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The Role of Matrix Metalloproteinases in the Pathogenesis of Atrial Fibrillation

Dan Li[1], Junru Zhang[2,*]

[1]Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi 712046, China.
[2]Shaanxi Traditional Chinese Medicine Hospital, Xi'an, 710003, China.

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***Corresponding author:** Junru Zhang, Shaanxi Traditional Chinese Medicine Hospital, Xi'an, 710003, China.

Abstract

Atrial fibrillation is a disease of atrial dysfunction caused by absolutely irregular atrial activation, and it is one of the most common arrhythmias in clinic. At present, it is believed that the pathogenesis of atrial fibrillation is mainly due to the occurrence of fibrosis in atrial tissue, which affects the conduction between myocardium and ultimately leads to the occurrence of irregular atrial pacing. Matrix metalloproteinases (MMPs) are a kind of complex degradation enzymes related to human tissue fibrosis. They participate in the pathogenesis of atrial fibrillation and affect the prognosis by degrading the extracellular matrix proteins of myocardium. This article mainly discusses the relationship between MMPs and the pathogenesis of atrial fibrillation, and further clarifies the mechanism of the occurrence and development of atrial fibrillation, in order to provide new research ideas for the prevention and treatment of atrial fibrillation.

Keywords

Atrial Fibrillation, Matrix Metalloproteinases, Pathogenesis

1. Atrial Remodeling

Atrial fibrillation is a common clinical arrhythmia. According to the latest survey, the prevalence of AF worldwide is 2%, and this figure is still rising [1]. Anxiety, fatigue and other discomfort caused by atrial fibrillation affect the physical and mental health of patients; The formation of cardiogenic thrombus seriously threatens the life safety of patients. At present, the pathogenesis of atrial fibrillation is not clear, and atrial remodeling is the pathological basis for the occurrence and maintenance of atrial fibrillation and plays an important role in many aspects such as complications, recurrence and prognosis of atrial fibrillation [2-3]. Matrix metalloproteinases (MMPs) are degradation enzymes related to extracellular matrix remodeling and play an important role in the heart of patients with atrial fibrillation. In this paper, the role of MMPs in the pathogenesis of atrial fibrillation was discussed to further clarify the pathogenesis of atrial fibrillation and provide new research ideas for the treatment of atrial fibrillation.

1.1. Introduction to matrix metalloproteinases

Matrix metalloproteinases are a degrading enzyme activatedby Zn^{2+}. The MMPs discovered and encoded by humans are divided into six categories [4]: collagenase, gelatinase, lysozyme, matrix lysin, membrane type (MT) - MMP and other MMPs that have not been named yet. Among them, MMP-1 in collagenase, MMP-2 and MMP-9 in gelatinase are closely related to atrial fibrillation. Different types of MMPs have slightly different domain arrangement, but they are roughly composed of five domains: signal peptide, propeptide, catalytic domain, heme binding protein like C-terminal domain and hinge region connecting the latter two. MMPs are usually derived from fibroblasts, endothelial cells, vascular smooth muscle, macrophages, cytotrophoblasts and other tissues and cells. By dissolving and renewing various extracellular matrix (ECM) proteins, MMPs maintain the normal structure and func-

tion of ECM and tissues. In addition, MMPs play an important role in the regulation of remodeling tissues and intercellular soluble factors, and participate in angiogenesis, apoptosis, immune response and other physiological and pathological processes.

The endogenous inhibitor of MMPs is named tissue inhibitor of metalloproteinases (TIMPs), and the amino terminus contained in its structure can specifically bind to the catalytic Zn^{2+} of MMPs, thereby inhibiting its activity. In addition, it also assists MT-MMP to activate proMMPs. There are only four kinds of TIMPs, and one TIMP can inhibit multiple MMPs at the same time. Therefore, it is not easy to regulate a single MMP with TIMPs as a target. More and more evidences show that TIMPs have diverse biological functions and may also regulate the growth and apoptosis of cardiac fibroblasts [5]. The ratio of MMP / TIMP is a measure of ECM protein degradation and tissue remodeling [4].

2. Significance of atrial remodeling in the development of atrial fibrillation.

Atrial remodeling is the pathological basis of the occurrence and maintenance of atrial fibrillation, including electrical remodeling, structural remodeling and autonomic nerve remodeling. Atrial fibrillation can lead to abnormal function of various ion channel proteins related to electrical conduction, such as K^+, Ca^{2+} and gap junction protein, and then abnormal myocardial electrical conduction, formation of reentrant loops in the atrium, electrical remodeling finally; Repeated atrial electrical remodeling can lead to abnormal metabolism of myocardial extracellular matrix and the formation of atrial fibrosis, which becomes the structure for the occurrence and maintenance of atrial fibrillation. At the same time, it may be accompanied by the disordered arrangement and accumulation of collagen fibers, stimulate the activation of surrounding profibrotic factors, and aggravate atrial fibrillation. As an adverse factor, the autonomic nervous system participates in the pathogenesis of AF, which is triggered by AF and further accelerates the progress of AF [1, 2, 6].

