

Research Progress on IL-6 / STAT 3 Signaling Pathway in Heart Failure

Junyi Li¹, Jing Liu^{2,*}, Jike Li², Ru Han², Juan Li²

¹*Shaanxi University of Chinese Medicine, Xiayang, Shaanxi, 712046, China*

²*Xi'an Hospital of Traditional Chinese Medicine, Xi'an, Shaanxi, 710021, China*

**Corresponding author*

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Abstract: Heart failure is the end stage of cardiovascular disease. It has the characteristics of high medical cost, high mortality and poor quality of life of patients. Its treatment is a difficult and hot topic in the field of cardiovascular research. In order to treat heart failure, it is necessary to understand the specific mechanism of its occurrence. With the continuous discussion and research on the mechanism of heart failure, signal pathways related to heart failure are also constantly being discovered. Interleukin-6 / signal transducer and activator of transcription 3 (IL-6 / STAT3) is one of the more novel pathways. In the early days, IL-6 / STAT3 signaling pathway was more used in the field of cancer. In recent years, more and more studies have shown that IL-6 / STAT3 signaling pathway can also affect the occurrence and development of heart failure by affecting myocardial inflammation, myocardial fibrosis, myocardial energy metabolism and so on. This article focuses on the relationship between IL-6 / STAT3 signaling pathway and heart failure.

1. Introduction

Heart failure (HF) is a syndrome of cardiac structural and (or) cardiac function abnormalities leading to impaired systolic or (and) diastolic function, leading to a range of clinical manifestations. It is characterized by high medical cost, high fatality rate and poor quality of life of patients. The etiology of HF is more complex, involving a variety of signals Conduction as well as protein expression. With the continuous exploration of heart failure, the signaling pathways related to heart failure are also being explored, and IL-6 / STAT 3 signaling pathway is more used in the research of cancer field in the early detection. It has also been closely linked to heart failure through various mechanisms such as inflammatory response and hormone secretion. This provides new ideas for the treatment of HF. This paper focuses on the IL-6 / STAT 3 signaling pathway in the development of heart failure mechanism of action.

2. Current Research Status on Heart Failure

2.1 Epidemiological Investigation of HF

In recent years, with the aging of the population, the increase of work pressure, the impact of bad

living habits and many other factors. The incidence of cardiovascular disease (CVD) also increases year by year, dying in urban and rural residents. Take the first place in the death composition ratio [1]. As the terminal stage of cardiovascular disease, heart failure is one of the main causes of death. In 2021, the overall crude incidence of HF in China was 248 /100,000 per year, the standardized prevalence of HF was 1.1% and 275 / 100,000 people per year. Therefore, it is estimated that for 12.05 million HF patients aged 25 and above, the standardized prevalence of HF in people over 35% was about 50% higher than that in 2000, and the incidence of 80 years old patients reached 1655 / 100,000 per year [2]. In addition to the high incidence, heart failure is not optimistic in prognosis, even worse compared to some malignancies [3]. According to a survey of patients with Heart failure with preserved ejection fraction (HFpEF) in 481 hospitals in 31 provinces in China released in 2022, The incidence of major clinical events was 16.4%, 1-year hospitalization rate for heart failure was 13.6%, cardiovascular mortality was 3.1%, all-cause mortality was 8.5%, and cardiovascular, non-cardiovascular and unexplained deaths were 36.7%, 37.2% and 26.1%, respectively [4]. The occurrence of heart failure not only seriously damage the health of patients, at the same time caused a heavy economic burden, in 2012, an estimated global heart failure overall economic cost of \$108 billion, the direct cost accounts for about 60% of total expenditure, indirect cost about 40% of the total expenditure, and with the global population aging, rapid growth and industrialization, this value will continue to rise [5]. It can be seen that the prevention and treatment of heart failure has become an important task in China's medical and health industry, and the exploration and research work of heart failure is urgent.

2.2 The Occurrence Mechanism of Heart Failure

HF is a clinical syndrome of myocardial causes [6], and ventricular remodeling is an important pathological process in the development of HF [7]. Cardiomyocyte apoptosis, vascular damage, and myocardial fibrosis caused by various causes may further aggravate ventricular remodeling, and eventually lead to heart failure.

