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MATRIX METALLOPROTEASES: A REVIEW ON THEIR PROANGIOGENIC AND METASTATIC POTENTIAL

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ABSTRACT

Matrix metalloproteases (MMPs) are involved in the dissolution of basement membrane and components of extracellular matrix (ECM). Metastasis is one of the leading causes of deaths in cancer. It is a critical step in the progression of cancer through dissolution of tissue barriers throughout the body and spread to distant sites. MMPs induce cancer progression by interacting with tumor suppressor genes and initiating abnormalities in normal cells. The regulation of MMPs is critical, since they have a role in tumorigenesis and metastasis. One of the most effective therapeutic strategies to overcome cancer progression is through downregulation of the expression of MMPs leading to anti-invasion and anti-metastasis. Tissue inhibitors of metalloproteinases (TIMPs) are the major in situ inhibitors of MMPs and they maintain homeostasis between ECM formation and destruction. However, TIMPs have limited efficacy as pharmacological agents due to their short half-lives *in vivo*. In the present review, the classification of MMPs and their significant roles in different types of cancers have been discussed. A number of synthetic MMP inhibitors (MMPIs) have been synthesized in the last few decades and have undergone rigorous clinical evaluation in an attempt to control abnormal MMPs expression in certain physiological conditions including cancer. Although limited success has been achieved in this respect, nevertheless, development of novel and effective MMPIs is an ongoing area of vigorous research and might prove to be a promising research area for both diagnostic and therapeutic purposes in future.

KEYWORDS: Matrixins, Endopeptidases, Extracellular matrix, Angiogenesis, Tumorigenesis, TIMP, MT-MMP.

INTRODUCTION

MMPs were observed for the first time in 1962 by Jerome Gross and Charles Lapiere in the tissue obtained from the tails of tadpoles *Rana catesbiana*, a North American species, that exhibited collagenolytic property and named it as MMP-1 or collagenase 1 (1). This collagenase enables the distribution of collagen in the tail of tadpole during metamorphosis, which facilitates transformation into the adult (1, 2). The ECM is modulated by a number of MMPs which have a profound effect on its migration, intravasation and extravasation. In the classical view, MMPs particularly help in ECM remodeling by causing release of growth factors bound to it. This eventually leads to creation of a microenvironment which aids the establishment of tumors (3). However, recent studies have revealed that the MMPs are responsible for regulating the level, activation and release of growth factors, chemokines, other bioactive molecules and antibiotic peptides that participate in physiological processes such as neurite growth, inflammation, bone remodeling, angiogenesis and innate and adaptive immune processes (4).

MMPs, also called matrixins, belong to a large metzincin group and are calcium and zinc-dependent endopeptidases which are involved in the dissolution of ECM components including fibronectin, fibrillar/nonfibrillar collagens, basement membrane and laminin by interfering with their protein components (5). In their catalytic sites, they share the conserved zinc-binding motif which requires Ca^{+} ion for enzyme activity. Most of the MMPs are secreted as zymogens whose activity is regulated by activators and inhibitors and these zymogens are required to be proteolytically cleaved in order to become active (6). Their expression and activity can be regulated at different levels including proenzyme activation, endogenous inhibition and gene transcription. Therefore, MMPs are expressed only at the time of tissue remodeling in events such as mammary gland development, vascular and bone remodeling. However, their abnormal expression is correlated with various pathological conditions including tumor cell invasion, rheumatoid arthritis, metastasis and periodontitis (7). A number of MMP genes are associated with different cancers, indicating their role

in carcinogenesis (8). In humans, MMP-1 consists of two pro-enzymes, one 52 kDa major and another 57 kDa minor, both of which undergo processing to generate two active enzymes of 47 kDa each. MMP-1 is unable to cleave basal membrane components as compared to other MMPs. On the basis of their substrate specificity and homology, MMPs can be classified as collagenases, gelatinases, stromelysins, matrilysins, membrane- type and other MMPs. The present review provides an update on the roles of MMPs in colon, breast, oral, lung, prostate and other types of cancers. Some recent studies focusing on regulation of MMPs and their therapeutic intervention in cancer have also been discussed. MMPs block several cell cycle inhibition pathways and thus, promote cancer progression. Firstly, the therapeutic significance of MMPs regulation in oral cancer is discussed. Oral squamous cell carcinoma (OSCC) contributes to about 94% of the total oral cancers prevalent throughout the world (9, 10). Secondly, the role of MMP-9 and MMP-2 in modulation of mitogen-activated protein kinase kinase kinase 3 (MEKK3), phosphate-extracellular signal-regulated kinases (p-ERK) signaling pathways in lung cancer proliferation is discussed (11). Thirdly, the involvement of steroid receptor coactivator 3/amplified in breast 1 (SRC-3/AIB1), MMP-2 and MMP-13 in promoting prostate cancer invasiveness is dealt with (12). Last but not the least, the role of erythropoietin-producing hepato-cellular receptor-2 (EphA2) and MT1-MMP in inducing ovarian cancer is dwelt upon (13).

CLASSIFICATION OF MMPs

MMPs form a large group of several proteins viz. MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, etc. Till date, 26 different MMPs have been identified including 23 in humans (Table 1) (14-17). These play critical roles in ECM degradation, angiogenesis, organogenesis and other cellular degradation and metastatic processes. MMP-3 and MMP-10 lead to breakdown of fibronectin, proteoglycans and laminin, whereas MMP-1, MMP-8 and MMP-13 degrade collagen type I, II and III. MMPs have been divided majorly into six major groups:

1. Collagenases (MMP-1, MMP-8, MMP-13 and MMP-18).These enzymes have the ability to cleave interstitial collagens I, II, and III at specific sites (17, 18).
2. Gelatinases (MMP-2 and MMP-9). These enzymatic proteins can readily digest denatured gelatins and collagens (17, 19).
3. Stromelysins (MMP-1, MMP-3, MMP-10 and MMP-11). Besides digesting ECM, these enzymes also play a role in activating pro-MMPs leading to generation of fully activated proteins (17, 21).
4. Matrilysins (MMP-7 and MMP-26). These enzymes help in processing various cell surface molecules such as TNF-α, E-cadherin, FAS-ligands etc (17).
5. Membrane-type MMPs (MMP-14, MMP-15, MMP-16 and MMP-24). These are type I transmembrane proteins and MMP-17 and MMP-25 are GPI linked proteins (17).
6. Other MMPs (MMP-12, MMP-19, MMP-20, MMP-22, MMP-23 and MMP-28). MMP-20 is known to digest amelogenin which is located in the tooth enamel (17, 22).

