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MATRIX METALLO PROTEINASES IN CARCINOMA OF CERVIX - A REVIEW

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ABSTRACT

Carcinoma Cervix is one of the most common cancers in women causing mortality in majority of them. Tumor invasion and metastasis is the commonest cause of death in these patients. Matrix Metalloproteinases [MMPs], are a set of zinc dependent endopeptidases, are responsible for the progression and dissemination of the tumor cells. Many MMPs are expressed in increased proportions in this malignancy and their level of expression correlates with stage and grade of the tumor. Human Papilloma Virus is undoubtedly the etiological factor for this neoplasm. Numerous studies have given the possible mechanisms which relate HPV infection to MMPs expression. In this review we have discussed various MMPs in cervical cancer, their expression patterns with an emphasis on their relation to HPV infection.

Key Words: Matrix Metalloproteinases, Carcinoma cervix, Human Papilloma virus

INTRODUCTION

Matrix Metalloproteinases (MMPS) are a distinct group of zinc dependent endopeptidases that play a vital role in various physiological and pathological disease processes in human tissues. Their role in pathogenesis of tumor and tumor metastasis are of great significance. This review elucidates the possible role of MMPS in pathobiology of initiation carcinoma cervix and its progression. Also an effort has been made to relate the increased expression of MMPS to human papilloma virus (HPV) which is the etiological agent for almost all the cases of carcinoma cervix and also prognostic implications of the MMPS.

Structure and function of MMPS

MMPS constitute a family of 26 endopeptidases which have a common protein sequences and each individual MMP contains a specific domain which imparts the substrate specificity to it (Ii, Yamamoto, Adachi, Maruyama, Shinomura 2006). These MMPS can be categorized in to four groups based on their substrate specificity.

Table 1: ***Matrix Metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and their preferred substrates (Wright, Harding 2009).***

Group	Members	Abbrev.	Substrate
Collagenases	Fibroblast collag.	MMP-1	fibrillar collagens

	Neutrophil collag.	MMP-8	fibrillar collagens
	Collagenase-3	MMP-13	fibrillar collagens
	Collagenase-4	Col 4	Collagens
Gelatinases	Gelatinase A	MMP-2	gelatin, elastin fibronectin, types IV–VI collagens
	Gelatinase B	MMP-9	gelatin, elastin, fibronectin, types I, IV & V collagens
Membrane-type	MT 1-MMP	MMP-14	pro-MMP-2, collagens, gelatin, elastin, casein, fibronectin, vitronectin, aggrecan
	MT 2-MMP	MMP-15	pro-MMP-2, collagens, gelatin, fibronectin, laminin, nidogen, tenascin
	MT 3-MMP	MMP-16	pro-MMP-2, collagens, gelatin
	MT 4-MMP	MMP-17	pro-MMP-2, collagens, gelatin
Stromelysins	Stromelysin-1	MMP-3	fibronectin, collagens, laminin, non-fibrillar
	Stromelysin-2	MMP-10	fibronectin, collagens, laminin, non-fibrillar collagens
	Stromelysin-3	MMP-11	gelatin, fibrillar collagens, 1 proteinase inhibitor (serpin)
	Macrophage	MMP-12	Elastin
	Metalloelastase		
	Matrilysin	MMP-7	fibronectin, collagens, laminin, non-fibrillar collagens, aggrecan, casein, decorin, insulin
Others	Enamelysin	MMP-20	Amelogenin
	Xenopus collag.	MMP-18	Unknown
	?	MMP-19	aggrecan, gelatin, tenascin C
		XMMP	Unknown
TIMPs		TIMP-1	all MMPs except MT1-MMP
		TIMP-2	all MMPs
		TIMP-3	all MMPs
		TIMP-4	all MMPs

