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MATRIX METALLOPROTEINASES AND THEIR ROLE IN BREAST CANCER: A MINI REVIEW

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ABSTRACT

Matrix metalloproteinases (MMPs) are members of metzincin group of zinc-dependent endopeptidases which are responsible for degrading and remodeling of extracellular matrix (ECM) during organogenesis, wound healing, angiogenesis, apoptosis, cell proliferation and cancer progression. MMPs are synthesized in cytoplasm as proenzymes with a cytoplasmic domain and can be divided into 6 groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type and other non-classified MMPs. They are found in cytosol, subcellular organelles, nucleus and extracellular regions and have several biological functions in all stages of cancer. MMPs play crucial roles in cell growth, survival, differentiation and motility. ECM degradation by MMPs not only increases tumor invasion but also affects tumor cell behavior and leads to metastasis and cancer progression. Thus, MMPs and their inhibitors can be considered as promising therapeutic target(s) against cancer.

KEYWORDS: Matrix metalloproteinases, Breast cancer, Extracellular matrix, Metastasis, Angiogenesis, Collagenases, Gelatinases.

INTRODUCTION

Matrix metallopeptidases (MMPs), also known as matrixins, are metalloproteinases that are calcium-dependent zinc-containing endopeptidases. Zinc proteases are subdivided according to the primary structure of their catalytic sites and include gluzincin, metzincin, inuzincin, carboxypeptidase and DD carboxypeptidase subgroups (1). The metzincin subgroup is further divided into serralysins, astacins, matrixins and adamalysins (2). MMPs are a group of enzymes that are responsible for the degradation of ECM proteins during organogenesis, growth and normal tissue turnover (3).

MMPs were described for the first time by Jerome Gross and Charles LaPiere during their experiments on tadpole tail metamorphosis in 1962 and isolated six years after their discovery by Arthur Z. Eisen and his co-workers (4, 5). Several types of proteinases are involved in ECM degradation; currently 24 MMPs have been identified in vertebrates including 23 in humans (4, 6). MMPs are categorized into following six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type and other non-classified MMPs (4). All MMPs consist of common domain structures which include pre-domain, pro-peptide domain, catalytic domain and a hemopexin domain which is linked to the catalytic domain by a flexible hinge-region (Fig. 1).

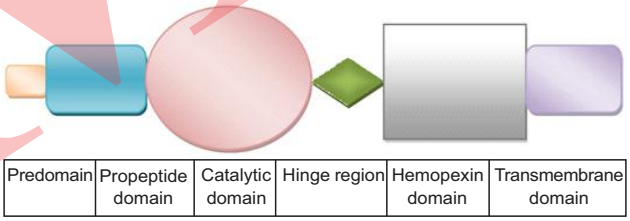

Fig 1: Structure of MMPs

The MMPs are synthesized as inactive zymogens with a pro-peptide domain which must be removed before the enzymes become active (7). Whereas the propeptide domain consists of 80 amino acids, the catalytic domain consists of about 170. A typical MMP contains a linker peptide known as a hinge region of variable length and a hemopexin domain of approximately 200 amino acids. Hemopexin is required for interactions with other MMPs and the tissue inhibitors of metalloproteinases (TIMPs).

Abnormal cell-cell and cell-matrix interactions are a major cause of pathological conditions occurring during cell transformation and carcinogenesis. In this regard, activity of MMPs plays an important role in tumor growth and is a multistep process including proteolytic degradation of ECM, alteration of the cell-cell and cell-ECM interactions, migration and angiogenesis (8). On the basis of substrate specificity, sequence similarity and domain organization vertebrate MMPs can be classified into 6 groups (Table 1).

