Biochemical features, pathophysiology and medicalsignificance of Matrix Metalloproteinase-9 (MMP-9): a review article

Abstract :

Matrix metalloproteinase (MMP)-9 (also known as gelatinase B) is a member of the MMP family of endopeptidases (zinc-dependent) that has been connected with tumor cell invasion and metastasis and tumor-induced angiogenesis, through its ability to remodel the extracellular matrix. Under physiological conditions, MMP-9 provides tissue homeostasis by controlling matrices degradation involved in different types of physiological processes such as wound healing process, angiogenesis, immune cell migration and regulation of tissue repair activity. On the contrary, deregulated expression and excessive activation of MMP-9 have been implicated in the pathogenesis of many diseases such as chronic inflammatory disorders, cardiovascular diseases, neurodegenerative disease. fibroses and cancers. MMP-9 is implicated in leukocyte infiltration and activation of inflammatory cytokines, disruption of basement membrane integrity, and increased pathological tissue remodeling. In oncology, up-regulation of MMP-9 expression is closely related to the tumor invasion/metastasis/angiogenesis and poor clinical prognosis which makes it an attractive diagnostic and therapeutic target. In a similar manner, elevated MMP-9 activity has been associated with the exacerbation of rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, diabetic complications and neurological disorders involving continuous degradation of the extracellular matrix and persistent inflammation. In addition to its pathological roles, MMP-9 has emerged as a potential biomarker for disease diagnosis, prognosis and monitoring of therapeutic responses because of its close association with severity/extentofpathological processesand tissue remodeling. Improved understanding of the biology of macrophage MMP-9 has enabled recent advances in molecular biology for a selective approach to MMP-9 inhibition (e.g. monoclonal antibodies, RNA-based therapeutics and nanotechnology-assisted drug delivery systems) for curbing pathological MMP-9 but at the

same time not interfering with physiological functions. However, difficulties still exist concerning selective inhibition, potential off-target effects and the fact that MMP-9 has context-dependent biological functions in various tissues at distinct time points during disease. Investigation of the molecular mechanisms underlying MMP-9 regulation with both inflammatory cytokines, growth factors, and tissue inhibitors of metalloproteinases (TIMPs) will enhance our understanding of its biological relevance, and allow the development of rationally designed, targeted therapies for inflammatory, fibrotic, and neoplastic disease states.
Keywords:MMP-9, ECM, TIMPs, VEGF, DMD

Introduction

Matrix metalloproteinase-9 (MMP-9),is a Zn^{+2} dependent endopeptidase that is synthesized and secreted in monomeric form as zymogen. It belongs to the MMPfamily, which is a large family of structurally similar enzymes that degrade substrates of extracellular matrix (ECM) (Patil & Kundu, 2006). The MMP-9 is released from different cell types like neutrophils, macrophages, fibroblasts, keratinocytes and endothelial cells; it significantly influences both physiological tissue homeostasis and pathophysiological processes associated with inflammation, fibrosis and tumorigenesis (Kessenbrock et al., 2010). It has been shown that under normal conditions, MMP-9 plays a critical role in embryonic development, wound healing and immune surveillance by tightly regulating its proteolytic activity. Dysregulation of it has been implicated in the pathogenesis of several diseases, such as cardiovascular disorders, neurodegenerative diseases, autoimmune diseases and malignancies; therefore, there is great interest within the biomedical research community (Rashid &Bardaweel, 2023).

The MMP-9 consists of complex protein with three functional domains: the N-terminal propeptide domain, the catalytic domain, and the C-terminal, the hemopexin-like domain. MMP-9 is synthesized in an inactive form, also known as zymogen (pro-MMP-9), and has to be cleaved by additional proteases, including MMP-2,kPlasmin or trypsin-like proteases for activation (Mathpalet al., 2022). Upon activation, MMP-9 cleaves ECM proteins such as type IV collagen, gelatin, and elastin to promote cell migration, tissue invasion, and angiogenesis. In addition to its canonical ECM-degrading functions, MMP-9 performs pleiotropic effects by cleaving a wide variety of non-ECM substrates, including cytokines, chemokines,

growth factors and cell surface receptors in such a way that multiplies its ability to regulate pathways associated with cell signaling and inflammation(Kessenbrock et al., 2010; Mondal et al., 2020).

