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MMP-9: A DUAL ROLE IN PHYSIOLOGY AND PATHOLOGY – THERAPEUTIC TARGETING AND DIAGNOSTIC POTENTIAL

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ABSTRACT

Matrix metalloproteinase-9 (MMP-9) is a vital enzyme involved in a variety of physiological activities, including tissue remodeling, immunological modulation and wound healing. However, dysregulation is linked to a wide range of clinical disorders, including cancer, cardiovascular disease and chronic inflammation. Because of its dual role in health and disease, MMP-9 has emerged as a promising therapeutic target and biomarker for disease detection and prognosis. While therapeutic techniques aimed at MMP-9, such as selective inhibitors, have showed promise, issues such as off-target effects and tissue-specific activities confound treatment approaches. Furthermore, MMP-9's potential as a biomarker opens up non-invasive diagnostic prospects, especially when paired with additional markers. Future research is required to address the limits of therapeutic interventions and improve the use of MMP-9 in clinical diagnostics and personalized medicine.

KEYWORDS

MMP-9, Matrix metalloproteinase-9, Therapeutic targeting, Disease biomarker, Tissue remodeling, Cancer, Cardiovascular diseases and Inflammation.

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INTRODUCTION

Macromolecules of the extracellular matrix (ECM) are crucial for establishing the cellular microenvironment necessary for morphogenesis and development metalloproteinases (MMPs) are zinc-dependent endopeptidases that play a role in both normal and pathological tissue remodeling. MMPs degrade all structural elements of the extracellular matrix (ECM) and process a wide range of non-ECM substrates. MMPs were initially given descriptive names based on substrate specificity and were divided into five groups: Collagenases,

gelatinases, stromelysins, matrilysins and membrane type[1]. MMPs, also known as matrixins, are expected to play a key part in these processes. Most matrixins are transcriptionally controlled by growth factors, hormones, cytokines, and cellular change. MMPs' proteolytic activity are tightly controlled during activation from precursors and inhibition by endogenous inhibitors, such as a-macroglobulins and tissue inhibitors of metalloproteinases (TIMPs). Table No.1 covers the currently known vertebrate matrixins. Additionally, non-vertebrate members have been found in sea urchins, Caenorhabditis elegans, soybean and Arabidopsis[2].

Physiological Role of MMP-9

MMP-9 is a zinc-dependent endopeptidase that is essential for the breakdown and remodeling of the extracellular matrix (ECM). It is engaged in a variety of physiological processes, such as tissue healing, angiogenesis, immunological response, and bone formation.

Extracellular Matrix (ECM) Remodeling

MMP-9 largely degrades ECM components like type IV and V collagen, elastin, and gelatin. This process is essential for normal tissue growth and repair, as well as preserving ECM homeostasis. During tissue injury, MMP-9 helps eliminate damaged ECM components, allowing tissue regeneration and remodeling[3]. Furthermore, MMP-9 plays an important function in embryonic development, controlling ECM turnover during organogenesis to ensure appropriate tissue formation[4].

Angiogenesis

MMP-9 is a crucial regulator of angiogenesis, the process of forming new blood vessels, which is necessary for wound healing, tissue growth, and pregnancy. By degrading the ECM, MMP-9 enables the release of vascular endothelial growth factor (VEGF) and other pro-angiogenic substances, increasing endothelial cell migration and blood vessel development[5,6]. MP-9-mediated angiogenesis is critical for activities such as wound healing and placental development[7].

Leukocyte Migration and Immune Response

MMP-9 also plays an important function in the immunological response, allowing leukocyte movement. It dissolves the ECM barriers, allowing immune cells like neutrophils and macrophages to travel toward sites of infection or injury[8]. This function is particularly crucial during acute inflammation, because MMP-9 stimulates the influx of immune cells into injured tissues to battle infection and promote healing Vu *et al*, 1998[9].

Bone Development and Remodeling

MMP-9 plays a role in bone formation and remodeling in the skeletal system. It is important for osteoclast-mediated bone resorption because it helps destroy bone ECM components, allowing for the clearance of old or diseased bone[10]. This role is especially important during growth plate development in children, where MMP-9 regulates the conversion of cartilage into bone, ensuring adequate bone growth[11].

Nervous System Development

MMP-9 is vital in the nervous system, especially for brain growth and plasticity. It modulates the ECM around neurons, which contributes to synaptic plasticity, learning and memory formation[11]. Furthermore, MMP-9 is involved in axon regeneration after nerve injury, which facilitates neuronal recovery[12].

Reproduction and Tissue Invasion

MMP-9 is also involved in reproductive processes, specifically ovulation and embryo implantation. It helps to degrade the follicular wall, which allows the oocyte to be released during ovulation[13]. During embryo implantation, MMP-9 assists in the invasion of the embryo into the uterine lining by remodelling the ECM, which is necessary for successful pregnancy Nothnick, 2008.

Pathological Role of MMP-9

When matrix metalloproteinase-9 (MMP-9) expression is abnormal, it plays an important role in a variety of pathogenic diseases. Overexpression or unregulated MMP-9 activity has been linked to tissue damage, inflammation and disease development in cancer, chronic wounds, cardiovascular illnesses and neurological disorders.

