Role of matrix metalloproteinase 9 in remodeling of the left ventricle myocardium

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Abstract: The article gives information about the role of matrix metalloproteinase 9 in remodeling of the left ventricle myocardium.

Keywords: matrix, metalloproteinase 9, ventricle myocardium

Relevance

Cardiovascular diseases (CVD) remain the leading cause of mortality and disability worldwide, despite significant advances in treatment and prevention [1]. The first place in the structure of mortality from cardiovascular diseases is occupied by chronic heart failure (CHF), which develops due to early left ventricular (LV) remodelling after infarction.

Myocardial remodelling that occurs after myocardial infarction (MI) is caused by changes in the structure of the extracellular matrix (ECM) [2].

Increase in the level of matrix metalloproteinases (MMPs) is associated with LV remodelling, its dysfunction and, as a consequence, the development of coronary heart disease.

The nature of myocardial remodelling after myocardial infarction depends on the degree of arterial channel damage, severity of inflammatory response and many other processes occurring during scar formation.

In response to cardiomyocyte injury, many defence mechanisms are triggered, including inflammation, cell proliferation and maturation [3].

Each of them contributes to temporary changes in the level of MMPs in myocardium.

MMPs in the scarred area are secreted by a variety of cells including neutrophils, macrophages, endothelial cells, damaged cardiomyocytes and fibroblasts.

The processes occurring in necrotic and ischaemic myocardium make MMPs important mediators of progressive LV myocardial remodelling [4-7].

Extracellular matrix and the process of LV myocardial remodelling

Extracellular matrix is the basis of connective tissue that provides mechanical framework of cells and transport of chemical substances (Table 1) [8].

Main components of ECM

Protein	Function	Localization
Collagen I	Strength and structure	ECM

Collagen III	Elasticity	ECM
Collagen IV	Maintaining basement membrane architecture	basement membrane
Collagen VI	Organization of ECM proteins, interaction with the basement membrane	ECM basement membrane
Elastin	Elasticity	ECM
Fibronectin	Collagen bonding, formation of fibrillar structure	ECM
Decorin	Collagen binding	ECM
Integrins	Transfer of signals from the ECM to cardiomyocytes	ECM
Laminin	Maintaining basement membrane architecture	basement membrane

The strength and elasticity of the ECM is achieved due to three-dimensionally organised structures connected to myocardial fibres.

Collagen and its types make up approximately 70-85% of the total mass of the ECM and determine its quality.

Type III collagen constitutes approximately 10% of the average total collagen content and assesses the stability of the ECM [9-13].

Myocardial remodelling in MI is pathophysiologically caused by cardiomyocyte death due to prolonged ischemia, which leads to MMP activation, which in turn leads to ECM degradation, violating its structural integrity.

All this ultimately leads to a decrease in both systolic (due to cardiomyocyte death) and diastolic (ECM destruction) function [8].

LV myocardial remodelling in the IM zone occurs in several stages [9, 10].

These stages (inflammation, proliferation and collagen deposition) are sequential and are important for delineating the infarct zone.

The outcome of myocardial remodelling depends on the severity of each of these stages and their interrelationship.

Cardiomyocyte homeostasis deteriorates immediately after ischaemia, leading to cell death within 30 minutes, resulting in neutrophil and macrophage activation and hence an acute inflammatory response [11-13].

Neutrophils and macrophages infiltrating MI areas release inflammatory mediators such as MMPs and tissue metalloproteinase inhibitors.

About 5 days after myocardial infarction, a collagen-rich scar begins to form to compensate for the loss of myocardial cells in the infarction zone [15].

Cardiomyocyte basement membrane

In addition to collagens of types I and III, which form the basis of the ECM, the basal membrane of cardiomyocytes contains proteins.

It also contains collagen types IV, V, VII, X, and XIV in the form of laminin [10].

The basal membrane is a dense network of various proteins surrounding the cardiomyocytes including laminin, type IV collagen and many proteoglycans [14, 15].

It is considered another form of the ECM because it contains type IV collagen, a layer that is present only in the basal membrane and separates the ECM from cardiac myocytes.

Fragmentation of the basal membrane occurs as early as 1 hour after myocardial infarction and persists up to 7 days after reperfusion [13].