S.No.	Group	MMPs	Common name & Enzyme	Cell types & Organs	Human Chromosome No.
1	**Collagenases**	MMP-1	Collagenase-1 (Interstitial Collagenase)	Skin (Fb and KC), EC, chondrocytes, osteoblasts, macrophages, hepatocytes	11q22-q23
		MMP-8	Collagenase-2 (Neutrophil Collagenase)	Primarily by neutrophils	11q21-q22
		MMP-13	Collagenase-3	Skin (Fb and KC), osteoblasts, osteocytes	11q22.3
		MMP-18	Collagenase-4		NA
2	**Gelatinases**	MMP-2	Gelatinase-A (72 kDa type IV Collagenase)	Skin (Fb and KC), EC, chondrocytes, osteoblasts, osteocytes, monocytes, alveolar macrophages, polymorpho-nuclear leukocytes, mammary gland	16q13
		MMP-9	Gelatinase-B (92 kDa type IV Collagenase)	Skin (Fb and KC), EC, chondrocytes, osteoblasts, osteoclasts, monocytes, alveolar macrophages, polymorpho-nuclear leukocytes, invading trophoblasts	20q11.2-q13.1
3	**Stromelysins**	MMP-3	Stromelysin-1	Skin (Fb and basal KC), epithelial cells, mammary gland	11q23
		MMP-10	Stromelysin-2	Skin (Fb and basal KC), epithelial cells	11q22.3-q23
		MMP-11	Stromelysin-3	Uterus, placenta and involuting mammary glands	22q11.2
4	**Matrilysins**	MMP-7	Matrilysin-1	Glandular epithelial cells in skin, parotid, liver, endometrium, mammary gland, prostate, pancreas, small intestine crypts, peribronchial glands and conducting airways in lungs	11q21-q22
		MMP-26	Matrilysin-2 (Endometase)	Kidney, uterus, placenta	11p15
5	**Membrane Type (MT)**				
	Trans membrane	MMP-14	MT1-MMP	Skin (Fb and KC), osteoblasts, osteocytes, articular cartilage	14q11-q12

Table 1: Classification of MMPs

	Trans membrane	MMP-15	MT2-MMP	Placenta, heart, brain	15q13-q21
	Trans membrane	MMP- 16	MT3-MMP	Lung, kidney, spleen, heart, skeletal muscle, chondrocytes, reproductive tissue, placenta, intestine	8q21
	Trans membrane	MMP-24	MT5-MMP	Brain, kidney, lung, pancreas	20q11.2
	GPI- Anchor	MMP-17	MT4-MMP	Brain, reproductive tissue, colon, leukocytes	12q24.3
	GPI- Anchor	MMP-25	MT6-MMP	Skeletal muscle, lung, spleen, testis, kidney	16p13.3
6	**Other MMPs**	MMP-12	Macrophage elastase	Macrophages, placenta	11q22.2-q22.3
		MMP-20	Enamelysin	Dental tissue	11q22.3
		MMP-23	CA-MMP	Reproductive tissues (ovary, testis, prostate)	1p36.3
		MMP-28	Epilysin	Skin (KC), brain, lung, heart, kidney, testis, placenta, colon, intestine, pancreas	17q21.1
		MMP-21	XMMP (Xenopus)	Fetal: brain, kidney, liver Adult: ovary, kidney, lung, liver, placenta, brain, peripheral blood leukocytes	ND
		MMP-27	CMMP (Gallus)	Bone, kidney, heart	11q24
		MMP-19	RASI	Skin (KC), skeleton muscle, liver, lung, kidney, thymus, spleen, brain, heart, reproductive tissue, mammary gland, placenta,, colon, small intestine, pancreas, leukocytes	12q14

Table 1: Classification of MMPs

Structure of MMPs

Collagenases

This group of enzymes includes MMP-1, MMP-8, MMP-13 and MMP-18 (Fig. 2). These enzymes cleave interstitial collagens I, II and III at a specific site three-fourths from the N- terminus (9).