S.No.	Group	Enzyme	MMP	Chromosome Location	Substrate	Cellular Location	Inhibitor(s) Synthetic/Natural
1.	Collagenases	Collagenase-1(interstitial collagenase)	MMP-1	11q22-q23	Collagens (I-III, VII,VIII, and X), gelatin, IL-1β, aggrecan, L- selectin, proteoglycans, ovostatin, MMP-2, MMP- 9, entactin	Secreted	Metastat (CMT-3), batimastat (BB-94), doxycycline, mino-cycline, BB- 1101, MMI270B, FN-439, ilomastat, marimastat (BB-2516)
2.	Gelatinases	Gelatinase-A (type IV collagenases)	MMP-2	16q13	Collagen IV VI, X, elastin, fibronectin	Secreted	TIMP-4, batimastat (BB-94), BB-1101, doxycycline ilomastat, marimastat (BB-2516), minocycline

Table 1: Classification of MMPs

3.	Stromelysins Stromelysin-1	MMP-3	11q23	Collagens (III-V and IX), aggrecan, prolecan, decorin, casein, gelatin, laminin, osteonectin, elastin, plasminogen, entactin, MMP-2/TIMP-2, MMP-9, MMP-8, MMP- 13, MBP, IL-1β	Secreted	BB-1101, MMI270B, doxycycline, batimastat (BB-94), ilomastat, FN-439, marimastat (BB-2516), minocycline
4.	Matrilysins Matrilysin (PUMP)	MMP-7	11q21-q22	Elastin,collagens(IV,X), gelatin,aggrecan,transferrin decorin,laminin,casein, plasminogen,fibronectin, β4-integrin,MMP-1,MMP-2, MMP-9,MMP-9/TIMP-1	Secreted	Batimastat(BB-94), BB-1101, minocycline, doxycycline, marimastat (BB-2516)
5.	Collagenases Collagenase-2/neutrophil	MMP-8	11q21-q22	Fibronectin, collagens (I-III, V, VII, VIII, and X), aggrecan, gelatin	Secreted	Doxycycline, TIMP-1, MMI270B, batimastat (BB-94), BB-1101, metastat (CMT-3), FN-439, marimastat (BB- 2516), ilomastat
6.	Gelatinases Gelatinase-A	MMP-9	20q11.2-q13.1	Osteonectin, collagens (IV, V, VII, X, and XIV), plasminogen, elastin, gelatin, entactin, aggrecan, fibronectin, MBP, IL-1β	Secreted	TIMP-1, minocycline, batimastat (BB-94), BB-1101, MMI270B, FN- 439, marimastat (BB-2516), ilomastat
7.	Stromelysins Stromelysin-2	MMP-10	11q22.3-q23	Aggrecan, collagens (III–V), gelatin, elastin, casein, MMP-1, MMP-8	Secreted	-
8.	Stromelysins Stromelysin-3	MMP-11	22q11.2	Unknown (casein)	Secreted	-
9.	Otherenzymes Macrophage metalloelastase	MMP-12	11q22.2-q22.3	Collagen IV, gelatin, elastin, casein, plasminogen, fibronectin, fibrinogen, vitronectin, laminin, entactin, fibrin	Secreted	BB-1101
10.	Collagenases Collagenase-3	MMP-13	11q22.3	Osteonectin, gelatin collagens (I–IV, IX, X, and XIV), plasminogen, perlecan, aggrecan, fibronectin, MMP-9	Secreted	BB-1101, metastat (CMT-3), MMI270B, doxycycline
11.	MT-MMP MT1-MMP	MMP-14	14q11-q12	Proteoglycans, Collagens (I–III), laminin, gelatin, entactin, casein, fibronectin, vitronectin, MMP-2, MMP-13	Membrane associated	Marimastat (BB-2516), TIMP-1, TIMP-2, ilomastat and BB-1101
12.	MT-MMP MT2-MMP	MMP-15	15q13-q21	Perlecan, entactin, fibronectin, laminin, aggrecan, MMP-2	Membrane associated	-

Cont. Table 1: Classification of MMPs

13.	MT-MMP	Homology to stromolysin-2	MMP-16	8q21	Collagen III, gelatin, casein, fibronectin, MMP-2	Membrane associated	-
14.	Stromelysins	MT4-MMP	MMP-17	12q24.3	-	Membrane associated	TIMP-1, TIMP-2
15.	MT-MMP	Collagenase-4	MMP-18	NA	Type I collagen	-	-
16.	Collagenases	RASI I	MMP-19	12q14	Type I collagen	-	-
17.	Other enzymes	Enamelysin	MMP-20	11q22.3	Amelogenin, aggrecan	Secreted	-
18.	Other enzymes	MMP identified on chromosome I	MMP-21	ND		Secreted	-
19.	Other enzymes	MMP identified on chromosome I	MMP-22	NA		-	-
20.	Other enzymes	From human ovary cDNA	MMP-23	1p36.3		Membrane associated	-
21.	MT-MMP	MT5-MMP	MMP-24	20q11.2	Fibronectin	Membrane associated	-
22.	MT-MMP	MT6-MMP	MMP-25	16p13.3	Progelatinase A	Membrane associated	TIMP-1, TIMP-4
23.	Matrilysins	Matrilysin-2	MMP-26	11p15	Collagen IV, gelatin, α (1)-proteinase inhibitor, fibronectin, fibrinogen	-	-
24.	Other enzymes	CMMP *(Gallus sp.)*	MMP-27	11q24	-	-	-
25.	Other enzymes	Epilysin	MMP-28	17q21.1	-	Secreted	-
26.	Other enzymes	Unnamed	MMP-29	NA	-		-

Cont. Table 1: Classification of MMPs

BIOLOGICAL FUNCTIONS OF MMPs

MMP-1 promotes colon carcinogenesis by activating the cytoplasmic transcription factor known as signal transducer and activator of transcription 3 (STAT-3) located in the nucleus and interacts with NF-KB subunit RelB (RELB proto-oncogene) forming an activation complex (23). MMP-2 has been found to play critical roles in various oral carcinomas. A study has demonstrated that pinostilbene hydrate (PSH), a methylated derivative of resveratrol, possesses the capacity to suppress MMP-2 activity by downregulating p38 mitogen-activated protein kinases/extracellular signal-regulated kinases 1/2 (p38/ERK1/2) pathway and thus, is an attractive agent against metastasis (24).