In cardiovascular disease (CVD), MMP-9 is recognized as an important mediator of pathological remodeling (Halade et al., 2013). Serum MMP-9 levels are a poor outcome predictor in acute inflammatory syndromes (examples: COVID-19); with ranges (most extreme vs non-extreme patients give large difference (Ding et al., 2023). Chronically elevated levels of MMP-9 and MMP-9/TIMP-1 ratios in patients with chronic obstructive pulmonary disease (COPD) have been associated with the FEV1 level (estimated by HDM challenge) supporting a role for MMP−9 in airway remodeling leading to functional decline (Dimic-Janjic et al., 2023). All data for this meta-analysis and Mendelian randomization analysis, demonstrating a causal, and thus likely direct, association of MMP-9 expression with thoracic and abdominal aortic aneurysm risk, support the potential for proteolytic imbalance as a mechanism for structural vascular failure. Hence, these data effectively place MMP-9 into dual roles as a marker of matrix repair turnover and a mechanistic effector for acute injury, chronic remodeling and progressive organ dysfunction(Qin et al., 2024).

MMP-9 has a strong clinical relevance, especially in oncology and cancer therapy. MMP-9 has been found to be strongly overexpressed in a variety of malignant tumors including colorectal cancer, breast cancer, gastric cancer and melanoma where it aids tumor angiogenesis, interrupts intercellular ECM bind, and helps in invasion & metastasis of the cancer cell (Kessenbrock et al., 2010; Rashid &Bardaweel, 2023). The expression of MMP-9 mRNA and protein in cancer tissue was significantly higher than that in pericardial carcinoma tissue, and the intensity of MMP-9 expression increased with lymphatic metastasis and tumor pathological stage in head and neck cancers such as hypopharyngeal carcinoma (Chen & Xu, 2022). Moreover, MMP-9 plays a role in psoriatic pathogenesis via activating vascular endothelial cells, recruiting inflammatory cells and modulating keratinocyte proliferation through ERK-1/2 and p38/MAPK signaling pathway (Baran et al., 2022). MMP-9 has been repeatedly shown to promote adaptation of tumor cells to the microenvironment of distant tissues by mediating infiltration of tumor cells into foreign tissue and release from the ECM of protumorigenic factors (Deryugina& Quigley, 2015).

The MMP-9 is positioned as a central catalyst of remodeling extracellular matrix (ECM), due to its extracellular localization and enzymatic accessibility, in comparison to conventional intracellular kinases or transcription factors (Wolosowicz et al., 2025). The approachability of its catalytic pocket and auxiliary domains permits therapeutic modalities such as small-molecule zinc chelators, domain-selective inhibitors, engineered TIMPs, and monoclonal antibodies (Rashid &Bardaweel, 2023). Moreover, in case of MMP-9 activity quantification; biofluids including plasma and CSF provide basic resources for non-invasive monitoring of MMP-9 levels, which may facilitate its investigation as a putative biomarker in disease severity, prognosis and therapy response. However, although MMP-9 has been evaluated as a promising therapeutic target for cancer due to its pro-tumorigenic properties, several challenges regarding specificity of inhibitors and off-target toxicity as well as context-specific functions of MMP-9 in different microenvironments in the same tissue have limited preclinical and clinical translation (Mondal et al., 2020). We summarize the biochemical properties, pathophysiology and clinical relevance of MMP-9 in the context of its increased recognition as a diagnostic biomarker and therapeutic target in numerous diseases.

MMP-9 in Tissue Homeostasis and Pathological Remodeling Many pathological conditions are related to MMP-9 such as tumor-induced angiogenesis, metastasis and invasion of tumor cells (Vandooren et al., 2013). The MMP-9 has an N-terminal propeptide domain with the cysteine-switch motif, a zinc-binding catalytic domain, three fibronectin type II repeats binding denatured collagen and elastin substrates and a hemopexin-like C-terminal domain governing substrate specificity and inhibition by tissue inhibitors of metalloproteinases (TIMPs) (de Almeida et al., 2022). The structural basis of MMP-9 presents the opportunity to cleave connective tissue substrates including type IV/V collagens, gelatin and fibronectin; all of which are essential aspects of physiological process such as embryonic development, wound healing, angiogenesis and leukocyte trafficking (Chakrabarti et al., 2005). The MMP-9 expression and activation is well-regulated, through transcription regulation, zymogen latency, and inhibition by tissue inhibitors of metalloproteinases (TIMPs), so as a result, the ECM remodeling occurs spatially and temporally restricted(Caley et al., 2015).

MMP-9 is involved in the regulated proteolytic turnover of matrix to maintain epithelial and vascular integrity in tissue homeostasis. MMP9 is upregulated during wound healing for a brief period to clear fibrin clots and also coordinates the mobilization of keratinocytes from the wound bed margin across the clot in an essential step for re-epithelialization (Caley et al., 2015). MMP-9 localized at synapses in neurons influences glutamatergic transmission by remodeling dendritic spines during synaptic plasticity processes in the CNS and is essential for learning, memory, and cortical plasticity (Rękość et al., 2024). The enzyme further regulates angiogenesis through the release of matrix-bound vascular endothelial growth factor (VEGF) and in generating conditions for the migration and lumen formation of endothelial cells (Dimic-Janjic et al., 2023). These key homeostatic processes underscore the necessity of tight control of MMP-9 activity for normal physiology of the tissues.

