MINI-REVIEW

Matrix Metalloproteinases and Cancer - Roles in Threat and Therapy

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Abstract

   Matrix metalloproteinases (MMPs) are a family of zinc dependent extracellular matrix (ECM) remodelling endopeptidases having the ability to degrade almost all components of extracellular matrix and implicated in various physiological as well as pathological processes. Carcinogenesis is a multistage process in which alteration of the microenvironment is required for conversion of normal tissue to a tumour. Extracellular matrix remodelling proteinases such as MMPs are principal mediators of alterations observed in the microenvironment during carcinogenesis and according to recent concepts not only have roles in invasion or late stages of cancer but also in regulating initial steps of carcinogenesis in a favourable or unfavourable manner. Establishment of relationships between MMP overproduction and cancer progression has stimulated the development of inhibitors that block proteolytic activity of these enzymes. In this review we discuss the MMP general structure, classification, regulation roles in relation to hallmarks of cancer and as targets for therapeutic intervention.

Keywords: MMPs - MMPI - TIMP - cancer - endopeptidases - microenvironment

Introduction

   Cancer is one of the leading causes of mortality and morbidity worldwide (Jemal et al., 2004) and in addition to genetic features, environmental factors are also important in modulating the individual susceptibility to it (Cao and Li, 2006).

   Carcinogenesis of head and neck is a multistep process (Chaudhary et al., 2010) and the molecular mechanism of complex interaction between the tumour cells and tumour microenvironment play an important role in this process (Gialeli et al., 2011). Matrix metalloproteinases (MMPs) have the ability to regulate the tumour microenvironment and their expression and activation is increased in almost all human cancers compared to normal tissue (Egeblad and Werb, 2002).

   MMPs are a family of structurally related zinc dependent endopeptidases collectively capable of degrading almost all components of extracellular matrix (Vihinen and Kahari, 2002). MMPs are important not only in normal, physiological and biological processes such as embryogenesis, normal tissue remodelling, wound healing and angiogenesis but also in diseases such as arthritis, cancer& tissue ulceration (Sekhon, 2010).

Structure and Classification

   Currently 24 different types of MMPs have been

identified among vertebrates, 23 of them have been found in humans (Overall and Lopez-otin, 2002; Vihinen and Kahari, 2002; Chau

dhary et al., 2010; Sekhon, 2010) (Table 1). Several MMPs have been localised to the same chromosomal location 11q23, a region that shows amplification in several solid tumours (Curran and Murray, 1999).

   On the basis of substrate specificity, sequence similarity and domain organisation vertebrate MMPs can be divided in to 6 groups-Collagenases, Gelatinases, Stromelysins, Matrilysins, Membrane Type MMPs and other MMPs (Visse and Nagase, 2003).

   MMPs contain several distinct domains (Figure 1) that are conserved among various members of the family and are as follows: *i*) Predomain or the secreation leader sequence (absent in MT-MMPs); *ii*) Propeptide that contains highly conserved PRCGVPDV sequence and proteolytic cleavage of which is required for enzymatic activation; *iii*) Catalytic domain which has a conserved
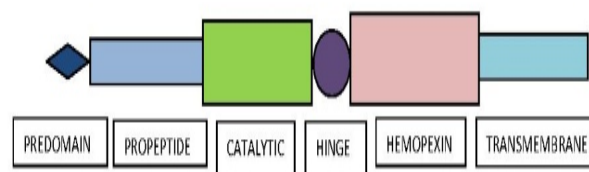

Figure 1. Different Domains of MMPs

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Table 1. Classification of MMPs, their Chromosomal Location and Substrate

