# Matrix Metalloproteinases (MMPS) and its Role in Cancers - A Review

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## Abstract

The main aim of this study is to analyze the role of Matrix metalloproteinases genes in cancer progression and metastasis. Matrix metalloproteinase genes were identified in humans, and many are involved in cancer. Extracellular matrix (ECM) degradation by matrix metalloproteinase not only enhances tumour invasion but also affects tumour cell behaviour and leads to cancer progression. This review highlights recent developments in the cellular and molecular mechanisms of matrix metalloproteinase that influence tumour cell growth, invasion, and metastasis. A review with recent information about matrix metalloproteinases and its role in cancer collected from search engines from the articles dated from 2000-2020. The recent articles discussed in this review help to gain knowledge and understanding of Matrix metalloproteinases in cancer invasion and progression, metastasis, angiogenesis, and aid in the analysis of the mutations caused which aid the medical field to prevent tumour progression.

***Keywords:*** *Matrix metalloproteinases, tumour growth, metastasis, angiogenesis, tumour invasion, matrix metalloproteinase inhibitors*

## Introduction

Cancer is one of the world's leading causes of illness and death. As a result, the past two decades of biomedical research have yielded vast quantities of knowledge about the molecular events that occur during carcinogenesis and the signalling pathways that participate in the development of cancer. A key role in this process is the molecular mechanisms of the complex interplay between the tumour cells and the tumour microenvironment[1].

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Matrix metalloproteinases consist of a multi-gene family of zinc-dependent extracellular matrix (ECM) remodelling endopeptidases involved in pathological processes such as carcinogenesis, physiological processes like wound healing, uterine involution, organogenesis, and pathological conditions such as inflammatory, vascular, and autoimmune disorders. Here, their activity plays a pivotal role in tumour growth and multi-stage invasion and metastasis processes, including proteolytic ECM degradation, cell-cell, and cell-ECM interactions, migration, and angiogenesis[2]. Matrix metalloproteinases are considered a possible biomarker of diagnosis and prognosis in many cancer forms and stages. An increasing number of matrix metalloproteinase inhibitors (MMPs) were subsequently developed and evaluated in various clinical trials[3].

While several proteases are involved in ECM degradation, it is known that a group of metalloproteinases called matrix metalloproteinases or matrixes play a major role. Diseases like arthritis, atherosclerosis, fibrosis, and cancer include ECM turnover associated with uncontrolled matrix activities.

Particular attention has been drawn to involving matrix metalloproteinase in cancer metastasis, as it increases the prospect of developing matrix metalloproteinase inhibitors as a new type of cancer treatment. Recent findings suggest that matrix metalloproteinase are also involved in vascularization and initial growth of tumours, in addition to involvement in metastasis. In this review, we discuss the current understanding of the role of matrix metalloproteinase in cancer metastasis and tumour progression[4]. The number of articles used in the present study was the articles that were collected from various search engines. The articles relevant to matrix metalloproteinase and its role in cancers were collected from the period of 2000 to 2020 (to date). It is a five-step process in the selection of articles – identification of clear objectives, identification of relevant articles, selection of data, data extraction, analysis and report.

## MATRIX METALLOPROTEINASES

Types of matrix metalloproteinase :

They are classified into collagenases, gelatinases, stromelysins, and matrilysins based on the specificity of matrix metalloproteinase for ECM components. Of the eight distinct matrix metalloproteinase structural classes: five are secreted, and three are matrix metalloproteinase (MT-Matrix metalloproteinase) of the membrane type[5]. MT-Matrix metalloproteinases are bound to the cell membrane by covalent bonds, the most obvious way to tether matrix metalloproteinase activity to the cell membrane. Another way of locating the cell surface is by binding the integrins in the form of secreted matrix metalloproteinase or CD44 or by interacting with cell-surface associated heparan sulfate proteoglycans, collagen type IV or extracellular metalloproteinase inducer (Matrix metalloproteinaseRIN)[6]

### Role of Matrix metalloproteinases:

Matrix metalloproteinase-1 (Interstitial collagenase):

Matrix Metalloproteinase 1 (MMP-1) degrades collagen type I, a major constituent of bone ECM Matrix metalloproteinase-1 was significantly down-regulated while TIMP-1 levels were increased in a smooth muscle cell (SMC) mechanical strain model, in a time- and pressure-dependent manner. The matrix metalloproteinase-1 expresses fibroblasts, keratinocytes, endothelial cells, monocytes, and macrophages. In addition, a bet-expression screen set up to identify the molecules needed for motoneuron development also led to matrix metalloproteinase1 being isolated. In primary culture, matrix metalloproteinase-1 encoding mRNA was expressed at significantly higher levels in Human OS cells than normal human bone cells.