Cancer Progression and Metastasis

MMP-9 promotes cancer growth by degrading the extracellular matrix (ECM), which facilitates tumor invasion and metastasis. It causes the breakdown of the basement membrane, which serves as a barrier to tumor cell dissemination, allowing cancer cells to penetrate nearby tissues and spread to distant organs. MMP-9, in particular, has been found to promote angiogenesis, which is essential for supplying nutrients and oxygen to developing tumors. This enzyme also secretes bioactive compounds including vascular endothelial growth factor (VEGF), which promotes angiogenesis and tumor survival[14]. Furthermore, studies have established a direct relationship between high MMP-9 expression and poor prognosis in numerous malignancies, including breast, lung and colorectal tumors[15].

MMP-9's significance in the epithelial-to-mesenchymal transition (EMT), which allows epithelial cells to migrate and invade, has also been highlighted. By degrading ECM components and altering cell adhesion molecules, MMP-9 promotes the phenotypic alterations essential for EMT, allowing metastasis in many malignancies[16].

Chronic Wounds and Impaired Healing

MMP-9 is required for normal healing of wounds because it clears damaged tissue and speeds up the remodeling process. However, excessive or prolonged MMP-9 activity is harmful in chronic wounds, such as diabetic ulcers and venous leg ulcers. High levels of MMP-9 contribute to the breakdown of newly created ECM and critical growth factors, impeding the healing process and resulting in non-healing wounds. Persistent wounds exudates frequently demonstrate increased MMP-9 levels, which are associated with poor healing outcomes[17].

Targeted suppression of MMP-9 in chronic wounds can promote healing by minimizing excessive ECM breakdown and promoting tissue repair[18]. Strategies that reduce MMP-9 activity are being investigated as potential therapeutic approaches for chronic wound management.

Cardiovascular Diseases

MMP-9 has a pathogenic involvement in cardiovascular illnesses such atherosclerosis, myocardial infarction and aneurysm development. In atherosclerosis, MMP-9 contributes to the degradation of the fibrous cap of atherosclerotic plaques, making them more prone to rupture. Plaque rupture can cause thrombosis and other cardiovascular events such heart attacks or strokes[19]. Furthermore, MMP-9 participates in the remodeling of the vascular wall, encouraging aneurysm formation and contributing to arterial stiffness.

MMP-9 has also been linked to post-myocardial infarction remodeling, where severe ECM degradation can result in ventricular dilation and heart failure. Increased plasma levels of MMP-9 during myocardial infarction have been associated with worse cardiac outcomes[19].

Neurodegenerative Disorders

MMP-9 contributes to synaptic plasticity and neuronal healing in the central nervous system. However, its overexpression has been linked to neurodegeneration, particularly in Alzheimer's disease (AD) and multiple sclerosis (MS). MMP-9 has been associated to tight circuit protein breakdown in Alzheimer's disease, which increases blood-brain barrier permeability and promotes neuroinflammation. This exacerbates the development of amyloid-β plaques, a disease characteristic[20].

MMP-9 is linked to the collapse of the barrier between the blood and the brain during MS, enabling immune systems to get into the brain's nerve cells and destroy myelin, the protective sheath that surrounds neurons. Increased MMP-9 levels in the cerebrospinal fluid of MS patients associated with disease severity and progression[21].

Inflammatory Diseases

MMP-9 has an important role in several inflammatory disorders, including rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD). MMP-9 in RA contributes to cartilage degeneration by degrading collagen and proteoglycans, resulting in joint deformities and

discomfort. It also encourages the migration of inflammatory cells into the joint synovium, which worsens inflammation[22].

In COPD, MMP-9 is overexpressed in response to persistent pulmonary inflammation. It destroys the ECM in the alveolar walls, causing tissue damage and decreased lung function. High levels of MMP-9 in COPD patients have been associated with greater disease severity and exacerbation frequency.

MMP-9 Regulatory Mechanisms

Matrix metalloproteinase-9 (MMP-9) is closely regulated on several levels, including gene expression, zymogen activation, and inhibition by tissue inhibitors of metalloproteinases. This multi-layered control keeps MMP-9 activity in check to prevent excessive extracellular matrix (ECM) disintegration, which can cause pathological conditions like cancer metastasis, persistent wounds and inflammation.

Transcriptional Regulation

Various stimuli, such as cytokines, growth hormones and environmental stressors, predominantly influence MMP-9 expression through transcription. Activator protein-1 (AP-1), nuclear factor-kappa B (NF-κB) and specificity protein 1 (SP1) activate transcription of the MMP-9 gene by binding to its promoter's area.

AP-1 and NF-κB Pathways

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) activate the NF-κB pathway, which enhances MMP-9 gene transcription[23]. These cytokines also activate the AP-1 pathway, predominantly via the MAPK signaling cascade, which results in the creation of AP-1 complexes (c-Jun/c-Fos) that bind to the promoter and stimulate MMP-9 production. AP-1 and NF-κB enhance MMP-9 synthesis, particularly during inflammation and tumor growth[23].