Membrane-anchored MMP-14 (MT1-MMP) plays a major role in the transition of tumor stage to invasive carcinoma by helping in penetration of basement membrane (25-28). Various studies have shown that most of MMP-14 expression is at the tumor and stroma interface rather than within the bulk of the tumor (3, 29-32). The major endogenous inhibitor of MMP-14 is tissue inhibitor of metalloproteinases 2 (TIMP-2) (33-35) and various soluble factors secreted by tumor cells

lead to its activation. One such factor is transforming growth factor beta-1 (TGFβ1) which helps in fibroblast differentiation and in stimulation, expression and activation of MMP-14 (36-39). As has been reported by Quintanilla et.al (2014), there is overproduction of TGFβ during later stages of tumorigenesis which leads to higher expression of MMPs (39).

ROLE OF MMPs IN ANGIOGENESIS

MMPs induce angiogenesis by degradation of the basal membrane with the help ECM-bound proangiogenic growth factors (bFGF, VEGF and TGFβ). ECM dissolution leads to exposure of integrin binding sites which trigger intracellular signaling of integrin contributing to survival and proliferation of endothelial cells (40). Hypoxia is an important pro-angiogenic signal that activates the hypoxia-inducible factor signaling pathway leading to increase in proangiogenic factors and inflammation. On the other hand, MMPs can also generate angiogenesis inhibitors. Therefore, MMPs have both pro- and anti-angiogenic effects.

ROLE OF MMPs IN CANCER

Upregulation in the level of several MMPs has been reported in virtually every type of cancer and the increase is correlated with metastasis, invasiveness and advanced stages (41,42). It has been demonstrated that tumor cells which show early expression of MMPs ultimately function in the remodeling of ECM and cause release of angiogenesis promoting factors and formation of primary tumors as shown Fig 1. In different model systems, both MMP-9 and MMP-2 have been found to have a role in the induction of an angiogenic switch in which a balance of proangiogenic factors (VEGF and bFGF) has been found to overcome the expression of angiogenic inhibitors (thrombospondins, IFNs and angiostatin) (42). MMP-9 and MMP-2 promote cell migration by exposure of new binding sites, removal of adhesion sites, cleavage of cell-matrix or cell-cell receptors and release of chemo attractants (43).

Breast cancer is a heterogeneous disease and one of the most common cancers in women worldwide. Millions of cases are reported annually with disparities in incidence (44, 45). In the past, several studies have revealed that MMP-9 and MMP-2 have roles in breast cancer progression (46). In particular, these MMPs have the capacity to break down most of the collagen containing components of the basement membrane around the tissue barrier (47, 48). In early stages of tumorigenesis, these enzymes initiate tumor growth by interacting with tumor suppressor genes (Fig 2).

