Advances in the ADAMTS Family in Cardiovascular Disease

Tianying Jin, Zhaohui Meng*

Laboratory of Molecular Cardiovascular Disease, Department of Cardiology, The First Affiliated Hospital of Kunming Medical University, Kunming 650032, China.

Abstract: Cardiovascular disease is a serious threat to human life and health. The number of people who die from cardiovascular disease is up to 15 million every year, ranking the first cause of all causes of death. ADAMTS family (A Disintegrin and Metalloproteinase With Thrombospondin Motifs, ADAMTSs) are matrix-associated zinc metallopeptidases with secretory function. It has diverse roles in tissue morphogenesis, pathophysiological remodeling, inflammation, and vascular biology. Controlling the structure and function of the Extracellular Matrix (ECM) is the central theme of the biology of ADAMTSs. ADAMTSs mainly play a biological role by regulating the structure and function of extracellular mechanisms, and the abnormal expression or dysfunction of some family members is associated with cardiovascular diseases. ADAMTS family plays an important role in the occurrence and development of various cardiovascular diseases. This paper aims to study the role of ADAMTS family in cardiovascular diseases.

Keywords: ADAMTSs; Dilated Cardiomyopathy; Acute Coronary Syndrome; Atherosclerosis

Introduction

The world's leading cause of death is now cardiovascular disease (CVD) : it kills more people each year than any other cause. More than three quarters of CVD-related deaths occur in low - and middle-income countries. According to the statistical study in the 2020 Report on Cardiovascular Health and Disease in China [1], the prevalence of cardiovascular disease in China is still on the rise. The report clearly estimated that the total number of cardiovascular diseases now reached 330 million, of which 13 million were stroke patients, 11.39 million were coronary heart disease patients, 8.9 million were heart failure patients, 4.87 million were atrial fibrillation patients, about 5 million were pulmonary heart disease patients, and 2.5 million were rheumatic heart disease patients. Congenital heart disease affects 2 million people, lower extremity arterial disease affects 45.3 million people, and hypertension affects up to 245 million people [1]. At present, the etiology of many cardiovascular diseases is not clear, and many patients have insidious onset without seeking medical treatment or being diagnosed, which poses a great threat to human health. At present, a large number of clinical and basic researches on various cardiovascular diseases have been carried out in clinical and scientific research, with the purpose of seeking efficient diagnosis and treatment methods, improving the prognosis of cardiovascular diseases, and summarizing the early prevention of cardiovascular diseases.

ADAMTS family is a secreted protease belonging to the Zn2 + -dependent metalloproteinase family [2]. The mammalian genome contains a total of 19 ADAMTS genes numbered 1 to 20, of which code 11 was not used because it was assigned to the gene previously identified as ADAMTS5. The ADAMTSs protease family shares the same structural domain, which includes a propeptide region, a metalloproteinase domain, a disintegrin-like domain, and a thrombospondin type 1 (TSP1) motif. It is only that individual members of this family differ in the number of C-terminal TSP1 motifs, with some having unique C-terminal domains [3]. The proprotein encoding ADAMTS has proteolytic processing function, which can

eventually form the mature procollagen N protease. This protease excises the N-propeptide of type I-III and type V protofibrillar collagen. ADAMTS and ADAM(A Disintegrin and Metallo pro-teinase) family activities can be inhibited by The Tissue Inhibitor of metalloproteinases Metallop-roteinases, TIMPs) and other endogenous inhibitors, whose activity can also be inhibited by synthetic small molecule inhibitors [4]. ADAMTS and ADAM have been shown to be potential therapeutic targets and important diagnostic biomarkers for cardiovascular diseases. [5] Among various proteinases in the human body, ADAMTS, Matrix Metallo proteinase (MMP) and ADAM play a crucial role in cardiovascular diseases. [5] Therefore, it is urgent to explore the role and related pathophysiological mechanism of ADAMTS family in the occurrence and development of cardiovascular diseases, which may bring new progress in the early diagnosis, targeted treatment, improvement of prognosis and long-term survival rate of cardiovascular diseases.