Hypoxia and HIF-1α

MMP-9 expression is increased in hypoxic circumstances, which are common in tumor microenvironments and ischemic tissues. HIF-1α binds to hypoxia-responsive elements (HREs) in the MMP-9 promoter and increases transcription. This modulation encourages tissue remodeling and angiogenesis in hypoxic environments[24].

Post-Transcriptional Regulation

MMP-9 mRNA stability and translation are influenced by a variety of microRNAs. Several miRNAs, notably miR-21 and miR-29, have been demonstrated to directly target the MMP-9 3'-untranslated region (3'-UTR) and regulate its expression[25]. For example, miR-21 increases MMP-9 expression by inhibiting phosphatase and tensing homolog (PTEN), which activates the PI3K/AKT pathway and leads to MMP-9 overexpression. In contrast, miR-29 inhibits MMP-9 by directly targeting its mRNA and inducing destruction[26].

Zymogen Activation

MMP-9 is produced and released as an inactive zymogen (pro-MMP-9), which must be activated before it can function properly. Other proteases, such as MMP-2, plasmin, or neutrophil elastase, usually catalyze the cleavage of its pro-domain during activation. This proteolytic activation ensures that MMP-9 is only active in tissue conditions that require proteolytic activity, hence restricting its activity to specific locations[27].

Reactive oxygen species (ROS)

ROS can activate MMP-9 by causing oxidative alteration of the pro-domain, making it more vulnerable to proteolytic cleavage (Sun *et al*, 2020). This process is especially important in inflammatory situations, where high ROS levels coexist with tissue remodeling and inflammation[28].

Regulation by TIMPs

MMP-9 activity is directly suppressed by tissue inhibitors of metalloproteinases (TIMPs), specifically TIMP 1. TIMPs bind to MMP's active sites, generating a 1:1 complex that blocks MMP-9 from interacting with its substrates. The balance of MMP-9 and TIMP-1 is essential for maintaining ECM homeostasis. An imbalance in MMP-9 activity compared to TIMP-1 levels might result in excessive ECM breakdown, whereas elevated TIMP-1 levels can inhibit normal tissue remodeling[29].

TIMP-1 Modulation

Inflammatory mediators and growth factors both control TIMP-1 expression. Interestingly, TIMP-1 not only suppresses MMP-9 but also regulates its gene expression via feedback processes, resulting in a finely tuned MMP control system[30].

Epigenetic Regulation

Epigenetic processes such as DNA methylation and histone changes also help to regulate MMP-9 production. Hypermethylation of the MMP-9 promoter region reduces expression, whereas hypomethylation increases expression. Histone acetylation, mediated by histone acetyltransferases (HATs), can also boost the accessibility of transcription factors to the MMP-9 promoter, hence enhancing its expression[31].

Regulation by Integrins and Cell Adhesion Molecules

MMP-9 activity is further influenced by its interactions with integrins and cell adhesion molecules on the cell surface. Integrins like αvβ3 and α2β1 interact with MMP-9, leading to its recruitment on the cell surface and regulated destruction of the extracellular matrix. These interactions are especially significant in cancer cell invasion and migration[32].

Therapeutic Effects of MMP-9 Inhibitors

The suppression of MMP-9 has therapeutic potential in a variety of diseases and disorders. MMP-9 plays an important function in tissue remodeling, inflammation and extracellular matrix breakdown. The inhibitors described in Table No.1 have detailed therapeutic effects, which are provided below.

Small Molecule Inhibitors (Sulfonamide and Thiadiazine)

Small compounds, such as sulfonamide and Thiadiazine derivatives, effectively target MMP-9 by binding to its active site and reducing its enzymatic activity. This inhibition is advantageous in cancer, as MMP-9 promotes metastasis by destroying the extracellular matrix. MMP-9 leads to tissue damage and persistent inflammation in inflammatory disorders (e.g., rheumatoid arthritis, Crohn's disease), hence blocking it helps alleviate these symptoms. Furthermore, these inhibitors help with wound healing, especially in diabetic foot ulcers and chronic wounds, by limiting excessive tissue breakdown and supporting normal tissue regeneration.

Cancer

These compounds inhibit MMP-9, preventing tumor cell invasion and metastasis. They prevent the degradation of collagen and other extracellular matrix components, which are crucial in cancer growth[33].

Inflammatory Diseases

MMP-9 plays an important part in inflammatory reactions by breaking down tissue in response to injury. Sulfonamide and Thiadiazine-based inhibitors assist minimize tissue degradation in chronic inflammatory illnesses, such as rheumatoid arthritis[34].

Wound Healing

MMP-9 over activity causes delayed wound healing, particularly in diseases such as diabetes. Inhibitors speed up wound closure by controlling matrix remodeling and minimizing excessive degradation[35].

Monoclonal Antibodies Targeting MMP-9

Monoclonal antibodies directed at MMP-9 provide a highly selective and effective suppression of its function. These antibodies are useful because they can selectively target MMP-9 while minimizing off-target effects. Their therapeutic effects are observed across a variety of diseases:

Cancer

MMP-9 helps cancer cells infiltrate surrounding tissues and disseminate to distant organs. Monoclonal antibodies that inhibit MMP-9 prevent invasion and limit metastatic potential, increasing overall survival[36].