Type	Common Name	Chromosomal Location	Substrate
Collagenases	MMP-1 Collagenase-1	11q$_{22.2-22.3}$	Collagen (I,II,III,VII,VIII,X),Casein,Perlecan,Entactin,Laminin,Pro-MMP-1,2,9 &Serpins
	MMP-8 Collagenase-2	11q$_{22.2-22.3}$	Collagen (I-III,V,VII,VIII,X), Gelatin,Aggrecan,Fibronectin.
	(Neutrophil Collagenases)		
	MMP-13 Collagenase-3	11q$_{22.2-22.3}$	Collagen(IIV,IX,X,XIV),Gelatin,Plasminogen,Aggrecan,Perlecan ,Fibronectin
	MMP-18 Collagenase-4	Not in humans	Type I Collagen
Gelatinases	MMP-2 Gelatinase A	16q13	Gelatin, Collagen(IV-VI,X), Elastin, Fibronectin
	MMP-9 Gelatinase B	20q$_{11.2-13.1}$	Gelatin,Collagens(IV,V,VII,X,XIV),Elastin, Fibrillin&Osteonectin
Stromelysins	MMP-3 Stromelysin-1	11q$_{22.2-22.3}$	Laminin,Aggregan,Gelatin,Fibronectin
	MMP-10 Stromelysin-2	11q$_{22.2-22.3}$	Collagens(III-V),Gelatin,Casein,Aggregan, Elastin,MMP-1,8
Stromelysin like MMPs	MMP-11 Stromelysin-3	22q 11.2	Fibronectin ,Laminin,Aggregan,Gelatin
	MMP-12 Metalloelastase	11q$_{22.2-22.3}$	Elastin,Gelatin,CollagenI,IV,Fibronectin, Laminin,Vitronectin, Proteoglycan
Matrilysins	MMP-7 Matrilysin	11q$_{22.2-22.3}$	Collagen(IV-X), Fibronectin, Laminin, Gelatin, Aggregan,Pro-MMP-9
	MMP-26 Matrilysin-2	11q 22.2	Gelatin,Collagen IV,Pro-MMP-9
Membrane type MMPs	MMP-14 MT-1 MMP	14q 12.2	Collagen(I,II,III),Gelatin,Fibronectin,LamininAggrecan,Tenascin.
	MMP-15 MT-2 MMP	16q 12.2	Fibronectin,Laminin,Aggrecan,Perlecan.
	MMP-16 MT-3 MMP	8q 21	Collagen III,Gelatin,Casein
	MMP-17 MT-4 MMP	12q24	Fibrinogen,TNF Precursor
	MMP-24 MT-5 MMP	20q 11.2	Proteoglycans
	MMP-25 MT-6 MMP	16p13.3	Collagen IV, Gelatin,Fibronectin,Fibrin
Other MMPs	MMP-19 -	12q14	Type I Collagen
	MMP-20 Enamelysin	11q22	Amelogenin,Aggrecan
	MMP-21 XMMP(Xenopus)	-	Gelatin
	MMP-22 CMMP(Chicken)	11q24	-
	MMP-23 Cysteine array	1p36.3	Gelatin
	MMP-27 -	11q24	-
	MMP-28 epilysin	17q11.2	Casein

three histidine sequence that is required for zinc chelation; *iv*) Hemopexin domain (except in MMP-7) that is involved in interactions with other MMPs and tissue inhibitors of metalloproteinases (TIMP) (Thomas et al., 1999).

A typical MMP consist of propeptide of about 80 AAs, a catalytic domain of about 170 AAs, a linker peptide of variable length [also known as hinge region] & a hemopexin domain of about 200 AAs (Nagase et al., 2006). Common properties of the MMPs include requirement of zinc in their catalytic site for activity and their synthesis as inactive zymogens that generally need to be proteolytically active (Rundhaung, 2003).

Regulatory Mechanisms of MMPs

There are 3 levels of regulation for MMPs: *i*) Gene transcription; *ii*) Proenzyme activation; *iii*) Inhibition of enzyme activity (Folgueras, 2004).