Conversely MMP-9 can become a pathological effector instead of a physiological mediator when its regulation is disturbed. Ongoing or exaggerated MMP-9 activity causes maladaptive tissue remodelling defined by excessive ECM degradation, barrier dysfunction and chronic inflammation. Notably, both increased serum levels of MMP-9 and increased MMP-9/TIMP-1 ratios correlate with decreased values of FEV1, a crucial measure that represents airway wall thickening, subepithelial fibrosis and further airflow limitation in chronic obstructive pulmonary disease (COPD) patients [9] (Dimic-Janjic et al., 2023). Similarly, alveolar macrophages in asthma overexpress MMP-9 compared to its inhibitor TIMP-1 in a manner that enhances airway hyperresponsiveness and predicts rapid lung function decline over time (Lommatzsch et al., 2019). In a 2024 Mendelian randomized analysis, the authors provide evidence that increased MMP-9 expression is causally associated with thoracic and abdominal aortic aneurysm, suggesting a role for proteolytic imbalance in the structural failure of vascular tissue that is central to cardiovascular disease. These data are being that MMP-9 is a marker of matrix turnover not only during but also plays an active role on disease progression(Qin et al., 2024).

atrix metalloproteinases (MMPs), and specifically MMP-9, have well-established functional roles in normal physiology and in the pathobiology of a number of diseases. In fact, it is the dysregulation of MMP activity, for example during fibrotic disorders, that has been proposed as a cause of progressive tissue destruction, leading to the notion of a vicious in

maintaining inflammation and scar tissue formation. In pulmonary fibrosis, MMP-9 promotes pathological fibroblast activation and disorganized alveolar remodeling and transitions adaptive repair into progressive organ failure (Shen et al., 2025). In rheumatoid arthritis, synovial fibroblasts and infiltrating neutrophils release high amounts of MMP-9, leading to accelerated cartilage erosion and joint destruction (Rashid &Bardaweel, 2023). Thereby, the enzyme also produces bioactive ECM fragments which is called (matrikines)and propagates inflammatory signaling and fibroblast recruitment, thus creating a self-sustained loop of tissue damage (Määttä et al., 2025). Dysregulated MMP-9 in the central nervous system (CNS) promotes blood-brain barrier injury, and is involved in leukocyte trafficking and neuroinflammation in diseases such as multiple sclerosis, stroke, traumatic brain injury (Rękość et al., 2024).

Although MMP-9 is a key player in homeostasis, dysregulated activity may lead to destruction of both normal and neoplastic tissues which presents enormous obstacles for future therapeutic targeting. Broad-spectrum, non-selective MMP inhibitors have endeavored and failed in clinical trials due to a myriad of factors that include lack of selectivity, toxicity, tolerability issues with systemic therapy, and interference with natural physiological tissue repair (Rashid &Bardaweel, 2023). Consequently, this has shifted an interest toward indirect modulation strategies—statins, angiotensin II receptor blockers, sub-antimicrobial dose doxycycline and glucocorticoids—that target the upstream signaling (+) pathways that attenuate MMP-9 expression while maintaining its transient reparative functions (Määttä et al., 2024).

MMP-9 as a Driver of Cancer Invasion, Metastasis, and Angiogenesis

One of the most differentially important aspects of cancer biology is the way in which non-invasive malignant tumors move into invasive tumor metastasis. Matrix metalloproteinase-9 (MMP-9) has been defined to be the catalyzing enzyme of this metastatic process, known to drive the migration and invasion of tumor cells(Xu et al., 2010). The MMP9 promotes the invasion of cancer cells by degrading components of basement membranes (Collagen, gelatin and last but not least laminin) that are actually physical barriers that restrict epithelial cells to its processing tissue (Kessenbrock et al., 2010). This proteolytic activity not only spares structural matrix components but MMP-9 also processes a wide variety of non-matrix

substrates including cytokines, chemokines, growth factors and adhesion molecules which together alter the tumor microenvironment thus promoting dissemination of cancer cells (Deryugina& Quigley, 2015). The MMP-9 expression is elevated in malignant tumors including breast, colorectal, lung, cervical and melanoma and high level of MMP-9 expression correlate with advanced tumor stage, lymph node metastasis and poor prognosis(Sharma et al., 2018; Rashid &Bardaweel, 2023).

The subsequent metastatic process includes several interdependent steps of local invasion, intravasation, circulation, extravasation and colonization, all of which are supported by proteolysis mediated throughMMP-9. Secreted by tumor cells, as well as macrophages and neutrophils within the tumor-associated stroma, MMP-9 produces tracks in the extracellular matrix allowing migration of cancer cells during local invasion (Deryugina& Quigley, 2015). Overexpression of MMP-9 mRNA and protein in head and neck cancers has been reported, particularly hypopharyngeal carcinoma (Huang et al., 2020), compared to normal tissues; the expression intensity is associated with lymphatic metastasis degree and pathological tumor stage. This clinical evidence validates the association between MMP-9 activity and the invasive potential of cancer cells(Chen & Xu, 2022).