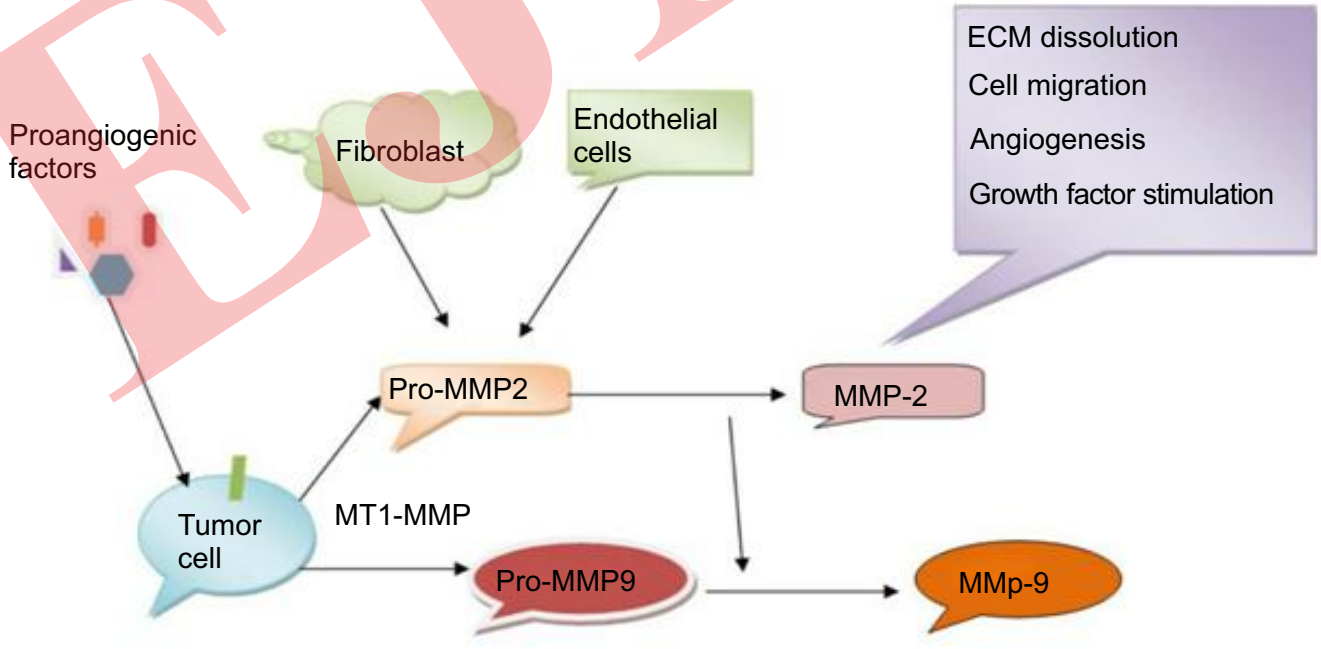

Fig 1: Functional Role(s) of MMPs in Cancer

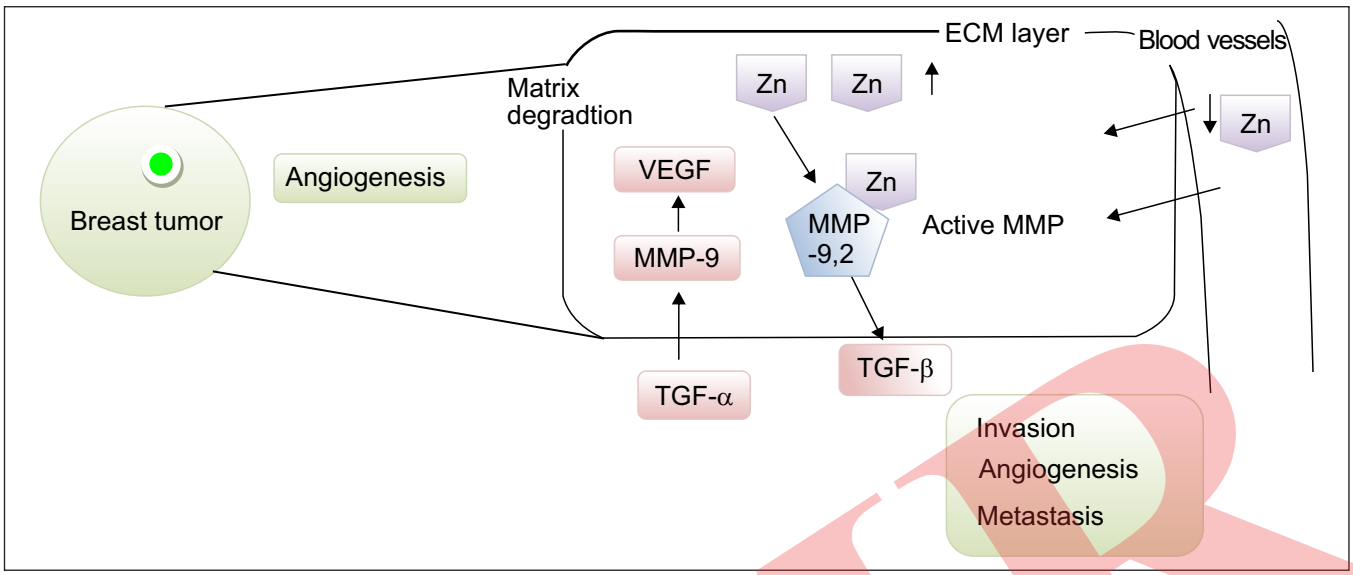

Fig 2: Biological Function(s) of MMPs in Breast Cancer

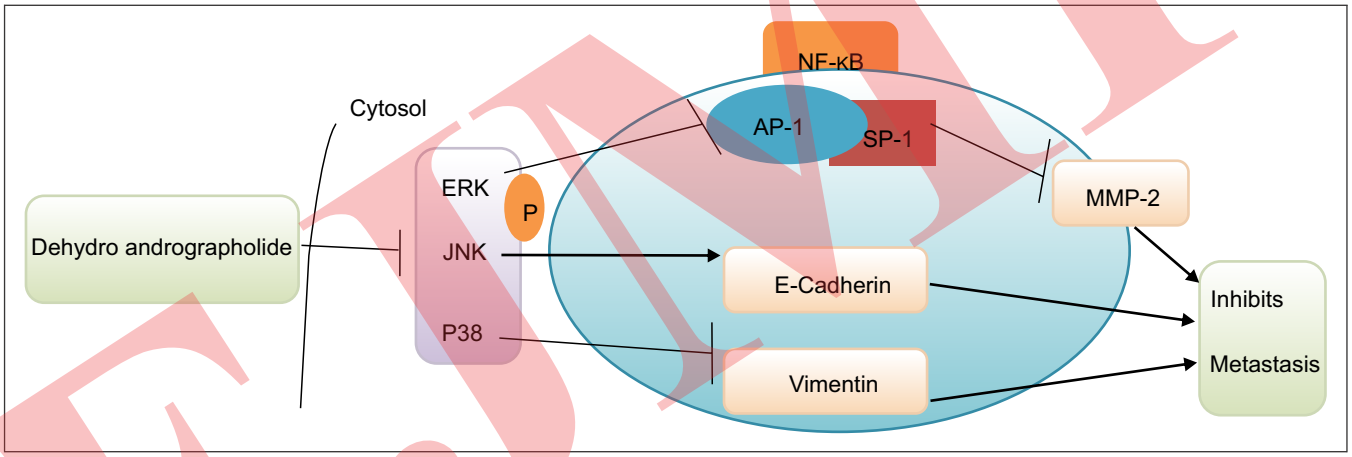

Fig 3: Regulation of Gene Expression by MMP-2

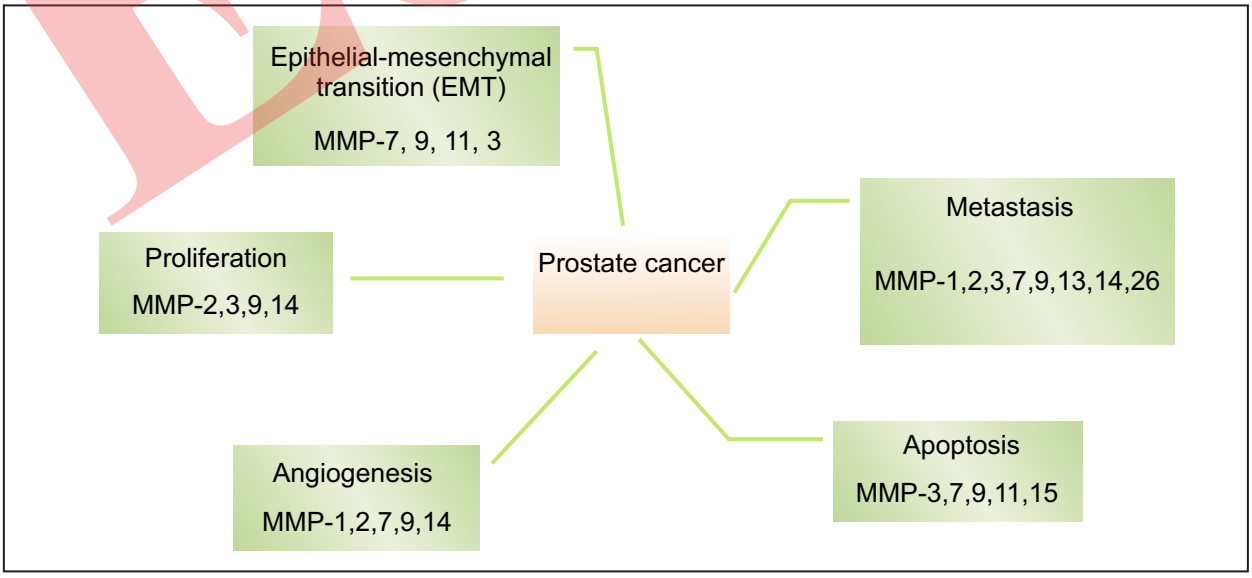

Fig 4: Biological Role(s) of Various MMPs in Prostate Cancer

As far as OSCC is concerned, increased expression of gelatinase A and gelatinase B has been found to cause increased collagen degradation and tumor invasion. Another study has demonstrated that 6-pyrrolidinyl-2-(2-hydroxyphenyl) - 4-quinazolinone (MJ-29), an anti-mitotic agent, has been found to drastically inhibit MMP-2 and MMP-9 expression. In ovarian cancer, transcription factors of mitogen-activated protein kinase/extracellular signal-regulated (RAS/MAPK), Ak strain transforming (AKT) signal pathway such as activator protein 1(AP-1) and ribosomal protein S6 kinase beta-1 (p70S6K), have also been found to regulate gene expression of MMP-2 and MMP-9 (49-52). Administration of dehydroandrographolide (a potential anti-cancer agent) has also been found to effectively suppress MMP-2 expression and tumor metastasis (Fig 3).

A recent study by Zeng et al. (2016) has indicated a significant elevation in MMP-7 levels induced by sphingosine-1-phosphate (S1P) leading to production of TGF-β1 in hepatocellular carcinoma (53). In prostate cancer, the nuclear MMP-7 forms a complex with alternate reading frame protein (ARF) to degrade E-cadherin and ultimately ECM (54). An increase in the expression of ARF has also been found to decrease the level of phosphatase and tensin homolog (PTEN) leading to tumorigenesis. Moreover, studies have revealed that MMP-7 reduces the ability of natural killer cells to recognize cancer cells, thus the cancer cells evade the immune system and proliferate immensely (55). MMPs are also regulated by receptors called low density lipoprotein receptor-related proteins 1 (LRP-1) which help in removal of ECM components and thus, providing access to the cell environment. A number of studies have revealed that presence of LRP-1 induces the decrease in the activity of MMP-2 and MMP-9 (56). A recent study on patients with advanced prostate cancer has revealed a correlation between increased levels of lectin-type oxidized LDL (LOX-1) receptor associated with obesity and atherosclerosis and oxidized low-density lipoprotein (oxLDL). This causes an epithelial to mesenchymal transition *via* up regulation of ECM markers MMP-2 and MMP-9 (57). The biological role(s) of different MMPs involved in prostate cancer have been outlined in Fig 4.