Transcriptional Mechanism

A wide variety of agents are responsible for spatial and temporal variation of MMP expression such as cytokines, growth factors and oncogenes (Westermarck and Kahari, 1999). Structural and functional analysis of the promoter region of several MMPs provided the understanding of the mechanisms that regulate their expression and studies revealed that inducible MMP genes posses an AP-1 binding site in their proximal promoter region (Pendas et al., 1997). AP-1 binding site is located approximately 70 bp upstream of the transcriptional activation site and considered to play an important role in the regulation of transcription of MMP promoter (Benbow and Brinckerhoff, 1997). Two extensively studied factors which influence the MMP transcription are IL-1β and TGF −β.IL-1 β stimulates, whereas TGF- β inhibits MMP gene expression (Figure 2) (Murphy and Reynolds, 1993).

Figure 2. Factors Affecting MMP Gene Expression

Proenzyme Activation

MMPs are synthesized as inactive zymogens and require activation.MMPs remain inactive by an interaction between cysteine-sulphydryl group of propeptide domain and zinc ion bound to the catalytic domain (Sternlicht and Werb, 2001). The cysteine –sulphydryl group within the propeptide domain of the latent MMPs forms a bridge with the catalytic zinc and blocks the enzymatic activity. Activation can occur by physical or chemical means (Stamenkovic, 2003) by disturbing the cysteine –zinc interaction of the cysteine switch (Chen et al., 1993).

MMP activation requires participation of other proteases to remove propeptide domain (Lijnen, 2001). Most MMPs are activated in pericellular space by tissue and plasma proteinases ,bacterial proteinases or other MMPs but MMP11,23,28 and MT-MMPs are activated intracellularly prior to secretion by Golgi associated furin proteases (Velasco et al., 1999). Activation of ProMMPs by plasmin is an important pathway in vivo and other mechanism of activation is via cell surface MT-MMPs (Basbaum and Werb, 1996).

Inhibition of Enzyme Activity

Proteolytic activity of MMPs can be inhibited specifically by TIMP and non-specifically by α1 proteinase inhibitor and α 2 macroglobin (Westermarck and Kahari, 1999; Brew et al., 2000).

TIMP are specific inhibitors that bind MMPs in a 1:1 stoichiometry (Brew et al., 2000). Four TIMPs have been identified in vertebrates in which TIMP 1 and 3 are

glycoproteins whereas TIMP2 and 4 are unglycosylated (Leco et al., 1994). TIMP 1, 2 and 4 are secreted and TIMP 3 is anchored in the ECM. TIMP have a conserved structure divided in to an N- and C- terminal domain containing three conserved disulfide bonds (Williamson et al., 1990). TIMP-1 is a 28.5 KD glycoprotein and inhibits all activated collagenases (Denhardt et al., 1993). TIMP2 is a 21 KD nonglycosylated protein which is an inhibitor of MMP 2 and can be secreted as complex with pro-MMP2 or in an unbound form (Stetler-stevenson et al., 1989). TIMP3 and 4 cloned from cDNA library (Uria et al., 1994; Greene et al.,1996).

MMPs in Cancer

In the context of tumour biology, the MMPs were initially believed to facilitate metastasis by breakdown of physical barriers provided by extracellular matrix and basement membrane, but now appear to have multiple biological functions in different steps of carcinogenesis including growth regulatory effects on both primary and secondary tumours (Chambers and Matrisian, 1997).

There are 6 fundamental alterations that underlie cancer progression. These are the self support in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, infinite replication, sustained angiogenesis and invasion and metastasis (Hanahan and Weinberg, 2000). Initially MMPs were thought to be important exclusively in invasion and metastasis, but recent studies demonstrated that MMPs are involved in several steps during carcinogenesis (Egeblad and Werb, 2002).

Regulation of Growth

MMPs can regulate the growth of tumour cells by the following mechanisms: *i)* By release of cell membrane bound precursors of some growth factors (Peschon et al., 1998); *ii)* By modulating the bioavailability of growth factors that are sequestered by ECM proteins. eg-IGF (Manes et al., 1997); *iii)* By indirectly regulating proliferative signals through integrins (Agrez et al., 1994). Because of the shedding of the E cadherin, β catenin translocates to the nucleus and leads to proliferation (Maretzky et al., 2005).