Angiogenesis is defined as the process of new blood vessel formation from pre-existing vasculature. This process is necessary for tumors to grow beyond approximately 1–2 mm^3 and represents a fundamental step in the metastatic cascade. Multiple mechanisms by which MMP-9 facilitates angiogenesis include degradation of the basement membrane of pre-existing vessels to allow for endothelial cell sprouting, liberation of matrix-bound vascular endothelial growth factor (VEGF) in a bioactive soluble form and mobilization into circulation of bone marrow-derived endothelial progenitor cells to incorporate into nascent tumor vasculatures (Deryugina& Quigley, 2015; Rashid &Bardaweel, 2023). Tumor-coordinated MMP-9 favors VEGF utilization in $CD45^+$ cells from bone marrow facilitating angiogenesis and controlling tumor invasion in glioblastoma (Long et al., 2023). Likewise, in melanoma, tumor-released MMP-9 enhances vascular permeability and aids the recruitment of pro-tumor granulocytic myeloid-derived suppressor cells to the lungs where they make a pre-metastatic niche that establishes after metastatic colonization (Long et al., 2023). In colorectal cancer, the elevation of MMP-9 and its inhibitors TIMP-1 and TIMP-2 along with angiogenin is persistent, the TIMP-1/TIMP-2/MMP-9 axis correlates to

angiogenesis and invasion; importantly, MMP-9 inhibits natural killer cell activity leading to inhibition of anti-tumor immune surveillance and tumor escape (Bruno et al., 2023).

The MMP-9 shapes the immune microenvironment of tumors towards a pro-metastatic state, in addition to its direct proteolytic activities. Proteolytic cleavage of chemokines such as CXCL9, CXCL10 and CXCL11 by MMP-9 restricts tumor-infiltrating lymphocytes trafficking which facilitates escape from the immune system (Rashid &Bardaweel, 2023). The MMP-9 also cleaves interleukin-2 receptor α (IL-2Rα/CD25) to produce a soluble antagonistic form of the receptor that inhibits tumor-reactive cytotoxic lymphocytes. These immune regulatory effects position MMP-9 as a multifunctional regulator of the tumor-stroma-immune axis, rather than just a matrix-degrading enzyme(Rashid &Bardaweel, 2023).

The MMP-9 has been validated as a clinically relevant biomarker for metastatic disease across cancer types. MMP-9 expression is markedly upregulated in triple-negative and HER2-positive subtypes of breast cancer, and its overexpression in lymph nodes with metastases obviously plays a role in lymphatic dissemination (Sharma et al., 2018). The MMP-9 is significantly higher in serum of non-small cell lung cancer patients as compared to healthy controls and also when combined with clinical parameters such age, gender and smoking history shows diagnostic utility for early detection (Sharma et al., 2018). MMP-9 immunohistochemistry is an independent predictor of poor overall survival in cervical cancer patients, consolidating its value as a predictive biomarker (Sharma et al., 2018).

The MMP-9 has an important role in invasion, angiogenesis and immune escapism, features which exaggerate its appeal as a therapeutic target for anti-metastatic therapy. Nonetheless, the selective targeting of MMP-9 has been labor-intensive due to the significant conservation of the active site among all MMPs and therefore treated with higher doses in clinical studies where broad spectrum inhibitors resulted in dose-limiting musculoskeletal toxicity (Rashid &Bardaweel, 2023). More recent advancements have focused on more selective strategies such as the monoclonal antibody andecaliximab (GS-5745), which targets MMP-9 distally from the active site, inhibiting its activity via a non-competitive mechanism. Andecaliximab decreased tumor growth and metastatic incidence in preclinical models of gastric and colorectal cancer, without the toxicity associated with small-molecule inhibitors and is being tested in phase II clinical trials. These

discoveries provide a translation of the efficacy of targeting MMP-9 in the metastatic cascade and potential for improving outcomes for patients with advanced malignancies(Rashid &Bardaweel, 2023).

Clinical Applications of MMP-9

Matrix metalloproteinases-9 (MMP-9) has received considerable attention as a clinically relevant biomarker for various diseases because of its extracellular residence, potential to be cleaved by other enzymes, and strong correlations with harmful remodeling of tissue. According to the National Institutes of Health, a biomarker is defined as any characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes or pharmacological response (Lindsey et al., 2013). MMP-9 thus acts as a proximal biomarker—directly linked to specific disease mechanisms such as cardiac remodeling or tumor invasion—and distal biomarkers. It is an indicatorof generalized inflammatory status that predict non-targeted disease outcomes. The ability to quantify its concentrations in serum, plasma and other human biofluids has allowed the introduction of this marker into routine diagnostic, prognostic and therapeutic follow-up (Huang, 2018).

