Review Article

# Pathophysiology of matrix metalloproteinases in breast cancer progression

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## Abstract

Matrix metalloproteinases (MMPs) are secretary or membrane type proteolytic enzymes that act on extracellular matrix protein components such as collagens, gelatins, elastins, laminins, fibronectins, and integrins. MMPs are synthesized as zymogens and are activated to functional forms on autoproteolysis or by other proteases. Naturally, the activity of MMPs was regulated by specific tissue inhibitors of metalloproteinases and transcriptionally regulated by miRNAs. MMPs have an important role in tissue remodeling by regulating cell death, morphogenesis, and wound healing activity. Overexpression of MMPs leads to various pathologies predominantly cancer, cardiovascular, and neurological diseases. Impact of MMPs on breast cancer progressions such as proliferation, angiogenesis, invasion, and metastasis are focused in this review.

**Keywords:** Angiogenesis, Breast cancer, Extracellular matrix, Invasion, Matrix metalloproteinases, Metastasis

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## INTRODUCTION

Cancer a long-standing disease is associated with fear for its pain, unpredictable course of progression and impotence of existing therapies, serious side effects and premature mortality (Global Action Plan for the Prevention and Control of NCDs 2013–2020).[1] Breast cancer is the leading type of cancer in women, accounting for 25.4% of all cancer diseased cases worldwide. According to the WHO, India has a cancer mortality rate of 79/100,000 deaths and accounts for 6% of total deaths. Breast cancer is at the highest incidence, mortality, and prevalence of cancers in India with 162,468 new cases, 87,090 deaths in 2018 and 5 years prevalence rate of 405,456 (Globocan 2018). Breast cancer is a dominant cause of women morbidity and mortality rate. The evidence suggests that cancer prevalence is the highest among the elderly and also among females in the reproductive age groups. Ongoing demographic data and epidemiological evolution infer that cancer is budding as a major public health concern in India.[1]

## BREAST CANCER

Cancer is a group of diseases involving uncontrolled cell growth/decreased apoptosis, differentiated into a tumor with a potentiality of invasion and spreads to other parts of the body in advanced stages is leading to the death of the organism. There are four main subtypes of breast cancer, such as luminal A, luminal B, human epidermal

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growth factor receptor 2 (HER2)-overexpression, and triple-negative breast cancer (TNBC). Luminal A type breast cancer is hormone-receptor positive estrogen-receptor (ER+), progesterone-receptor (PR+), and HER2 negative, showed with low levels of Ki-67 protein, luminal A tumors tend to have the best prognosis, with fairly high survival rates and fairly low recurrence rates. In case of luminal B type, it is hormone-receptor positive (ER+, PR+), and HER2 (positive or negative) with high levels of Ki-67. Luminal B cancers generally grow slightly faster than luminal A cancers, and their prognosis is slightly worse. TNBC is hormone receptor negative (ER and PR negative) and HER2 negative as regards 15%–20% of breast cancers are triple negative/basal-like.[2]

The treatment procedures of cancer include surgery, chemotherapy, and radiotherapy. The therapeutics used were failed considerably to treat cancers as well as induces rendered toxic side effects on patients. The major hallmark for cancerous deaths is metastasis, a property of malignant tumor migration by destroying the tissue barriers forming secondary malignancies. Cancer cases and mortality rates are enhancing mostly due to the lack of awareness, very high treatment costs, poor chances of survival, particularly diagnosed at advanced stages.