MMPs can also inhibit growth by the following mechanism: *i)* By activation of TGF-β; *ii)* By generation of proapoptotic molecules. e.g. Fas ligand or TNF α (Egeblad and Werb, 2002).

Regulation of Apoptosis

MMPs perform both the apoptotic and antiapoptotic action. Antiapoptotic actions are mediated by the following mechanisms: *i)* By cleaving the Fas ligand (Mitsiades et al., 2001); *ii)* Byproteolytic shedding of tumour associated MHC complex class I related protein (Waldhauer et al., 2008); *iii)* By activating serine/threonine kinase, AKT/ Protein kinase B (Gialeli et al., 2009).

Apoptotic actions are mediated by changing the ECM composition. MMPs cleave the adhesion molecules and leads to apoptosis (Gialeli et al., 2011).

Regulation of Angiogenesis

Angiogenesis is a complex process by which new blood vessels form from existing vessels (Rundhaung, 2003) and this process is essential for tumour growth (Hanahan and Folkman, 1996). MMPs have dual role in the process of angiogenesis – they promote as well as inhibit angiogenesis. MMPs that play important role in angiogenesis are MMP 2,9&14 whereas MMP1&7 plays a minor role (Rundhaung, 2003).

MMPs promote the process of angiogenesis by the following mechanism: *i)* By degradation of basement membrane and other ECM components (Stetler-Stevenson, 1999); *ii)* By releasing ECM bound pro-angiogenic factors (Stetler-Stevenson, 1999). MMP 9 plays key role in angiogenic switch by increasing the bioavailability of important angiogenic factors such as VEGF b – FGF (Cornelius et al., 1998); *iii)* By triggering the integrin intracellular signalling (Stetler-Stevenson,1999).

MMPs inhibit the process of angiogenesis by the following mechanism: *i)* By cleavage of plasminogen which releases angiostatin (Cornelius et al., 1998); *ii)* By cleaving collagen XVIII which produces endostatin (Ferreras, 2000); *iii)* By shedding of cell surface bound urokinase type plasminogen activator receptors which are required for the endothelial cell invasion in to fibrin (Koolwijk et al., 2001).

Regulation of Invasion and Metastasis

Tumour invasion is a multistep process in which cell motility is coupled with proteolysis and involves interaction of cells with ECM (Zhang et al., 2012). During invasion malignant cells detach from primary tumour and invade through basement membrane and stromal ECM (Vihinen and Kahari, 2002). Proteolytic degradation of basement membrane and ECM is an essential step for invasion and requires proteases (Sekhon, 2010). The steps involved in the process of invasion are shown in Figure 3.

Cadherin are cell adhesion molecules that mediate cell-cell adhesion in normal mucosal cells and maintain epithelial integrity (Choi and Myers, 2008) and its deregulation is associated with cancer progression (Birchmeier et al.,1996). Decreased expression of E-cadherin causes loss of cell adhesion and contributes to cell dissociation, increased motility and invasion (Takeichi, 1991).

E-cadherin is cleaved by MMP3 and 7 (Noe et al., 2001) and this cleavage also triggers the epithelial to mesenchymal transition(EMT) (Birchmeier et al., 1996).
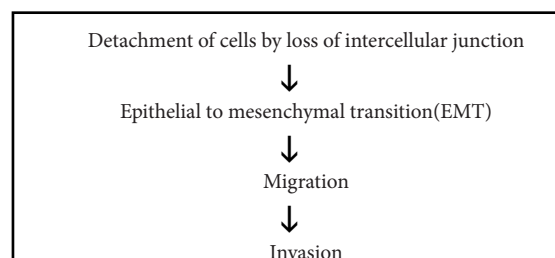

Detachment of cells by loss of intercellular junction
↓
Epithelial to mesenchymal transition(EMT)
↓
Migration
↓
Invasion

Figure 3. Flow Chart

Epithelial mesenchymal transition is a process in which epithelial cells change from epithelial phenotype to mesenchymal phenotype leading to loss of epithelial integrity, increased migration, invasion and ultimately metastasis (Thiery, 2002). MMP28 causes the proteolytic activation of TGF –β which is a powerful inducer of EMT (Illman et al., 2006).