MMP-9 is a well-described strong predictor of adverse remodeling in the setting of myocardial infarction (MI) in cardiovascular disease. Acute increases in plasma MMP-9 levels post-MI, peaking within the first week, correlate with left ventricular volumes and ejection fraction (Kelly et al., 2007; van den Borne et al., 2009), as well as the risk for cardiac rupture. In the Framingham Heart Study, plasma MMP-9 linked to clinical cardiovascular risk factors and echocardiographic left ventricular measures, therefore, confirms its value in risk stratification (Sundstrom et al., 2004). In addition, increased MMP-9 in patients with acute coronary syndromes has been shown to correlate with poorer long-term outcomes and conventional therapeutic agents for heart failure (e.g. aldosterone antagonists, ACE inhibitors, and beta-blockers) have been shown to decrease circulating levels of MMP-9 implying a potential role for its monitoring as guidance for the therapeutic decision-making process. Because high MMP-9 levels are associated with joint destruction, cartilage erosion and disease activity in rheumatoid arthritis, synovial fluid MMP–9 might serve as a surrogate marker of therapeutic response (Tchetverikov et al., 2003).

Equally compelling oncological utility of MMP-9 as a biomarker. Higher levels of serum and tissue MMP-9 have been consistently reported to be associated with poor prognosis as reflected by tumor stage and lymph node metastasis, while lower overall survival rates can further be correlated in several malignancies including breast, colorectal, lung, cervical and head neck cancers (Sharma et al., 2018). MMP-9 is associated with the prognosis of various cancers as well, such as hypopharyngeal carcinoma, in which a stronger expression of MMP-9 is positively correlated with the clinicopathological stage and lymphatic metastasis (Chen & Xu, 2022). Higher serum MMP-9 concentrations in the patients with non-small cell lung cancer over healthy controls, also has been found to be significant and MMP-9 adds diagnostic value to clinical parameters (age, sex and smoking history) pertaining to early detection of disease . A unique versatile biomarker which can both reflect tumor burden and inflammatory profile of the host, this is relevant not only in theory but has potential in practice as a means to monitor disease [progression] and/or response to therapy (Blanco-Prieto et al., 2017).

MMP-9 may therefore have prospective biomarker relevance for multiple disease outside of cancer and heart disease, particularly neurological diseases and inflammation. Owing to its biological role in the pathogenesis of DMD, serum MMP-9 levels are significantly higher in the poorly regenerative, degenerative muscle of DMD patients than healthy controls, with MMP-9 also being associated with age and disease severity, distinguishing between ambulant and non-ambulant patient subgroups (Nadarajah et al., 2011). In contrast, the MMP-9 but not TIMP-1 levels were elevated with age, as shown longitudinally over 4 years (Nadarajah et al., 2011), leading to the proposal that MMP-9 serves as a convenient biomarker to monitor disease progression and therapeutic response in DMD. We have found notable associations between MMP-9 serum levels and major depressive disorder and bipolar disorder and schizophrenia in patients with psychiatric and neurodevelopmental disorders, as serum MMP-9 correlates with clinical measure of disease severity and may be one of the biomarker for impairment of blood-brain barrier function/neuroinflammation. These findings expand the clinical potential of MMP-9 to systemic and central nervous system pathology beyond root conceptions of organ-specific disease (Vendrusculo et al., 2023).

However, while it is indeed an exciting area of investigation, the clinical implementation of MMP-9 as biomarker is not without its challenges. The main factor limiting comparability of studies as well as clinical laboratories is the absence or vice versa, non-unified approaches in the stages of pre-analytical, analytical and post-analytical processes (Lindsey et al., 2013). MMP-9 is also displayed in three different conformations proMMP-9, active MMP-9 and MMP-9TIMP-1 complexes, which have distinct biological importance and are rarely individually separated in common laboratory assays. Assays designed for MMP-9 that is active, and not total MMP-9, could increase clinical specificity (Rashid &Bardaweel, 2023). Additionally, the inclusion of MMP-9 into multi-biomarker panels along with established markers of cardiac injury and failure (troponins, B-Type Natriuretic Peptide [BNP] and CRP) should allow us to achieve a higher diagnostic and prognostic accuracy over that possible with a single marker. In further studies it needs prospective validation to assess the advantages of MMP-9 compared with the gold standard with reference ranges establishing in other populations/diseases (Vorovich et al., 2008).