Wound Healing

By suppressing MMP-9, these antibodies promote wound closure and tissue repair in chronic wounds, such as diabetic foot ulcers[35].

Inflammatory Diseases

Monoclonal antibodies against MMP-9 improve joint damage in rheumatoid arthritis by inhibiting

excessive matrix disintegration during inflammation[37].

Peptide-Based Inhibitors (Peptoids)

Peptoid-based inhibitors are a new type of small chemical that shares the structure and activity of peptides. These inhibitors effectively bind to MMP-9's active site, inhibiting its capacity to breakdown the extracellular matrix.

Cancer

Peptoid inhibitors provide a focused strategy to cancer treatment by limiting matrix degradation and tumor spread. They effectively limit metastasis by reducing MMP-9's enzymatic activity[35].

Wound Healing

Peptoids, like other MMP-9 inhibitors, accelerate wound healing by limiting excessive matrix breakdown and supporting normal tissue repair processes[38].

Inflammatory Diseases

By inhibiting MMP-9, these inhibitors can minimize tissue damage caused by chronic inflammation, particularly in rheumatoid arthritis[39].

Nanoparticle-Based Inhibitors

Nanoparticle-based methods provide tailored delivery of MMP-9 inhibitors, increasing their efficacy while limiting side effects. The use of nanoparticles to administer MMP-9 inhibitors is an emerging field of study, particularly in cancer and wound healing.

Cancer

These technologies improve the selectivity and bioavailability of MMP-9 inhibitors, enabling direct administration to tumor locations. This focused method helps to reduce tumor invasiveness and metastasis[38].

Wound Healing

Nanoparticle-based inhibitors provide regulated release at the wound site, promoting faster and more efficient tissue regeneration, particularly in chronic wounds[36].

Natural Product-Derived Inhibitors (e.g., Curcumin)

Curcumin is a natural substance that has been identified as a powerful MMP-9 inhibitor. Curcumin, a turmeric-derived substance, suppresses MMP-9 while also acting as an anti-inflammatory and antioxidant.

Cancer

Curcumin inhibits MMP-9, which reduces cancer cells capacity to spread. Its multi-target activity makes it a promising addition to cancer therapy[35].

Wound Healing

Curcumin, a natural MMP-9 inhibitor, helps to speed up wound healing by lowering collagen degradation and promoting tissue regeneration in chronic wounds, such as those seen in diabetes patients[39].

Inhibitory RNAs (siRNA for MMP-9)

Small interfering RNAs (siRNAs) that precisely target MMP-9 have been created as a gene therapy technique. MMP-9 expression is silenced with siRNAs, which prevents its negative impact in a variety of disorders.

Cancer

By downregulating MMP-9 expression, siRNA therapies reduce tumor cell invasion and metastatic spread, improving cancer treatment outcomes[36].

Cardiovascular Diseases

SiRNAs that target MMP-9 in cardiovascular disease can avoid arterial remodeling and rupture by modulating matrix degradation[35].

Wound Healing

Silencing MMP-9 in wound sites can promote faster healing by preventing excessive matrix breakdown and tissue destruction[39].

MMP-9 as a Biomarker for Disease Diagnosis and Prognosis

Matrix metalloproteinase-9 (MMP-9), also known as gelatinase B, is a key enzyme in extracellular matrix (ECM) degradation and tissue remodeling. It is involved in several physiological processes, including embryogenesis, wound healing and angiogenesis. However, its dysregulation is significantly linked to a number of pathological illnesses, including cancer, cardiovascular disease, chronic inflammatory diseases and neurological disorders. Given its importance in these processes, MMP-9 has emerged as a possible biomarker for illness diagnosis, prognosis and treatment monitoring. The next sections go over MMP-9's

diagnostic and prognostic significance in various conditions.

Cancer

MMP-9 is well recognized as a cancer biomarker, with overexpression associated to tumor growth, invasion, metastasis, and angiogenesis. MMP-9 promotes the breakdown of ECM components, allowing cancer cells to penetrate adjacent tissues and spread to distant organs.

Diagnostic Marker in Cancer

MMP-9 levels in serum or plasma are elevated in a variety of cancer types, including breast, colorectal, lung and prostate. MMP-9 levels have been linked to disease progression and a poor prognosis in breast cancer, with greater levels indicating aggressive phenotypes and metastasis (Li *et al*, 2019). A meta-analysis of various cancer research revealed that MMP-9 may serve as a viable biomarker for cancer detection and early diagnosis[40].

Prognostic Value

MMP-9 levels have been linked to poor clinical outcomes, such as lower survival rates and an increased risk of metastases in certain malignancies. For example, in non-small cell lung cancer (NSCLC), higher MMP-9 levels are associated with advanced-stage tumors and a poor prognosis[41]. Similarly, in colorectal cancer, elevated MMP-9 expression indicates enhanced invasive potential and a higher risk of recurrence. As a result, MMP-9 functions as both a diagnostic and prognostic marker in many cancers, assisting in risk stratification and treatment decision-making[42].