MMPs are involved in the cell migration by removing sites of adhesion, exposing new building sites, cleaving cell-cell or cell-matrix receptors and releasing chemo attractants from ECM (McCawley and Matrisian, 2001). MMP2&14 degrades laminin5 and reveals a cryptic site that triggers motility (Egeblad and Werb, 2002).

The ability to invade and establish colonies at remote site is a characteristic of malignant neoplasm (Curran and Murray, 1999). For neoplastic lesion to invade and metastasize, neoplastic cells must be capable of degrading the extracellular matrix and accessing blood vessels and lymphatics (Thomas et al., 1999). Proteolytic enzymes play a fundamental role in cancer progression providing an access for tumour cells to vessels and lymphatic system and thus support the growth and metastasis (Chambers et al., 2002). It is known that basement membrane which separates the epithelial and mesenchymal compartments represent first barrier to invasion (Thomas et al., 1999). MMP2 and 9 both can degrade type IV collagen of basement membrane and thus helps in invasion (Ikebe et al., 1999).

To promote invasion there is localisation of MMPs in specialised surface protrusion known as invadopodia. MMPs which localise to invadopodia are MMP 2, 9, and 14 that help in the degradation of basement membrane (Thomas et al., 1999). Once cancer cells cleave basement membrane then degradation of interstitial collagen is essential for further spread. MMP1 plays an important role in metastasis by degrading the interstitial collagen (Murray et al.,1996). During metastasis cancer cells cross several ECM barriers, first they cross basement membrane then invade surrounding stroma, enter blood vessels or lymphatics and then after extravasation establish new colonies (Egeblad and Werb, 2002). Several studies indicate that MMP9 is required for intravasation (Kim et al., 1998) and similar to intravasation, MMPs are necessary for the circulatory tumour cells to be able to exit the blood vessels (extravasation), although this step is not rate limiting for the establishment of metastasis. At the distant site, MMPs are required for local migration, establishment of a microenvironment conducive for metastatic growth and angiogenesis for sustained growth (Rundhaung, 2003).
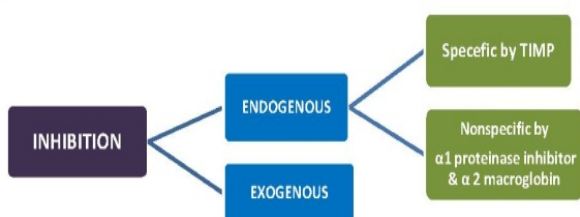
Regulation of Immune Surveilliance

Figure 4. Different Mechanisms of Inhibition of MMPs

Once in the circulation, tumour cells are particularly vulnerable to destruction by innate and adaptive immunity (Kumar et al., 2004). Immune system is capable of recognising and attacking cancer cells and to survive cancer cells develop many ways to escape immune surveillance (Gialeli et al., 2011).

Tumour specific cytotoxic T cells, natural killer cells, neutrophils and macrophages are the inflammatory cells that are capable of recognising and attacking cancer cells (Egeblad and Werb, 2002). When T cells are activated by antigen they secrete locally acting protein called cytokines. Under the influence of cytokine called interleukin 2 (IL-2), T- cells proliferate (Kumar et al., 2004). MMPs can cleave the IL-2Rα and thereby suppressing their proliferation (Sheu et al., 2001). TGF β is a cytokine that down regulate the immune responses by affecting the lymphocyte growth, activation and differentiation (Kumar et al., 2004). MMPs activate TGF β and thus indirectly regulate the T lymphocyte function (Gorelik and Flavell., 2001). Chemokines are family of small protein that act primarily as chemo attractants for specific types of leucocytes (Kumar et al., 2004). Several chemokines are targets of MMPs so MMPs can indirectly affect the leukocytes action (Egeblad and Werb, 2002).