Some studies have shown that inflammatory cytokines such as IL-6 and IL-1 can further lead to the occurrence of myocardial remodeling by affecting cardiac contractility, inducing mast cells, and promoting cell apoptosis and fibrosis, and ultimately causing heart failure [8-9]. Coronary microvascular endothelial cells (CMEC) impairment causes coronary microvascular dysfunction (CMD). CMD will cause excessive coronary microvasoconstriction, impaired diastolic function, and vascular structure changes, leading to increased coronary microcirculation resistance and increased myocardial energy consumption. The activated endothelial cells aggravate myocardial fibrosis through endothelial-mesenchymal transition to promote the progression of ventricular remodeling, which then leads to the development of HFpEF [10-13]. Cardiomyocyte apoptosis is also considered to be an important process in the progression of HF. Mitochondria and Cysteiny l aspartate specific proteinase (Caspase) enzymes play an important role in this process [14-15]. Mitochondrial permeability changes when myocardial cells are stimulated by ischemia and hypoxia. Cytochrome c, Smac / DIABLO and other substances are released into the cytoplasm from mitochondria. Cytochrome c binds to the cytoplasmic protein apaf1 to form an oligomer Apaf-1 / cytochrome c complex, which activates caspase-9 and then triggers caspase-3 activation. In this process, the released Smac / DIABLO also promotes the activation of caspase-9 by inhibiting the expression of apoptosis inhibitory factors (IAPs). The two work together to promote cardiomyocyte apoptosis [16]. In addition, long-term abnormal glucose metabolism in diabetic patients can also lead to problems such as decreased vascular wall elasticity, myocardial dysfunction, and cardiac energy metabolism disorders, and ultimately induce the occurrence of heart failure. For every 1 % increase in glycated hemoglobin (HbA1c), the risk of heart failure increases by 8 % [17-18].

3. Current Status of STAT 3 and IL-6

The STAT family of proteins has functions in signal transduction and transcriptional activation. STAT 3, discovered in 1994, is activated by tyrosine phosphorylation, acting as a DNA binding protein for epidermal growth factor (EGF) and IL-6, but does not respond to interferon γ (IFN- γ) [19]. STAT 3 includes multiple isoforms, including long STAT3 α , truncated STAT3 β and STAT3 γ , and STAT3 δ , various isoforms derived from a gene within chromosome 1 through alternative splicing of transcript 17 q 2, which can be affected by multiple factors, and signals triggered by pH, pO₂ and IL-3 each converge on STAT 3 through independent mechanisms, using the flexibility conferred by different STAT 3 isoform expression and phosphorylation diversity to regulate different granulocytic responses [20]. Study [21] found that STAT 3 is a key transcriptional regulator of β -adrenergic receptor-mediated cardiac stress adaptation, pathological remodeling and heart failure, which, through G α protein and Src protein kinase activation, alleviated the ventricular remodeling generated by β AR activation. Moreover, it has been shown that [22] deubiquitination enzymes can lead to inflammatory response, fibrosis and hypertrophy in cardiomyocytes by inducing deubiquitination of STAT 3. There have also been studies [23] that inhibition of STAT3 activity in mice attenuates ventricular remodeling induced by angiotensin II (AngII). Some studies [24] found that the subacute myocardial infarction mice after STAT 3 knockout had an aggravation of cardiac fibrosis, decreased capillary density, increased superoxide production, increased mortality and caused severe cardiac hypertrophy after a period of time. Therefore, it can be seen that the expression of STAT 3 is not solely harmful to the body, but is complex and bidirectional.

IL-6 is a multifunctional cytokine with pro-inflammatory and anti-inflammatory efficacy and plays an important role in host defense. When infection or tissue damage occurs, IL-6 is rapidly produced by monocytes and macrophages and through various responses to remove infectious agents and restore damaged tissue [25]. But excessive IL-6 production can lead to chronic inflammation and autoimmune diseases [26]. The level of IL-6 during the development of HF is also strongly associated with HF severity [27]. IL-6 can exert its effects on the heart through multiple pathways. IL-6 can act on the megakaryocytes, generation stage leading to increase the release of platelets, which is not only more easily lead to the formation of coronary artery thrombosis, but also through the platelet rich chemokine ligand 4 (CXCL 4) to promote macrophage secreted phosphoprotein 1 (Spp 1), fibronectin 1 (Fn 1) and arginase 1 (Arg 1) expression to aggravate damaged myocardial fibrosis, speed up the process of heart failure [28-29]. In addition, IL-6 may also induce the production of vascular endothelial growth factor (VEGF), which can lead to increased vascular permeability and enhanced angiogenesis, thus to slow the development of heart failure [30-31]. Taken together, the mechanisms of the influence of IL-6 on HF are also complex.

