# Mechanistic Research and Therapeutic Advances of the JAK/STAT Signaling Pathway in Myocardial Infarction

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**Abstract:** Myocardial infarction (MI) is a critical heart disease with high incidence and mortality. Current treatments like coronary reperfusion have limitations, including risks of reperfusion injury and bleeding. Understanding MI's molecular mechanisms is vital for developing new strategies. The JAK/STAT pathway plays a key role in MI by regulating inflammation, apoptosis, fibrosis, oxidative stress, and angiogenesis. This article reviews its role in MI pathophysiology and its therapeutic potential, laying a foundation for innovative treatments. As research progresses, modulating JAK/STAT shows promise in reducing myocardial damage and inflammation, offering hope for future effective therapies.

***Keywords*:** janus kinase (JAK), signal transducer and activator of transcription (STAT), myocardial infarction (MI), therapeutic strategies

## 1. Introduction

Myocardial Infarction (MI), a severe consequence of Coronary Artery Disease (CAD), usually results from atherosclerotic plaque rupture causing acute coronary occlusion, leading to myocardial ischemia and necrosis[1]. This event abruptly interrupts myocardial blood flow, inducing prolonged ischemia and widespread cardiomyocyte necrosis and apoptosis[2]. Rapid restoration of oxygen and blood supply is crucial for emergency and long-term management. MI triggers inflammation and necrotic cell clearance by macrophages, and can lead to severe complications such as heart failure, ventricular aneurysms, septal rupture, arrhythmias, and sudden cardiac death, increasing mortality risk. Thus, key goals in MI management include restoring blood flow, reducing infarct size, enhancing cardiac function, and lowering mortality. Coronary reperfusion therapy is the gold standard for acute MI, but high mortality and morbidity rates persist, along with complications like hemorrhage, ischemia-reperfusion injury, and restenosis[3]. Therefore, focusing on post-ischemic cardiac repair and protection—such as reducing inflammation, inhibiting cardiomyocyte apoptosis, and promoting angiogenesis—is vital for MI treatment and prognosis. Investigating the molecular mechanisms underlying these strategies is essential for developing novel and effective therapies, a core mission in cardiovascular research.

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway is an essential intracellular network regulating inflammatory responses, myocardial cell apoptosis, and angiogenesis, making it a promising therapeutic target for MI , This review explores the pathogenic consequences of JAK/STAT pathway activation in MI and provides an overview of JAK/STAT inhibitors' application in MI management, emphasizing their potential to mitigate severe effects and guide therapeutic approaches. By doing so, it aims to contribute to ongoing scientific discourse and foster the development of more effective MI therapies

## 2. Overview of JAK/STAT pathway

Discovered three decades ago, the JAK/STAT signaling pathway, activated by cytokines, has become a research hotspot. It transmits signals from the cell membrane to the nucleus, promoting transcription of key genes for cellular responses and serving as a central communication node in mammalian cells[4]. This pathway is linked to various diseases, including autoimmune, oncological, cardiovascular, inflammatory bowel, and neurodegenerative conditions. It plays a crucial role in cytokine signaling, immune response modulation, and cell proliferation and differentiation, supporting hematopoiesis, immune balance, and tissue homeostasis[4,5]. Unlike other cascades, JAK/STAT has a streamlined mechanism involving three key components: tyrosine kinase-associated receptors, JAK, and STAT.

### 2.1 Tyrosine kinase associated receptor

A diverse array of cytokines and growth factors, including interleukins 2 through 7 (IL-2 to IL-7), granulocyte-

macrophage colony-stimulating factor (GM-CSF), growth hormone (GH), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and interferons (IFNs), utilize the JAK-STAT signaling pathway for signal transduction. These signaling molecules possess specific receptors on the cell membrane. A distinctive feature of these receptors is their lack of intrinsic kinase activity; however, their intracellular segments are equipped with binding sites for the tyrosine kinase JAK. Following ligand binding, the associated JAK is activated, initiating a phosphorylation cascade on tyrosine residues of various target proteins, thus facilitating the signal transmission from the extracellular environment to the intracellular milieu.

## 2.2 JAK

JAKs are a class of cytoplasmic tyrosine kinases that are connected to the intracellular regions of membrane-bound receptors. They are non-receptor tyrosine kinases that can phosphorylate their associated cytokine receptors and a variety of specific signaling molecules with Src homology 2 (SH2) domains. The JAK family includes four members: JAK1, JAK2, JAK3, and TYK2[6]. JAK1, JAK2 and TYK2 are expressed in the heart, while JAK3 is mainly expressed in the lymphatic system and bone marrow[7]. Each of these kinases performs a different biological function[4]. Specifically, JAK1 is primarily responsible for the binding of cytokines to their receptors. JAK2 mediates signal transduction between extracellular ligands and receptors. Similar to JAK1, JAK3 is involved in the binding process of cytokines to their receptors, but its expression is restricted to hematopoietic cells and some endothelial tissues. TYK2 plays a regulatory role in lymphocytes, particularly in the signaling of type I interferons (IFN-α/β) and IL-12. Structurally, JAKs consist of four domains: FERM, SH2, Pseudokinase, and Kinase.