Conclusion

Matrix metalloproteinase-9 (MMP-9 or gelatinase B) is a zinc-dependent endopeptidase that contributes to homeostasis of normal tissues and pathological remodeling, and its dysregulation has been associated with the development of cancer, cardiovascular disease and inflammatory disorders. With its multi-domain structure (propeptide, catalytic domain, fibronectin-like and hemopexin-like domain), MMP-9 possesses a large substrate specificity that enables it to degrade matrixes broadly and process non-matrix proteins as well. The MMP-9 mediates cancer progression by promoting basement membrane degradation, angiogenesis and immune evasion. Its overexpression correlates with advanced stage and overall poor prognosis. Clinical studies reported increased serum and tissue MMP-9 levels are true clinical biomarkers for the severity of diseases, the therapeutic response of some malignant tumors, cardiovascular diseases and neuromuscular disorders as well as prognostic stratification. The MMP−9/TIMP−1 imbalance is an important pathophysiological mechanism in several chronic diseases, such as COPD and heart failure, and acts as a quantitative index of disease activity and tissue destruction. While MMP-9 inhibitors could be established therapeutic targets, the clinical translation is

hampered by candidate agents with poor selectivity and high off-target musculoskeletal toxicity as well as a lack of understanding of how the functions of these promiscuous enzymes depend on their context. Novel strategies for targeting monocyte-derived MMP-9, including monoclonal antibodies (e.g., andecaliximab) as well as selective small-molecule inhibitors and indirect modulators may offer more targeted knockdown of MMP-9 release with improved safety profiles.

References

1. Baran, A., Stepaniuk, A., Kiluk, P., Kaminski, T.W., Maciaszek, M. and Flisiak, I. (2022) 'Potential predictive value of serum pentraxin 3 and paraoxonase 1 for cardiometabolic disorders development in patients with psoriasis—Preliminary data', *Metabolites*, 12(7), p. 580. doi: 10.3390/metabo12070580.
2. Blanco-Prieto, S., Barcia-Castro, L., Páez de la Cadena, M., Rodríguez-Berrocal, F. J., Vázquez-Iglesias, L., Botana-Rial, M. I., Fernández-Villar, A., & De Chiara, L. (2017). Relevance of matrix metalloproteases in non-small cell lung cancer diagnosis. *BMC cancer*, *17*(1), 823. https://doi.org/10.1186/s12885-017-3842-z\
3. Bruno, A., Bassani, B., d'Uva, G., Digiacomo, G., Cassinotti, E., Pelissero, A., Baci, D., Mortara, L., Borsotti, P., Albini, A. and Noonan, D.M. (2023) 'MMP-9 is a novel player in the polarization of the immune system: Focus on the tumor microenvironment', *Cancers*, 15(14), p. 3704. doi: 10.3390/cancers15143704.
4. Caley, M.P., Martins, V.L. and O'Toole, E.A. (2015) 'Metalloproteinases and wound healing', *Advances in Wound Care*, 4(4), pp. 225–234. doi: 10.1089/wound.2014.0581.
5. Chakrabarti, S., Patel, A. and Patel, K. (2005) 'Matrix metalloproteinase-2 (MMP-2) and MMP-9 in pulmonary pathology', *Experimental Lung Research*, 31(6), pp. 599–621. doi: 10.1080/019021490944232.
6. Chen, X. and Xu, X. (2022) 'The role of MMP-2 and MMP-9 in the metastasis and development of hypopharyngeal carcinoma', *Brazilian*

Journal of Otorhinolaryngology, 88(4), pp. 642–650. doi: 10.1016/j.bjorl.2020.07.003.

