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Review Article

Comprehensive Insights into Matrix Metalloproteinase (MMP) Regulation and Inhibition Strategies in Cancer Therapeutics: A Review

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Abstract: Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that play a major role in extracellular matrix (ECM) components degradation, enabling tissue remodeling and cellular migration. In cancer, overexpression and activation of MMPs, leadingly MMP-2 and MMP-9, contribute to tumor progression, invasion, metastasis, angiogenesis, and modulation of the tumor microenvironment. This article provides insights into the mechanisms of MMP regulation, including the influence of oncogenic signaling pathways, cytokines, growth factors, and hypoxic conditions within the tumor niche. The complex interplay between MMPs and their inhibitors is discussed. Furthermore, we explore a broad spectrum of MMP inhibition strategies, ranging from synthetic inhibitors and monoclonal antibodies to emerging natural compounds, such as flavonoids and nonsteroidal anti-inflammatory drugs (NSAIDs), highlighting their potential to modulate MMP activity with reduced toxicity. Although several synthetic MMP inhibitors have failed in clinical trials due to off-target effects and poor efficacy, recent advances in in-silico screening, drug repurposing, and combination therapies offer renewed promise. In conclusion, targeting MMPs through a multifaceted and personalized approach could significantly enhance the efficacy of current cancer therapies, reduce metastasis, and improve patient outcomes. Future research should focus on refining inhibitor specificity and validating combinatorial treatments in preclinical and clinical settings.

Keywords: Cancer, Matrix Metalloproteinase (MMPs), Angiogenesis, Metastasis, Small molecule inhibitors, Clinical trials.

1. INTRODUCTION

1.1 Background on Matrix Metalloproteinase (MMPs)

The Matrix Metalloproteinase (MMP) belongs to the zinc-dependent proteolytic enzyme family that has been extensively studied since 1962, covering an enzyme in the mammalian uterus that degrades collagen in various animal and tissue models (Woessner, 1962). MMPs have been researched across disciplines like biochemistry, cell biology, pathology, immunology, physiology, and computational biology, focusing on diseases like arthritis, cancer, periodontal diseases, and cardiovascular diseases. In the late 1980s, additional MMPs were discovered and given the name MMPs (Okada *et al.,* 1990). The International Union of Biochemistry and Molecular Biology assigned each MMP member an enzyme number and designated MMPs with unique names. The MMP family has 25 members, but not all of them are found in humans. The family is divided based on sequence homology and substrate characteristics into collagenases, gelatinases, matrilysins, stromelysins, and membrane-type MMPs (Iyer *et al.,* 2012). These all are capable of degrading components of the ECM including collagen, fibronectin, laminin, and proteoglycan protein core (Cabral-Pacheco *et al.,* 2020).

All MMPs have a protease domain and a conserved sequence HEXGHXXGXXHS/T with three histidine residues making a complex with a catalytic Zn atom and a regulatory conserved sequence domain PRCGXPD important for binding of cysteine to the Zn at active site found in the protease domain of MMPs (Nagase *et al.,* 2006).

1.2 Importance of MMPs in Cancer Progression and Metastasis

Cancer is a group of diseases that is a major cause of death worldwide. Studies have shown that

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extracellular matrix remodeling proteases-Metrix metalloproteinases (MMPs) play a crucial role in the changes seen in the microenvironment during cancer advancement. (Page-McCaw *et al.,* 2007). During the development of cancer, tumor cells interact with the tumor microenvironment, including the growth factors, cytokines, and extracellular matrix and surrounding cells such as fibroblasts, endothelial cells, macrophages, neutrophils and mast cells (Murphy, 2008), (Deryugina & Quigley, 2006). The four processes of cancer – migration, invasion, metastasis, and angiogenesis depend on this microenvironment. The MMPs expression in tumor microenvironment depends on cancer and stromal cells. MMPs have proteolytic activity and degenerate ECM physical barriers causing angiogenesis, invasion, and metastasis. The growth factors and cytokines signaling molecules cause tumor growth and angiogenesis. These factors are easily accessed by MMPs in cancer cells and cancer microenvironment.