Matrix metalloproteinase-2 (Gelatinase-A, 72 kDa gelatinase):

Whole-mount RNA hybridization in situ characterized matrix metalloproteinase2 ‘s pattern of expression. Matrix metalloproteinase2 expression takes place widely in the embryonic CNS which contrasts with matrix metalloproteinase 1 Matrix metalloproteinase-2 expression and beta-catenin loss have a part to play in ESC pathogenesis and progression. It has recently been shown that the expression of the enzymes in vitro and the size of the C6-glioma in vivo in the animal model was reduced by DNAzyme produced against matrix metalloproteinase-2 mRNA. Decreased E-cadherin plays a significant role in the development of both the ESC and EEC[7]

Matrix metalloproteinase-3 (Stromelysin 1) :

The size of IGFBP-3 degradation products produced by matrix metalloproteinase-3 is identical to that produced by serum during pregnancy. Subgroup E stromelysin contains stromelysin-1 (MMP-3). In recent research on atherosclerotic plaque stability, a series of apoE / matrix metalloproteinase double knockout mice were used to show that matrix metalloproteinase-3 restricts plaque growth and improves plaque stability, thus playing a protective role[8].

Matrix metalloproteinase-7 (Matrilysin, PUMP 1):

Matrix metalloproteinase-7 (MMP-7), the matrix-degrading enzyme, plays a major role in cancer invasion and metastasis. Studies have shown that antisense oligonucleotides to matrix metalloproteinase-7 inhibit a higher rate of spread of H-infected gastric gland cells. Cultures PyloriMatrix metalloproteinase-7 mRNA was expressed in 53 percent of primary stomach cancers but not in the normal stomach mucosa, fibroblasts, or mesothelial cells. Induction of matrix metalloproteinase-7

occurs during epithelial cell response to bacterial infection[9]

Matrix metalloproteinase-8 (Neutrophil collagenase):

In most mammals, the connective tissue contains neutrophil collagenase, a collagen cleaving enzyme[10]. It is often referred to as MMP-8 or MNL-CL[11]. This has an exclusive pattern of expression in inflammatory conditions and is thus unique in the metalloproteinase matrix family MMPMatrix metalloproteinase-8 mRNA and protein have been expressed in all 3 forms of human in situ atheroma cells[12].

Matrix metalloproteinase-9 (Gelatinase -B, 92 kDa gelatinase):

It is also known as collagenase IV type 92 kDa, gelatinase B (GELB) 92 kDa matrix metalloproteinase-9 releases skit and this allows BM repopulating cells to be translocated to a permissive vascular niche that facilitates the differentiation and reconstitution of the stem/progenitor cell stream[13].

Stromelysin 2 (MMP10):

For humans, the matrix metalloproteinase10 gene encodes the Stromelysin-2 enzyme, also known as the matrix metalloproteinase-10 or transin-2 matrix[14].

Matrix metalloproteinase-10 (Stromelysin 2):

For humans, the matrix metalloproteinase10 gene encodes the Stromelysin-2 enzyme, also known as the matrix metalloproteinase-10 or transin-2 matrix[15].

Stromelysin-3 (MMP11):

The gene matrix metalloproteinase11 encodes Stromelysin-3 (SL-3) or (MMP-11) in humans[16]. The role of Matrix metalloproteinase-11 in neointima formation was tested in wild-type (MMP-11+/+) and matrix metalloproteinase-11–deficient (MMP-11−/−) mice using a vascular injury model matrix metalloproteinase-11 overexpression has possibly been linked with ovarian carcinoma aggressiveness[17].

Matrix metalloproteinase-11 (Stromelysin-3) :

The gene matrix metalloproteinase11 encodes Stromelysin-3 (SL-3) or (MMP-11) in humans. The role of Matrix metalloproteinase-11 in neointima formation was tested in wild-type (MMP-11+/+) and matrix metalloproteinase-11–deficient (MMP-11−/−) mice using a vascular injury modelMatrix metalloproteinase-11 overexpression has possibly been linked with ovarian carcinoma aggressiveness[18].

Matrix metalloproteinase-12 (Macrophage metalloelastase):

Animal models conducted research into the role of matrix metalloproteinase-12 in the development of COPD in humans smokers and suggested a predominant role for matrix metalloproteinase-9 and matrix metalloproteinase-12 in pulmonary inflammation pathogenesis[19].

Matrix metalloproteinase-13 (Collagenase 3):

The human gene matrix metalloproteinase13 encodes the enzyme Collagenase 3. Expressed into human OA and RA by chondrocytes and synovial cells, matrix metalloproteinase-13 is thought to play a crucial role in cartilage degradation. It has been documented that the degradation of the connective tissue growth factor in wound tissue was prevented transiently in matrix metalloproteinase-13 KO miceMatrix metalloproteinase-13 remains the primary matrix metalloproteinase released by chondrocytes, when stimulated with retinoic acid, to degrade their matrix[20].

Matrix metalloproteinase-14 (MT1-matrix metalloproteinase) :

Membrane type 1-matrix metalloproteinase (MT1-matrix metalloproteinase or matrix metalloproteinase-14) is a major pro-matrix metalloproteinase-2 activator and is essential for the development of the skeleton. Cleavage of membrane-bound native MT1-matrix metalloproteinase with several recombinant matrix metalloproteinases including both active MT1-matrix metalloproteinase and matrix metalloproteinase-2 is generated in vitro[21].