## MATRIX METALLOPROTEINASES

In general, extracellular matrix (ECM) possesses several tough proteoglycans or extracellular molecules secreted by cells provide mechanical strength and biochemical support to the surrounding cells for cell adhesion, cell-cell communication, and differentiation. The animal ECM contains interstitial matrix majorly made up of fibrous proteins, and basement membrane comprises sheet-like structures where epithelial cells rely. The fibrous components make interlocking mesh-like network in ECM include collagens, gelatins, elastins, fibronectins, integrins, and laminins. Human matrix metalloproteinases (MMPs) are matrixins, a family of 23 structurally related extracellular/cell-surface-anchored zinc endoproteases.[3] They are classified into collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10, MMP-11, MMP-27), matrilysins (MMP-7, MMP-26), membrane type (MT) MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, MMP-25), metalloelastase (MMP-12), enamelysin (MMP-20), and others (MMP-19, MMP-21, MMP-23, MMP-27, MMP-28). Functions of MMPs extend beyond the matrix and MMPs act as regulators of diverse processes by cleaving nonmatrix extracellular proteins.[4]

All the MMPs are multidomain enzymes containing signal sequence, propeptide, catalytic, hemopexin (except matrilysin, MMP-7) domains, transmembrane, and cytosolic domains for MT-MMPs. A cysteine residue, strictly conserved in the propeptide domain of all MMPs has been shown to be essential for maintaining the MMPs in an inactive state.[5] It has been suggested that the sulfhydryl group of cysteine residue is coordinated to catalytic zinc ion and interrupt the interaction causing activation through cysteine switch mechanism. Physiological activation of MMPs is probably initiated by proteases that cleave-specific sites within the propeptide, but final processing to the mature form of the active MMP that lacks the entire propeptide often requires intermolecular, autoproteolytic cleavage by the target MMP. When triggered with sulfhydryl-reactive compounds, such as organomercurials that interrupt the cysteine to zinc coordination, processing of proMMPs to the active form can be entirely autoproteolytic. The C-terminal hemopexin-like domain of MMPs is linked to the catalytic domain by a hinge peptide, and it determines the substrate specificity.[6,7] The activated MMP with catalytic triad (zinc, three histidines, and glutamic acid) brought proteinase activity between glycine and isoleucine repeats of ECM proteins in the presence of water. In general, MMPs activity over ECM proteins was endogenously controlled by tissue inhibitors of metalloproteinases in a stoichiometric fashion of 1:1. This regulation was unbalanced in cancers, on extreme secretion or production of MMPs.

ECM acts as a barrier and prevents the cells from transition, but in case of cancer, the balance between proteolytic actions predominate the antiproteolytic activity by extreme production of MMPs. They cleave ECM proteins and mediate both normal tissue remodeling processes during early developmental ages and pathological tissue remodeling processes on overexpression in cancers.[8]

Cancer progression is a sequential process where normal cells exhibit molecular aberrations that introduce indefinite tumor growth, angiogenesis, invasion, and metastasis behavior observed in cancerous condition.[9] The paper findings documented various roles of MMPs in breast cancer progression and emphasized some crucial MMPs that are ideal targets involved in all stages of breast cancer progression for therapeutic design.

## ROLE OF MATRIX METALLOPROTEINASES IN CELL PROLIFERATION

Cancer cell proliferation is a major hallmark of cancer, where the cells will never cease to death with infinite cell divisions forming uncontrolled tumor growth or

malignancy. MMP-2 and MMP-9[10,11] are involved in breast cancer cell proliferation and tumor growth. MMP-2 and MMP-9 cause tumorigenicity in TNBC.[12,13] MT1-MMP, multifunctional protease is involved in the activation of pro-MMP-2, leading to tumor growth.[14,15] MMP-7, MMP-11, and MMP-13 are also involved to mediate tumor growth or breast cancer proliferation with the help of MMP-2, MMP-9, and MMP-14.[16]

The crucial cell proliferation pathways are mediated by RAS/RAF/mitogen-activated protein kinase (MAPK) and JAK/STAT pathways. MMPs are downstream signaling enzymes activated in breast tissue proliferation. HER2 causes 30% of breast cancer cases through RAS/RAF/MAPK pathway.[17] ERs also have a pivotal role in breast cancer growth and progression. Moreover, ERβ exhibited a significant role on the gene expression of numerous matrix mediators, including the syndecans-2/-4, proteoglycans, and serglycin, MMP-2 and 9, components of plasminogen activation system as well as receptor tyrosine kinases.[18] The down-regulation of ERβ through tyrosine kinase receptors of epidermal growth factor receptor/insulin-like growth factor-I receptor (EGFR/IGF-IR) and the JAK/STAT signaling pathways reduces the migration of breast cancer cells.

