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# A SHORT REVIEW OF MATRIX METALLOPROTEINASE – 9

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## ABSTRACT
Matrix metalloproteinases (MMPs) are group of zinc-dependent peptidases molecule. These are capable of degrading all extracellular matrix. MMPs help in process a variety of non-ECM substrates. They are responsible for physiological and pathological tissue remodeling. MMP-9 belongs to the gelatinase subgroup of MMPs. MMP-9 are involved in tissue growth and morphogenesis. MMP-9 activity is required during embryological development and maintenance of physiology, help in cell migration, modulation of the activity. Various experimental cell line and clinical studies have implicated role of MMP9 in many human diseases including respiratory diseases, cardiovascular disorders, neuropsychiatric disorder, autoimmune diseases, and cancer. This article highlight the nature MMP-9, including chemical structure, genes involved in formation, role in physiological function and role in various diseases including respiratory, cardiovascular and cancer.

**KEYWORDS:** Matrix metalloproteinases (MMPs),

## INTRODUCTION
Matrix metalloproteinases (MMPs) are group of zinc-dependent endopeptidases. These are capable of degrading all extracellular matrix (ECM) components as well as process a variety of non-ECM substrates. They are responsible for physiological and pathological tissue remodeling. They are expressed in neutrophils, endothelial cells, eosinophils, macrophages, and T lymphocytes.[1] In 1962, Woessner demonstrated a protein enzyme in mammalian uterus that could degrade collagen. Later on Jerome Gross and Charles Lapiere identified a matrix metalloproteinase. They showed collagenolytic activity in the skin, gut, and gills of the tadpole during metamorphosis. Later the International Union of Biochemistry and Molecular Biology designated the family with a unique name MMP. In 1974, MMP-9 was first isolated in neutrophils and also coined as "neutrophil gelatinase".[2]

### Gene Transcription and Regulation of Expression
MMP-9 gene is mapped on chromosome 20q11.2-q13.1. Regulation of MMP-9 is a coordinated attempt of gene transcription, proenzyme activation, and endogenous inhibitors. Regulation of the gene expression is mainly at transcriptional level besides epigenetic and posttranscriptional regulation. Classical activation includes disruption of the interaction between the zinc molecule in the catalytic domain and the cysteine switch in the pro-domain of MMP9. This leads to cleavage of the prodomain and production of active enzyme. However, pro-MMPs can be activated by two mechanisms – proteolytic cleavage and allosteric activation. Furthermore, tissue inhibitor metalloproteinases (TIMP), endogenous inhibitors also regulate MMP expression.[1,2,3]

### Protein Structure and Distribution
MMP-9 belongs to the gelatinase subgroup of MMPs. The constitutive physiological MMP expression is normally low, transient higher expression could be expected during homeostasis linked matrix remodeling or specific developmental events. MMP-9 is secreted by a wide number of cell types, including neutrophils, macrophages, and fibroblasts. MMP-9 is also expressed by osteoblsts as its expression thought to be expressed by RUNX-2, it also supports its expression in osteoblasts.[4] The main structural components of human MMP-9 are an NH2-terminal pro-domain, a catalytic domain, a linker domain, and a COOHterminal hemopexin-like domain. The catalytic domain of MMP-9 contains two zinc ions, five calcium ions, and three repeats homologous to the type II module of fibronectin. The zinc ions of the catalytic domain along with cysteine rich motif of the pro-domain of MMP-9 are structurally coordinated to keep the molecule inactive. The fibronectin-like domain is heavily O-glycosylated and

also responsible for binding to denatured collagen or gelatin. Hemopexin-like domain, which shares a sequence similarity to plasma hemopexin, forms a tight complex with TIMP-1 and TIMP-3 though their COOH terminal domains in pro-MMP-9. This complex formation occurs in Golgi apparatus before its secretion which leaves amino terminus capable of inhibiting other MMPs.[5]

**MMP-9 in Physiology**

MMPs have a well established role in degradation of extracellular matrix. Thus, MMP-9 are involved in tissue growth and morphogenesis. MMP-9 activity is required during embryological development and maintenance of physiology. MMP-9 degradation of ECM molecules and allow cell migration, modulation of the activity of biologically active molecules by direct cleavage, release from bound stores, or the modulating of the activity of their inhibitors.[6]

**Cell Migration**

ECM behaves as a barrier for cell migration during early phase of embryogenesis. The in vitro studies using assays of cell migration observed the secretion of MMP-9 by trophoblast during implantation suggesting its potential to mediate physiological migration of cell by acting on specific substrate. In addition, during development of nervous system, MMP-9 also plays a crucial role in neurite growth, a phenomenon through which neurons extend their processes over long distances to form connections. In long bone development, migration of preosteoclastic cells is largely mediated by their increased MMP-9 expression so that they can invade the cartilage to initiate the process of endochondral ossification.[7]

**Modulation of Bioactive Molecules**

Several biological active molecules get cleaved by MMP-9 to acquire new activities. Angiostatin is a fragment of plasminogen produced by cleavage mediated by MMP-9 to act as a potent angiogenesis inhibitor. MMPs may also cleave cell surface molecules, thereby modulating their activity. An example is alteration in signal tansducing property of gelactin-3. Cleavage of galectin-3 by MMP-9 alters the carbohydrate recognition domain of galectin-3 and reduces selfassociation of the galectin molecules. MMP-9 cleaves and activates many immune-related molecules such as interleukin-8 to its more potent truncated form and activates IL-1b and transforming growth factor b. Proteomics techniques revealed a role of active MMP-9 in shedding b2 integrin from macrophages. Besides these contributions, MMP-9 has been described to release the biologically active form of vascular endothelial growth factor (VEGF) which is complemented by the direct proteolytic degradation of vascular basement membrane proteins, indicating that MMP-9 may play a crucial role in the formation of new blood vessels.[8]