Matrix metalloproteinase-15 (MT2-matrix metalloproteinase) :

Ueno et al. identified a correlation between the positive nodal status and the 15 mRNA expression. On E10 hypocellular ECs. Mice with targeted snail

knockdown were exhibited and associated with decreased expression of mesenchyme cell markers and downregulation of the family member of the matrix metalloproteinase MMP, matrix metalloproteinase15[22].

Matrix metalloproteinase-16 (MT3-matrix metalloproteinase):

This is the new name for MT3-matrix metalloproteinase [Membrane-type matrix metalloproteinase-3], according to a numerical nomenclature for the matrix metalloproteinases. MT3-matrix metalloproteinase expression in human cartilage is elevated in end-stage osteoarthritis. Under pathological conditions, PDGF and fibronectin can upregulate the expression of matrix metalloproteinase-16 through cultured vascular smooth muscle cells[23].

Matrix metalloproteinase-17 (MT4-matrix metalloproteinase) :

The matrix metalloproteinase-17 (MT4-matrix metalloproteinase) is a member of the subfamily MT-matrix metalloproteinase. Eyes are anchored to the plasma membrane via a glycosyl-phosphatidylinositol (GPI) anchor that provides these enzymes with a specific collection of regulatory and functional mechanisms separating them from the rest of the matrix metalloproteinase family[24].

Matrix metalloproteinase-18 (Collagenase 4, xcol4, Xenopus),:

Matrix metalloproteinase-18 is expressed in migratory macrophages, and bands for matrix metalloproteinase-18 corresponding to mRNA are found in CB tissue[25].

Matrix metalloproteinase-19 (RASI-1, occasionally referred to as stromelysin-4) :

Matrix metalloproteinase-19 was revealed in laser capture microscopy as a novel mediator followed by microarray analysis in the hyperplastic epithelial cells adjacent to biotic regions. This has functions in cell proliferation, migration, angiogenesis, and adhesion, expressed in human epidermis and endothelial cells. For this gene, Yu et al. , 2012, identified several transcript variants that encode different isoforms.[26]

Enamelysin (MMP20):

An amelogenesis imperfecta was associated with a matrix metalloproteinase-20 mutation which alters the normal splice pattern and results in premature ending of the encoded protein.[27]

Matrix metalloproteinase-21 (X-matrix metalloproteinase):

Matrix metalloproteinase-21 increases the ability of certain solid tumours to enter and metastasize tumour matrix metalloproteinase-21 expression was examined on immunohistochemistry assay in 296 cases of gastric cancer.[28]

Matrix metalloproteinase-23A (MMP-CA):

Matrix metalloproteinase 23a does not have the signal chain, as opposed to other matrix metalloproteinases. It is suggested it could function intracellularlyMatrix metalloproteinase-23 has a short prodomain and contains a single cysteine residue that may be part of the cysteine-switch process working to preserve the latency of the enzymes.[29]

Matrix metalloproteinase-24 (MT5-matrix metalloproteinase):

TIMPs inhibit all matrix metalloproteinase, except matrix metalloproteinase-24, matrix metalloproteinase25 (MT6-matrix metalloproteinase). Membrane-type matrix metalloproteinase (MMP -25, also known as MT1-, MT2-, MT3-, MT4-, MT5-, and MT6-matrix metalloproteinase) are structurally similar to other matrix metalloproteinase types but are anchored to the cell membrane ‘s exterior. It is highly expressed in leukocytes and some tissues of cancer.[30]

Matrix metalloproteinase-26 (Matrilysin-2, endometase):

Matrix metalloproteinase-26 has 998 mRNA nucleotides and no type of transcript. RT-PCR, the study of immunofluorescence, and cytometry determined the matrix metalloproteinase-26 mRNA and protein expression by. This is the minor part of the metalloproteinase matrix. E encoded protein degrades type IV collagen, fibronectin, fibrinogen, casein, vitronectin, alpha-1-antitrypsin, alpha-2-macroglobulin, and insulin-like growth factor-binding protein 1, and activates matrix metalloproteinase9 through cleavage [31].

Matrix metalloproteinase-27 (MMP-22, C):

The matrix metalloproteinase-27 mRNAs are usually expressed at a lower level[32].

Matrix metalloproteinase-28 (Epilysin):

Matrix metalloproteinase-28 (MMP-28, epilysine) is highly expressed in the skin by keratinocytes, the nervous system developing and regenerating, and a variety of other normal human tissues. Matrix metalloproteinase-28 expression is associated with cell proliferation during epithelial repair and is spatially and temporarily tightly regulated during wound repair matrix metalloproteinase-28 expression is upregulated in primary keratinocytes by TNF-alpha therapy [33].