MMPs, STAT3, AKT, ERK, and NF-kB are downstream targets of EGFR and IGF-IR. The activation of EGFR upregulates the downstream targets and enhances ERα+ and ERα− breast cancer progression.[19] TNBC cells treated with *Nelumbo nucifera* leaves extract to suppress MMP-2 and VEGF in turn reduce PI3K-AKT-ERK activation, which decreases the growth of the tumor.[20]

## ROLE OF MATRIX METALLOPROTEINASES IN ANGIOGENESIS

Angiogenesis is the development of new blood vessels with the differentiation of endothelial cells. This is an essential process in cancers as the most solid tumors contain regions of hypoxia in which increased cell proliferation promotes oxygen consumption. This condition is further exacerbated as cancer cells become localized far from a functional blood vessel, decreasing the oxygen supply which necessitates the angiogenesis.[21] Increased expression of transforming growth factor-beta 1, tumor necrosis factor, and interleukin 1 beta cytokines in fibroblasts leads to overexpression of MMP-9 and induces tumor cell growth by promoting tumor vasculature.[22] MMP-2 and MMP-9 secreted by human umbilical vein endothelial cells are the major angiogenic mediators of VEGF signaling.[23-25]

## ROLE OF MATRIX METALLOPROTEINASES IN CELL INVASION

Cell invasion refers to the degradation of ECM by MMPs to promote metastasis through invadopodia formation. MMP-2 and MMP-9 in the vesicles are responsible for extending invadopodia during breast cancer cell invasion.[26] MMP-1,[27] MMP-2,[28,29] MMP-3,[30,31] MMP-7,[17,32] MMP-9,[26,33-36] MMP-11,[3,37] MMP-13,[38,39] MMP-14,[28,40] and MMP-17[41] are known to be involved in cell migration and invasion of breast cancers.

The inhibition of thrombin activatable fibrinolysis activator increases secretion of MMP proenzymes by endothelial breast cancer cells which results in a series of cell invasion, cell migration, tube formation and collagen degradation by the activation of the protein kinase C α/nuclear factor-κB (PKCα/NF-κB) pathway.[42,43] Overexpression of MMP-2 activates p38 MAPK-MK2-HSP27 signaling leads to actin polymerization and induces cell migration in invasive breast carcinoma tissues.[44] MMP-9 degrades ECM in metastatic cancers as it plays a major role in cancer cell invasion.[43] Cell invasion was enhanced through activation of MMP-9 associated with the epithelial–mesenchymal transition of ER+ breast cancer cells.[45] Caspase-6, an important apoptotic signaling enzyme modulates invasion by modulating MMP-2 and MMP-9 expression in breast cancer cells.[34] MMP-2 and MMP-9 expressions were upregulated and PKD1 downregulation in invasive breast cancer.[36] Invasion of breast cancer occurs by the activation of MMP-2 through JAK/STAT pathway, and MMP-9 by PKC-α activation further activates c-Src, Akt, and finally, NF-kB leads to invasion of breast cancer cells.[46]

## ROLE OF MATRIX METALLOPROTEINASES IN METASTATIC CONDITION

Metastasis involves the spread of cancer cells from their primary location to surrounding tissues and to distant organs and is the primary cause of cancer morbidity and mortality.[47] In metastatic cascade, cancer cells detach from the primary origin, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, invade and proliferate in distant organs. MMPs are capable of contributing to every step of the metastatic cascade.[48] BACH1 (BTB and CNC homology 1) is a transcriptional factor which promotes the migration and invasion of breast cancer cells by upregulating MMP-1 expression.[49] MMP-1,[49-51] MMP-2 and MMP-9,[20,52-54] MMP-3,[51,55] MMP-13,[56] MMP-14[57] are the key proteases involved in metastatic breast cancer progression.