Cardiovascular Diseases

MMP-9 is implicated in the pathogenesis of several cardiovascular disorders, most notably atherosclerosis and heart failure. The enzyme contributes to plaque instability, which increases the risk of plaque rupture and subsequent cardiovascular events.

Atherosclerosis and Acute Coronary Syndromes

Elevated MMP-9 levels in atherosclerosis patients are associated with plaque instability and rupture susceptibility. Studies have indicated that patients with acute coronary syndromes (ACS), such as myocardial infarction, have considerably greater blood MMP-9 levels than those with stable coronary artery disease. MMP-9 can be used as a biomarker to predict plaque rupture and acute cardiovascular events[43].

Heart Failure

MMP-9 leads to unfavorable cardiac remodeling, which is defined by the breakdown of ECM components, resulting in fibrosis and left ventricular dysfunction. MMP-9 levels in plasma have been found to be elevated in heart failure patients, which is related with poor clinical outcomes and an increased risk of hospitalization and death (Kwon et al., 2020). MMP-9 thus provides predictive significance in identifying patients with a higher probability of bad outcomes in heart failure[44].

Neurological Disorders

MMP-9 disrupts the blood-brain barrier (BBB) and causes neuronal damage, making it a possible biomarker in neurological illnesses such multiple sclerosis (MS), stroke, and Alzheimer's disease (AD).

Stroke

In ischemic stroke, MMP-9 contributes to the breakdown of the BBB, exacerbating brain damage and facilitating hemorrhagic transformation. Elevated MMP-9 levels in cerebrospinal fluid (CSF) and serum have been linked to poorer clinical outcomes in stroke patients, such as increased infarct size, hemorrhagic transformation and poor neurological recovery. MMP-9 is consequently regarded as a valuable predictive marker for stroke severity and recovery[45].

Multiple Sclerosis

MMP-9 contributes to the etiology of MS by increasing leukocyte migration across the BBB and causing demyelination and axon destruction. MMP-9 levels in serum and cerebrospinal fluid have been found to be elevated in individuals with relapsing-remitting multiple sclerosis (RRMS), particularly during relapse episodes. MMP-9 levels are therefore being examined as a measure of disease activity and responsiveness to treatment in MS patients[46].

Chronic Inflammatory Diseases

MMP-9 plays an important function in ECM breakdown and tissue remodeling in chronic inflammatory disorders such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), which contribute to disease progression.

COPD

MMP-9 has a role in the development of COPD by destroying alveoli and remodeling the airways. Elevated levels of MMP-9 in sputum, bronchoalveolar lavage (BAL) fluid, and serum have been linked to greater disease severity and airflow limitation in COPD patients. MMP-9 has thus been proposed as a biomarker for evaluating disease progression and therapy response in COPD[47].

Rheumatoid arthritis (RA)

MMP-9 contributes to cartilage deterioration and joint degeneration. MMP-9 levels in serum and synovial fluid have been found to correlate with disease activity and severity in people with RA. Higher MMP-9 levels, in particular, are linked to more aggressive illness and increased joint injury. As a result, MMP-9 functions as both a diagnostic and prognostic marker in RA, guiding therapy decisions and tracking disease progression[48].

Diabetic Complications

MMP-9 has a role in the pathogenesis of diabetic complications, specifically diabetic nephropathy and diabetic foot ulcers, by contributing to ECM remodelling and tissue destruction.

Diabetic Nephropathy

Patients with diabetic nephropathy have elevated urine MMP-9 levels, which are linked to glomerular basement membrane breakdown and podocyte injury. MMP-9 levels have been linked to higher albuminuria and more severe kidney damage, making it a promising biomarker for detecting and predicting the course of diabetic nephropathy[49].

Diabetic Foot Ulcers

In diabetic wound healing, MMP-9 is involved in excessive ECM breakdown, which impairs healing and leads to chronic wound development. MMP-9 levels were shown to be elevated in the wound fluid of individuals with non-healing diabetic foot ulcers, which were linked to poor wound healing outcomes. Thus, MMP-9 acts as a predictive marker for wound healing in diabetes patients, assisting doctors in identifying individuals at risk for chronic, non-healing wounds[50].

Future Perspectives and Challenges in MMP-9 Research and Therapeutics

Matrix metalloproteinase-9 (MMP-9) remains a focus of research in both basic and clinical sciences due to its important role in a variety of physiological and pathological processes, particularly in disease progression such as cancer metastasis, cardiovascular disease, and chronic inflammation. Despite decades of research, there are still significant hurdles to completely understanding MMP-9's molecular roles and efficiently addressing it therapeutically. This section discusses future views and the hurdles that must be overcome in order to fully realize MMP-9's promise as a biomarker and therapeutic target.

Precision Medicine and Personalized Therapy

One of the growing topics in MMP-9 research is its incorporation within the context of precision medicine. MMP-9 expression and activity vary among individuals and disease situations, implying that MMP-9 therapy must be tailored to the individual. Identifying the genetic and epigenetic mechanisms that control MMP-9 expression in various populations and disease states is critical for designing individualized treatment options.

