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Research Progress of IL-33/ST2 Signaling Pathway in Cardiovascular Disease

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Abstract. Soluble ST2 (sST2) is a protein of interleukin-1 (IL-1) receptor family, IL-33 is the special ligand of ST2, IL-33/ST2 signaling has a significantly effect in the inflammation and immunology diseases. It certified that ST2 can be secreted by the myocardial cells on the mechanical overload, and it can inhibit the anti-Hypertrophy and anti-fibrosis of IL-33, can induce the cardiac remodeling. New researches indict that ST2 effects on the process of atherosclerotic and is associated with incident hypertension. Higher sST2 is related to disease activity and adverse in coronary artery disease and heart failure. Aldosterone receptor antagonist plays an important role in the IL-33/ST2 pathway.

Introduction

IL-33/ST2 signaling pathway plays an important role in myocardial remodeling after myocardial infarction and heart failure as a new mechanism for myocardial fibroblast - myocardial cell information exchange. The study found that serum level of ST2 is associated with the prognosis of myocardial infarction and heart failure; The latest edition of the American heart failure guidelines has recommended ST2 as a biomarker that provides additional risk stratification value. In addition, ST2 has the effect of causing early atherosclerosis, and high concentration of ST2 is associated with the risk of hypertension in the future [1]. Aldosterone receptor antagonist can reduce ST2 level and indirectly increase IL-33 expression, enhance IL-33/ST2 signaling pathway, and reduce inflammation and fibrosis of myocardium after infarction[2]. The mechanism of IL-33/ST2 signaling pathway in vivo is complex, and this paper will review the research progress of this pathway in recent years.

Biological Characteristics of IL-33/ST2 Signal Transduction Pathway

Biological Characteristics of IL-33

IL-33 belongs to the family of IL-1, and human IL-33 gene is located in chromosome 9, which is mainly expressed in matrix cells of barrier tissues such as skin, lungs and intestines. IL-33 is a biologically active precursor that is activated by the shear of Caspase-1 in inflammatory conditions such as cell damage or necrosis, and delivers early warning information; In the process of normal cell apoptosis, Caspase-3 and Caspase-7 can be inactivated IL-33, so as to avoid autoimmune injury[3]. IL-33 is a bifunctional protein. On the one hand, it is located in the nucleus as a transcription factor, on the other hand, IL-33 can be secreted out of the cell and play the role of cytokines by binding with ST2L. The study confirmed that IL-33 is a paracrine signaling molecule between fibroblasts and cardiac myocytes, which is mainly secreted by cardiac fibroblasts, and the expression of IL-33 is upregulated when the circulation tension increases.

Biological Characteristics of ST2

ST2 gene was discovered by Tominaga in 1989. It is located in human chromosome 2q12 and has the Toll/IL-1R structural domain and is a member of IL-1 receptor family. ST2 gene encodes 4 different subtypes: sST2, ST2L, ST2V and ST2LV. sST2 and ST2L are derived from a dual promoter that promotes differential mRNA expression. ST2L is a transmembrane type, including an extracellular domain, a transmembrane segment and a Toll/IL-1R intracellular domain. It has

immunomo- dulatory function and plays an important role in T cell mediated immune diseases. ST2V and ST2LV are two splicing bodies of ST2L. sST2 has no transmembrane sequence and is soluble ST2, which can inhibit inflammatory reaction. As a decoy receptor, sST2 can competitively bind to IL-33 and inhibit IL-33/ST2 signal transduction. ST2 is mainly expressed in mast cells, activated Th2 cardiomyocytes, lymphocytes and macrophages. Expression was different in different tissues: 114kb transcript was expressed in skeletal muscle, brain, heart and pancreas, 215kb and 412kb in liver, lung and kidney [3]. The expression of sST2 and ST2L can be induced by myocardial cells and fibroblasts under mechanical stretch.

Il-33 /ST2 Signal Transduction Pathway with Atherosclerosis and Hypertension

Both IL-33 and sST2 are expressed in vascular endothelial cells and play an important role in early atherosclerosis. The possible mechanism of IL-33 against atherosclerosis is as follows: 1） IL-33 promotes Th1 conversion to Th2, resulting in an increase of Th2, while atherosclerosis is primarily driven by Th1 cells; 2） Macrophage derived foam cells are involved in the formation of atherosclerosis. IL-33 can regulate the polarity of macrophages and make them change from M1 type with anti-inflammatory function to M2 type, which can reduce the inflammatory reaction **[4]**. 3） IL-33 can promote vascular regeneration and increase vascular permeability. Apolipoprotein E knockout of the vascular regeneration, resulting in increased vascular permeability. Experiments on mice with apolipoprotein E knockout confirmed that atherosclerosis was less common in the experimental group treated with rIL-33 after a high-fat diet, and foam cell production was reduced. However, in the experimental group treated with sST2, the effect was reversed, and the atherosclerotic plaque increased significantly **[5]**.

sST2 is associated with high blood pressure risk. Ho**[1]** et al. found in a community-based study of 1834 Framingham offspring that high sST2 concentration was associated with the risk of hypertension in the next three years. The systolic blood pressure of individuals in the upper quartile increased by 2.6mmHg (1mmHg= 0.133kpa) compared with those in the lower quartile, and the pulse pressure increased by 1.8mmHg. The concentration of sST2 has been characteristic of the progression of age and arterial sclerosis.