MMP- 1, 8, 13, 18

Fig 2: Domain Structure of Collagenases

Gelatinases

This group of enzymes includes Gelatinase A (MMP-2) and Gelatinase B (MMP-9). These enzymes digest the denatured collagens and gelatins (Fig. 3). The enzymes have three repeats of a type II fibronectin domain inserted into the catalytic domain which binds to gelatin, collagens and laminin and a hinge region with the hemopexin domain attached to it (9).

MMP- 2, 9

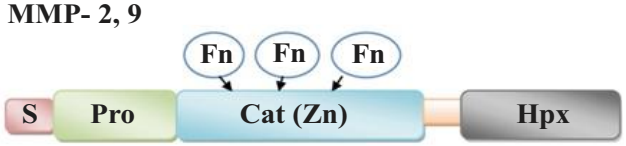

Fig 3: Domain Structure of Gelatinases

Stromelysins

This group of enzymes includes Stromelysin 1 (MMP-3), Stromelysin 2 (MMP-10) and Stromelysin 3 (MMP-11). These enzymes digest ECM components and activate a number of pro-MMPs (9) Fig. 4

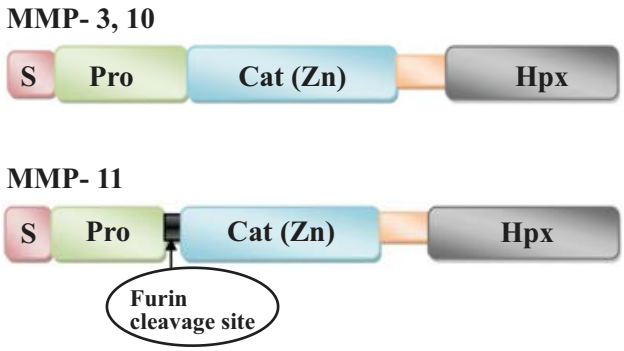

Fig 4: Domain Structure of Stromelysins

Matrilysins

This group includes Matrilysin 1 (MMP- 7) and Matrilysin 2/Endometase (MMP-26), which are characterized by the lack of a hemopexin domain (Fig. 5). Besides degrading ECM matrix, MMP-7 aids cell surface molecules such as Fas-ligand, pro-tumor necrosis factors (TNF-α), pro- α-defensin and E-cadherin in binding to their respective receptors (9).

Fig 5: Domain Structure of Matrilysin

Membrane-type MMPs

This group (Fig. 6) has six membrane-bound MMPs (MT-MMPs) including type I transmembrane proteins (MMP-14, MMP-15, MMP-16, MMP-24) and glycosyl- phosphatidyl-inositol (GPI) anchored proteins (MMP-17, MMP-25). Besides degrading the ECM matrix, these enzymes are capable of activating pro MMP-2 (9).

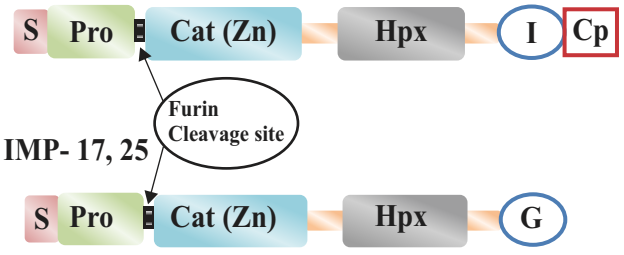

Fig 6: Domain Structure of Membrane-type MMPs

OTHER MMPs

This enzymatic group (Fig. 7) includes Metalloelastase (MMP-12), MMP-19, Enamelysin (MMP-20), MMP-22, MMP-23, MMP- 21 and MMP- 28 (9).