Genomic and epigenomic Insights

Future study should investigate how genetic variations in the MMP-9 gene or its promoter regions influence illness risk and treatment responses. For example, single nucleotide polymorphisms (SNPs) in the MMP-9 gene have been linked to variable risks of cardiovascular disease and cancer in different populations. (Blankenberg *et al*, 2003[51]. Epigenetic changes, such as DNA methylation or histone acetylation, may similarly affect MMP-9 production, complicating its role as a diagnostic and therapeutic target[52].

Tailored Therapeutic techniques

As we gain a better knowledge of these genetic and epigenetic factors, developing tailored therapeutic techniques to target MMP-9 will become increasingly important. For example, some patients may benefit more from direct MMP-9 inhibitors, while others may respond better to medicines that target upstream regulators, such as microRNAs or transcription factors that govern MMP-9 expression[53].

Development of Selective MMP-9 Inhibitors

One of the most serious issues in MMP-9 therapy is the lack of selectivity among existing MMP inhibitors. Broad-spectrum MMP inhibitors frequently cause undesirable side effects because they block other MMPs involved in normal physiological functions like tissue healing and immunological control. Developing selective inhibitors that target only MMP-9 while sparing other MMPs remains an important aim.

Structural and functional insights

In order to build more selective inhibitors, we must first get a better understanding of MMP-9's structural biology. Recent advances in cryo-electron microscopy and X-ray crystallography have permitted molecular studies of MMP-9, revealing the protein's particular active sites and regulatory regions. These findings will help in the development of small-molecule inhibitors or monoclonal antibodies that preferentially bind to MMP-9, decreasing off-target effects[54].

Biological Agents and Antibodies

Future study could concentrate on biological agents such monoclonal antibodies, which have showed potential in selectively targeting MMP-9. For example, GS-5745, a monoclonal antibody that targets MMP-9, has showed promising outcomes in preclinical tests for cancer and inflammatory illnesses. However, there are still hurdles to optimizing the dose, administration, and long-term safety of these medicines in clinical settings[55].

MMP-9 in Tissue-Specific Pathologies

MMP-9 is involved in a variety of disorders, however its function varies greatly depending on the tissue and disease environment. One key difficulty moving forward is better understanding MMP-9's tissue-specific activities, particularly in illnesses where it promotes and inhibits disease development.

Cancer and Tumor Microenvironment

MMP-9 has a well-established role in cancer, promoting tumor invasion and metastasis; however, recent studies have revealed that MMP-9 can also exhibit antitumor effects in certain contexts, such as promoting immune infiltration and activating anti-tumor immunity. This duality complicates therapeutic targeting because blocking MMP-9 may accidentally diminish the body's immunological response to tumors. Future study should focus on determining when MMP-9 promotes cancer progression and when it may play a preventive role[56].

Cardiovascular Diseases

MMP-9 has an important role in ECM remodeling in cardiovascular disorders, which can be beneficial or harmful depending on the illness stage and tissue environment. For example, MMP-9 has been demonstrated to contribute to plaque rupture in atherosclerosis, which can lead to severe cardiovascular events. However, in the early phases of atherosclerosis, MMP-9 may promote positive adaptive remodeling. The problem is timing the therapeutic intervention-targeting MMP-9 too early may impede required remodeling, while postponing intervention may allow for pathological ECM disintegration[57].

Diagnostic and Prognostic Biomarkers

Another potential objective is to improve the diagnostic and prognostic capabilities of MMP-9 as a biomarker. Although higher MMP-9 levels have been linked to disease severity in a variety of illnesses, MMP-9's specificity and sensitivity as a biomarker remain limited. For example, high MMP-9 levels are found in a range of disorders, making it difficult to distinguish between distinct pathologies based solely on MMP-9 levels.

Combining Biomarkers

To improve diagnosis accuracy, future research should look into combining MMP-9 with other biomarkers to create biomarker panels that can

more accurately reflect certain diseases or states. For example, combining MMP-9 with inflammatory cytokines, growth factors, or ECM degradation products may provide a more complete picture of disease development and response to therapy[58].

Non-Invasive Biomarker Testing

Another promising area for expansion is the development of non-invasive or minimally invasive testing methods for assessing MMP-9 levels in patients. Currently, MMP-9 levels are frequently tested using blood or tissue biopsies, which can be invasive and inconvenient for routine monitoring. Future study should look into the viability of detecting MMP-9 in bodily fluids including urine, saliva, or exhaled breath condensate, which could lead to easier and more frequent monitoring Martu *et al*, 2022)[59].

Overcoming Therapeutic Resistance

Therapeutic targeting of MMP-9 has often resulted in resistance or poor success. One possible explanation is the activation of compensatory mechanisms that can overcome MMP-9 suppression. In cancer, blocking MMP-9 may cause the overexpression of other proteases, such as MMP-2 or MMP-14, which can continue ECM destruction and tumor invasion.

Combination Therapies

To overcome resistance, future therapeutic options may require the combination of MMP-9 inhibitors and additional medicines targeting complimentary pathways. Combining MMP-9 inhibitors with immunotherapies, such as checkpoint inhibitors, can improve antitumor responses by targeting MMP-9's proteolytic and immune-modulatory roles. Additionally, targeting other ECM-degrading enzymes with MMP-9 may limit the activation of compensatory mechanisms, hence boosting therapeutic effects[60].