MMP-1 and MMP-9 overexpressions are crucial in invasion, vascular intravasation, and metastasis of ER+ and TNBC.[58] MMP-2 and MMP-9 are proposed as therapeutic targets for metastatic breast cancer in 4T1 cells.[52] COX-2 genes as key contributors to cancer progression by augmenting pro-tumorigenic, angiogenic, and metastatic enzymes such as MMP1 and MMP3.[50] Bone is one of the most common sites of breast cancer metastasis and a major cause of high mortality in these patients. Sterol regulatory element-binding protein 2 (SREBP-2) plays in osteoclast formation a function, and in breast cancer metastasis and found to be highly expressed in breast cancer tissues and correlated with a poor prognosis. SREBP-2 regulates the expression of MMPs, key degradative enzymes involved in bone metastases with osteolytic bone lesions by breast cancer cells.[59]

CD147 promotes breast cancer cell proliferation, metastasis, and invasion by modulating MMP-9 and VEGF expression.[60] Anti-angiogenic and anti-tumor activities of 4-vinylphenol in beta-catenin, EGFR and AKT signaling pathways which activates MMPs in higher tumorigenic and metastatic potential breast cancer.[61] ETS transcription factor (ELK3) play a positive role in the metastasis of breast cancer by indirectly regulating MT1-MMP expression.[62]

## ROLE OF MATRIX METALLOPROTEINASES IN ANTI-APOPTOSIS

Caspase-6 is an important enzyme in the apoptotic signaling pathway which could regulate breast cancer cell invasion by modulating MMP-2 and MMP-9 expression in 4T1 tumor-associated macrophages.[34] Apoptotic signals including processed caspase-8, caspase-7, poly ADP-ribose polymerase, Bax and Bcl-2, and MMP-9 expression cause invasive and migration potential through ICAM-1 suppressed transcriptional activity in MCF-7 breast cancer cells. An anti-metastatic agent (*Oldenlandia diffusa*) suppresses the metastatic response by targeting p-ERK, p-38, and NF-κB, thus reducing the invasion capacity of MCF-7 breast cancer cells through inhibition of MMP-9.[63]

Up-regulation of pro-apoptotic protein BAX along with the down-regulation of anti-apoptotic proteins (BCL-XL, Survivin), migration-associated proteins (p-FAK, MMP-3) and cancer stem cell markers (CD44, Oct-4), mediated by AKT/c-Jun pathway essential for anti-apoptosis pathways were observed in gemcitabine-based chemotherapy. Gemcitabine-based chemotherapy remains one of the standards in the management of metastatic breast cancer. However, intrinsic and acquired resistance to gemcitabine inevitably occurs. Inhibition of src and siRNA could partially reverse gemcitabine resistance and attenuate resistance-associated anti-apoptosis, migration, and stem cell capacities.[64]

In the overall MMPs, the outweighed MMPs involvement in breast cancer progression was highlighted in this review. MMP-9 and MMP-11 were highly expressed by cancer-associated fibroblasts in luminal A tumors.[65] Increased levels of MMP-1, MMP-3, and MMP-10 by 5–8 folds in luminal breast cancers were also reported.[66] MMP-14 in luminal B tumors was highly expressed. Overexpression of MMP-9 by mononuclear inflammatory cells (MICs) in HER-2-positive tumors as well as MMP-2/9 by MICs is crucially significant for TNBC.[67,68]

## FUTURE DIRECTIONS

The present therapeutics developed in cancers are based on receptors in Ras and JAK/STAT-mediated pathway signaling molecules and hormone receptors such as ER and PR. Among the 23 MMPs, 10 MMPs are mainly involved in breast cancer metastasis, whereas gelatinases are involved in all stages of breast cancer progression. Hence, the 10 MMPs can be targeted to design therapeutics or combination drugs along with the existing drugs to overcome drug resistance.

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### Conflicts of interest

There are no conflicts of interest.

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