4. IL-6 / STAT 3 Signaling Pathway and Heart Failure

4.1 Current Status of IL-6 / STAT 3 Signaling Pathway

The IL-6 / STAT 3 signaling pathway was early identified as a key oncogenic pathway. With the expansion of the role of this signaling pathway, this pathway is no longer only limited to cancer. Some studies have shown that endotoxin can cause the production of tumor necrosis factor α (TNF- α) to strengthen the inflammatory response and recruit inflammatory cells, leading to increased cardiomyocyte apoptosis and tissue damage, while IL-6 can activate STAT 3 through gp 130 to reduce the production of TNF- α and combat the negative effects of endotoxin on the myocardium [32]. This study shows that this signaling pathway has an important role in the development of heart failure.

4.2 Specific Mechanisms of the IL-6 / STAT 3 Signaling Pathway in the Process of Heart Failure

Inflammatory response is an important mechanism leading to heart failure, and the IL-6 / STAT 3 signaling pathway can have adverse effects on the myocardium by enhancing the inflammatory response. It is shown that IL-6 binds to the IL-6 receptor (IL-6R) to form a complex to bind the agonist protein gp 130, which then induces its dimerization and initiates intracellular signaling through the JAK / STAT pathway, and the IL-6 / gp 130 / STAT 3 axis is the basic condition of the inflammatory response [33]. Animal experiments [34] have shown that IL-6 / STAT3 signaling is up-regulated in HF mice induced by aortic coarctation. After inhibiting IL-6 / STAT3 signaling, the development of inflammation, MF, and myocardial hypertrophy in cardiomyocytes has also been inhibited. This indicates that IL-6 / STAT3 signaling can increase the release of IL-6 from cardiomyocytes and cardiac fibroblasts and promote STAT3 phosphorylation. This will lead to the accumulation of inflammatory factors and inflammatory cells, increased local inflammatory response, increased myocardial cell damage, and ultimately promote the progress of HF. At the same time, IL-6 / STAT 3 signaling pathway can also aggravate the iron death of cardiac microvascular endothelial cells (CMVECs), induce myocardial remodeling and cause cardiac dysfunction by strengthening the up-regulation of iron level and lipid peroxidation mediated by AngII [35].

Myocardial fibrosis (MF) is also an important pathological process in heart failure. However, IL-6 / STAT 3 can promote the development of MF by upregulating the level of fibronectin and collagen, thus leading to aggravated heart failure. Some studies [36] found that miR-320 activated IL 6 / STAT 3 pathway promotes the overexpression of cardiac hypertrophy and fibrosis. This process may be related to increased type I and III collagen in the left ventricular tissue. And Hikmet Nural-Guvener et al [37] was found that congestive heart failure (CHF) could be used by Mocetinostat by inhibiting class I histone deacetylase to reduce the phosphorylation of IL-6 and STAT 3 at Y705, and then reduced the levels of fibronectin and collagen in cardiac fibroblasts and increased the ability against myocardial fibrosis, indicating that the activation of IL 6 / STAT3 could aggravate the degree of myocardial fibrosis.

IL-6 / STAT 3 pathway can also affect cardiomyocytes through the myocardial energy metabolism pathway. Someone [38] found that IL-6 / STAT 3 can increase the expression of mitochondrial outer membrane protein FUNDC1 in cardiomyocytes, and the formation of mitochondria-related endoplasmic reticulum membrane can cause cardiac dysfunction.

IL-6 / STAT 3 not only has a negative effect on the heart, but also has a protective effect on the heart when heart failure occurs. For example, in the occurrence of heart failure, the liver can inhibit ventricular remodeling through the IL-6 / STAT3 pathway, which leads to the lack of mineralocorticoid receptors (MR) in hepatocytes and then up-regulates the expression of fibroblast growth factor 21 (FGF21) in liver to treat heart failure and MI. Similarly, hepatocyte IL-6 receptor deficiency and Stat3 deficiency can aggravate cardiac injury by regulating the MR / FGF21 axis[39].

5. Conclusions

Heart failure is the end-stage route of many cardiovascular diseases. Delaying the development of heart failure, reducing the morbidity and mortality of heart failure have become the focus of cardiovascular disease research today. With the development of science and technology, the signaling pathways related to HF have been gradually explored, and the in-depth discussion of the different mechanisms of HF causes is helpful to find new solutions. IL-6 / STAT 3 pathway has been tested to affect the development of heart failure through many factors, such as inflammatory response, energy metabolism, myocardial fibrosis and myocardial fibrosis. Most studies have

shown that the activation of the IL-6 / STAT3 pathway can lead to heart failure or aggravate heart failure, but this effect is not a single, but a complex two-way. We believe that we will find more and more comprehensive content if we continue to dig deeper into the upstream and downstream of the signaling pathway. It provides more theoretical support for the clinical treatment of heart failure and drug development.

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