Studies have shown that mucosal thickness increases, contributing to impaired oxygen diffusion and the development of hypoxic stress .

In addition, after the onset of myocardial infarction, the production of antibodies against type IV collagen begins, which also causes disruption of the structural integrity of the basal membrane, leading to endothelial cell dysfunction.

Proteins formed after laminin degradation stimulate healing and angiogenesis of necrotic areas [13].

On the contrary, proteins formed during the degradation of type IV collagen play an important role in the inhibition of angiogenesis, disruption of the structural integrity of blood vessels and intercellular interactions after myocardial ischaemic injury.

Matrix metalloproteinases

MMPs are a family of zinc-dependent endopeptidases that regulate the metabolism of connective tissue proteins and also influence the normal development and remodelling processes of LV. MMPs have been widely studied as predictive markers of LV remodelling and heart failure development after MI [14, 15]. Many publications emphasise the importance of this enzyme in the list of promising and important biomarkers that can be used to improve the diagnosis of CHF and increase the effectiveness of treatment .

MMP-9 or gelatinase B is one of the most well-studied proteases controlling the processes of pathological remodelling.

MMP-9 plays an important role in the degradation of ECM in various physiological and pathophysiological processes, including tissue remodelling.

MMP-9 is secreted by various cells such as cardiomyocytes, endothelial cells, neutrophils, macrophages and fibroblasts.

For the first time, MMP-9 was used as a novel prognostic biomarker for the development of LV dysfunction and late survival.

Together with other investigators, they showed an association between elevated MMP-9 levels and high plasma concentrations of interleukin-6, C-reactive protein and fibrinogen, indicating a high prognostic value of MMP-9.

MMP-9 regulates myocardial remodelling by directly degrading VSMCs and activating cytokines and chemokines .

Exposure to MMP-9 is both deleterious and beneficial for regeneration of the affected area. On the other hand, under the influence of MMP-9, macrophage phagocytosis is reduced and neutrophil inflammatory response is prolonged, resulting in increased LV after IM .

On the other hand, osteopontin is cleaved, resulting in the formation of two bioactive peptides that increase the rate of cardiac fibroblast migration, thereby

promoting healing of the infarcted area. Thus, the use of MMP-9 as a diagnostic marker at different days after myocardial infarction may be useful in predicting and preventing LV dysfunction after myocardial infarction. In addition, the role of MMP-9 in the degradation of collagen, especially type IV collagen, in the basal membrane of cardiomyocytes should be noted.

In a recently published study, the authors used immunohistochemical methods to demonstrate that MMP-9 in the cytoplasm of cardiomyocytes is associated with partial or complete destruction of the cardiomyocyte basement membrane formed by type IV collagen.

Conclusion

Cardiovascular disease is the leading cause of death in developed countries [15], and myocardial infarction is a significant contributor to cardiovascular disease mortality.

According to various estimates, the prevalence of cardiovascular diseases is expected to increase by 10% over the next two decades, leading to 23.6 million deaths per year worldwide by 2030. In addition, healthcare costs associated with MI are expected to triple over the next 20 years.

After myocardial infarction, the LV undergoes many changes at the molecular and cellular level. The extracellular matrix also changes, changing the shape of the LV and impairing its function over time. ECM degradation determines early and late prognosis after MI.

Assessing the ECM at various time points after myocardial infarction provides an early diagnosis or prognostic indicator of LV remodeling and allows the stratification of patients into groups depending on individual risk and subsequent treatment.

Currently, various biomarkers are used for the timely diagnosis of myocardial infarction, but their use is limited due to insufficient specificity and selectivity. Determining the role of MMP-9 in remodeling after MI is an important challenge. A better understanding of the pathophysiological processes, including the biological functions of MMP-9, may allow the development of new strategies for the diagnosis and treatment of patients with myocardial infarction. Biomarkers of ECM remodeling, which can be detected in structural changes during myocardial infarction, may be useful for predicting the further development of CHF.

In particular, one of these markers may be type IV collagen, which is located in the basement membrane of cardiomyocytes and is destroyed by MMP-9. Simultaneous analysis of the level of MMP-9 and the content of type IV collagen in the myocardium will allow us to determine criteria for predicting survival in this group of patients, determine treatment tactics, and better understand the processes of remodeling.