1. ADAMTSs and the occurrence and development of cardiovascular diseases

1.1 ADAMTSs and dilated cardiomyopathy and heart failure

Dilated Cardiomyopathy (DCM) is characterized by enlargement of the left or right ventricle or both ventricles with systolic dysfunction. Some patients may have congestive heart failure during the process of the disease, and most of them have ventricular or atrial arrhythmias. The etiology of DCM is unknown, and the disease is progressive, and death can occur at any stage of the disease. At present, there is no targeted treatment for DCM. According to the 2021 China Cardiovascular Health and Disease Report, the prevalence of dilated cardiomyopathy (DCM) in China was 19/100 000 according to the survey of 9 provinces (autonomous regions) [6]. Recent studies have shown that the imbalance of ADAMTS1 and MMP2/TIMP1 ratio interferes with the synthesis of extracellular matrix and participates in ventricular remodeling in terms of collagen degradation and angiogenesis, which may promote the further development of myocarditis into dilated cardiomyopathy [7]. In the same year, Huang et al. [8] found that ADAMTS7 could degrade cartilage matrix protein (COMP) in cardiomyocytes, thereby promoting the migration of vascular smooth muscle cells (VSMC) and participating in the process of myocardial remodeling, proving that ADAMTS7 plays an important role in the occurrence and development of DCM. Subsequent studies found that ADAMTS2 expression was up-regulated in the failing human heart and hypertrophic mouse heart, and ADAMTS2 gene could also drive isoproterenol induced cardiac hypertrophy in mice [9]. ADAMTS2 attenuated endothelin (ET) -induced cardiomyocyte hypertrophy in neonatal rat cardiomyocytes. Blocking the phosphoinositide 3-kinase (PI3K)/Akt pathway can improve the hypertrophic response caused by ADAMTS2 deficiency [10]. Based on the above studies, it is hypothesized that ADAMTS1, 2, and 7 are abnormally important in the ventricular remodeling process of DCM.

Heart failure (HF) is a clinical syndrome caused by structural or functional diseases of the heart, which leads to impaired filling and/or ejection function, insufficient cardiac output to meet the metabolic needs of body tissues, congestion of pulmonary and/or systemic circulation, and insufficient blood perfusion of organs and tissues. Omura[11] et al. found that ADAMTS8 knockout mice exhibit improved right ventricular failure under conditions of chronic hypoxia, enhanced angiogenesis, and reduced right ventricular ischemia and fibrosis. This suggests that ADAMTS8 may be associated with the occurrence and development of HF.

1.2 ADAMTSs and atherosclerosis and acute coronary syndrome

Atherosclerosis is characterized by the accumulation of lipids and complex saccharides in the intima of the involved arteries, followed by hemorrhage, thrombosis, fibrous tissue hyperplasia and calcinosis. Over time, the middle layer of the

arteries gradually changes and calcifications. If the lesion progresses to occlusion of the arterial lumen, ischemia and necrosis will occur in the area supplied by the artery. Acute Coronary Syndromes (ACS) refers to the rupture or erosion of unstable plaques, incomplete or complete occlusion of coronary arteries, and acute myocardial ischemia on the basis of coronary atherosclerotic lesions. At present, ACS is clinically divided into 3 categories: Unstable angina, ST-segment elevation acute myocardial infarction, and non-ST-segment elevation acute myocardial infarction.

Studies have found that ADAMTS1, 4, 5 and 13 can be expressed in carotid plaques, especially in smooth muscle cells and macrophages, while ADAMTS1 expression is higher and ADAMTS4 and 5 expression is slightly increased in unstable plaques [12]. Jonsson-Rylander [13] et al. found through immunohistochemistry and other experiments that ADAMTS1 may promote the occurrence of atherosclerosis by cutting extracellular matrix proteins and inducing vascular smooth muscle cell migration. Pehlivan[14] et al. showed that ADAMTS1 was diffusely distributed in the myocardium of individuals who died of myocardial infarction or trauma, as analyzed by staining of cardiomyocytes from postmortem patients. Another study showed that the immune response area of ADAMTS2, 3 and 13 was very large in acute myocardial infarction, and subsequently ADAMTS2, 3, 13 and 14 were listed as the culprit of acute myocardial infarction [15]. ADAMTS4 can generally diffuse into the plasma after cardiovascular injury. Elevated plasma ADAMTS4 levels have been found in patients with ACS[16-19] and atherosclerosis [19-23]. Some of these studies have linked elevated plasma levels of ADAMTS4 to increased ACS severity [18-21] and plaque instability [23]. Elevated ADAMTS4 levels have also been found in macrophage-rich regions of human atherosclerotic plaques and unstable coronary plaques [20-23]. Plasma ADAMTS4 levels are significantly increased in acute coronary syndrome, and continue to increase with the progression from stable angina to UA, NSTEMI, and STEMI. Studies have shown that continuous measurement of plasma ADAMTS4 may be a marker of plaque instability in acute coronary syndrome [19].

Studies in mice have shown that ADAMTS7 acts early in the development of atherosclerosis, possibly in response to TNF in an inflammatory environment [24]. Corresponding analyses of human atherosclerotic lesions have shown that ADAMTS7 localizes to smooth muscle cells, but not macrophages in lesions, and localizes them to their cell surface and pseudopodia [25]. ADAMTS7 colocalizes with macrophages and smooth muscle cells in coronary and carotid atherosclerotic plaques and stains throughout the plaque, including the shoulder, cap, and core [26,27]. Plasma ADAMTS7 is elevated in patients with severe obstructive coronary artery disease [27]. Various findings suggest that ADAMTS7-related advanced atherosclerosis may be associated with the degradation of cartilage oligomeric matrix protein (COMP), a protein secreted by vascular smooth muscle cells [28-30]. Previous studies have shown that ADAMTS7 can promote vascular muscle cell migration and intimal thickening after vascular injury, and can also degrade COMP, so it plays an important role in atherosclerosis and restenosis after atherosclerosis [31-34]. Bengtsson[35] et al. analyzed the expression of ADAMTS7 in human carotid plaques by immunohistochemical method and analyzed its correlation with the components of plaque vulnerability. The results showed that ADAMTS7 levels were increased in plaques of symptomatic patients compared with those of asymptomatic patients.