Il-33 /ST2 signaling pathway with coronary heart disease

Coronary heart disease (CHD) is considered to be a kind of inflammation and autoimmune diseases, is the result of the humoral regulation, cell regulation, IL-33/ST2 signaling pathway is involved in the inflammation process, to protect ischemic myocardial cells, improve heart function. IL-33 inhibits the cascade reaction of Caspases, inhibits the apoptosis of ischemic myocardial cells, and protects myocardial cells from ischemic injury. IL-33 can also induce the expression of anti-apoptotic factors, XIAP, CIAPI and survivin, and improve cardiac function. sST2 can partially inhibit the protective effect of IL-33 on myocardium. Seki[6] et al. confirmed that IL-33 could improve the left ventricular function by reducing the myocardial fibrosis around 15d after myocardial infarction, thus improving the survival rate of myocardial infarction in wild mice and ST2 knockout mice. ST2 level and IL-33/ST2 ratio in the blood of patients with acute myocardial infarction were correlated with prognosis at 6 months.

IL-33/ST2 signaling pathway is involved in the process of myocardial remodeling after myocardial infarction. sST2 is involved in regulating the remodeling and inflammatory processes of extracellular matrix, which can cause arrhythmias and other negative cardiovascular events **[7]**. In acute myocardial infarction, a series of complex, extensive and rapid cellular and extracellular matrix remodeling reactions are initiated to activate the aldosterone system, which has strong fibrogenic effects on the heart, including compensatory fibrosis in the infarction area and reactive fibrosis in the non-infarction area. Aldosterone receptor antagonist can enhance IL-33/ST2 signaling pathway by low expression of sST2, reduce postinfarction collagen synthesis, reverse myocardial fibrosis, prevent myocardial remodeling, improve prognosis, etc. Weir**[8]** studies have found that sST2 level after myocardial infarction is positively correlated with norepinephrine and plasma aldosterone level, independent of NT-pro BNP. Lax et al.**[2]** observed in the rat model of acute myocardial infarction (descending branches before ligation) that IL-33 expression level and the concentration of fibrosis and inflammatory markers in myocardial cells after infarction were

higher than those in the control group, and the levels of fibrosis and inflammatory markers were decreased after treatment with aldosterone receptor antagonists.

Il-33 /ST2 signaling pathway with heart failure

Currently, the gold standard for the diagnostic and prognosis of heart failure is the BNP and the NT-pro BNP, because it's susceptible to various factors, like the age, sex, the left ventricle, the ventricle, the atrial fibrillation, the atrial fibrillation, myocardial ischemia, the hypooxygenemia, the hepatic and the high metabolic risk factors, whose clinical reference value is limited[9]. As a new type of marker, sST2 can not only reflect the pathological and physiological process of myocardial injury, inflammatory reaction and myocardial remodeling after heart failure[10], but also not affected by age, body mass index, kidney function damage[11]. The 2013 new ACC/AHA heart failure guidelines and 2014 China heart failure diagnostic and therapy guide have introduced sST2 to the recommendation of biomarkers; The latest edition of the American heart failure guide has recommended it as a biomarker that provides additional risk stratification value [12].

sST2 is a strong index for the independent prediction of short term mortality in a heart failure patient, and the SST 2 can be better used in the diagnosis of heart failure, risk stratification and prognostic evaluation, in combination with NT-pro BNP. Ahmad et al.[13] found that sST2 was a strong independent predictor of pump failure and sudden cardiac death through observation of 813 patients with systolic heart failure who received emergency treatment. So, Zilinski[14] have been able to detect the prognosis of the ICU in the advanced ICU in the course of the pulmonary catheterization of the pulmonary artery, and the elevated sST2 in 48h can predict the prognosis of the 90d. Zhang et al.[15] found that sST2 was a strong independent predictor of hospitalized patients with heart failure and could significantly increase the value of nt-pro BNP in risk prediction by tracking 1528 hospitalized patients with heart failure for 19.1 months (all cause death and heart transplantation as negative events). Because of the molecular mechanism, the diagnostic value of sST2 protein in idiopathic dilated cardiomyopathy in chronic heart failure is higher than that of ischemic cardiomyopathy. sST2 is also associated with the risk of cardiovascular disease in diabetics, and the IL-33/ST2 signaling pathway may play an important role in the inflammatory response to diabetes. Fousteris[16] in 158 cases of normal systolic function of the volunteers in the study found that sST2 in Ⅱ diabetes patients blood concentrations higher than control group, with left ventricular diastolic dysfunction of its concentration is higher in patients with diabetes, sST2 associated with blood glucose control level obviously; This may be related to the secretion of sST2 by vascular endothelial cells under the stimulation of a large number of inflammatory factors. Huang Chenhua etc[17] research shows that the level of serum sST2 associated with Ⅱ diabetes patients in cardiovascular disease risk factors such as age, plasma fibrinogen, Framingham cardiovascular risk stratification ten years were positively correlated. Left ventricular diastolic dysfunction in patients with type Ⅱ to assess the diagnostic value of serum ST2 is better than that of the BNP [18]. Abston et al. [19] found that IL-33 can induce eosinophilic pericarditis, and IL-33 has adverse effects on cardiac function through its receptor binding. Meanwhile, sST2 can prevent the growth of eosinophils and improve cardiac contractility. This poses a challenge to IL-33/ST2 signaling pathway in the treatment of heart disease and heart failure.

Conclusion

With the deepening of the study on IL-33/ST2 signaling pathway, ST2 is gradually recognized by people. sST2, as a kind of inflammatory cytokines in acute or chronic infectious diseases, allergic disease, pulmonary embolism, stroke, acute trauma, connective tissue diseases and tumor diseases can be increased, thus limits its alone as a specific myocardial markers and used in clinical. IL-33/ST2 signaling pathways in the body mechanism is complex, has a positive role in protecting the body from disease, also have negative effect to promote the development of disease, it is subject to our further in-depth study.

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