Tumor metastasis is a complex process where cancer cells spread from the original tumor to other parts of the body. This involves the cells acquiring specific traits to escape the primary tumor, travel through the bloodstream, and form new tumors in distant organs. The process requires survival and communication skills from tumor cells. Overcoming physiological barriers is crucial for successful metastasis (Chambers *et al.,* 2002, Pantel & Brakenhoff, 2004, Geho *et al.,* 2005). At the stage of metastasis, tumor cells interact with various components like extracellular matrix, protein growth factors, and cytokines during metastasis. These interactions occur with different structures such as the basement membrane, blood vessels, and the microenvironment of secondary sites. These interactions contribute to the displacement of normal tissue and the formation of metastatic foci.

MMPs have an important role in metastasis (Deryugina & Quigley, 2006, Quintero-Fabián *et al.,* 2019). Regulation and dysregulation of MMPs in cancer involves various mechanisms that alter their expression, activation, and function. In many cancers, MMPs are often overexpressed, leading to increased ECM degradation, which facilitates tumor invasion and metastasis. This upregulation can be mediated by various factors such as growth factors (e.g., TGF-β, EGF), cytokines (e.g., TNF-α), and oncogenic signaling pathways (e.g., MAPK, PI3K-Akt) as well as by cytokines and growth factors present in the tumor microenvironment (Egeblad & Werb, 2002). DNA methylation and histone modifications can influence MMP expression patterns in cancer cells. For example, hypermethylation of promoter regions of certain MMP genes can lead to their silencing, while hypomethylation can contribute to their overexpression (Nagaset & Woessner, 1999). MMP activity can be modulated by post-translational modifications such as glycosylation, phosphorylation, and proteolytic processing. These modifications affect MMP activation, stability, and cell and ECM microenvironment localization. MicroRNAs (miRNAs) play a critical role in regulating MMP expression post-transcriptionally. Certain miRNAs can target MMP mRNAs for degradation or inhibit their translation, thereby modulating MMP levels in cancer cells, (Fabbri *et al.,* 2007). TIMPs are endogenous inhibitors of MMPs that maintain the balance between MMP activity and ECM integrity. Dysregulation of TIMPs, either through reduced expression or increased degradation, can lead to excessive MMP activity and ECM degradation in cancer (Mustafa *et al.,* 2022). The tumor microenvironment, characterized by hypoxia, inflammation, and interactions with stromal cells, influences MMP expression and activity. Hypoxia-inducible factors (HIFs) and cytokines released by tumor-associated immune cells can upregulate MMP production, promoting tumor invasion and metastasis. (Sun, 2010).

2. Extracellular Matrix Remodeling by MMPs

The ECM is commonly composed of structural proteins (collagen and elastin), glycosaminoglycan, proteoglycan, and connecting proteins (fibronectin and laminin) (Yuan *et al.,* 2023). The most common functions performed by the ECM are cell proliferation, differentiation, and maintenance of tissue homeostasis (Chakraborty & Edkins, 2021).

MMPs are produced as soluble or membrane-anchored enzymes that cleave components of the extracellular matrix (ECM). MMPs bind with the various ECM proteins for the remodeling of connective tissue (Laghezza *et al.,* 2020). The overexpression of MMP-2, MMP-3, MMP-9, and MMP-14 are associated with the remodeling of ECM in many of the malignant tumors (Luo *et al.,* 2021). The degradation of collagen IV is responsible for the invasion of tumor cells into the basement membrane mediated by MMP-2 and MMP-9. It causes tumor metastasis and diffusion (Taleb *et al.,* 2006). The collagen degradation also causes the remodeling of ECM biomechanical properties. The collagen dissolution around tumor cells is induced by MMP-14. It is an important factor for cell invasion and migration (Chen *et al.,* 2020).