Targeting Upstream Regulators

Targeting upstream regulators of MMP-9 expression, such as transcription factors like NF-κB and AP-1 or microRNAs like miR-21 and miR-146a, is a potential approach (Ravi *et al*, 2021). Targeting the signaling mechanisms that control MMP-9 expression may allow for better long-term therapeutic effects while limiting compensatory overexpression of other proteases (Shen *et al*, 2015)[61].

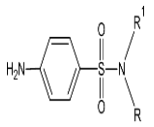
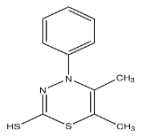
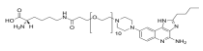
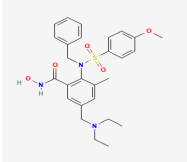
Table No.1: Vertebrate members of the matrix in family

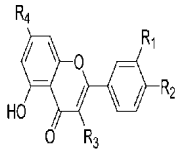
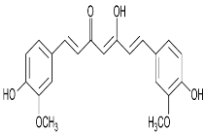
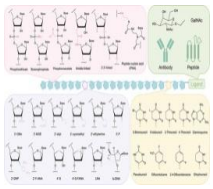
S.No	Protein	MMP	Domain composition
1	Collagenase 1	MMP-1	B
2	Gelatinase A	MMP-2	C
3	Stromelysin 1	MMP-3	B
4	Matrilysin	MMP-7	A
5	Collagenase 2	MMP-8	B
6	Gelatinase B	MMP-9	D
7	Stromelysin 2	MMP-10	B
8	Stromelysin 3	MMP-11	E
9	Macrophage elastase	MMP-12	B
10	Collagenase 3	MMP-13	B
11	MT1-MMP	MMP-14	F
12	MT2-MMP	MMP-15	F
13	MT3-MMP	MMP-16	F
14	MT4-MMP	MMP-17	F
15	Collagenase 4 (*Xenopus*)	MMP-18	B

16	(No trivial name)	MMP-19	B
17	Enamelysin	MMP-20	B
18	XMMP (*Xenopus*)	MMP-21	G
19	CMMP (chicken)	MMP-22	B
20	(No trivial name)	MMP-23	H

(Nagaset and Woessner, 1999)

MMP-9 inhibitors and their patents with chemical structures

S.No	Category	Patent	MMP-9 Inhibitor Type	Structures	Disorders Treated	Patent number	Sources
1	Small Molecule Inhibitors	Sulfonamide Derivatives	Synthetic Small Molecule		Cancer, Inflammatory Diseases, Cardiovascular Disorders, Wound Healing	US 8507009B2 (2013)	Shi Z, Li J, Shi L, discovery, X. L. on anti-cancer drug, 2012, undefined, (2012). An updated patent therapeutic agents targeting MMPs.
2		Thiadiazine Derivatives	Synthetic Small Molecule		Cancer, Inflammatory Diseases, Cardiovascular Disorders, Wound Healing	WO 2012045811A1 (2012)	Khare T, Palakurthi S, Shah B S. P.-I. Journal of, 2020, undefined. (2020). Natural product-based nanomedicine in treatment of inflammatory bowel disease.
3	Monoclonal Antibodies	Humanized Monoclonal Antibodies	Antibody-Based		Cancer, Inflammatory Diseases, Wound Healing	US 8664537B2 (2014)	Goffin L, Fagagnini S, Vicari A C M.-I. bowel, 2016, undefined. (2016). Anti-MMP-9 antibody: A promising therapeutic strategy for treatment of inflammatory bowel disease complications with fibrosis.
4	Peptide-Based Inhibitors	Peptoid MMP-9 Inhibitors	Peptide-based Small Molecule		Cancer, Inflammatory Diseases, Wound Healing	WO 2013028305A1 (2013)	Austin M J, Schunk H, Watkins C, Ling N, Chauvin J, Morton L, Rosales A M. (2022). Fluorescent Peptomer Substrates for Differential Degradation by Metalloproteases.

5	Nanoparticle-Based Inhibitors	MMP-9 Inhibiting Nanoparticles	Nanoparticle-based Inhibitors		Cancer, Inflammatory Diseases, Wound Healing	US 9795609B2 (2017)	Fan C, Joshi J, Li F, Xu B, Khan M, Yang J, Zhu W. (2020). Nanoparticle-Mediated Drug Delivery for Treatment of Ischemic Heart Disease
6	Natural Product Derivatives	MMP-9 Inhibitors from Natural Products (e.g., Curcumin)	Natural Product-Derived		Inflammatory Diseases, Cancer, Wound Healing	US 8143290B2 (2012)	Wang Z, Liu Z, Qu J, Sun Y, Zhou W. (2024). Role of natural products in tumor therapy from basic research and clinical perspectives
7	Inhibitory RNAs	Small Interfering RNA (siRNA) for MMP-9	RNA-Based		Cancer, Cardiovascular Diseases, Neurodegenerative Diseases, Wound Healing	US 20170323920A1 (2017)	Almarghalani, D, therapy Z S G, 2023, undefined. (2023). Progress on siRNA-based gene therapy targeting secondary injury after intracerebral hemorrhage.