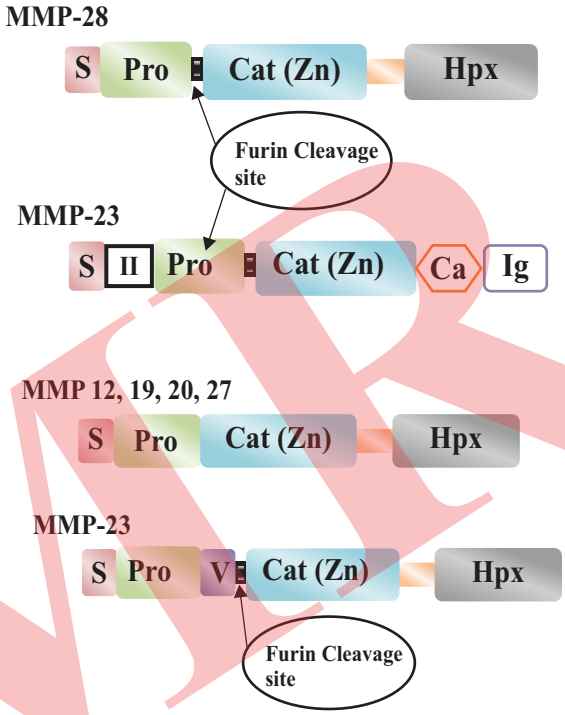

Fig 7: Domain Structure of other MMPs

Modulation of Gene Expression oF MMPs

MMPs are involved in embryogenesis, trophoblast implantation, bone growth, wound healing, angiogenesis and tissue regeneration. The MMPs are expressed at low levels in tissues and their activation and inhibition is based on controlled cascade processes. They are not synthesized until needed. Transcription can be induced by several signals such as mechanical stress, growth factors, cytokines, hormones and growth factors. A few of these are transforming growth factor (TGF-β), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), etc. (6,10). Most of the MMPs are secreted as inactive zymogens, so they need to be converted into their active forms by selective and specific proteolysis at their NH_2-terminal prodomains. Some MMPs are activated by other serine proteases such as plasmin and furin, while others can activate other members of their family (10).

Inhibitors of MMPs

MMP inhibitors include endogenous and exogenous inhibitors. TIMPs are endogenous inhibitors which

can either be attached with ECM components (TIMP-3) or secreted (TIMP-1, TIMP-2, TIMP-4) in the ECM. Sequence similarity between different TIMPs is about 40% and these display overlapping abilities in inhibiting various MMPs (11). The N-terminal domains of TIMPs act as inhibitory domains by tightly binding to the active site of the MMPs *via* non-covalent interactions (7, 11). Exogenous inhibitors include hydroxamic acid derivatives and thiirane-based gelatinase inhibitors SB-3CT. The expression of MMP inhibitors is induced by retinoic acid, heparin, corticosteroids and interleukin- 4 (IL-4) (6).

(9) and flavonoids (16) have an inhibitory effect on MMP-3 and -9 and these naturally occurring compounds shave shown potential against drug resistance. Natural products have been hailed as important sources for antitumor drug discovery and development (14). MMPs have also been considered as potential diagnostic and prognostic biomarkers for anti-metastasis in many types of cancer (15).

Tumor growth triggers an angiogenic switch which causes up-regulation of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor

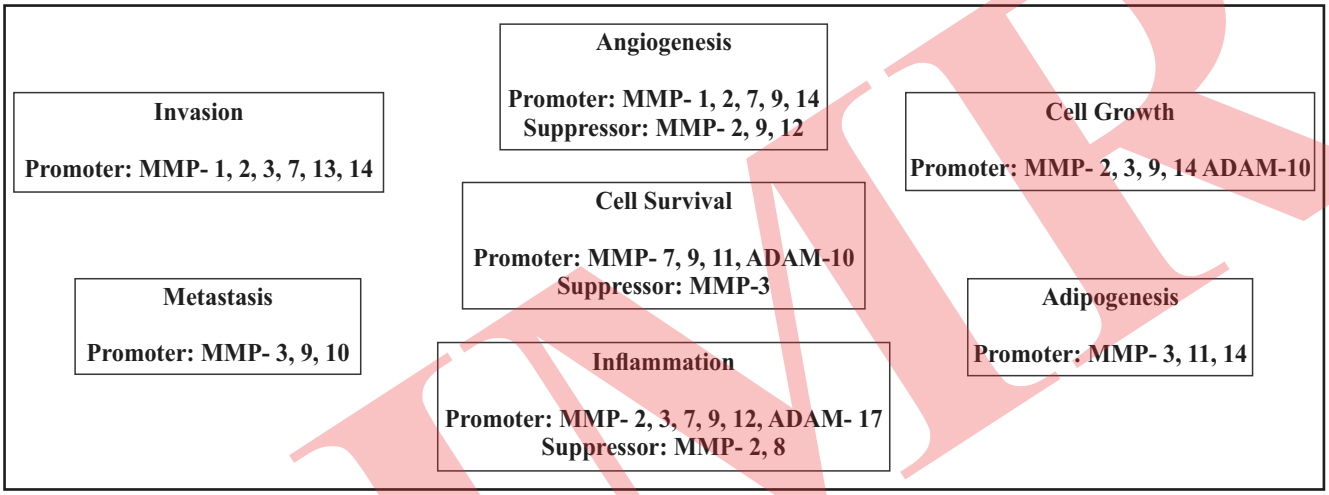

Fig 8: Different Roles of MMPs

MMPs and Their Role in Cancer

Cancer is one of major causes of mortality and morbidity around the world. Biomedical research has revealed various molecular pathways which participate in cancer progression (8). Several studies have reported that MMPs play an important cause of variations and remodeling observed in the ECM during cancer progression (12, 13). MMPs provide a favorable microenvironment for primary tumor growth *via* remodeling the ECM or by releasing membrane bound growth factors (10).

In particular, MMP-9 has attracted widespread attention by virtue of its presence in the vicinity of metastatic tumors. MMP-9 also acts as a precursor to the action of other endopeptidases (4-6,8,12,14) and as an inducer of angiogenesis where its expression is controlled by some growth factors and regulated by intracellular signaling pathways (13,15). Therefore, MMP-9 has the potential to serve as a potential target for synthesis of novel anticancer and antimetastasis drugs and its downregulation may help augment the therapeutic spectrum and range of existing chemotherapeutic drugs. Recent studies have revealed that some naturally occurring phenolics viz. lignans

(VEGF) that overcomes the expression of angiogenic inhibitors viz. interferons-α/β, endostatin, angiostatin, thrombospondins and decorin (17). Up-regulation of MMPs expression degrades the basal membrane region allowing the tumor cells to penetrate the stroma zone and enter the circulation. MMPs also play an important role in cell migration by removing adhesion sites, allowing new binding sites, cleaving cell matrix and releasing chemotactic chemicals to attract the macrophages for degrading ECM and, thus, are involved in cancer progression and metastasis (18). Some MMPs also inhibit cancer progression viz. MMP-8 has been found to exert a protective effect against breast cancer metastasis (19). On the other hand, MMP-9 promotes tumor progression. A recent study has reported the carcinogenic role of insulin and its synergistic effect with KRAS mutation in pancreatic cancer (20). Introduction of the mutated KRAS gene has been found to increase the migration and invasion ability of HPNE (immortalized human pancreatic duct-derived cells, hTERT-HPNE E6/E7/st) cells together with an increase in expression of MMP-2. Simultaneous administration of insulin has been found to further enhance these effects through activation of PI3K/AKT and ERK1/2 pathways with

MMP-2 gelatinolytic activity playing a vital role in ECM remodeling ECM (20). These findings may be of use in future for providing a novel therapeutic intervention for pancreatic cancer having a background of hyperinsulinemia Fig. 8 summarizes varios roles of MMPs.