Role of matrix metalloproteinase in Cancer Progression :

Tumour cells participate in many tumour microenvironmental interactions involving extracellular matrix ( ECM), ECM-associated growth factors, and cytokines, as well as surrounding cells (endothelial cells, fibroblasts, macrophages, mast cells, neutrophils, pericytes, and adipocytes) during carcinogenesis formation. The local microenvironment relies on four cancer hallmarks that include migration, invasion, metastasis, and angiogenesis [34].

Matrix metalloproteinase is an important molecule in these processes as they degrade specific molecules of cell adhesion and thus modulate interactions between cells and cells and ECM. The development of cancer includes multiple steps, including tumour growth and multi-step invasion, metastasis, and angiogenesis processes, all of which can be modulated by a matrix metalloproteinase. The tumour microenvironment expression of matrix metalloproteinase depends not only on the cancer cells but also on the neighbouring stromal cells [35]Matrix metalloproteinase exercise their proteolytic activity and break down the physical barriers, promoting angiogenesis, invasion of tumour cells, and metastasis. Tumour growth and angiogenesis often rely on the increased availability of signalling molecules, such as growth factors and cytokines, by making those factors more available to cancer cells and the tumour microenvironment. This occurs either by extracting them from the ECM (IGF, bFGF, and VEGF) or by shedding them out of the cell surface (EGF, TGF-α, HB-EGF) [36].

Angiogenesis is also strongly modulated by the release of angiogenesis negative regulators, such as angiostatin, tumstatin, endostatin, and endorepellinMatrix metalloproteinase also modulate cell-cell and cell – ECM interactions by manipulating E-cadherin and integrins, influencing both cell phenotype (EMT) and cell migration, respectively. The over-expression of matrix metalloproteinase in the tumour microenvironment depends not only on the cancer cells but also on the neighbouring stromal cells that are induced in a paracrine manner by the cancer cells [37]. Cancer cells stimulate host cells such as fibroblasts to form an essential source of matrix metalloproteinase through interleukin secretion and growth factors, and direct signalling by extracellular matrix metalloproteinase inducers. Therefore the cellular source of matrix metalloproteinase may have important effects on its role and operation. In this regard, for example, neutrophils express matrix metalloproteinase-9 free of TIMP-1, which leads to more readily activating the proteinase.[38]

Specifically, they may promote or inhibit the development of cancer depending on the tumour stage, tumour site (primary, metastasis), enzyme localization (tumour cells, stroma), and substrate profile among other factors. For example, matrix metalloproteinase-8 provides a protective effect in the metastatic cycle, decreasing the metastatic potential of breast cancer cells when overexpressed. Similarly, the expression of matrix metalloproteinase-8 in tongue squamous cell carcinoma is associated with improved patient survival, and it is proposed that this protective action is possibly associated with the role of estrogen in tongue sq growth.[39]On the other hand, in some particular circumstances, matrix metalloproteinase-9 may act as a tumour promoter in the carcinogenesis cycle, as well as an anticancer enzyme at later stages of the disease. This dual function is based on the results in animal models, where matrix metalloproteinase-9 knockdown mouse models showed a reduced incidence of carcinogenesis whereas tumours developed in matrix metalloproteinase-9 mice were substantially more aggressive.

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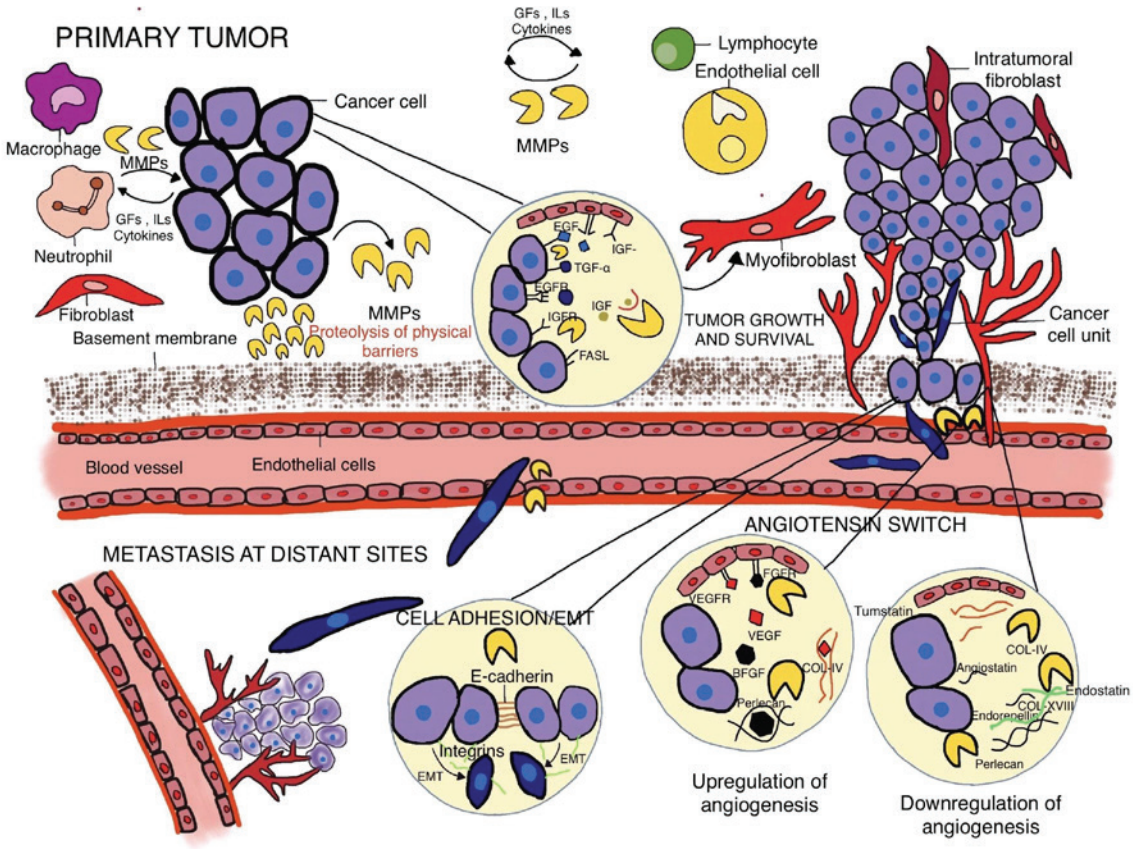