MMPS have ~ 20-aminoacid residue signal peptides and are initially in inactive pro forms which have to be activated to execute their functions. These pro forms consist of a ~ 80-residue N-terminal prodomain followed by ~ 170 residue catalytic domain. The later is in turn linked to a ~ 195 residue C-terminal hemopexin like domain .This hemopexin like domain is vital for cleavage of triple helical collagen. The structure of these MMPS can be demonstrated by X-ray crystallography which visualizes the active sites of these MMPS. Different MMPS have similar catalytic domain structure but the configuration of active site cleft differs and this is responsible for their substrate specificity. This cleft harbours the "Catalytic Zinc" and it also separates the two parts of catalytic domain of MMPS, the smaller "lower domain" and larger "upper domain". Besides catalytic zinc, all MMPS also posses a structural zinc and two bound calcium ions (Bode, Fernandez-Catalan, Tschesche, Grams, Nagase, Maskos 1999). Almost all MMPS have similar catalytic domain structure with the exception of MMP-7 and MT-1 MMP which show mild deviations. The site of glycosylation a is specific for individual MMP (Douglas, Shi, Sang 1997). As already mentioned MMPS are initially in pro-peptide form and they have to be cleaved to reveal the active catalytic domain. In an inactive Pro MMP, Zinc atom is bond to the cystein residue of propeptide region (Wright, Harding 2009). Disruption of this

bond by activation factors exposes a form of MMP which itself by autocatalysis cleaves the propeptide region (Birkedal-Hansen, Moore, Bodden et al. 1993). The activation factors include plasminogen activators, (Malemud 2006), kallikrien, Thrombin and other MMPS themselves (Sternlicht, Werb 2001). Expression of MMPS is regulated at both transcriptional and post transcriptional level (Birkedal-Hansen et al. 1993).

MMPS are multitask enzymes with maintenance and reconstruction of extra cellular matrix (ECM) being the important function. They play a vital role in embryogenesis, tissue remodeling (Bulbule, Saraswati, Kundu 2011) in progression of diseases such as atheroma, arthritis and chronic tissue ulcer (Nagase, Visse, Murphy 2006). Their role in immunological functions is proved by their demonstration in polymorphonuclear leucocytes and macrophages (Kessenbrock, Brown, Werb 2011). However their role in tumorigenesis of gynecological cancers and metastasis is of utmost importance (Kallakury, Karikehalli, Haholu, Sheehan, Azumi, Ross 2001) and it is a complex multi step process. The level of expression of these MMPS varies from tumor to tumor and a relationship has been established between their expression level and clinico-pathological outcome. In the next few paragraphs we have discussed the various MMPS expressed in carcinoma cervix, their relevance to HPV infection and prognosis of the patient. MMPS in different tissue samples can be measured by IHC [Immunohistochemistry], RT-PCR [real Time Polymerase chain reaction], western and Northern blot analysis, ELISA [Enzyme-Linked Immunosorbent assay] and zymography (Szarvas, vom, Ergun, Rubben 2011).

Tissue Inhibitors of Metalloproteinases (TIMP):-

These are a group of glycoproteins with four members (TIMP 1-4) which form tight non covalent complexes with MMPS and thus inhibit their activity (Skiles, Gonnella, Jeng 2001). TIMPS are two domain proteins linked by three disulfide bonds and have shape of an elongated contiguous wedge (Bode, Fernandez-Catalan, Tschesche, Grams, Nagase, Maskos 1999). TIMP contains 12 cysteine residues which form six loop structures through disulfide bonds. The N-terminus of TIMPs 1-4 binds to the catalytic domain of most activated MMPs and inhibits function. The C-terminus of TIMP1 and TIMP2 binds to the hemopexin domain of proMMP2 and proMMP9, respectively; this binding regulates MMP function (Overall, Lopez-Otin 2002) (Figure 1). TIMPS are found in different tissues and body fluids. They are expressed by various normal and also transformed cells (Birkedal-Hansen et al. 1993). TIMPS and their recombinant forms are of interest in present researches because they can be of therapeutic use in various diseases and malignancies where curtailing the activities of MMPS would treat clinical condition. However, in several occasions their dual role as promoter and inhibitor of tumor cell has been demonstrated. Recombinant TIMPS have been expressed in various cell lines. TIMP concentrations generally far exceed the concentration of MMPs in tissue and extracellular fluids, thereby limiting their proteolytic activity to focal pericellular sites.