2.1 MMP-Mediated Angiogenesis and Vasculogenesis

Angiogenesis and vasculogenesis are two fundamental processes involved in the formation of blood vessels. Angiogenesis refers to the formation of new blood vessels from pre-existing ones (Bajbouj *et al.,* 2021). Vasculogenesis is the de novo formation of blood vessels from endothelial progenitor cells during embryonic development or in postnatal tissues under certain pathological conditions (Kovacic & Boehm, 2009). Both processes are critical for normal physiological functions like wound healing and embryonic development. However, in pathological conditions like cancer, it contributes to tumor growth and metastasis by supplying nutrients and oxygen to the tumor cells (Lugano *et al.,* 2020).

MMPs are central to both angiogenesis and vasculogenesis, as they facilitate the remodeling of the ECM, which is crucial for endothelial cell (EC) migration, proliferation, and differentiation (Kubis & Levy, 2003). MMPs also modulate the bioavailability of growth factors and cytokines, thereby regulating the signaling pathways that drive angiogenesis and Vasculogenesis (Mott & Werb, 2004).

MMP-2 and MMP-9 are important in angiogenesis and Vasculogenesis due to their ability to degrade type IV collagen, a component of the basement membrane. The basement membrane acts as a barrier to cell migration, and its degradation by MMP-2 and MMP-9 is a critical step in the formation of new blood vessels (Shoari, 2024). These MMPs are often upregulated in response to pro-angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-β), facilitating the migration of ECs during angiogenesis and the mobilization of endothelial progenitor cells during Vasculogenesis (Pathak *et al.,* 2024). VEGF is a potent pro-angiogenic factor that stimulates EC proliferation, migration, and survival. MMP-9 has been shown to release VEGF from the ECM, increasing its bioavailability and enhancing its angiogenic effects. This interaction is crucial for the initiation of both angiogenesis and vasculogenesis, as VEGF signaling is essential for the recruitment and differentiation of endothelial progenitor cells during vasculogenesis and for the sprouting of new blood vessels during angiogenesis (Ghalehbandi *et al.,* 2023).

TGF-β plays a dual role in angiogenesis and vasculogenesis, acting as both a pro-angiogenic and anti-angiogenic factor depending on the context. TGF-β is secreted in a latent form bound to latency-associated peptide (LAP), which keeps it inactive. MMPs, particularly MMP-2 and MMP-9, can cleave LAP, releasing active TGF-β. The activation of TGF-β by MMPs contributes to the regulation of angiogenesis by influencing EC proliferation and differentiation, as well as the recruitment of pericytes and smooth muscle cells to stabilize newly formed vessels (Neel *et al.,* 2012).

MMPs influence angiogenesis and vasculogenesis by modulating signaling pathways through the proteolytic processing of signaling molecules and receptors. Thus, MMPs can either activate or inactivate signaling pathways, for fine-tuning the angiogenic and vasculogenic response. MMP-14 is a membrane-bound MMP that plays a crucial role in the activation of pro-MMP-2. It is expressed on the surface of endothelial cells (ECs) involved in angiogenesis and vasculogenesis. It activates pro-MMP-2 by cleaving its Propeptide, converting it into the active enzyme that degrades type IV collagen and other ECM components (J. H. Chang *et al.,* 2016). it is crucial for the invasive capacity of ECs during angiogenesis and the differentiation of endothelial progenitor cells during vasculogenesis.

MMPs can cleave VEGFR-2, modulating its activity and the downstream signaling pathways involved in EC proliferation and migration. This cleavage can result in either the activation of VEGFR-2 signaling or its inhibition, depending on the specific MMP involved. The regulation of VEGFR-2 by MMPs is critical for maintaining the balance between angiogenesis and vasculogenesis, (X. Wang & Khalil, 2018), (Ceci *et al.,* 2020).

3. MMP Inhibition Strategies

MMP Inhibition Strategies involve developing and applying methods to prevent or reduce the activity of MMPs to treat or manage the diseases. MMP activity can be crucial in treating diseases where MMPs contribute to tissue damage, such as cancer, arthritis, and cardiovascular diseases.