**FIGURE 1: Role of matrix metalloproteinase in cancer progression.**

Matrix metalloproteinases and Cancer Invasion :

The ECM is a dynamic structure that orchestrates the cells' actions through interaction with them. A cancer cell requires the proteolytic activity of matrix metalloproteinase to degrade physical barriers during local expansion and intravasation in nearby blood vessels, extravasation, and remote invasion. Localization of matrix metalloproteinase to specific cell surface structures, called invadopodia, is necessary during invasion for their ability to promote invasion. Such structures reflect the place where there is a significant degradation of the ECM. Invadopodia uses proteinases related to transmembrane invadopodia, like matrix metalloproteinase-14 (figure 2) [41].

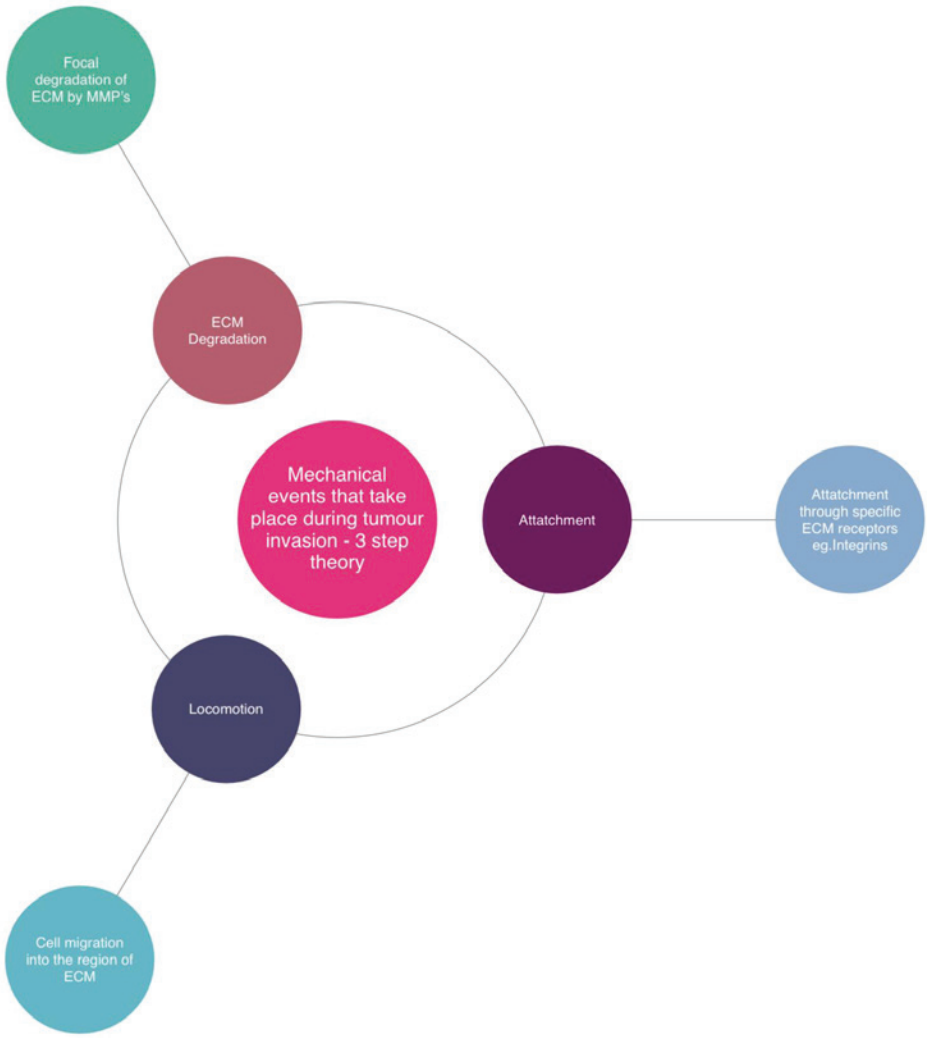


**FIGURE 2: Role of matrix metalloproteinase and ECM in tumour invasion.**

Matrix metalloproteinases and Tumour Angiogenesis :

