to play role in metastasis.¹⁰

Depending upon the spatio-temporal factors the role MMP-11 in metastasis will occur. In a study they also found that there is a increased frequency of lymphnode metastasis in OSCC patients with at least one polymorphic allele of MMP-11.

MMP-11 which contain cysteine that binds with catalytic zinc ion and inhibiting the enzyme, when this cysteine ion is dissociated from zinc ion, releases peptide which activates the enzyme which in turn found to affect the function of MMP-11 this leads to increased activity of MMP-11 in tumor cells and surrounding fibroblast which in turn enhances the proliferation and metastasis of oral cancer.¹¹

When expression of MMP- 11 in tumor specimen of 177 OSCC patients where study they found positive expression for 70 percentage of samples. in another study when 220 OSCC patients and 90 precancerous lesions where studied for MMP 11 expression and they found that expression of MMP-11 and pro angiogenic factors are indicators for progression from free cancer stage to frank malignancy. also there is evidence in study conducted in Taiwan that strong expression of MMP-11 is correlated

with poor survive in OSCC patients also that study they found that a FAK/src a signalling pathway is involved in MMP-11 mediated cell metastasis in oral squamous cell carcinoma.¹¹

In a study it has been found that expression of ST-3 in stromal fibroblast also in, epithelial cells that are undergoing mesenchymal transition.¹² this has been related with progression of phenotypic alteration which are required yearly during malignant transformation of oral epithelium pathway.¹³ Thus stating that MM-11 can serve as a potential target in designing molecular therapeutics in early intervention of oral tumorigenesis.

Conclusion

MMP's are one of the proteins that remodel the host tissue, by degrading various ECM components. MMP's also promote the proliferation and invasion of cancer cells. MMP-11(ST-3) favours epithelial proliferation in areas of intense remodeling, where the regenerating cells remain viable through an anti apoptotic signal. This physiological role of ST-3 is hampered in malignancy. Need further studies to well establish the role of MMP-11 in Oral squamous cell carcinoma.

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