3.1 Small Molecule Inhibitors of MMP Activity

Batimastat (BB-94) is a synthetic broad-spectrum small molecule inhibitor of MMP activity including MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, and MMP-13 extensively studied for its therapeutic potential. The structure of Batimastat includes a hydroxamate group that binds to the zinc ion in the active site of MMPs. This interaction is critical for the inhibition of the enzyme proteolytic activity (Hernandez-Pando *et al.,* 2000). Batimastat was administered in oral and intravenous routes, but its clinical use has been limited due to poor bioavailability and dose-limiting toxicities. It disrupts ECM remodeling by binding to the active site of MMPs and chelates the zinc ion essential for MMP activity and preventing the degradation of extracellular matrix components (Brew & Nagase, 2010).

Marimastat (BB-2516) is a next-generation oral broad-spectrum inhibitor, it inhibits MMP-1, MMP-2, MMP3, MMP-7, and MMP-9 activity. The structure of Marimastat has a Hydroxymate, that acts as a zinc chelator of the active sites of MMPs. Marimastat was studied in pancreatic, non-small cell lung, breast, colorectal, gastric, glioblastoma brain, and prostate cancer (Bramhall *et al.,* 2002).

Other inhibitors including tanomastat Carboxylate zinc chelator, inhibits MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13, prinomastat Hydroxymate zinc chelator inhibitor, inhibits MMP-2, MMP-3, MMP-9, MMP-13, and MMP-14, and rebimastat Sulfhydryl based mercaptoacyl zinc chelator inhibitor of MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-13, MMP-14 (Winer *et al.,* 2018), all these inhibitors were studied in ovarian, pancreatic, lung, breast, and prostate carcinomas. All these inhibitors were found small inhibitory activity and failed in clinical trials for the positive effect on survival.

3.2 Antibody-Based Therapies Targeting MMPs

Antibody-based therapies targeting MMPs represent a promising approach to treating many diseases where MMP dysregulation is critical. Monoclonal antibodies (mAbs) are engineered proteins that can bind to specific antigens, such as MMPs, it is designed to selectively inhibit a single MMP with high affinity, greater specificity, reduced side effects, and the ability to exploit the immune system for therapeutic benefit (Alaseem *et al.,* 2019).

The antib REGA-3G12 and REGA-2D9 are target MMPs (Liu & Khalil, 2017), (Fields, 2019). The REGA3G12 inhibits MMP-9 by affecting the catalytic domain and the N-terminal region, rather than the catalytic zinc ion of the fibronectin region (K. Li *et al.,* 2020). Additionally, monoclonal antibodies AB0041 (Andecaliximab-GS-5745 humanized version with clinical trails) and AB0044 also target MMP-9 and have demonstrated the ability to inhibit tumor growth and metastasis through pro-MMP-9 activation and non-completely inhibits MMP-9 activity in colorectal carcinoma models.

3.3 Natural Compounds as MMP Inhibitors

Natural products are an important source of bioactive molecules for developing therapeutic applications. In some cases, it becomes approved as a drug and useful for the development of new derivatives (Newman & Cragg, 2012). Many of the metabolites and small natural products are known for the inhibition of MMPs expression including MMP-2 and MMP-9 (Mudit & El Sayed, 2016), (Gentile & Liuzzi, 2017), (Eun Lee *et al.,* 2019) including the flavonoids and polyphenols.