3. Relationship between MMPs and myocardial remodeling in atrial fibrillation.

3.1. MMPs and atrial electrical remodeling.

Atrial electrical remodeling is the first factor driving atrial abnormal pacing, which is mainly related to impaired calcium processing, enhanced inward rectifier potassium current and gap junction abnormalities. It has been found that MMP-2 can directly affect calcium and potassium channels, inhibit calcium influx and myocardial contraction [4]. The influx of Ca2 + caused by MMP acting on venous tissue may lead to hyperpolarization and relaxation of venous tissue [7], which may cause abnormal blood supply and oxygen supply of cardiomyocytes and further affect the electrical conduction in the atrium. Some studies have shown that MMP-2 can degrade a series of myofilament proteins related to contractility, resulting in decreased sensitivity of myofilaments to Ca2 +, and subsequent contractile dysfunction [8]. This change in contractile function is irreversible when severe. Gap link is a low resistance channel of myocardial electrical conduction, which enables electrical signals to reach the whole heart quickly and synchronously. Cx45 is mainly expressed in the sinoatrial node, and Cx40 and Cx43 are also contained in atrial cells [9]. Atrial fibrillation causes abnormal expression of gap link protein, hinders electrical conduction, and promotes the formation of reentrant waves and fibrosis in atrial tissue. This further indicates that MMPs play an important role in the process of myocardial electrical remodeling.

3.2. MMPs and atrial structural remodeling

MMPs participate in the fibrosis and remodeling of atrialtissue, and then affect the occurrence and development of atrial fibrillation. MMPs are encoded, transcribed and expressed in the extracellular matrix in the heart. When stimulated, MMPs activate, cleave collagen to rearrange them, or promote myocardial fibrosis to repair myocardial necrosis. The elevation of MMPs before and after the onset of AF represents the persistence of remodeling of cardiac extracellular matrix [10]. Jia, M. et al. found that the level of MMP-7 in myocardial cells of dogs with atrial fibrillation was increased, negatively correlated with left ventricular ejection fraction and positively correlated with myocardial fibrosis [11]. A study found that compared with the sinus rhythm group, the contents of collagen VI, MMP-2, MMP-9 and TIMP-1 in the left atrial tissue of the atrial fibrillation group were significantly increased [12]. The newly discovered MMP-28 content in patients with atrial fibrillation is significantly higher than that in sinus rhythm and is related to the left atrial diameter [13]. However, in the study of inhibiting the activity of MMP in atrial tissue of dogs with atrial fibrillation, it was found that the susceptibility to atrial fibrillation was weakened and cardiomyocyte hypertrophy and fibrosis were reduced [14]. TIMP as a natural inhibitor of MMPs, also has similar effects. Some studies suggest that the decreased expression of TIMP-2 may be the cause of ECM abnormal de-

position, structural remodeling and atrial fibrosis [15]. MMPs interfere with the process of atrial remodeling in many ways and affect the occurrence and maintenance of atrial fibrillation. In recent years, through in-depth research on MMPs, it has been found that MMPs not only have the role of promoting fibrosis, but also play the role of anti fibrosis. When Foronjy et al implanted MMP-1 in mice with ventricular remodeling caused by hypertension, the myocardial fibrosis in the mouse model was alleviated, and the specific mechanism is still unclear [16].

3.3. MMPs and autonomic nerve remodeling

Autonomic nerve remodeling intervenes the electrical conduction and structural remodeling of atrial remodeling through the neural regulatory system, and stimulates the process of atrial remodeling by regulating some cytokines, thus playing an important role in the occurrence and development of atrial fibrillation. Some studies have shown that the atrial sympathetic nerve in the canine model of persistent atrial fibrillation is significantly increase [17, 18]. Also, vagal tension can shorten the time of action potential and stabilize the reentry related rotor by affecting acetylcholine dependent potassium current [19]. It can be seen that the tension of the vagus nerve has a positive relationship with the occurrence of atrial fibrillation. Avoiding the stimulation of the vagus nerve may reduce the onset of atrial fibrillation. One study found that, β Adrenergic receptor activation can increase the permeability of Ca2 + channels in diastole, leading to Ca2 + loss, delay depolarization and stimulate ectopic beats, which is similar to β Receptor blockers have the same purpose of controlling ventricular rate. Other trials suggest that inhibition of autonomic nerve signals can improve the effect of pulmonary vein isolation in a specific population with AF, which provides a new entry point for the prevention and treatment of AF. TIMP-3 is thought to be an upstream mediator of neuronal apoptosis and may lead to neuronal loss in ALS patients [20]. Coincidentally, it has been found that multiple MMPs are related to the pathophysiology of various neurons. Their expression and activation may affect the function of local nerves, may be related to the degradation of extracellular matrix by MMPs, and the inflammatory reaction caused by MMPs may cause irreversible effects on nerve cells [21, 22, 23]. Therefore, the complex relationship between MMPs and TIMPs and autonomic nerve reflects the complexity of MMPs participating in the progression of AF. Therefore, we can also think that we can achieve our goal by regulating one party and controlling the change of the other.