Similarly, glial-cell invasion is also known to be protease dependent and abnormal MMPs expression and activation leads to degradation of the ECM and eventually, metastasis and invasion. The levels of MMP-2, MMP-9 and MT1-MMP have been found to be elevated in gliomas as compared to the normal brain tissue (6). Colorectal cancer (CRC) is among the leading causes of mortality and morbidity, particularly in the western countries (58, 59). MMP-2 and MMP-9 are important prognostic markers for colon cancer and synthetic MMIs have been found to have considerable potential against colon cancer. Emodin, a naturally occurring anthraquinone-based anticancer agent has been found to act through suppression of NO-mediated upregulation of MMPs. Another study has reported that positive regulation of MMP-1 is dependent on signal transducer and activator of transcription 3 (STAT-3) and activator protein-1(AP-1) family of transcription factors. It has been observed that constitutive knock down of transcription factors STAT-3 and RelB in the nuclei of colon cancer cells leads to a decrease in the level of MMP-1 (60). Table 2 delineates recent studies *in vitro* / in vivo on MMPs

S.No	MMP	*In vitro*	*In vivo*	Protective compound	Protective knockdown/ pathway	Cause of Cancer	References
1.	MMP-2	FTC133 (Follicular thyroid carcinoma)				Perfluoroocta noic acid (PFOA)	Saejia et al., 2019 (61)
2.	MMP-2/-9	HeLa (Cervical carcinoma)		Praeruptorin-B (Pra-B)	Suppression of p-AKT/NF-κB		Hung et al., 2019 (62)
3.	MMP-1, MMP-9	A2058 (Melanoma)			Knockdown of DLL3		Ding et al., 2019 (63)
4.	MMP-2, MMP-9	HCT116, Ht29, and Caco-2 (Colon carcinoma)				Ethanol up regulates survival of colon cancer	Cernigliaro et al., 2019 (64)
5.	MMP-2, MMP-9	LOVO and HCT116(Colon carcinoma)			HYAL1 and HYAL2 suppress progression		Jin et al., 2019 (65)

Table 2: Brief outline of the Role(s) of Different MMPs in Various Cancer Types

6.	MMP-2, MMP-9	Epithelial ovarian cancer (EOC) tissues, four ovarian cancer cell lines, and human skin fibroblasts (HSF)					Jeleniewicz et al., 2019 (66)
7.	MMPs	Lung cancer	Lung cancer models		FBXW2 (E3 ligase for β-catenin) and promotes β-catenin ubiquitylation and degradation		Yang et al., 2019 (67)
8.	MMP-2, MMP-9	C33A, Siha, Caski, HeLa and HCC94 (Cervical carcinoma)				FABP5 expression up regulates cancer progression	Zhan et al., 2019 (68)
9.	TGIF/MMP2	Human breast carcinoma				Long term cadmium (Cd) exposure	Wang et al., 2019 (69)
10.	MMP-9		Diethyl nitrosamine (DEN)-induced hepato cellular carcinoma(HCC) in rats	gallium nanoparticles (GaNPs) combined with low level of gamma radiation (IR)			Moawed et al., 2019 (70)
11.	MMP11, MMP13	Colorectal carcinoma(CRC) and cancer-associated fibroblasts (CAFs)					Eiro et al., 2019 (71)
12.	MMP-2	SCC-15		Nano doxorubicin-indocyanine green matrix metalloproteinase (MMP)-responsive hydrogel (denoted as NDIMH)			Wang et al., 2019 (72)
13.	MMP-13	Breast carcinoma				Golgi membrane protein 1 (GOLM1)	Zhang et al., 2019 (73)
14.	MMP-2	Hepatocellular carcinoma (HCC)			Tripartite motif containing 55 (TRIM55)		Liet al., 2019 (74)
15.	MMP-2, MMP-9	BcPAP (Thyroid cancer-derived cell line)			Podoplanin (PDPN) is a mucin-type transmembrane glycoprotein		Sikorska et al., 2019 (75)

