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JAK/STAT Pathway as a Double-Edged Sword in Myocardial Ischemia-Reperfusion Injury

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Abstract: Myocardial ischemia-reperfusion injury (MIRI) is a serious injury to ischemic myocardium after blood flow recovery, and it is the focus and difficulty of cardiovascular disease treatment. The JAK/STAT signaling pathway is a double-edged sword in MIRI. The activation of STAT1 can promote cardiomyocyte apoptosis and aggravate myocardial injury. STAT3 can reduce myocardial injury by up regulating anti apoptotic protein, but inhibiting the activation of the JAK2/STAT3 signaling pathway under oxidative stress can protect myocardium.

1. Introduction

Myocardial ischemia-reperfusion injury (MIRI) refers to the severe damage inflicted upon ischemic myocardium following the restoration of blood flow after acute myocardial infarction (MI), utilizing thrombolytic drugs or percutaneous coronary intervention, among other methods, which is a focal point and challenge in the treatment of cardiovascular diseases[1]. MIRI often presents with increased myocardial injury such as no-reflow, myocardial stunning, and severe lethal arrhythmias, as well as increases the risk of serious complications such as heart failure and sudden cardiac death[2]. Reperfusion-induced myocardial injury has been reported to account for nearly 50% of the final myocardial damage in acute myocardial infarction[3], posing a significant threat to patients' lives and health. The pathogenesis of MIRI is complex and may be associated with increased myocardial oxidative stress, calcium overload leading to myocardial apoptosis, decreased mitochondrial membrane stability, autophagy, myocardial inflammation, and disordered energy metabolism[4]. Previous studies have shown that the Janus protein tyrosine kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway plays a significant role in the mechanisms of MIRI. JAK is a cytoplasmic tyrosine kinase that, upon interaction with activated

cytokine receptors, undergoes autophosphorylation and subsequently phosphorylates STAT, promoting its translocation into the nucleus to regulate the expression of target genes, thereby modulating apoptosis in cardiomyocytes and influencing the pathological progression of MIRI[5]. Understanding the role of the JAK/STAT pathway in MIRI can aid in the advancement of potential drug research.

2. Biological Characteristics of the JAK/STAT Pathway

The JAK/STAT signaling pathway is a ubiquitously expressed intracellular signal transduction pathway, considered one of the central communication hubs in cellular function[6]. As signal transducers and activators of transcription, JAK proteins transduce signals from extracellular ligands (e.g., cytokines and growth factors) to the nucleus to orchestrate cellular responses. Structurally, JAK possesses seven highly conserved homology (JH) domains, among which the JH1 domain contains the genetic sequence required for activation and autophosphorylation, regulating kinase activity and serving as a binding site for STAT proteins[7].STAT, a substrate of JAK, is activated by phosphorylation of serine Ser727 and tyrosine Tyr705 and plays a central role in signaling from the plasma membrane to the nucleus and mitochondria[8]. The process of JAK-STAT signaling pathway can be summarized as follows: (1) cytokines such as interleukins, interferons, and colony-stimulating factors bind to transmembrane receptors, phosphorylating and activating JAKs; (2) JAKs activate the tyrosine phosphorylation of STATs; (3) STATs enter the nucleus in the form of homodimers or heterodimers, and bind with the promoters of target genes to regulate the gene expression. This pathway is widely involved in biological processes such as cell proliferation, differentiation, apoptosis, inflammation, and immune regulation, playing a significant role in MIRI and myocardial protection[9].

3. Role of the JAK/STAT Pathway in Myocardial Ischemia-Reperfusion Injury

During the onset of MIRI, Ca^{2+} concentration in cardiomyocytes increases significantly, leading to mitochondrial dysfunction, which in turn activates cysteine asparaginase 3 (Caspaes3) and promotes apoptosis of cardiomyocytes, exacerbating myocardial injury; concurrently, the accumulation of reactive oxygen species (ROS), disturbance of cellular ionic homeostasis, and inflammatory response to cell death can cause further damage to ischemic tissues[10]. The pathological processes of oxidative stress, inflammatory response, and apoptosis involved in the process are all closely related to the JAK/STAT pathway[10]. Studies have found that all members of the STAT family have some degree of distribution in the heart, among which STAT1 and STAT3 have opposite effects on cardiomyocyte survival during ischemic injury[11]. When STAT1 expression is upregulated, the apoptotic pathway in cardiomyocytes is overactivated, aggravating myocardial injury, while STAT3 can exert a cardioprotective effect by upregulating the expression of anti-apoptotic and cytoprotective proteins[11]. (1) JAK2/STAT3 signaling pathway: studies have shown that in a myocardial ischemia model of mice treated with the JAK2 inhibitor AG490, the number of apoptotic cardiomyocytes and the infarct area in ischemia-reperfusion injury mice significantly increased, suggesting that myocardial injury and infarction in MIRI may be associated with the inhibition of the JAK2/STAT3 pathway[12]. Additional evidence shows that the activation of the JAK2/STAT3 signaling pathway is crucial for cardiac protection after ischemia. The ischemic preconditioning state can activate mitochondrial STAT3 by increasing levels of cardiac adiponectin (APN), thereby improving mitochondrial function, promoting an increase in ATP content, reducing myocardial oxidative stress, and ultimately alleviating ischemic myocardial injury[13]. In contrast, some researchers have proposed that inhibiting the JAK2/STAT3 pathway can also be beneficial for myocardial injury. They found that under oxidative stress, inhibiting the phosphorylation and