**MMP-9 in Diseases**

Various experimental cell line and clinical studies have implicated role of MMP9 in many human diseases including respiratory diseases, cardiovascular disorders, neuropsychiatric disorder, autoimmune diseases, and cancer.[8]

Recently, MMP9 has been shown to be increasingly important in several aspects of central nervous system activity. Furthermore, a pathogenic role for this enzyme has been suggested in such neuropsychiatric disorders as schizophrenia, bipolar illness, and multiple sclerosis. Genetic aspect of etiopathogenic role of MMP-9 suggests the relation between T allele of the 1562 polymorphism of MMP9 gene to its increased transcriptional activity of the gene especially in aforementioned diseases and disorders.[8]

**Respiratory Diseases[9]**

The role of gelatinases in pathology has been studied extensively, especially in lung diseases like asthma and chronic obstructive pulmonary disease (COPD). If not in chronic asthma, increased MMP-9 and the MMP-9/TIMP-1 ratio are found to be useful indicator in exacerbations of acute asthma. This phenomenon may be explained by increase in MMP-9 concentration in infiltrating neutrophils that is released during the asthmatic attack. Degranulation of neutrophil granule leads to an increase in the local concentration of proteolytically active MMP-9, which contributes in the symptoms observed in acute asthma via various mechanisms like airway obstruction due to desquamation of epithelial cells and increased mucus production by goblet cells. Ability of MMP-9 to cause ECM destruction and degradation of a1-protease inhibitor is thought to be an important factor in COPD development and its progression. MMP-9 is further capable of chemotaxis of neutrophils (a major source of MMP-9) by production of the biologically more active truncated form of IL-8, causing a vicious circle of MMP-9 activity in the lung pathology.

**Cardiovascular Diseases[9]**

In cardiovascular diseases like coronary artery diseases, hypertrophic cardiomyopathy, aortic aneurysm, and hypertensive diseases, serum MMP-9 has been considered to be a valuable prognostic indicator. In plaque formation, one of the important pathogenic roles of MMP-9 includes increased migration and proliferation of vascular smooth muscle cells through elastic lamina into the intimal space. Likewise, both human and animal studies have shown a relationship between elevated MMP-9 levels and abdominal aortic aneurysms. Altered level of MMP-9 and its genetic polymorphism were found to be related with poorer prognosis of coronary heart disease.

**MMPs in Cancer[10]**

Since its first isolations, evidences supporting the close association of MMP-9 and various domains of

carcinogenesis (cell proliferation, survival, association with inflammation, angiogenesis, cell migration, metastatic niche formation) are mounting up in various cancers like ovarian, gastric, oral, and breast cancer. MMP-9 is a proteolytic enzyme that degrades basal membrane and the extracellular matrix which are prerequisite steps of carcinogenesis. Sequentially it has the ability to promote cancer progression by increasing cancer cell proliferation, migration, invasion, metastasis, and angiogenesis by exploiting its physiological role like cleaving a diverse group of substrates, including structural components of the extracellular matrix, growth factor-binding proteins, growth factor precursors, receptor tyrosine kinases, cell-adhesion molecules, and other proteinases. Expression of MMP-9 by both tumor and stromal cells make the scenario more complex as both bidirectional talks between these cells via MMP-9 influences the cancer biology to a large extent.

**REFERENCES**


1. Fanjul-Fernández M, Folgueras AR, Cabrera S, López-n Otín C. Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models. Biochim Biophys Acta., 2010; 1803(1): 3–19.
2. Iyer RP, Patterson NL, Fields GB, Lindsey ML. The history of matrix metalloproteinases: milestones, myths, and misperceptions. Am J Physiol Heart Circ Physiol., 2012; 303(8): H919–30. doi:10.1152/ajpheart.00577. 2012.
3. Hadler-Olsen E, Fadnes B, Sylte I, Uhlin-Hansen L, Winberg JO. Regulation of matrix metalloproteinase activity in health and disease. FEBS J., 2011; 278: 28–45. doi:10.1111/j.1742-4658.2010. 07920.x.
4. Löffek S, Schilling O, Franzke C-W. Biological role of matrix metalloproteinases: a critical balance. Eur Respir J., 2011; 38: 191–208. doi:10.1183/09031936. 00146510.
5. Yabluchanskiy A, Ma Y, Iyer RP, Hall ME, Lindsey ML. Matrix metalloproteinase-9: many shades of function in cardiovascular disease. Physiology, 2013; 28: 391–403.
6. Klein T, Bischoff R. Physiology and pathophysiology of matrix metalloproteases. Amino Acids., 2011; 41(2): 271–90. doi:10.1007/s00726-010-0689-x.
7. Bruni-Cardoso A, Johnson LC, Vessella RL, Peterson TE, Lynch CC. Osteoclast derived matrix metalloproteinase-9 directly impacts angiogenesis in the prostate tumor-bone microenvironment. Mol Cancer Res., 2010; 8(4): 459–70. doi:10.1158/1541-7786.MCR-09-0445.
8. Vu TH, Werb Z. Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev., 2000; 14(17): 2123–33.
9. Rybakowski JK. Matrix metalloproteinase-9 (MMP-9) – a mediating enzyme in cardiovascular disease, cancer, and neuropsychiatric disorders. Cardiovasc Psychiatry Neurol., 2009; 2009: 1–7.
10. Wu Q-W, Yang Q-M, Huang Y-F, She H-Q, Liang J, Yang Q-L, Zhang ZM. Expression and clinical significance of matrix metalloproteinase-9 in lymphatic invasiveness and metastasis of breast cancer., 2014; 9(5): e97804. doi:10.1371/journal.