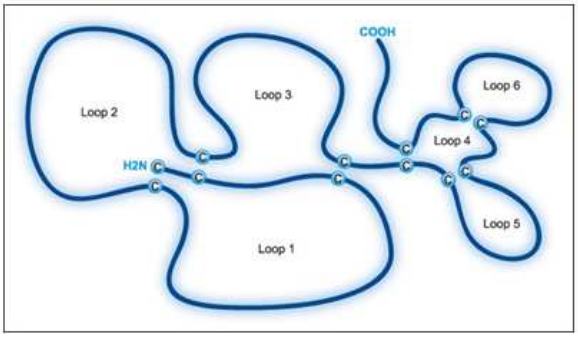

Figure 1: ***Schematic representation of TIMP structure.***

Main focus is the cell types responsible for producing MMPs in cancer. Contrary to expectations, most MMPs in tumors are produced by stromal cells rather than the cancer cells (Figure 2). One explanation for this phenomenon is that cancer cells produce Extracellular Matrix Metalloproteinase Inducer (EMMPRIN), a cell surface glycoprotein, which directly stimulates fibroblasts (through direct cell contact) to produce MMP1, 2, 3, and MMP14 (Figure 1)(Yan, Zucker, Toole 2005).

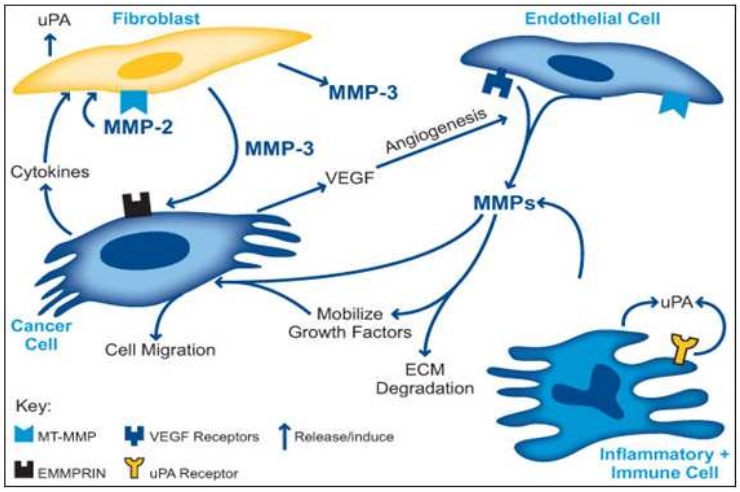

Fig 2. ***Schematic diagram of interaction between cancer cells and stromal within a tumor with a focus on role of MMPs.***

Carcinoma Cervix:-

Carcinoma cervix is the second common cancer in females and the most common malignancy of the female genital tract (Cannistra, Niloff 1996). Diagnosis and treatment at an early stage is important because if affects younger age group resulting in mortality at an early age (Petignat, Roy 2007). Hence there is a need for more comprehensive and liable diagnostic modalities and effective therapeutic strategies.

Carcinoma cervix is a classical example for gradual evolution of a malignancy in a normal epithelium because it has a spectrum of morphological patterns in the process of malignant transformation. The lesions in the early phase are called intraepithelial neoplasia (CIN). Grading of CIN was an ambiguity until a new revised Bethesda system 2001, quoted a new two grade system (Colgan 2001). Earlier it was a three grade system with CIN-I, II, III but due to extreme interobserver variation and poor reproducibility it has been revised and a new two grade system 'Low grade' and 'High grade' are adopted (Heatley 2002). Cervix biopsy is the most importance investigation in diagnosis cervical cancer (Petignat, Roy 2007).

Out of all the primary tumors of the cervix, Squamous cell carcinoma is the most common tumor (Cannistra, Niloff 1996) and adenocarcinoma comes next. The fact that HPV is the commonest etiological factor for cervical cancer has been substantiated by numerous studies (Thomison, III, Thomas, Shroyer 2008).