activation of the JAK2/STAT3 pathway can eliminate ROS generated during focal myocardial I/R, maintain cellular redox status, and prevent oxidative damage[14], implying that the JAK2/STAT3 pathway is not an absolute protective factor in MIRI. (2) The JAK2/STAT1 signaling pathway: The JAK2/STAT1 pathway is a detrimental factor for MIRI prognosis, and inhibition of this pathway can attenuate the damage of MIRI. In in vivo/in vitro IR rat models, inhibiting the activity of JAK2 and STAT1 can increase the antioxidant capacity of myocardial tissue and reduce cell apoptosis; whereas, after combining the JAK2 inhibitor AG490 or the STAT1 inhibitor S1491, the expression of Caspase-3 and pro-apoptotic protein Bax was decreased, and the expression of the anti-apoptotic protein Bcl-2 was increased, and the anti-apoptotic effect of HSYA was significantly enhanced, indicating that inhibiting the JAK2/STAT1 pathway can strengthen myocardial protection[15].

In conclusion, the inhibition or activation of the JAK/STAT pathway may be one of the key factors in the occurrence of MIRI. As the course of MIRI progresses or the severity of the condition changes, the activity and levels of JAK2, STAT1, and STAT3 also change. The activation of STAT1 can promote apoptosis in cardiomyocytes and exacerbate myocardial injury, while STAT3 can alleviate myocardial injury by upregulating anti-apoptotic proteins. However, inhibiting the JAK2/STAT3 pathway under oxidative stress can maintain cellular redox status and prevent oxidative damage. Therefore, the JAK/STAT signaling pathway is a double-edged sword in MIRI, and the rational regulation of JAK/STAT pathway signaling to inhibit apoptosis in cardiomyocytes and alleviate myocardial cell injury may become a breakthrough point in the treatment of MIRI.

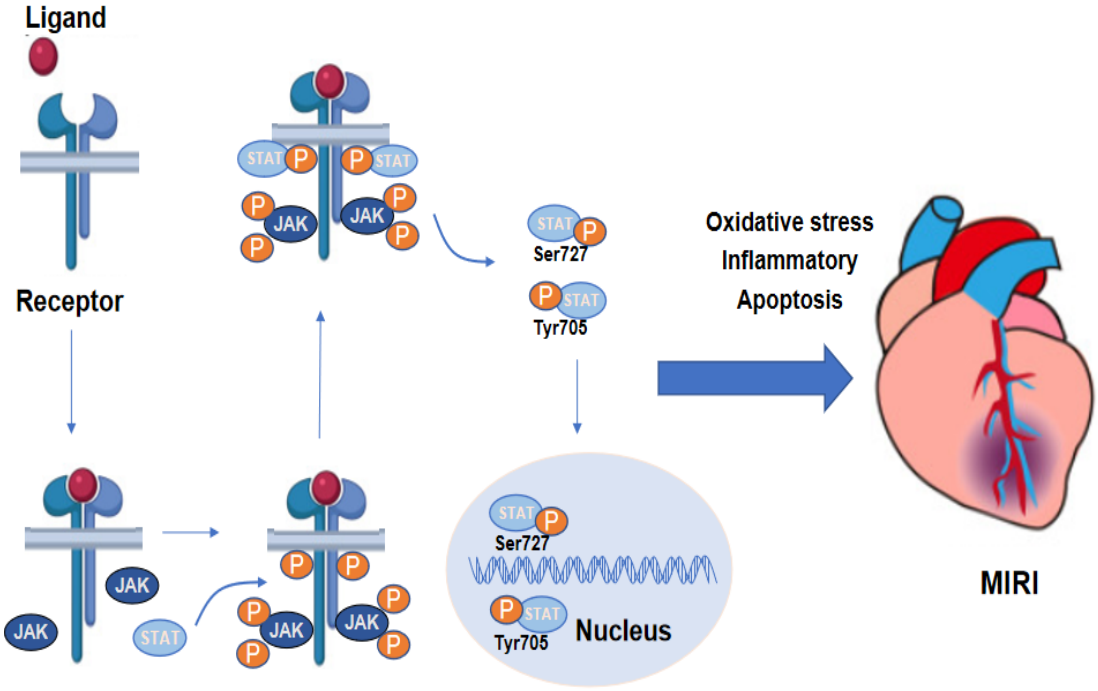

Fig.1 Mechanism of JAK/STAT pathway in MIRI

4. Conclusion

In recent years, a growing body of evidence has indicated that the JAK/STAT signaling pathway is an important mechanism in the development of MIRI. The activation or inhibition of this pathway has been confirmed as a significant factor leading to the occurrence of MIRI. Activation of STAT1 can promote apoptosis in cardiomyocytes, thereby exacerbating myocardial damage, while STAT3 can mitigate myocardial injury by upregulating anti-apoptotic proteins. However, under conditions

of oxidative stress, inhibiting the JAK2/STAT3 pathway activation can paradoxically serve a protective role for the myocardium. Thus, the JAK/STAT signaling pathway is a double-edged sword in MIRI.

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