Kaempferol a polyphenol has anticancer, antidiabetic, anti-inflammatory, antiaging, and antiallergic properties (Imran *et al.,* 2019). It prevents the nuclear translocation of the AP-1 transcription factor to the MMP-2 promoter, which suppresses the production of MMP-2 in human tongue squamous cell carcinoma cells (SCC4 cells) and stops propagation and invasion (Lin *et al.,* 2013). Thus, reducing cancer development and carcinogenesis (Lee *et al.,* 2017). Naringenin has anti-inflammatory and anticancer activity extracted from fruits. It reduces the nuclear translocation of NF-κB transcription factor in MMP-2 and MMP-9 and controls inflammation and cancer metastasis (H. L. Chang *et al.,* 2017). Luteolin has been found to inhibit cell proliferation, metastasis, and angiogenesis and can sensitize cancer cells to therapeutic-induced cytotoxicity by suppressing phosphatidylinositol 3′-kinase (PI3K)/Akt and nuclear factor kappa B (NF-κB) and suppresses MMP-2 and MMP-9 expression in A375 human melanoma cells (Yao *et al.,* 2019). Myricetin regulates the activity of MMP-2 and MMP-9 and reduces the MMP-2 production and expression in colorectal cancer cells (COLO 205). It reduces and inhibits metastasis in breast cancer cells (MDA-Mb-231) by reducing the expression of MMP-2 and MMP-9 activity (Ci *et al.,* 2018). it also reduces the growth and propagation of lung cancer cells (A549-IR) by reducing MMP-2 and MMP-9 expression and stops the growth and movement of cancer (Kang *et al.,* 2020).

Research conducted on quercetin flavonoids for its anti-inflammatory and anticancer activities which reduce propagation and invasion in human hepatocarcinoma cell lines (HCCLM3 cells). It suppresses MMP-2 and MMP-9 expression (Lu *et al.,* 2018) in human oral cancer cells (HSC-6 and SCC-9) (Zhao *et al.,* 2019). Genistein has antitumor, antibacterial, and antioxidant, properties. It inhibits angiogenesis and tumor cell programmed death. The in vivo study in mice identifies the growth and migration of tumors in HCT116 human colon cancer cell line by inhibition of MMP-9 activity (W. Li *et al.,* 2013). Silibinin stops skin cancer and affects metastasis in breast cancer by inhibiting the expression of MMP-9 in mice through suppression of the MEK/ERK cascade. It protects ECM by the control of MMP-9 expression in thyroid and breast cancer cell migration (S. Kim *et al.,* 2009). Caffeic acid is an active transcription inhibitor and MMP-9 activity inhibitor was obtained from a plant *Euonymus alatus* (Kuo *et al.,* 2015). Pterostilbene has antiproliferative, anti-inflammatory, anticancer, and antioxidant activities similar to Resveratrol, obtained from blueberries and other grape varieties (Rimando *et al.,* 2002), (McCormack & McFadden, 2012).

4. Clinical Trials Assessing MMP Inhibition in Cancer Therapy

Matrix metalloproteinase inhibitors (MMPIs) ranged from normal, natural, and synthetic chelating agents. Many experiments and clinical trials support that MMPs participate in tumor invasion, angiogenesis, and metastasis, thus MMP acts as potential targets for cancer therapy. These experimental and clinical trials have been studied in several experimental models. The results of experiments and trials give the possibilities as classes of anticancer drugs.

Batimastat (BB-94) - Batimastat is a Hydroxymate (zinc chelator) type of inhibitor and one of the most widely explored MMPs (MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-13) inhibitors as preclinical models (Chirvi *et al.,* 1994). Batimastat inhibits the regrowth of human breast cancer (MDA-MB-435) in the mammary fat pads, metastasis of the lung (Sledge *et al.,* 1995), growth of colon tumors, organ invasion, and metastasis. Batimastat has been tested on ovarian carcinomas, both alone and with traditional chemotherapy drugs (BROWN, 1994). Batimastat was the first explored MMP inhibitor, tested in an I-phase clinical trial and canceled in a Phase III clinical trial, due to low solubility and local toxicity. All the trials were stopped due to some general tissue reactions.

Marimastat (BB-2516) - Marimastat is a low-molecular-weight MMP including (MMP-1, MMP-2, MMP-7, and MMP-9) Peptidomimetic inhibitor that, has a similar action mechanism as Batimastat, with a 20% to 50 % oral bioavailability. The preclinical trial of Marimastat reached phases II and III in pancreatic, lung, breast, colorectal, brain, and prostate cancer(Levin *et al.,* 2006), (Rosenbaum *et al.,* 2005), Ongoing phase II results using Marimastat singly or in combination with other cytotoxic agents are producing promising results.