Pathogenesis of HPV Infection:-

It is essential to have knowledge about the mechanism of HPV infection for an explicit understanding of the events occurring in the cervical epithelium in the course of malignant transformation. High risk oncogenic HPV are major cause of almost all cases of carcinoma cervix and among these HPV 16 is the most prevalent one (Lace, Anson, Turek, Haugen 2008). After entering the epithelial cells of the cervix, HPV DNA initially replicates for which E1 and E2 proteins are essential, E1 serves as replicator initiator. Viral genome is interrupted at this E1/E2 reading frame which normally represses the expression of E6 and E7. Hence interruption of E1/E2 over express E6 & E7. E6 protein plays pivotal role in pathogenesis of the virus. E6 acts mainly be degrading P53, a tumor suppressor gene via Ubiquitin dependent proteolysis

(Syrjanen, Syrjanen 1999). E7 protein, on the other hand, binds to RB gene which is also another tumor suppressor gene and disrupts E2F/RB complex and eventually degrades the protein. Thus E6 and E7 proteins of high risk HPVs regulate the cell cycle by degrading the tumor suppressor gene. This mechanism is believed to be responsible for tumorigenesis. Also other events like methylation of DNA and Telomerase activation contribute to the viral pathogenesis (Holowaty, Miller, Rohan, To 1999). A careful study of these proteins is of immense utility in therapeutic modalities where blockage of these proteins would prevent infection. Prophylactic vaccines for HPV infection are designed to target these two proteins (Massimo, Calcagno, Battaglia, Pistorio 2009).

HPV infection of cervix is a continuous pathological process with a spectrum of morphological changes from latent subclinical stage to fatal malignancy (Li, Meng, Ting, Shen, Ma 2010). In addition to HPV other risk factors for carcinoma cervix are hormones, smoking and immunity (Ponten, Guo 1998).

Expression of MMPS in Carcinoma Cervix and their Relation to HPV Infection:-

The role of MMPS for progression and distant metastasis of tumor has been studied extensively in many types of tumors (Coussens, Werb 1996; Curran, Murray 1999; Stetler-Stevenson, Aznavoorian, Liotta 1993). Here we discuss their pattern of expression, actions and their relation to HPV infection in carcinoma cervix. A set of MMPS are expressed in the tissue of carcinoma cervix which act by interacting with stromal cells. Degradation of ECM and remodeling enables the tumor cells to invade in to the tissues and migrate (Stetler-Stevenson, Aznavoorian, Liotta 1993). The whole process is quite complex. Initially tumor cells should first mobilize, attach to the vessel wall, extravasate, invade the adjacent tissue and then should survive and proliferate in the new tissue. The key promoter for the whole process is a glycoprotein called 'laminin' in ECM (Engbring, Kleinman 2003). The contribution of MMPS to tumor progression and metastasis was substantiated by their role in angiogenesis promotion, growth factor stimulation and down regulation of inhibitory factor (Duffy, Maguire, Hill, McDermott, O'Higgins 2000). However, their ability to inhibit angiogenesis was also noticed when they were able to synthesize Angiostatin, an inhibitor of angiogenesis (Hiraoka, Allen, Apel, Gyetko, Weiss 1998). Thus tumor- stromal cell interaction is the event which trigger MMPs production and leading to the above mentioned sequence of events .Invitro studies have also substantiated that the cell of cervical cancer invades by utilizing MMPS produced by cervical fibroblast (Sato, Sakai, Noguchi, Takita, Hirakawa, Ito 2004).

Another member which has to be mentioned here is EMMPRIN (Extracellular Matrix metalloproteinase inducer) or CD 147, this is an immunoglobulin which when over expressed on tumor cells promote not only invasion and metastasis but also prolongs survival of tumor cells (Sato, Ota, Watanabe, Imada, Nomizu, Ito 2009; Yang, O'Neill, Jin et al. 2006). Hence MMP expression can be used as a marker for occurrence of carcinoma cervix irrespective of the type of the tumor (Nasr, Ayyad, El-Lamie, Mikhail 2005). However intensity of expression may vary. For example, MMPS are strongly expressed in Squamous cell carcinoma than in adenocarcinoma (Davidson, Goldberg, Liokumovich et al. 1998; Yoshida, Sumi, Hyun et al. 2003).