## 2.3 STAT

STAT proteins are central transcriptional regulators in the immune response and serve as downstream targets of the JAK family kinases. They play an essential role in processes such as cellular immunity, apoptosis, proliferation, and differentiation[8]. The seven members of the STAT protein family-STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6—are usually made up of 750-900 amino acid residues[7,9].Although these STAT family members share structural similarities, each is encoded by a distinct gene and is expressed in the heart. The structure of STAT proteins is composed of six conserved domains that collectively determine their functional properties. From the N-terminus to the C-terminus, the domains are the nitrogen-terminal domain, coiled-coil domain, DNA-binding domain, junction domain, SH2 domain, and transcription-activation structure[10,11].

## 2.4 The JAK/STAT pathway

The JAK/STAT pathway modulates signaling from membrane receptors to the nucleus through these steps: cytokines bind to receptors, causing dimerization and activation of associated JAKs via cross-phosphorylation; activated JAK phosphorylates receptor tyrosine residues, creating docking sites for STAT proteins; STAT binds to these sites, gets phosphorylated by JAK, and dissociates from the receptor; phosphorylated STAT molecules then dimerize, expose their nuclear localization signal, and translocate to the nucleus to regulate gene expression[6,8].

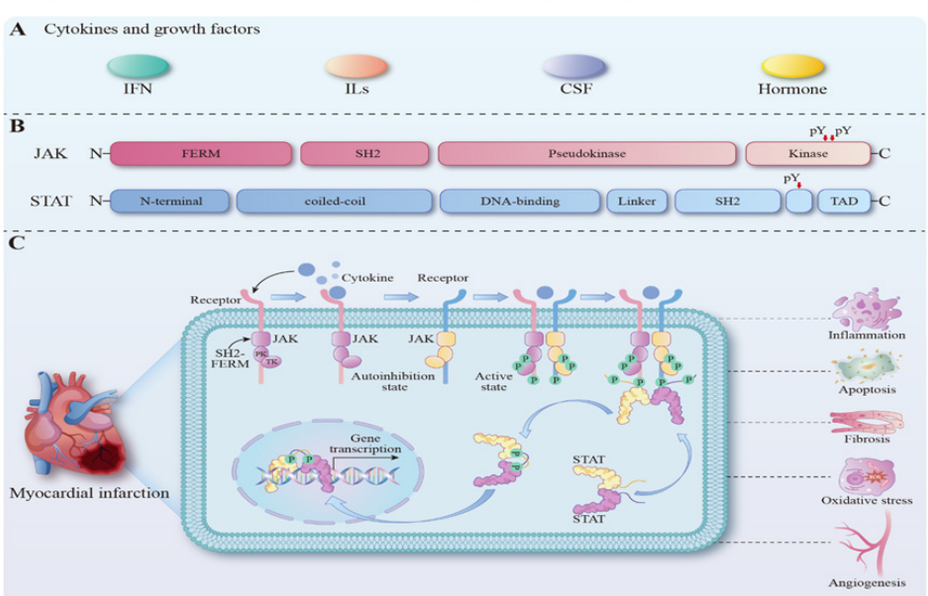


**Figure 1. JAK-STAT signaling pathway after MI**

Figure 1. The JAK-STAT pathway includes cytokines, receptors, JAKs, and STATs. JAKs have FERM, SH2, pseudokinase, and kinase domains, while STATs consist of an N-terminal domain, coiled-coil domain, DNA-binding domain, linker region, SH2 domain, and transcriptional activation domain. Cytokine binding activates JAKs, which phosphorylate and recruit STATs. Activated STATs dimerize and move to the nucleus to regulate target gene expression.

# 3. The regulatory mechanisms of JAK/STAT in MI

MI is a multidimensional pathological condition, the complexity of which stems from interactions at the cellular and molecular levels. Extensive research from animal experiments and clinical trials has been conducted on various pathophysiological processes of MI, including inflammation, fibrosis, oxidative stress, angiogenesis, and apoptosis, which are key components. The following content will provide a detailed summary of the specific regulatory mechanisms of the JAK/STAT signaling pathway in MI, thereby further revealing its diverse and complex roles in heart disease.