Matrix metalloproteinase has a dual role in tumour vasculature as they can function as both positive and negative angiogenesis regulators depending on the time point of expression during tumour angiogenesis and vasculogenesis as well as the availability of substrates. The matrix metalloproteinase family's main players involved in tumour angiogenesis are mainly matrix metalloproteinase-2, -9, and matrix metalloproteinase-14 and, to a lesser degree, matrix metalloproteinase-1 and -7. For cancer cells to keep growing and begin migrating, new blood vessels need to be created [42]. The first step in this cycle is to remove the physical obstacles by degrading the ECM and produce pro-angiogenic factors thereafter. Indeed, matrix metalloproteinase-9 participates in the angiogenic transition as it increases the bioavailability of essential factors in this cycle, such as the most effective tumour vascular endothelial growth factor ( VEGF) and the specific fibroblast growth factor (bFGF), by degrading extracellular components such as collagen type IV, XVIII and perlecan, respectively [43].

matrix metalloproteinase tightly controls the angiogenic balance, but they can also down-regulate the formation of blood vessels by producing degradation fragments that inhibit angiogenesis. These molecules include tumstatin, endostatin, angiostatin, and endorepellin, which are produced by type IV, XVII collagen, plasminogen, a serine proteinase plasmin inactive precursor, and perlecan cleavage (figure 3) [44].

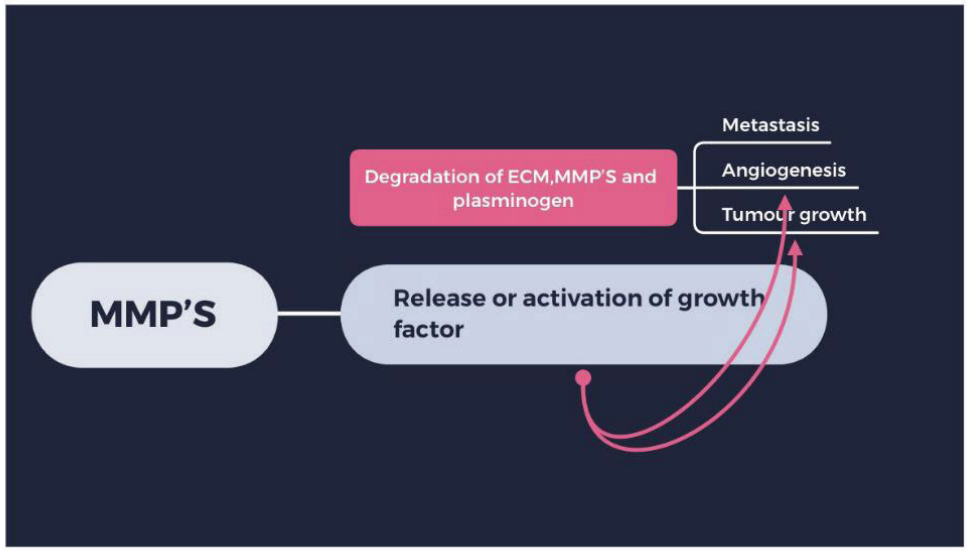


**FIGURE 3: Role of matrix metalloproteinase In tumour angiogenesis.**

Matrix metalloproteinase and Cancer Proliferation:

matrix metalloproteinase contributes to tumour cell proliferation by many pathways. In particular, they can modulate growth factor bioavailability and cell-surface receptor function. Even the ADAM family is interested in the above operation. Members of the matrix metalloproteinase and ADAM families that release cell-membrane-precursors of multiple growth factors such as insulin-like growth factors (IGFs) and epidermal growth factor receptor (EGFR) ligands promoting proliferation; Several matrix metalloproteinases (MMP-1,-2,-3,-7,-9,-11 and-19) and ADAM12 break down IGF-binding proteins which regulate the growth factor 's bioavailability [45]. Cell proliferation mediator EGFR is implicated in cancer development as it is over-expressed in over one-third of all solid tumours. With the action of matrix metalloproteinase-3, -7, ADAM17 or ADAM10, increased shedding of EGFR membrane-anchored ligands, including heparin-binding EGF (HB-EGF), transforming growth factor (TGF)-α, and amphiregulin was observed during cancer progression[46]Matrix metalloproteinase and ADAM also regulates proliferation signals through integrins since the shedding of E-cadherin results in translocation of β-catenin to the nucleus, leading to cell proliferation. It is worth noting that the inactive proform of TGF-β, an important molecule in cancer, is proteolytically activated by matrix metalloproteinase-9, -2, -14 in a similar way [47].