MMP-2 is most common metalloproteinase in carcinoma cervix (Wang, Ko, Tsai et al. 2008). Its association with the stage and grade as well as recurrence of the tumor has been established (Ahmed, Salahy, Tawfiq, Khalifa, Hassan 2004; Sato, Sakai, Noguchi, Takita, Hirakawa, Ito 2004) and plasma levels of MMP-2 can be used as the denominator for clinical correlation. MMP-9 is another MMP which is significantly expressed in Carcinoma cervix. Studies were conducted to compare the levels of expression of these two MMPs and also their role in clinical outcome. Higher values of MMP-9 than MMP-2 were found to be associated with progression of disease to higher grade, where as low values indicate a low risk of carcinoma (Yang, Wang, Lin et al. 2007). On the contrary, when the expression of MMP-2 &

9 were studied on tissues and their prognostic implications were evaluated and compared, MMP-2 was found to be associated with high grade tumor and unfavorable outcome. Also there could be a possibility that these two MMPS have different role in cervical cancer (Stevens, Tabrizi, Quinn, Garland 2006). Other MMPS that are expressed at mRNA level are MMP-1, -3, -7, -8, -11, -13, -14, -15, -17, 23 and 24. At the protein levels, MMP-1 & 11 are in active form, MMP-15 is in inactive from and MMP 9, -13, - 23 exist both in active and inactive forms (Schropfer, Kammerer, Kapp, Dietl, Feix, Anacker 2010) MMP 14 & 15 are mainly involved in activation of Pro MMP-2 (Sheu, Lien, Ho et al. 2003). Sometimes paired expression of MMPs is observed. MMP-2 is expressed in correlation with MMP-14 and MMP3 with MMP-15. Coexistence of MMP-2 and MMD 14 increase the grade of the tumor (Gilles, Polette, Piette et al. 1996).

TIMPS have also been proved to be involved in tumorigenesis and progression of cervical cancer. TIMP-1 & TIMP-2 (Davidson et al. 1998) are the most common members of this group to be linked to cervical cancer. TIMP-2 as a member of alfa-3, MT-1, MMP-2 complex is supposed to play a part in activating MMP-2 (Sato, Sakai, Noguchi, Takita, Hirakawa, Ito 2004). TIMP-4 expression levels are also found to be high in cervix carcinoma (Lizarraga, Espinosa, Maldonado, Melendez-Zajgla 2005). Thus other than antagonizing the actions of MMPS they also help in tumor progression. However, a balance between MMP and TIMPS is always desirable to have a better outcome of the tumor. As the value of MMP: TIMP ratio increases the prognosis worsens (Nuovo, MacConnell, Simsir, Valea, French 1995). Recently synthetic TIMPs have come in to use. Among these the hydroxamic acid based class of components [Hydroxamates] are widely used and they act by binding to the zinc ion present in MMPs (Yadav, Gupta, Sharma, Patil 2011). An extensive research is going on to identify the exact mechanism of correlation of HPV with MMP expression. The association of HPV and MMP is strongly supported and demonstrated in several studies. It has been documented that HPV infection precedes the elevation of MMP levels and this actually triggers the MMP production leading to tumor progression (da Silva Cardeal, Brohem, Correa et al. 2006). Several possibilities have been quoted to relate HPV with MMP. Studies on MMP-9 expression in carcinoma cervix showed that HPV E2 along with transcription factor NF Kappa B regulate the expression of MMP-9 (Gasparian, Fedorova, Kisselev 2007). In fact few studies as such failed to demonstrate any relation between HPV & MMPS (Branca, Ciotti, Giorgi et al. 2006). cDNA arrays done to study gene expression in cervical cancer showed that two genes, il-6 and MMP 10, were consistently over expressed (Vazquez-Ortiz, Pina-Sanchez, Hidalgo et al. 2005). Another breakthrough in this issue was when, in the keratinocytes infected with HPV 16 or 18, E7 protein induced expression of MTI-MMP (Smola-Hess, Pahne, Mauch, Zigrino, Smola, Pfister 2005).

CONCLUSION

Carcinoma cervix is an extremely common cancer worldwide and there is every need to prevent and cure it. Several studies done to explore the etiopathogenesis of cervical cancer concluded that HPV is the causative agent and MMPS have a vital role in tissue pathology in cervix. It has also been to some extent substantiated that HPV and MMPS accentuate each other's actions and raise the damage to the tissues multifold resulting in malignancy. The status of HPV and MMP expression has prognostic implications in carcinoma cervix. Hence a knowledge regarding their association and mode of action would be of great significance and it would also lay a path for the production of new therapeutic agents targeting HPV and MMPs. New research projects have to be conducted with this background.

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Conflict of Interest:
Authors declare that there is no conflict of Interest.

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