4. Relationship between MMPs and related factors of atrial remodeling

4.1. MMPs and inflammatory response

The injury and necrosis of myocardial tissue must be accompanied by local inflammatory reaction, while the whole process of myocardial remodeling in atrial fibrillation is accompanied by the occurrence of inflammatory reaction. Some people have even studied the prevention and treatment of atrial fibrillation by inhibiting the inflammatory reaction. The inflammatory response will stimulate the body to secrete a large number of MMPs and other enzymes to phagocytize myocardial necrotic tissue. However, continuous inflammatory stimulation will lead to excessive MMPs, destroy the stability of ECM [5], and promote atrial remodeling. Many studies have directly or indirectly shown that MMP-2 and MMP-9 have pro-inflammatory and anti-inflammatory properties; The level of MMP-9 is also directly related to the activities of C-reactive protein, fibrinogen and IL-6, and is considered as a novel inflammatory marker of coronary heart disease [24]. TIMP-3 is involved in the pathogenesis of vascular inflammation [25]. Even some MMPs are secreted by inflammatory cells and stimulated by inflammatory factors to accelerate the secretion process [4]. This series of evidence shows that MMPs are closely related to the inflammatory response. They promote each other and participate in the process of fibrosis and remodeling of atrial tissue.

4.2. MMPs and oxidative stress

At present, people have clearly recognized the importance of oxidative stress in the occurrence and development of atrial fibrillation. Combined with the current research results, it is speculated that the mechanism may be related to the interference of electrical remodeling, atrial remodeling and fibrosis, and the damage of oxidative stress to myocardial protein, lipid, DNA, etc. In addition, oxidative stress can stimulate inflammatory response, induce tissue damage and aggravate atrial fibrillation. In the myocardium of atrial fibrillation, it is often found that the oxidative stress products are significantly increased, the mitochondria are damaged and even the expression of redox genes is dysregulated. It has been found that hypoxia can promote the mRNA expression of MMP-2 and MMP-9 [26], and tissue inhibitors of MMPs favors Collagen accumulation. Oxidative stress produced in vascular endothelial cells leads to increased expression and activity of MMP-9 and so on [27]. In short, oxidative stress can stimulate MMPs and promote the occurrence of atrial fibrillation by participating in the fibrosis of atrial tissue.

4.3. MMPs and other factors

The transcription, expression and activation of MMPs in vivo are affected by various cytokines such as platelet-derived growth factor DD, epidermal growth factor (EGF), tumor necrosis factor [4], which play an important role in the pathogenesis, maintenance and prognosis of AF. MMPs and its inhibitor TIMPs regulate the activation of many inflammatory cells, cytokine release, cardiomyocyte proliferation and apoptosis, and participate in the occurrence and development of atrial fibrillation.

5. Summary

The pathophysiological mechanisms of AF include electrical remodeling, structural remodeling, autonomic nerve remodeling, excessive inflammatory environment, metabolic stress, chemokines and paracrine effect of epicardial adipose tissue [28]. Among them, atrial remodeling is the main pathogenesis and pathological basis of atrial fibrillation. Starting with MMPs, this paper analyzes the pathological mechanism related to atrial remodeling layer by layer in order to further clarify the decisive role of atrial remodeling in the development of atrial fibrillation and the important role of inflammatory factors, oxidative stress and other factors in this process. Myocardial fibrosis affects the occurrence, maintenance and recurrence of AF, and atrial structural remodeling is the main reason for the occurrence and maintenance of AF [29]. Studies have shown that the pro fibrotic pathway and inflammatory response are considered to be the most likely factors to induce the recurrence of AF after catheter ablation [30]. At present, many MMPs have been found to be biomarkers for predicting the risk of AF, recurrence after cardioversion and prognosis, which still needs long-term and large-scale investigation and research in clinical practice. A clearer understanding of atrial remodeling can further clarify the pathogenesis of atrial fibrillation and help prevent and treat atrial fibrillation earlier and more effectively. At present, there are many drugs targeting MMPs under research. At present, there are many kinds of drugs used to treat atrial fibrillation in the domestic and foreign guidelines for atrial fibrillation. In further pharmacological studies, it is also found that there is a subtle relationship between these drugs and MMPs. In conclusion, the role of matrix metalloproteinases in the pathogenesis of atrial fibrillation cannot be ignored. However, with the in-depth and detailed study of MMPs, people find that the mechanism of action is more complex, and this complexity brings new challenges and ideas. Therefore, in the future research, we need to pay more attention to the meticulous factors such as temperature, environment and stimulation factors to make the experiment more accurate and effective.

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