Cont. Table 2: Brief outline of the Role(s) of Different MMPs in Various Cancer Types

16.	MMP-9	HepG2 (Liver carcinoma)		Momordin Ic			Wang et al., 2019 (76)
17.	MMP-2	Lung carcinoma				Fine Particulate Matter (PM_25)	Chen et al., 2019 (77)
18.	MMP-2, MMP-9	Pancreatic adenocarcinoma and Lung adenocarcinoma				Nectin-3	Xu et al., 2019 (78)
19.	MMP-9	Pituitary adenomas					Han et al., 2019 (79)
20.	MMP-9	Glioblastoma multiforme (GBM)				Tumor necrosis factor receptor-associated factor 6 (TRAF6)	Sun et al., 2019 (80)
21.	MMP-2, MMP-9	H157, H1975, and A549 (Human NSCLC cell lines)			IL-17A/IL-17RA signaling		Wu et al., 2019 (81)
22.	MMP-2	Cervical squamous cell carcinoma (CSCC).				Nck1 gene expression	Xia et al., 2019 (82)
23.	MMP-2, MMP-9	Ht1197 (Bladder carcinoma)	Male C57B/L 6 mice	Melatonin			Chen et al., 2019 (83)
24.	MMP-9	HT-29 (human colorectal carcinoma)		7−allylamino−17−demethoxy geldanamycin (17-AAG)were studied alone and in combination with Capecitabine (Cap) and/or Irinotecan (IR)			Zeynali-Moghaddam et al., 2019 (84)
25.	MMP-2, MMP-9	MCF-7 (breast carcinoma)			EGFR-EGF interactions might render such cancers less invasive		Majumder et al., 2019 (46)
26.	MMP-11	Breast cancer					González et al., 2019 (85)
27.	MMP-2	Human gastric carcinoma				Increases expression of CDH17/NF-κB/MMP-2 axis	Jiang et al., 2019 (86)
28.	MMP-9/12		Rat models	AZD3342 inhibitor			Gibson et al., 2018 (87)
29.	MMP-1	MG-63 (Osteosarcoma)					Tang et al., 2018 (88)

Cont. Table 2: Brief outline of the Role(s) of Different MMPs in Various Cancer Types

30.	MMP-2	KKU-M156 (Cholangiocarcinoma Cell)		Rhinacanthin-C Extracted from *Rhinacanthus nasutus (L.)*			Boueroy et al., 2018 (89)
31.	MMP-14	Gastric cancer					Kasurinen et al., 2018 (90)
32.	MMP-9	Papillary thyroid cancer					Zarkesh et al., 2018 (91) Roncevic et al., 2019 (92)
33.	MMP-9		HER2-driven breast cancer (Hc11-NeuT) in immunocompetent mice				Juric et al., 2018 (93)
34.	MMP-2	Lung cancer				TRPM7 overexpression by Hsp90 α/uPA/ MMP2 signaling pathway.	Liu et al., 2018 (94)
35.	MMP-9	MCF-7 (Breast carcinoma)		Orientin (luteolin 8-C-β-D- glucopyranoside)			Kim et al., 2018 (95)
36.	MMP-9	SGC-7901 and MKN-45 (Gastric carcinoma)				Intraflagellar transport (IFT) proteins	Wang et al., 2018 (96)
37.	MMP-2, MMP-9	Head and neck squamous cell carcinoma (HNSCC)			Early Growth Response-1 (ERG-1)		Kim et al., 2018 (97)
38.	MMP-20	Endometrial carcinoma					Zhao et al., 2018 (98)
39.	MMP-7	UOK146 (Renal cell carcinoma-RCC)		Monensin is a metal ionophore			Verma et al., 2018 (99)
40.	MMP-9	HeLa (Cervical carcinoma)		Terminalia catappa leaf extracts (TCE)	Inhibiting ERK1/2 pathway		Lee et al., 2019 (100)
41.	MMP-9	Triple-negative breast cancer (TNBC).					Wang et al., 2018 (101)
42.	MMP-2, MMP-9	SHG44 (Human glioma)		Isoliquiritigenin			Dang et al., 2018 (102)

Cont. Table 2: Brief outline of the Role(s) of Different MMPs in Various Cancer Types

43.	MMP-2	MC3T3-E1 (mouse osteoblast)					Yu et al., 2018 (103)
44.	MMP2/9	A549 (Lung carcinoma)		PG-SG-Ptx micelles			Wang et al., 2018 (104)
45.	MMP-9	Breast cancer				Tumour necrosis factor receptor superfamily member 12A (TNFRSF12A)	Yang et al., 2018 (105)
46.	MMP-9	Pca (Pancreatic carcinoma)					Mandel et al., 2018 (106)
47.	MMP-9	MCF-7 (breast carcinoma)		7-Methoxy-luteolin-8-C-β-6-deoxy-xylo-pyranos-3-uloside (mLU 8C-PU)is a glycosyl flavone of luteolin isolated from Arthraxon hispidus			Kim et al., 2018 (107)
48.	MMP-2	HepG2 (Liver carcinoma)				C-C chemokine receptor type2 (CCR2) promotes epithelial−to−mesenchymal transition (EMT)	Li et al., 2018 (108)
49.	MMP-9	CRL-1739 (Gastric adenocarcinoma)		Rosmarinic acid (RA			Radziejewska et al., 2018 (109)
50.	MMP-14	Neural crest cells (NCCs)				neural crest EMT and migration	Garmon et al., 2018 (110)
51.	MMP-2, MMP-9	4T1 and JC (Breast carcinoma)		A flavonoids called fisetin			Tsai et al., 2018 (111)
52.	MMP-1	HT29 (Colon carcinoma)				STAT3 and ReB isminimal activator complex for positive regulation of MMP-1.	Jiang et al., 2018 (22)
53.	MMP-13	Lung cancer				Thrombospo ndin (TSP)-2	Liu et al., 2018 (112)
54.	MMP-2/9	B16-F1 (Mouse melanoma)		PD-1-based recombinantly tailored fusion protein (dFv-ePD1)			Wei et al., 2018 (113)