7. de Almeida, L.G.N., Thode, H., Eslambolchi, Y., Chopra, S., Young, D., Gill, S., Devel, L. and Dufour, A. (2022) 'Matrix metalloproteinases: From molecular mechanisms to physiology, pathophysiology, and pharmacology', *Pharmacological Reviews*, 74(3), pp. 712–768. doi: 10.1124/pharmrev.121.000349.
8. Deryugina, E.I. and Quigley, J.P. (2015) 'Tumor angiogenesis: MMP-mediated induction of intravasation- and metastasis-sustaining neovasculature', *Matrix Biology*, 44–46, pp. 94–112. doi: 10.1016/j.matbio.2015.04.004.
9. Dimic-Janjic, S., Hoda, M.A., Milenkovic, B., Kotur-Stevuljevic, J., Stjepanovic, M., Gompelmann, D., Jankovic, J., Miljkovic, M., Milin-Lazovic, J., Djurdjevic, N. et al. (2023) 'The usefulness of MMP-9, TIMP-1 and MMP-9/TIMP-1 ratio for diagnosis and assessment of COPD severity', *European Journal of Medical Research*, 28, p. 127. doi: 10.1186/s40001-023-01094-7.
10. Ding, L., Guo, H., Zhang, C., Jin, H., Guo, X. and Li, T. (2023) 'Elevated matrix metalloproteinase 9 expression is associated with COVID-19 severity: A meta-analysis', *Experimental and Therapeutic Medicine*, 26(5), p. 545. doi: 10.3892/etm.2023.12244.
11. Halade, G. V., Jin, Y. F., & Lindsey, M. L. (2013). Matrix metalloproteinase (MMP)-9: a proximal biomarker for cardiac remodeling and a distal biomarker for inflammation. *Pharmacology & therapeutics*, *139*(1), 32–40. https://doi.org/10.1016/j.pharmthera.2013.03.009
12. Huang, H. (2018). Matrix Metalloproteinase-9 (MMP-9) as a Cancer Biomarker and MMP-9 Biosensors: Recent Advances. Sensors, 18(10), 3249. https://doi.org/10.3390/s18103249
13. Kelly, D., Cockerill, G., Ng, L.L., Thompson, M., Khan, S., Samani, N.J. and Squire, I.B. (2007) 'Plasma matrix metalloproteinase-9 and left ventricular remodelling after acute myocardial infarction in man: A prospective cohort study', *European Heart Journal*, 28(6), pp. 711–718. doi: 10.1093/eurheartj/ehm003.
14. Kessenbrock, K., Plaks, V. and Werb, Z. (2010) 'Matrix metalloproteinases: regulators of the tumor microenvironment', *Cell*, 141(1), pp. 52–67. doi: 10.1016/j.cell.2010.03.015.

15. Lindsey, M.L., Iyer, R.P., Zamilpa, R., Yabluchanskiy, A., DeLeon-Pennell, K.Y., Hall, M.E., Kaplan, B.S., Bradshaw, A.D., Suckow, M.A. and De Castro Brás, L.E. (2013) 'A novel collagen matricryptin reduces left ventricular dilation post-myocardial infarction by promoting scar formation and angiogenesis', *Journal of the American College of Cardiology*, 61(15), pp. 1664–1674. doi: 10.1016/j.jacc.2012.12.045.
16. Lommatzsch, M., Schubert, S.C., Knecht, S., Stoll, P., Schröter, S., Zingler, C., Stoll, R., Schuff-Werner, P. and Virchow, J.C. (2019) 'Increased ratio of matrix metalloproteinase-9 (MMP-9)/tissue inhibitor metalloproteinase-1 from alveolar macrophages in chronic asthma with a fast decline in FEV1 at 5-year follow-up', *Journal of Clinical Medicine*, 8(9), p. 1451. doi: 10.3390/jcm8091451.
17. Long, Y., Li, J., Zhang, Y., Guo, Y., Sun, Y., Li, X., Yin, X., Liu, M., Wang, Y., Zhang, W. and Cai, L. (2023) 'Applications of matrix metalloproteinase-9-related nanomedicines in tumors and vascular diseases', *Cancers*, 15(7), p. 2118. doi: 10.3390/cancers15072118.
18. Määttä, J., Kallio, M., Nikkola, J., Salo, T. and Sorsa, T. (2025) 'Matrix metalloproteinase-9 (MMP-9) as a therapeutic target', *Cells*, 14(11), p. 1005. doi: 10.3390/cells14111005.
19. Mathpal, S., Sharma, P., Joshi, T., Pande, V., Mahmud, S., Jeong, M. K., Obaidullah, A. J., Chandra, S., & Kim, B. (2022). Identification of Zinc-Binding Inhibitors of Matrix Metalloproteinase-9 to Prevent Cancer Through Deep Learning and Molecular Dynamics Simulation Approach. *Frontiers in molecular biosciences*, *9*, 857430. https://doi.org/10.3389/fmolb.2022.857430
20. Mondal, S., Adhikari, N., Banerjee, S., Amin, S.A. and Jha, T. (2020) 'Matrix metalloproteinase-9 (MMP-9) and its inhibitors in cancer: A minireview', *European Journal of Medicinal Chemistry*, 194, p. 112260. doi: 10.1016/j.ejmech.2020.112260.
21. Nadarajah, V.D., van Putten, M., Chaouch, A., Garrood, P., Straub, V., Guglieri, M., Bushby, K., Lochmüller, H. and Aartsma-Rus, A. (2011) 'Serum matrix metalloproteinase-9 (MMP-9) as a biomarker for monitoring disease progression in Duchenne muscular dystrophy (DMD)', *Neuromuscular Disorders*, 21(8–9), pp. 569–576. doi: 10.1016/j.nmd.2011.05.011.