Subsequently, in animal model experiments, it was found that ADAMTS13-deficient mice had a larger myocardial infarction area when myocardial ischemia was induced than wild-type mice [36-38]. Another small case-control study showed that ADAMTS13 may also play a role in coronary atherosclerotic heart disease [39]. Using a meta-analysis approach, Maino[40] et al. also demonstrated that low ADAMTS13 levels increased the risk of myocardial infarction.

In summary, we found that ADAMTS1, 2, 3, 4, 7, 10, 13, 14, 17 were all more or less related to atherosclerosis or acute coronary syndrome, which provided evidence for us to study the relationship between ADAMTSs and atherosclerosis and acute coronary syndrome.

1.3 ADAMTSs and hypertension

Hypertension is a cardiovascular syndrome characterized by elevated systemic arterial pressure, defined as office systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg. Hypertension is one of the most frequent chronic diseases in the world, and it is also one of the most important risk factors for cardiovascular and cerebrovascular diseases. In 2018, Lu Chenling [41] et al. found that the G-C mutation at rs402007 site of ADAMTS1 gene may increase the risk of essential hypertension by affecting the expression of ADAMTSl protein. Other studies have shown that ADAMTS2 promotes the occurrence and development of hypertensive disorders complicating pregnancy [42]. ADAMTS7 has been shown to affect vascular remodeling and thus reduce the occurrence of PIH, and the normal expression of ADAMTS7 has a protective effect on the occurrence of severe eclampsia [42]. ADAMTSs may be closely related to the occurrence, development and treatment of hypertension.

1.4 ADAMTSs and atrial fibrillation

Atrial fibrillation (AF) is one of the most common arrhythmias, which is more common in middle-aged and elderly people. Af is the regular and orderly loss of atrial electrical activity, which is replaced by rapid and disordered fibrillation waves, forming many new atrial reentry loops, leading to atrial rhythm disorder. Severe atrial electrical rhythm disorder leads to atrial pumping dysfunction and abnormal atrioventricular junction electrical conduction, resulting in highly irregular ventricular response and impaired cardiac function. In 2012, Cervero [43] et al. showed that the expression of ADAMTS18 was down-regulated in a pig model using rapid atrial pacing to simulate atrial fibrillation, suggesting that the reduction of ADAMTS18 may play a role in the process of thrombosis in AF. Freynhofer[44] et al. reported in 2013 that a high ratio of plasma vWF /ADAMTS13 could independently predict major adverse cardiovascular events in AF patients. Recent studies have shown that ADAMTS13 gene polymorphism may be related to the progression of hypertensive atrial fibrillation, and the detection of ADAMTS13 gene polymorphism can predict the progression of the disease [45]. Therefore, vWF and ADAMTS13, 18 May play an important role in the progression of AF.

1.5 ADAMTSs and valvular heart disease

Valvulopathy is the abnormal structure (leaflet, annulus, chordae tendines, or papillary muscles) or function of single or multiple valves caused by a variety of reasons, which eventually leads to valve stenosis and/or insufficiency. The development of myxomatous mitral valves in ADAMTS5-deficient and ADAMTS9-haplodeficient mouse models suggests that alterations in complex proteolysis are the origin of abnormal valve development [46-47]. The loss of ADAMTS19 can also cause progressive, non-syndromic valvular heart disease [48]. ADAMTS19 has been identified as a new pathogenic gene of autosomal recessive valvular heart disease, mainly affecting the aortic valve and pulmonary valve [49]. In addition, 38% of homozygous ADAMTS19 knockout mice were found to exhibit progressive aortic valve disease, characterized by aortic valve stenosis and incompetence [49]. This suggests that ADAMTS5, 9 are associated with valve development, and ADAMTS19 may be a pathogenic gene for valvular heart disease.

2. Summary and Prospect

In summary, with the continuous development of technology, we have found more and more members of ADAMTS family, and have a certain understanding of its structure and function. A large number of literatures have pointed out that ADAMTSs are involved in the occurrence and development of cardiovascular diseases through a variety of ways, which provides a basis for us to understand the pathogenesis, early diagnosis, and molecular treatment of cardiovascular diseases. However, cardiovascular diseases have multiple pathogenic factors, and how ADAMTSs are involved in them still needs to

be further explored. These studies may provide new ideas for the diagnosis and treatment of cardiovascular diseases.

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