References

1. Kurbanov F. Sh., Rakhimova D. A. Condition of the periodontium in patients with chronic obstructive pulmonary disease // Nargiza Mirza Bakhtiyarkhonovna Abdurakhmanova, & Khalmurad Sadullaevich Akhmedov. – P. 70.

2. Kytikova O. Yu., Gvozdenko T. A., Antonyuk M. V. Modern aspects of the prevalence of chronic bronchopulmonary diseases // Bulletin of Physiology and Pathology of Respiration. – 2017. – No. 64. – pp. 94-100.

3. Mamaeva M. G. et al. Markers of systemic inflammation and endothelial dysfunction in patients with chronic obstructive pulmonary disease // Siberian Medical Review. – 2014. – No. 1 (85). – pp. 12-19.

4. Kholzhigitova, Mukhayo Berdikulovna, et al. "Clinical and bronchoscopic characteristics of the inflammatory process in patients with chronic obstructive bronchitis." Issues of Science and Education 25 (74) (2019): 55-63.

5. Kholzhigitova M. B., Aralov N. R., Dusanov A. D. Level of local immunity factors in chronic obstructive bronchitis in adolescents // Tyumen Medical Journal. – 2016. – T. 18. – No. 1. – pp. 52-55.

6. Kholzhigitova M. B. et al. Clinical and bronchoscopic characteristics of the inflammatory process in patients with chronic obstructive bronchitis // Issues of science and education. – 2019. – No. 25 (74). – pp. 55-63.

7. Ziyadullaev Sh. Kh. et al. The role of some regulatory cytokines in the immunopathogenesis of exogenous allergic alveolitis // Health of clinical and experimental medicine. – 2017. – No. 1. – pp. 38-41.

8. Rubenovna AI et al. Assessment Of The Degree Of Endothelial Dysfunction In Patients With Chronic Obstructive Pulmonary Disease Complicated By Chronic Heart Failure //Int. J. of Aquatic Science. – 2021. – T. 12. – No. 3. – pp. 2917-2922.

9. Ziyadullaev S. et al. The effect of budesonide on the quality of life in patients with bronchial asthma //European Journal of Molecular & Clinical Medicine. – 2020. – T. 7. – No. 2. – S. 1760-1766.

10. Fazilova G. et al. The role of certain regulatory cytokines in the immunopathogenesis of extrinsic allergic alveolitis. – 2018.

11. Kholliyev R. et al. The role of antioxidant enzymes in the pathogenesis of asthma and the formation of the features of its clinical course. – 2015.

12. Ismailov JA et al. Yurak yetishmovchiligini barvaqt aniqlash samaradorligi //Science and Education. – 2023. – T. 4. – No. 6. – pp. 91-109.

13. Dusanovich DA et al. NONSPESIFIK YARALI KOLITNING KLINIK VA IMMUNOLOGIK XUSUSIYATLARI //JOURNAL OF BIOMEDICINE AND PRACTICE. – 2022. – T. 7. – No. 5.

14. Mirzaev, Rizamat Ziyadullaevich, Eleonora Negmatovna Tashkenbaeva, and Gulnora Alievna Abdieva. "PROGNOSTIC CLINICAL MARKERS OF RENAL

FAILURE IN METABOLIC SYNDROME." Journal of Cardiorespiratory Research SI-2 (2022).

15. Tashkenbaeva Eleonora Negmatovna, Abdieva Gulnora Alievna Features of ischemic heart disease in association with climacteric cardiopathy // European science review. 2018. No. 3-4.

16. Yusufovna K. N. et al. Pharmacogenetics-A New Word in the Treatment of Rheumatoid Arthritis //Annals of the Romanian Society for Cell Biology. – 2021. – С. 259-265.

17. Rubenovna A. I. et al. Assessment Of The Degree Of Endothelial Dysfunction In Patients With Chronic Obstructive Pulmonary Disease Complicated By Chronic Heart Failure //Int. J. of Aquatic Science. – 2021. – Т. 12. – №. 3. – С. 2917-2922.

18. Rubenovna A. I. et al. Study of cardiovascular status and risk of heart failure in chronic obstructive pulmonary disease //Asian journal of pharmaceutical and biological research. – 2022. – Т. 11. – №. 2.