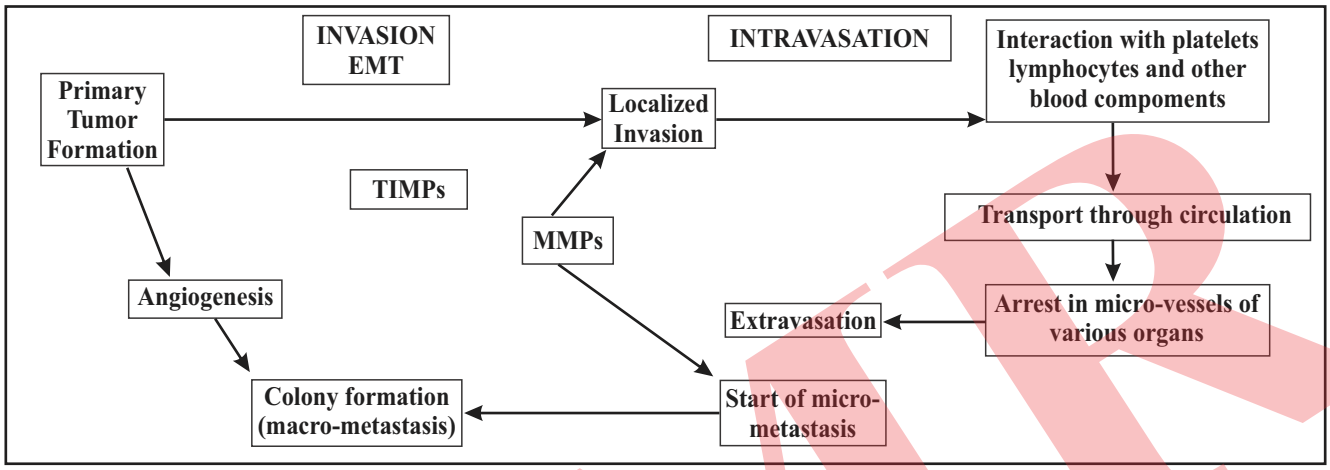

Fig 9: MMPs and Cancer Metastasis

Role of MMPS in Invasion and Prolif-eration

During the process of invasion, MMPs are localized at special cell surface structures called as invadopodia which promote invasion. Invadopodia utilize MMP-14, MMP-2 and -9, which facilitate cell invasion and metastasis (8, 19). Tumor growth and angiogenesis also depend on the increased availability of signaling molecules such as growth factors and cytokines as MMPs allow these factors more access to the cancer cells and the tumor microenvironment through ECM degradation (Fig. 9).

Tumor proliferation depends upon the bioavailability of growth factors and the function of cell-surface receptors. MMP-1-3, 7-9, -11 and -19 and ADAM12 (ADAM metallopeptidase domain 12) are involved in the cleavage of insulin-like growth factor-binding proteins (IGF-BPs) that regulate the bioavailability of the growth factors (21, 22). Since epidermal growth factor receptor (EGFR) signaling pathway is involved in the control of cell survival, proliferation, metastasis and angiogenesis, therefore inhibition of EGFR has become an attractive strategy for target-based cancer therapy since it is expressed in a variety of solid tumors (colorectal, breast, head and neck, etc.) (23). Moreover, MMP-3, 7, ADAM17 and ADAM 10 have been observed in the increased exudation and release of membrane-anchored ligands of EGFR such as heparin-binding EGF (HB-EGF), transforming growth factor (TGF)-α and amphiregulin (24, 25). In addition, MMP14-containing exosomes have also found to be involved in the regulation of corneal neo-vascularization through degradation of vascular endothelial growth factor receptor1 (VEGFR1) causing vascular endothelial growth factor A (VEGFA)-induced migration and proliferation of vascular endothelial cells (26). A study has reported simultaneous expression of MMP-14 and CD-44 with poor prognosis as well as correlation of CD-44 with vimentin expression in ovarian cancer patients (27, 28). Inside a cell, EMT-like changes are caused due to CD-44 linkage with actin skeleton leading to alterations in spindle shape and morphology. CD-44 expression has been found to induce EMT-like changes that result in down-regulation of epithelial markers such as E-cadherin and cytokeratins and increased expression of mesenchymal markers such as vimentin that cause cell migration and invasion. (27, 29-31).