22. Patil, D. P., & Kundu, G. C. (2006). *MMP9 (matrix metallopeptidase 9 (gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase)).* Atlas of Genetics and Cytogenetics in Oncology and Haematology. http://atlasgeneticsoncology.org/gene/41408/mmp9-(matrix-metallopeptidase-9-(gelatinase-b-92kda-gelatinase-92kda-type-iv-collagenase))
23. Qin, T., Zhong, J., Li, P., Liang, J., Li, M. and Zhang, G. (2024) 'Matrix metalloproteinase and aortic aneurysm: A two-sample Mendelian randomization study', *Annals of Vascular Surgery*, 105, pp. 227–235. doi: 10.1016/j.avsg.2024.02.011.
24. Rashid, Z.A. and Bardaweel, S.K. (2023) 'Novel matrix metalloproteinase-9 (MMP-9) inhibitors in cancer treatment', *International Journal of Molecular Sciences*, 24(15), p. 12133. doi: 10.3390/ijms241512133.
25. Rękość, N., Kucharczyk, K., Karpowicz, P., Strzałkowski, R., Ożarowski, M., Szymański, P. and Markowicz, M. (2024) 'The link between matrix metalloproteinases and Alzheimer's disease pathophysiology', *Molecular Neurobiology*, 61, pp. 1–15. doi: 10.1007/s12035-024-04315-0.
26. Sharma, B., Verma, H., Singh, D., Maheshwari, D., Sharma, P.K., Singh, C., Kaur, S., Bhatia, A., Banerjee, S., Kaushik, D. and Singh, T.G. (2018) 'Matrix metalloproteinase-9 (MMP-9) as a cancer biomarker and MMP-9 biosensors: Recent advances', *Sensors*, 18(10), p. 3249. doi: 10.3390/s18103249.
27. Shen, D., Lin, L., Su, Y., Xu, J., Jiang, W., Zhang, Z., Fang, Y., Ding, X. and Xu, X. (2025) 'Inhibition of matrix metalloproteinase-9 attenuates kidney fibrosis and cellular senescence in the transition from acute kidney injury to chronic kidney disease', *Renal Failure*, 47(1), p. 2499897. doi: 10.1080/0886022X.2025.2499897.
28. Sundstrom, J., Evans, J.C., Benjamin, E.J., Levy, D., Larson, M.G., Sawyer, D.B., Siwik, D.A., Colucci, W.S., Sutherland, P. and Wilson, P.W. (2004) 'Relations of plasma matrix metalloproteinase-9 to clinical cardiovascular risk factors and echocardiographic left ventricular measures: The Framingham Heart Study', *Circulation*, 109(25), pp. 2850–2856. doi: 10.1161/01.CIR.0000129318.79570.84.
29. Tchetverikov, I., Lard, L.R., DeGroot, J., Verzijl, N., TeKoppele, J.M., Breedveld, F.C. and Huizinga, T.W. (2003) 'Matrix

metalloproteinases-3, -8, -9 as markers of disease activity and joint damage progression in early rheumatoid arthritis', *Annals of the Rheumatic Diseases*, 62(11), pp. 1094–1099. doi: 10.1136/ard.62.11.1094.

30. van den Borne, S.W., Cleutjens, J.P., Hanemaaijer, R., Creemers, E.E., Smits, J.F., Daemen, M.J. and Blankesteijn, W.M. (2009) 'Increased matrix metalloproteinase-8 and -9 activity in patients with infarct rupture after myocardial infarction', *Cardiovascular Pathology*, 18(1), pp. 37–43. doi: 10.1016/j.carpath.2007.12.012.
31. Vandooren, J., Van den Steen, P. E., &Opdenakker, G. (2013). Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): The next decade. *Critical Reviews in Biochemistry and Molecular Biology*, *48*(3), 222–272. https://doi.org/10.3109/10409238.2013.770819
32. Vendrusculo, F.M., et al. (2023) 'Metalloproteinases as biomarkers and sociomarkers in human health and disease', *Biomedicines*, 11(12), p. 3193. doi: 10.3390/biomedicines11123193.
33. Vorovich, E. E., Chuai, S., Li, M., Averna, J., Marwin, V., Wolfe, D., Reilly, M. P., & Cappola, T. P. (2008). Comparison of matrix metalloproteinase 9 and brain natriuretic peptide as clinical biomarkers in chronic heart failure. *American heart journal*, *155*(6), 992–997. https://doi.org/10.1016/j.ahj.2008.01.007
34. Wolosowicz, M., Prokopiuk, S., & Kaminski, T. W. (2025). Matrix Metalloproteinase-9 (MMP-9) as a Therapeutic Target: Insights into Molecular Pathways and Clinical Applications. *Pharmaceutics*, *17*(11), 1425. https://doi.org/10.3390/pharmaceutics17111425
35. Xu, D., McKee, C. M., Cao, Y., Ding, Y., Kessler, B. M., &Muschel, R. J. (2010). Matrix metalloproteinase-9 regulates tumor cell invasion through cleavage of protease nexin-1. *Cancer research*, *70*(17), 6988–6998. https://doi.org/10.1158/0008-5472.CAN-10-0242