MMP Inhibition Strategies

The relation of MMPs overproduction and tumour progression has prompted the development of various strategies aimed to block the proteolytic activity of these enzymes (Folgueras et al., 2004). By understanding the steps involved in regulation of this proteolytic system there can be different strategies by which MMPs can be inhibited. There are three major levels of regulation of these enzymes: *i*) Transcription; *ii*) Activation; *iii*) Inhibition.

Targeting the transcription again can be at three levels as shown in Figure 5, first by interfering with the extracellular factors for e.g. interferon inhibit the transcription of MMPs (Kuga et al., 2003), second by blocking the signal transduction pathway such as MAPK pathway and ERK pathway (Folgueras et al., 2004) and third is by targeting the nuclear factors of transcription for e.g. AP-1 and NF-kβ (Karin and Chang, 2001) that influence the expression of MMP.

MMPs are secreted as zymogens and its activation is an important regulatory step of MMP activity (Nagase et al.,
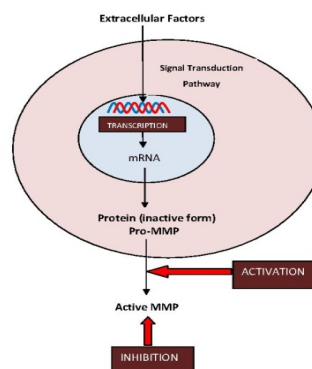

Figure 5. Different Steps in Regulation of MMPs

2006). MT1 –MMP is important in pro-MMP activation so anti-MMP monoclonal antibodies can be an effective strategy for MMP inhibition (Folgueras et al., 2004).

After the activation the activity of MMPs can be regulated by its inhibition which can be endogenous or exogenous. Endogenous inhibition can be nonspecific for e.g. by α-2 macroglobulin, or specific by TIMP (Vihinen and Kahari, 2002).

Human α-2 macroglobulin is a plasma glycoprotein of 725 KDa consisting of 4 identical subunits of 180 KDa (Strickland et al., 1990). TIMP consist of 21-29 KDa protein and besides their inhibitory activity they posses other biological capacities as well (Ganea et al., 2007).

Synthetic Inhibitors

Taking in to consideration the important roles that MMPs play in multistep process of carcinogenesis, various synthetic agents are developed in an attempt to control the activity of MMPs. Several generation of MMPI are tested in phase III clinical trials in humans, including synthetic peptides, nonpeptidic molecules, chemically modified tetracyclines and bisphosphonates (Vihinen and Kahari, 2002).

Side effects of drugs include musculoskeletal pain due to inhibition of TNF-α converting enzyme (TACE) and shedding of TNF-α receptor II (TNF-RII) (Nelson et al., 2000).

Peptidomimetic MMPI

These are pseudopeptide derivatives that mimic the cleavage site of MMP substrates (Wojtowicz-praga et al.,1996). They act as competitive inhibitors which inhibit the MMP activity by interacting with the Zn^{2+} in catalytic sites and then chelating it (Gialeli et al., 2011). This category includes Batimastat (BB-94), Marimastat (BB-2516) and Salimastat (BB-3644) (Chaudhary et al., 2010).

Batimastat is the first MMPI which was tested in humans, (Wojtowicz-praga et al., 1996) but it has broad spectrum of inhibition and low water solubility because of which its intraperitoneal administration is required. To overcome these drawbacks Marimastat was introduced which can be orally administered but associated with the side effects of musculoskeletal pain (Steward and Thomas, 2000).