Cont. Table 2: Brief outline of the Role(s) of Different MMPs in Various Cancer Types

55.	MMP-20	Oral cancer stem cell (OCSC)			DSPP(dentin sialophospho protein)/MM P20 silencing		Nikitakis et al., 2018 (114)
56.	MMP-13	Breast cancer				ETS transcri ption factor ETV4 promotes MMP-13	Dumortier et al., 2018 (115)
57.	MMP2/9	Zl55 malignant mesothelioma cells			ADP causes the cleavage and inactivation of poly-ADP-ribose polymerase-1		Muscella et al., 2018 (116)
58.	MMP-2, MMP-9			Bisdemethoxy curcumin (BDMC)		BDMC did not inhibit MMP-2, MMP-9	Liao et al., 2018 (117)
59.	MMP-8	Colorectal carcinoma					Böckelman et al., 2018 (118)
60.	MMP-9	A549 (Lung carcinoma)		Three novel phenols, named selaphenins A-C (1-3), two known selaginellin derivatives (4 and 5) and seven biflavonoids (6-12) were isolated from Selaginella tamariscina	Increases the expression of Bax and caspase-3		Wang et al., 2018 (119)
61.	MMP-2	Prostate cancer		Sb225002 (a specific CXCR2 receptor antagonist)	Particularly bone sialoprotein (BSP) and osteopontin (OPN) expression decreases		Xu et al., 2018 (120)
62.	MMP-9	Poly cystic ovary syndrome (PCOS)		Clomiphene citrate	Increases the levels of nitric oxide and interleukin-10		Sylus et al., 2018 (121)
63.	MMP-9	IOMM-Lee and CH157-MN (Malignant meningeoma)				Long noncoding RNA LINC00460	Xing et al., 2018 (122)
64.	MMP-9	MCF-7 (Breast carcinoma)			Cd147 siRNA had no effect on MMP-2 but decreased cell proliferation		Li et al., 2018 (123)

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65.	MMP-9	A549 (Lung carcinoma)		Linarin isolated from Chrysanthemm morifolium flowers		Regulated NF-κB activity	Jung et al., 2018 (124)
66.	MMP-9	Acute Lymphoblastic Leukaemia (ALL)		Prodigiosin			Sam et al., 2018 (125)
67.	MMP-2, MMP-9	Gallbladder cancer (GBC)			Tripartite motif (TRIM) 31 inactivates PI3K/Akt signaling		Li et al., 2018 (126)
68.	MMP-9	B16F10 (Mouse melanoma) and LL2 (Mouse lung tumor)	Tumor mouse model		Salmonella treatment inhibits the AKT/mTOR pathway		Tsao et al., 2018 (127)
69.	MMP-2	Lung cancer				High mobility group box protein 1 (HMGB1) induced cancer	Wu et al., 2018 (128)
70.	MMP-2/9	A2780 (Ovarian carcinoma)				Perfluorooctano ic acid (PFOA) activates activation of ERK/mTOR	Li et al., 2018 (129)
71.	MMP-2, MMP-9	C643 (Thyroid carcinoma)		Sphingosine 1-phosphate (S1P)			Asghar et al., 2018 (130)
72.	MMP-11	Hepatocellular carcinoma (HCC)					Wang et al., 2018 (131)
73.	MMP-2, MMP-9	HCCLM3 (Human hepatocellular carcinoma)		Quercetin	Down redulated protein levels of p-Akt1, MMP-2, and MMP-9		Lu et al., 2018 (132)
74.	MMP-9	MCF-7 (Breastcarcinoma)				Casein kinase 2 (CK2)	Kim et al., 2018 (133)
75.	MMP-7	Epithelial ovarian cancer.		Fibulin 5 (FBLN5)			Manders et al., 2018 (134)
76.	MMP-9	Bladder cancer					Wu et al., 2018 (135)
77.	MMP-7	Glioblastoma				Phosphatase of regenerating liver-3 (PRL-3)	Mu et al., 2018 (136)
78.	MMP3, MMP7	Colorectal cancer(CRC)		Celastrol	Knockdown PI3K/AKT signaling pathway		Bufu et al., 2018 (137)

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79.	MMP-2/-9	U87 and SF767 (Human glioblastoma)	Nude mice	Sinomenine hydrochloride (SH)			Jiang et al., 2018 (138)
80.	MMP-2/9	MDA-Mb-231Br(Breast carcinoma)	Lung metastasis in a mouse model	Myricetin			Ci et al., 2018 (139)
81.	MMP-9	Du145 (Prostate carcinoma)		Piperine	Ly294002, an protein kinase B (Akt) inhibitor		Zeng et al., 2018 (140)
82.	MMP-3	MCF-7 (Human breast carcinoma)			Downregulation of miR-519d		Chu et al., 2018 (141)
83.	MMP-9	MHCC97L and PLC/PRF/5 cells (Hepatocellular carcinoma)		Wogonin			Hong et al., 2018 (142)
84.	MMP-9	Esophageal squamous cell carcinoma (ESCC)		Inhibitor of growth 5 (ING5)	Regulation of the Akt/NF-κB/ MMP-9 signaling pathway		Zhang et al., 2018 (143)
85.	MMP-2, MMP-9	Du145 and Pc3 (Prostate carcinoma)				Hepatoma-derived growth factor (HDGF)	Yang et al., 2018 (144)
86.	MMP-2, MMP-9	A2780 and SKOV3 (Human ovarian carcinoma)		Iloprost ,a lipid prostacyclin (PGI2)			Ahn et al., 2018 (145)
87.	MMP-2	HeLa (Cervical carcinoma)	Mouse model	CuS@mSiO2-PEG Nanoparticles			Deng et al., 2017 (146)
88.	MMP-2/MMP-9	Choroidal melanoma					Wang et al., 2018 (147)
89.	MMP-2	Colorectal cancer(CRC)			Suppressing PI3K/ Akt signaling pathway		Zhang et al., 2018 (148)
90.	MMP-9, MMP-2	Human fibroblasts, breast carcinoma (MDA-MB-231), andmi crovascular endothelial carcinoma (HMEC-1)		Alternagin-C (ALT-C)			Moritz et al., 2018 (149)
91.	Mt1-MMP (MMP-14)	Squamous cell carcinoma					Timoshenko et al., 2017(150)
92.	MMP-9	Rat C6 astroglial cells (C6)					Abe et al., 2016 (151)
93.	MMP-9	Colon carcinoma		Extra-pure formulation of EPA as Free Fatty Acid (EPA-FFA)	Antagonizes the effect of inflammation on NOTCH1 signalling		Fazio et al., 2016 (152)