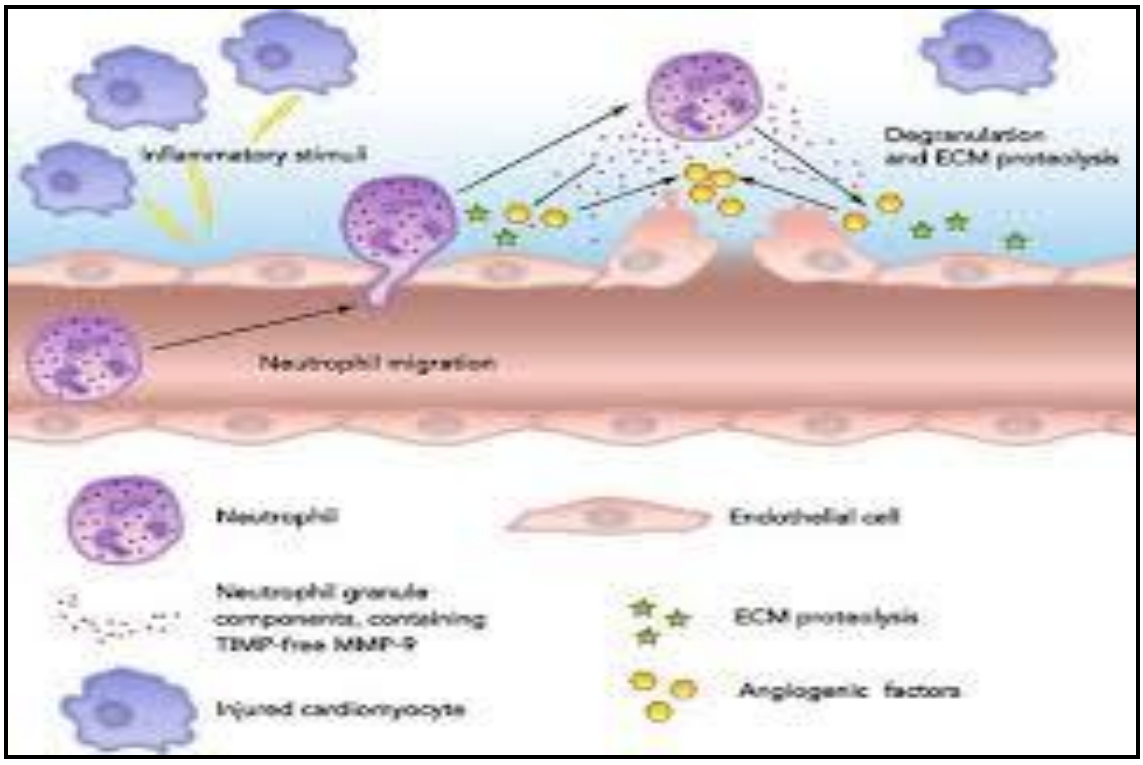


Figure No.1: Physiological Role of MMP-9

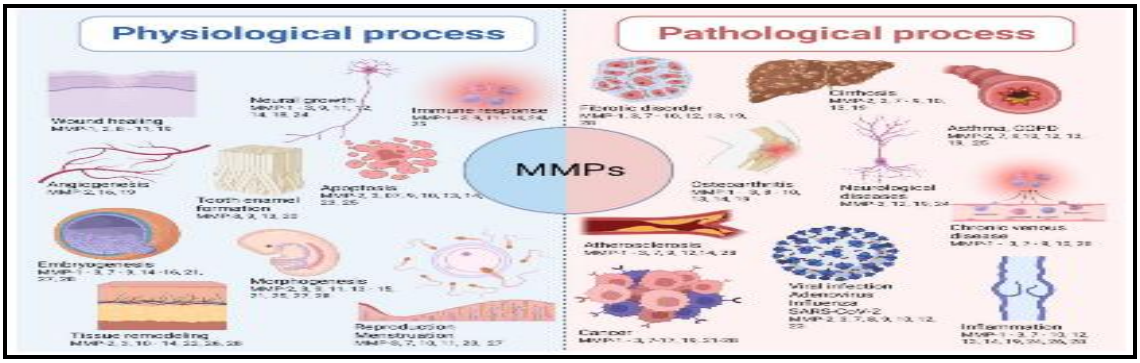


Figure No.2: Pathological Role of MMP-9

CONCLUSION

Matrix metalloproteinase-9 (MMP-9) is an important player in both normal physiological processes and disease progression, making it a prospective target for therapeutic intervention as well as a diagnostic and prognostic biomarker. Despite the introduction of MMP-9 inhibitors and other therapeutic techniques, obstacles like as selectivity, off-target effects and tissue-specific functions impede therapeutic targeting. MMP-9's potential as a biomarker for early illness identification and therapy response is intriguing. Moving forward, more precise drug design and non-invasive diagnostic approaches are required. Further research is required to fully realize MMP-9's potential in clinical settings.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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