Nonpeptidomimetic MMPI

These are more specific than peptidomimetic because these are based on the three dimensional X ray crystallographic confirmation of Zn binding site (Chaudhary et al., 2010).Oral bioavailability is better than peptidomimetic inhibitors (Vihinen and Kahari, 2002) and this category include Prinomastat (AG-3340), Tanomastat (BAY12-9566), BMS-275291(D2163) and MMI 270 B (CGS 27023 A) (Chaudhary et al., 2010).

Prinomastat is a low molecular wt MMP inhibitor, structure of which mimic collagen. It inhibits the activity of MMP1,2,3,7,9 and 14 (Hidalgo and Eckhardt, 2001).

BAY inhibits the activity of MMP -2,3,9 and 13 (Vihinen and Kahari, 2002). BMS lacks the musculoskeletal side effects (Lockhart et al., 2003) orally bio available and inhibits the angiogenesis by inhibiting the MMP-2 and MMP-9 activity (Vihinen and Kahari, 2002). MMI is in phase I clinical trial and inhibits the activity of MMP 1,2&3 (Chaudhary et al., 2010).

Tetracycline Derivatives

This category includes Metastat (COL-3,CMT-3), Minocycline and Doxycycline (Gialeli et al., 2011). Metastat has limited systemic toxicity and lacks the antimicrobial activity (Lokeshwar et al., 2001) because of the removal of the dimethyl amino group (Hidalgo and Eckhardt, 2001). Mode of inhibition of MMP activity is by binding to metal ions such as Zn^{2+} (Sapadin and Fleischmajer, 2006).

Bisphophonates

Bisphosphonates were originally developed to inhibit bone resorption, but it also inhibits MMP-2 secretion by indirectly acting through TIMP (Vihinen and Kahari, 2002).

Natural MMP Inhibitors

This category include Neovastat (AE 941),extracted from shark cartilage (Chaudhary et al., 2010) and has antiangiogenic and antimetastatic effects (Falardeau et al., 2001) by inhibiting MMP-2,9,12,13 and VEGF (Chaudhary et al., 2010). Another agent is Genistein a soy isoflavonoid similar to estradiol which interferes with the expression of several MMPs and TIMPs (Kousidou et al., 2006).

Strategies to Improve the Efficacy of MMPI

i) Should be used as preventive drugs, for e.g. in patients with genetic predisposition of cancer or postoperatively in a patient in which there is no metastasis (Eccles et al.,1996); *ii*) It would be better to target specific MMPs because at a high tolerated dose drugs lose their selectivity for MMP (Egeblad and Werb, 2002); *iii*) Precise identification of set of proteases, that should be targeted in a specific situation, with the importance of cancer degradome (Lopez-otin and Overall, 2002). i.e. the complete set of proteases produced by a specific tumour at a specific stage of development; *iv*) Drugs targeting the specific exosites should be used. Exosites are the binding sites related to substrate selection of MMPs, which are present outside the active domain (Overall, 2002).

Future Considerations

Several studies have demonstrated that MMPs not only participate in tumour invasion and metastasis or the late stages of the carcinogenesis but they are also involved in early stages in both favourable and unfavourable manner.

MMPs are a diverse group of enzymes with overlapping

and complex expression and functions in different types and stages of tumour so thorough consideration of type and stage of tumour should be done prior to administration of MMPI. According to current concept, MMPs play important role in maintaining the tumour microenvironment so MMPI would be more effective in a cancer where stroma plays an important role. Because the area and mode of action of MMPs is not very clear, so MMPs should be used as an adjuvant with chemotherapy. In different steps of carcinogenesis some MMPs have stimulatory whereas some have inhibitory effect so the concept of degradome should be utilize frequently and accordingly specific MMPI should be used so that the effects that are in favour of host are not blocked, and to minimize the side effects, specific inhibitors ,preferably targeting the specific exosites should be used.

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