One of the main findings that emerged from several studies is the crucial role of glycosaminoglycan (GAG)-matrix metalloproteinase-GF interactions, leading to the activation of pro matrix metalloproteinase and their subsequent proliferative effects. Notably, GAGs chains may recruit matrix metalloproteinase to release growth factors from the cell surface and, as a result, induce cancer cell proliferation matrix metalloproteinase-7, for example, exerts a high affinity for sulfate chains in heparan. Based on this notion, heparan sulfate chains on cell surface receptors, such as some CD44 variant isoforms, anchor the proteolytically active matrix metalloproteinase-7, resulting in the HB-EGF cleavage[48].

Matrix metalloproteinase and Cancer Cell Apoptosis:

Degrading matrix enzymes impart both apoptotic and antiapoptotic action matrix metalloproteinase and ADAMs, especially matrix metalloproteinase-7 and ADAM10, relay anti-apoptotic signals from the cell surface to cancer cells by cleaving Fas ligand, a death receptor Fas transmembrane stimulator. This proteolytic activity inactivates the Fas receptor and causes apoptosis resistance and chemical resistance to cancer cells or encourages apoptosis of neighbouring cells depending on the method. In addition, proteolytic shedding of tumour-

associated major histocompatibility proteins with ADAM17-related complex class-I proteins will inhibit natural killer ( NK) cytotoxicity to cancer cells[49]Matrix metalloproteinase can, in particular, contribute to the anti-apoptotic effect by indirectly activating serine/ threonine kinase Akt / protein kinase B via the EGFR and IGFR signalling cascadesMatrix metalloproteinase also facilitates apoptosis, most likely indirectly by altering the composition of the ECM; for example, by splitting laminin, which affects the signalling of the integrin [50].

Matrix metalloproteinase and Cell Adhesion, Migration, Epithelial to Mesenchymal Transition :

Cell movement is strongly correlated with matrix metalloproteinase and ADAMs proteolytic activity, regulating the complex ECM – cell and cell-cell interactions during migration. Initially, mysterious peptide production through the degradation of ECM molecules such as collagen type IV and laminin-5 promotes cancer cell migration. In controlling cell migration, some integrins play an important role as they can serve as substrates for matrix metalloproteinase [51].

Several matrix metalloproteinases (MMP-2,-3,-9,-13,-14) has been over-expressed in association with epithelial-mesenchymal transition (EMT), a highly conserved and fundamental morphological transition phase. In particular, epithelial cells are actively down-regulating cell-cell adhesion systems during this event, losing their polarity and acquiring a mesenchymal phenotype with reduced intercellular interactions and increased migratory ability. Contact between the cells is hindered by ADAM10 shedding of E-cadherin, resulting in disrupted cell adhesion and EMT induction, accompanied by increased cell migration. By cleaving E-cadherin, matrix metalloproteinase-1 and -7 also appear to contribute to this morphological transition[52]. Recent studies indicate the implication of matrix metalloproteinase-28 in the proteolytic activation of TGF-β, a strong inducer of EMT, leading to EMT.

It should be remembered that the interaction between hyaluronan and its main cell surface receptor, CD44, contributes to the activation of signalling molecules such as Ras, Rho, PI-3 kinases and AKT, thereby facilitating the progression of cancer[53,54]. A recent study indicated that hyaluronan promotes cancer cell migration and increased metalloproteinase matrix secretion through Rho kinase-mediated signalling, specifically the increased active form of matrix metalloproteinase-2 [55].

Matrix metalloproteinase and Immune Surveillance :

By recruiting tumour-specific T-lymphocytes, NK cells, neutrophils, and macrophages, the host immune system is able to recognize and attack cancer cells. Cancer cells, by contrast, evolve mechanisms of escape using matrix metalloproteinase to gain immunity [56]. Matrix metalloproteinase shed T-lymphocyte interleukin-2 receptors-α to inhibit their proliferation. In addition, TGF-β is released as a result of matrix metalloproteinase activity, a major suppressor of T-lymphocyte reaction against cancer cells. Likewise, matrix metalloproteinase reduces the vulnerability of cancer cells to NK cells by producing a bioactive fragment from an inhibitor of 1-proteinase[57]. A number of studies have also demonstrated the ability of matrix metalloproteinase to effectively cleave or control the mobilization of many members of the CC (β-chemokine) and CXC (α-chemokine) chemokine subfamilies, affecting leukocyte infiltration and migration [58]

Pharmacological Targeting of matrix metalloproteinase :

Hence, matrix metalloproteinase is suitable for therapeutic intervention by synthetic and natural inhibitors, giving prospects for future studies. Multiple therapeutic agents, called inhibitors of matrix metalloproteinase (MMPs), were developed to target matrix metalloproteinase in an attempt to control their enzymatic activity. Even though clinical trials with these compounds in most cases do not produce the anticipated effects, the field of matrix metalloproteinases is still in development.