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94.	MMP-9	U251 and SHG44 (Glioma)		Quercetin	Suppressing the Ras/MAPK/ ERK and PI3K/ AKT signalling pathways		Pan et al., 2015 (153)
95.	MMP-9	AGS (Gastric cancer)		Chrysin	Blocking the JNK1/2 and ERK1/2 pathways		Xia et al., 2015 (154)
96.	MMP-3	DU-145 (prostate carcinoma)			Blocking eotaxin-1 and CCR3 would be effective		Zhu et al., 2014 (155)
97.	MMP-2	B16 4A5 (Melanoma)		JaZ-30			Romanchi-kova et al., 2014 (156)
98.	MMP-9	MDA-MB-231, MCF-7, and U87		Adenosine dialdehyde (AdOx)			Kim et al., 2013 (157)
99.		MCF-7 (Breast carcinoma)		Sulforaphane(1-isothiocyanato-4-(methylsulfinyl)-butane)	Increased NF-κB and AP-1 DNA binding activity		Lee et al., 2013 (158)
100.	MMP-9	Medulloblastoma cells				Urokinase plasminogen activator receptor (uPAR)	Kotipatruni et al., 2012 (159)
101.	MMP-2	HeLa and prostate PC-3 cells.	Mouse model	Stable derivative of Withaferin A, 3-azido Withaferin A (3-azidoWA)	Attenuated internal phospho-ERK and phospho-Akt expression		Rah et al., 2012 (160)
102.	MT1-MMP	HeLa and HT-1080 (fibrosarcoma)				Phorbol 12-myristate 13-acetate	Williams et al., 2011 (161)
103.	MMP-9	MCF-7 and MDA-MB-231 (Breast carcinoma)		Sesamin	Downregulating ERK, JNK, phosphatidylinositol 3-kinase, and NF-κB-mediated pathways		Lee et al., 2011 (162)
104.	MMP-13	U251 and C6 cells		Glial cell line-derived neurotrophic factor (GDNF)	Increased by the MEK/ERK and JNK, c-Jun and AP-1 pathways		Lu et al., 2010 (163)

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105.	MMP-9		Glioma xenografts in nude mice				Veeravalli et al., 2010 (164)
106.	MMP-9	KB (Human oral epidermoid)		*Kaempferia pandurata (Roxb.)*	Downregulating MAPK phosphorylation, inhibiting transcriptional expression, blocking AP-1 and NF-kappaB activities.		Yanti et al., 2009 (165)

Cont. Table 2: Brief outline of the Role(s) of Different MMPs in Various Cancer Types

MMPs REGULATION

Since, MMPs have a broad substrate spectrum; therefore, they are subjected to regulation in order to maintain tissue homeostasis. Since these enzymes are involved in ECM degradation, both their expression and activity need to be tightly controlled in order to avoid tumor progression and metastasis. The activity of MMPs is controlled at four different levels:

1. By non-specific proteinase inhibitors (a2-macroglobulins and TIMPs);
2. Transcriptional and post-transcriptional regulation along with gene expression;
3. MMPs released from a different cell type or tissue and their extracellular localization (compartmentalization); and
4. Activation of pro-enzymes by removal of pro-domains.

As soon as the MMPs get activated, they induce the activation of other zymogens and cause the degradation of inhibitors and deactivation of other proteases (166, 167). Plasmin and furin are serine proteases which activate some MMPs, which in turn, cause activation of other members of the family. The transcriptional control of MMPs is influenced chromatin remodeling which is a consequence of epigenetic changes like DNA methylation and histone acetylation. A study has revealed that MMP promoter hypomethylation causes an increase in MMP-3 and MMP-9 expression in colon cancer and lymphoma cells, respectively (168). On the contrary, nuclear hormone retinoid X receptor (RXR) has been found to cause histone deacetylation which is accompanied by a concomitant decrease in AP-1 binding leading to decreased MMP-1 and MMP-13 expression (169).

MAINTENANCE OF HOMEOSTASIS

It is a well-known fact that in order to maintain homeostasis, it is necessary to regulate the activity of enzymes involved in tissue and ECM modeling failure to do so results in tumorigenesis, inflammation, dysregulated cell growth and metastasis. TIMPs and a2-macroglobulins are the two main classes of MMP inhibitors. The mode of action of human a2-macroglobulin is entrapment of MMPs followed by endocytosis (170). On the other hand, TIMPs bind non-covalently to the active site(s) of MMPs in a 1:1 ratio (171, 172). Additionally, increased generation of ROS during inflammation is known to be a potent blocker of MMPs expression (173).

CONCLUSION

Since cancer has become a scourge in modern times, therefore, extensive amount of research is being conducted in nearly all aspects of cancer. MMPs play a crucial role in cancer progression and hence, are considered to be important targets for newly synthesized anti-cancer drugs. However, in most clinical trials, many such targeted agents have resulted in poor outcomes which have been in contradiction to preclinical studies (174). There might be several reasons for these poor outcomes. Firstly, it is a known fact that different MMPs have different roles at different stages of cancer development. Some MMPs particularly, MMP-1 and MMP-14 are even known to possess a protective role against cancer (175). Therefore, the use of broad-spectrum MMPIs in such cases may result in poor clinical outcomes (176). Secondly, synthetic MMPIs might have associated side effects and toxicity which might drastically reduce the therapeutic spectrum of the drug compound on account of its being administered at lower doses in

order to avoid the toxic effects. For these reasons, development of highly selective MMPIs that do not cross-react with other MMPs is the need of the hour (177). Since MMP expression is usually associated with expression of other molecules in pathological processes, one possible strategy for increasing the specificity of MMPIs is using MMPIs in combination with other drugs that target co-expressed molecules viz. miR-98 (178), VEGF (179), and cyclooxygenase-2 (COX-2) (180). This combination therapy might prove to have more efficacy than the use of MMPIs only (181). In conclusion, the major take home message from the above discussion is that greater emphasis should be laid on the improvement of methodology for synthesis of novel MMPIs, in order to avoid or minimize the side effects. Development of a new generation of effective and selective MMPIs is an emerging and promising prospect of future research in this area.

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