MMPs and Their Role in Breast Cancer

Breast cancer is the most common malignancy in females. In the US, breast cancer is the second leading cancer in women after skin cancer. As per the latest statistics for 2018; 2,34,087 new cases of breast cancer were reported and there were 41,904 breast cancer-related deaths in the US alone (32). In India, as per the NICPR report; 1,62,468 new breast cancer cases and 87,090 deaths were reported for breast cancer in 2018 (33). Most of these deaths were due to distant metastases from the primary tumor site via the blood circulation.

Several studies have demonstrated the importance of MMPs in ECM remodeling (Fig. 10). MMP-2 has been considered as a breast cancer indicator (34). MMP-2 is converted to the active form and complexes with MT1-MMP to activate pro-MMP-2, the active form of which activates pro-MMP-9, in turn. MMP-2 and MT1-MMP together degrade the ECM causing invasion and metastasis of breast cancer cells (35). MMP-2 degrades the cellular network cemented by adhesion molecules E-cadherin and ALCAM/CD166 resulting in increased

metastasis (36, 37). Recent studies have indicated that MMP-9 degrades type IV collagen (component of basal membrane in human tissues) and allows the tumor cells to invade and metastasize (38). MMPs expression levels have been found to be regulated by tumor stroma interactions *via* CD147 (extracellular matrix metalloproteinase inducer; EMMPRIN) (39). A study has reported the association of CD147 and MMP9 expression in women with basal-like breast cancer (BLBC) *via* immuno-histochemistry (40). In addition, the tumor suppressor protein p53 has been found to inhibit Nutlin-3 (a small-molecule inhibitor of MDM2 (mouse double minute 2; an essential negative regulator of p53; nutlin-3 blocks the p53-binding domain of MDM2 resulting in p53 stabilization and p53 activation) and several TGF-β3-induced targets involved in tumor cell invasion such as MMP-2, MMP-9 and integrin-β3 in MCF-10A1 and MCF-10CA1 breast cancer cells (41). Another study has revealed that several P-glycoprotein substrates have been found to enhance tumor metastasis of MCF7 and MCF7/AdrR breast cancer cells *via* up-regulation of expression of CD147/EMMPRIN, MMP-2 and MMP-9 (42). MMP-1 (collagenase) has been found to be associated with fibrillar interstitial collagen degradation, MMP-2 (gelatinase) degrades and denatures type IV collagen whereas MMP-3 (stromelysin) has also been found to be associated with degradation of matrix components such as proteoglycans, laminin and non-helical regions of collagens (43). Recent studies have reported that the methanolic extract of *Leucobryum bowringii* has been found to stall growth of human breast carcinoma cells MCF-7 *via* partial inhibition of MMP-2 and MMP-9 activity (44). The role of MT1-MMP in resistance against collagen-induced apoptosis in basal-like breast carcinoma cells (MDA-MB-231) has recently been investigated. On the other hand, MT1-MMP has been found to exert a protective effect on noninvasive luminal-like breast carcinoma cells through the degradation of type I collagen and/or DDR1 (discoidin domain receptor) cleavage (45). Functional invadopodia formation requires polarized membrane trafficking driven by Rho GTPase-mediated cytoskeletal remodeling. This Rho GTPase-activating protein deleted in liver cancer 3 (DLC3; also known as STARD8), is an integral component of the endosomal transport and sorting machinery (46). DLC3 knockdown in MDA-MB-231 cells has been found to increase metalloproteinase-dependent matrix degradation which can be decreased by RhoB (Rho-related GTP-binding protein) co-depletion. This has unraveled a novel role for DLC3 in the suppression of MT1-MMP-dependent matrix degradation by inactivating RhoB signaling (46). Another clinicopathological study has reported expression of MMP-9 and VEGF-C in biopsy samples of breast cancer and benign breast disease. Expression of MMP-9 and VEGF-C has been found to be significantly associated with lymph node metastasis. This may help in providing valuable information in prognosis of breast cancer patients with lymph node metastasis (47). In another recent study, human SLFN5 (schlafen family member 5) has been found to inhibit cancer progression in breast cancer cell line MCF7, colorectal cancer cell line HCT116, lung cancer cell line A549, fibrosarcoma cell line HT1080 and clear cell renal cell carcinoma (ccRCC; the most lethal form of kidney cancer) based cell line 786-0 through suppression of MT1-MMP expression *via* AKT/GSK-3β/β-catenin signaling pathway (48). It has been recently reported that MT4-MMP over expression in MDA-MB-231 cells modulates the expression of 65 miRNAs related to pathways associated with tumor formation and progression viz. p53, TGF-β, MAPK, ErbB and Wnt pathways (49).