Prinomastat (AG 3340) - Prinomastat (AG 3340) is a Nonpeptidomimetic hydroxamic acid derivative MMP inhibitor that targets MMP-2, MMP-3, MMP-9, MMP-13, and MMP-14 and participates in tumor invasion and metastasis (Shalinsky *et al.,* 1999). In advanced prostate cancer patients, a Phase I clinical study of Prinomastat (AG 3340) in combination with mitoxantrone and prednisone is underway. The arthralgia and body aches were the most common side effects reported in the phase I clinical trial (Hidalgo & Eckhardt, 2001).

Rebimastat (BMS-275291) - Rebimastat (BMS-275291) is a broad-spectrum sulfhydryl-based mercaptoacyl (zinc chelator) orally bioavailable MMP inhibitor that targets MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-13, and MMP -14 in Phase I clinical trials (Sikic, 1999). Rebimastat (BMS-275291) has strong inhibitory activity against MMP-2 and MMP-9.

Tetracycline Derivatives- The tetracycline derivatives can inhibit the activity by binding with zinc and calcium ions and production of MMP (Fisher & Mobashery, 2006). The chemically modified tetracycline-like Doxycycline is the only FDA-approved MMP inhibitor that targets MMP-7 and MMP-8 (Kivelä-Rajamäki *et al.,* 2003)

Doxycycline - Doxycycline is one of the tetracyclines that act as an anticancer agent and inhibit the activity and production of several MMPs. It inhibits the secretion and activity of MMP-2 and MMP-9 in MDA-MB-435 cancer cell lines culture. In in-vitro studies, it inhibits the growth and development of the U2OS osteosarcoma, PC-3 prostate, and MDA-MB-435 breast cancer cell lines. it also starts apoptosis and suppresses the invasion and metastatic of the MDA-MB-435 breast cancer and B16F10 melanoma cell lines, (Fife *et al.,* 1998). In phase I clinical trial studies on cancer patients, oral doses of 400 mg administered twice a day resulted consisted of fatigue, confusion, nausea, and vomiting as in dose-limiting toxicity (Nanda *et al.,* 2016).

Natural MMP inhibition compounds

Neovastat (AE-941) - Neovastat (AE-941) orally administrated compound, has anti-angiogenic and anti-metastatic activity, and is extracted from shark cartilage. Several studies have shown his effect on the inhibition of vascular endothelial growth factor (VEGF) and enzymatic activity of MMPs (FALARDEAU, 2001). The high-dose administration of neovastat in Phase I and Phase II clinical trials shows their survival benefit in cancer patients (F. E. Mott *et al.,* 2003). The toxicity effects of neovastat are nausea, flatulence, diarrhea, vomiting, constipation, and rash. In breast cancer, colorectal cancer, kidney cancer, and stage III non-small cell lung cancer patients Phase III trials were started.

Genistein is an isoflavonoid (polyphenol) that has anti-tumor, anti-inflammatory, and anticancer activity. It inhibits the activity of MMPs (MMP-2 and MMP-9) including growth of the tumor and invasion (Huang *et al.,* 2005). In the case of breast and prostate cancers, there are several studies explaining that genistein has expressed a lower risk of cancer development and cancer patient death (Gu *et al.,* 2005).

5. CONCLUSION

The development of MMP inhibitors has been fraught with challenges, including issues of selectivity, toxicity, lack of efficacy, pharmacokinetics, and biomarker identification. MMPs may have overlaying substrates and biological functions, thus inhibiting one MMP may not fully block the pathological process. This redundancy can reduce the efficacy of MMP inhibitors as therapeutic agents, especially in complex diseases like cancer, where multiple MMPs are involved in tumor progression and metastasis. Clinical trials of early MMP inhibitors, such as Marimastat, showed promising results. Advanced drug designing, targeted delivery systems, and biomarker discovery may eventually overcome these challenges and limitations, leading to more effective MMP-based therapies.

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