**TABLE 1: Potential matrix metalloproteinase inhibitors**

| Matrix metalloproteinases | Type of Drug/source | Enzymes Inhibited |
|---|---|---|
| Synthetic inhibitors | | |
| Batimastat | Peptidomimetic | matrix metalloproteinase-1,-2,-3,-7,-9 |
| Marimastat | Peptidomimetic | Broad Spectrum |
| Tanomastat(BAY12-9666) | Non Peptidomimetic | matrix metalloproteinase-2,-3,-9 |
| Prinomastat(AG3340) | Non Peptidomimetic | matrix metalloproteinase-2,-3,-7,-9,-13 |
| BMS-275291 | Non Peptidomimetic | matrix metalloproteinase-2,-9 |
| CGS27023A | Non Peptidomimetic | matrix metalloproteinase-1,-2,-3 |
| Minocycline | Chemically modified tetracycline | matrix metalloproteinase-1,-2,-3 |
| Metastat(COL-3) | Chemically modified tetracycline | matrix metalloproteinase-1,-2,-8,-9,-13 |
| SB-3CT | Reform proenzyme structure | matrix metalloproteinase-2,-9 |
| INCB7839 | Small molecule sheddase inhibitor | ADAM-10,-17 |
| Off Target inhibitors | | |
| Bisphosphonates | Analogue of PPi | matrix metalloproteinase-1,-2,-7,9,MT1,MT2matrix metalloproteinase |
| Letrozole | Nonsteroidal inhibitors of aromatase | matrix metalloproteinase-2,-9 |
| | | |
| Neovastat(AE-941) | Extract from shark cartilage | matrix metalloproteinase-1,-2,-7,-9,-13 |
| Genistein | Soy isoflavone | matrix metalloproteinase-2,-9,MT1-,MT2-,MT3-matrix metalloproteinase |

Matrix metalloproteinases Inhibition and Anticancer Therapy :

Matrix metalloproteinase synthesis is inhibited by multiple agents that prevent them from interacting with molecules that direct their action to the cell surface or inhibit their enzymatic activity [59].

Inhibition of matrix metalloproteinases synthesis :

Matrix metalloproteinase synthesis is inhibited directly by transfecting mRNA or oligonucleotide antisense cells or by attacking mRNA with RIBOZYMES. This means it has been used in mouse models to downregulate matrix metalloproteinase7 or 9 to reduce the stress or metastasis of tumours. Indirect strategies for reducing matrix metalloproteinase expression are signal transduction pathways inhibition that induces matrix metalloproteinase transcription. Several medicines in clinical trials inhibit signals of tyrosine kinase receptors and levels of matrix metalloproteinase. Halofuginone, a COCCIDIOSTAT used in poultry, is a drug that controls the expression of the matrix metalloproteinase genes and the experimental metastasis of cancer cells. Coccidiostat is a drug used to treat coccidiosis, which is a protozoan-induced intestinal disease[60].

Inhibiting interactions between matrix metalloproteinase and other proteins:

Matrix metalloproteinase-2 is prevented from binding to αvβ3 integrin so as to inhibit matrix metalloproteinase interaction with other proteins. This form of strategy may be evaluated in clinical practice by directly targeting the cancer-promoting feature, and the compound shows promising results in animal experiments [61]

. Exploiting matrix metalloproteinase activity:

This has developed many cytotoxic agents that are activated by a matrix metalloproteinase. It is effective for treating tumours. Cytotoxic agents, such as recombinant proteins containing ANTHRAX TOXIN fused to a matrix metalloproteinase cleavage site, are activated by cell surface matrix metalloproteinase cleavage and internalized by the cell, followed by cell death[62]

Blocking of matrix metalloproteinase :

Common endogenous inhibitors (TIMPs), comprising a family of four protease inhibitors, inhibit the matrix metalloproteinase:

• TIMP-1

• TIMP-2

• TIMP-3 and

• TIMP-4TIMPs

might have matrix metalloproteinase-independent cancer-promoting activities [63]

Future Perspective :

Perspective research into neoepitopes will provide important and novel means for cancer diagnosis, prognosis, and increased efficacy of treatment. However, in order to take full advantage of neoepitopes as highly useful biomarkers of cancer, understanding the physiological processes and signalling pathways that control their generation is very critical. And the ultimate aim of modern diagnostic studies would be to use highly accurate biomarkers based on non-invasive mechanisms. Currently, receptors, cell adhesion molecules, growth factors, and enzymes with their associated protein substrates (e.g., matrix metalloproteinase and extracellular matrix components) are all hot areas of study in cancer drug production and diagnostic assays [64].

CONCLUSION :

Thus, this review gives a clear knowledge about different types of matrix metalloproteinases and their role in cancer progression and metastasis to analyze the gene mutations in cancer cells in order to prevent and reduce cancer progression in the future.

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Ethical Clearance

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