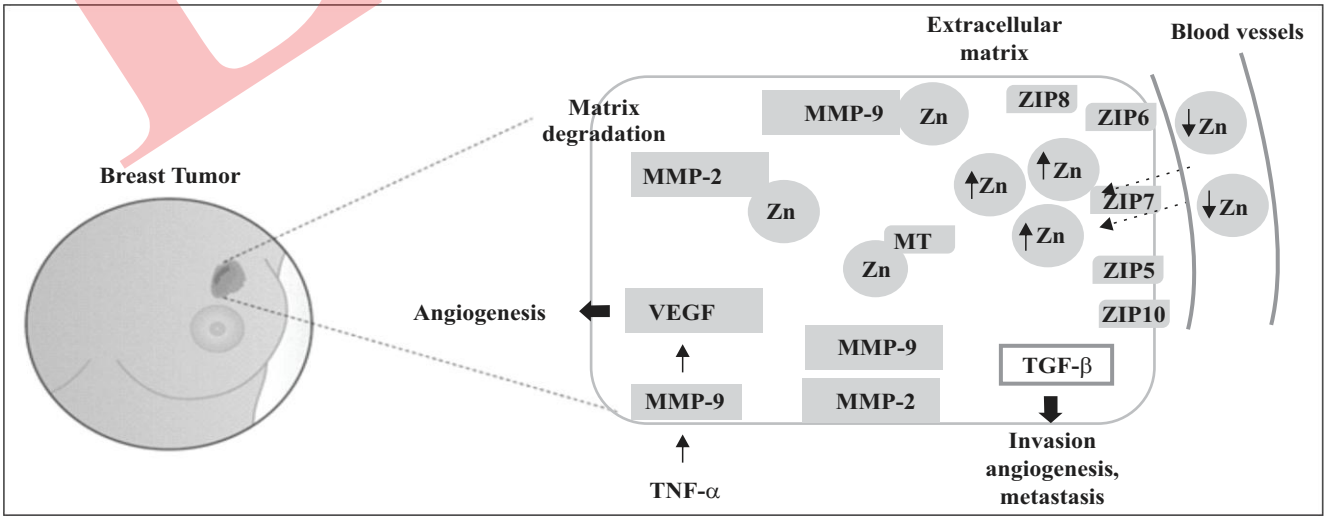

Fig 10: MMPs and Breast Cancer. Image Courtesy: Holanda et al. (1992) (50)

CONCLUSION

Cancer is a leading cause of mortality around the world**.** Therefore, researchers are always on a look out for novel strategies to combat cancer. As MMPs play a crucial role in ECM remodeling, cancer metastasis and progression, they are fast becoming promising targets for anticancer drug design and development. Several *in vitro* and *in vivo* studies have been done in the past concerning the role and significance of MMPs in breast carcinoma. The aim of this mini review was to shed light upon the structure, classification, role and significance of MMPs in breast cancer progression and metastasis and provide an update on its potential as a future anticancer drug candidate for breast cancer.

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