## 3.1 Inflammation

MI initiates a complex process of myocardial remodeling, in which inflammation plays a crucial role. The inflammatory response triggered by MI can lead to pathological cardiac remodeling, activating specific immune cells and generating a plethora of cytokines within the cardiac tissue. Macrophages are particularly active in this series of reactions and are one of the most critical cell types throughout the various stages post-MI. Inhibiting pro-inflammatory macrophages or increasing reparative macrophages through various means can play a protective role in myocardial remodeling post-MI[12]. It is worth noting that the JAK/STAT signaling pathway plays a significant role in regulating the differentiation of macrophages being one of the key pathways in this process.[13,14]

IL-33, by activating the JAK/STAT pathway, significantly increases the number of M2 macrophages in the infarct area, thereby reducing the size of the infarction[15]. Hyaluronic Acid Oligosaccharides (o-HA) also leverage the JAK/STAT signaling pathway to effectively promote the polarization of M2 macrophages and reduce the proportion of pro-inflammatory M1 macrophages, contributing to the recovery of cardiac function[16].Additionally, in the early stages of MI, RNF149 (RING finger protein 149) is highly expressed in cardiac macrophages of both mice and humans. The function of RNF149 is closely related to the Jak/Stat pathway. Activation of STAT1 induces the transcription of RNF149, which then counteracts type II interferon signaling by destabilizing the IFNGR1 protein, thereby maintaining immune homeostasis and promoting cardiac repair following MI[17]. Xiaohui N et al.'s study[18] found that α7 nicotinic acetylcholine receptor (α7nAChR) activation inhibits pro-inflammatory monocytes/macrophages via the STAT3 pathway, improving cardiac function and remodeling. STAT6 activation under specific conditions (e.g., hCVPC-CdM medium or hESC-CVPC-implanted hearts) enhances macrophage polarization for repair. However, in STAT6-deficient MI mice, this effect is diminished[19]. In summary, the JAK/STAT pathway is crucial for macrophage polarization and cardiac repair, providing new therapeutic strategies and targets for MI. These findings enhance our understanding of cardiac disease mechanisms and guide future clinical treatments.

## 3.2 Fibrosis

Cardiac fibrosis is a component of most myocardial pathological states, characterized by the accumulation of extracellular matrix in cardiac muscle cells. Extensive ventricular fibrosis is particularly common after MI. The sudden loss of a large number of cardiac muscle cells triggers an inflammatory response, leading to the proliferation of collagen-based scar tissue, which can ultimately lead to heart dysfunction and even the development of heart failure[20]. Among the numerous signaling pathways implicated in fibrosis, the JAK/STAT pathway stands out as a critical one that reacts to a variety of pro-fibrotic factors. These include Transforming Growth Factor beta ( TGF-β1)[21], Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), Interleukin-6 (IL-6), Angiotensin II (AngII), 5-Hydroxytryptamine (5-HT), and Endothelin-1 (ET-1)[22,23]. Upon activation by these mediators, the JAK/STAT signaling pathway stimulates the proliferation and differentiation of cardiac fibroblasts, leading to excessive deposition of the extracellular matrix (ECM), thereby exacerbating the process of myocardial fibrosis[24,25].

STAT1 and STAT3 are critical signaling molecules involved in regulating fibroblast activity, predominantly exhibiting pro-fibrotic effects in cardiac fibrosis. STAT1 drives fibrosis progression by mediating inflammatory responses and promoting fibroblast proliferation and activation, resulting in excessive extracellular matrix (ECM) production. Persistent STAT1 activation in cardiac tissue is strongly linked to the upregulation of fibrosis-related genes, including COL1A1 and COL3A1[26,27]. This process contributes to myocardial scar formation, increased tissue stiffness, and compromised cardiac function. Furthermore, STAT1's pro-fibrotic effects are often amplified through interaction with the TGF-β signaling pathway, further intensifying pathological fibroblast activity[28]. STAT3, on the other hand, aggravates fibrosis by promoting the

transformation of fibroblasts into myofibroblasts. These myofibroblasts are characterized by enhanced ECM production, including excessive secretion of collagen and fibronectin, as well as increased contractility, which exacerbates cardiac tissue stiffness[29,30]. Additionally, sustained STAT3 activation zupregulates Tissue Inhibitor of Metalloproteinases-1(TIMP1), inhibiting ECM degradation and accelerating ECM deposition[31]. STAT1 and STAT3 act as pivotal pro-fibrotic regulators in cardiac fibrosis, operating through distinct yet complementary mechanisms. Targeting the STAT signaling pathway represents a promising therapeutic strategy, where precise modulation tailored to the specific pathological stage of fibrosis could be crucial for achieving optimal clinical outcomes.

## 3.3 Oxidative stress

Oxidative stress, resulting from an imbalance between pro-oxidant and antioxidant systems in the body, is characterized by an overproduction of free radicals and reactive oxygen species (ROS) that exceeds the body's natural defense mechanisms. This state of disequilibrium poses a severe threat to cellular structures, particularly causing damage to proteins, lipids, and DNA, leading to cellular dysfunction and even cell death. MI, a serious cardiac event caused by obstruction of blood flow in the coronary arteries, results in ischemia and hypoxia of the myocardial tissue and necrosis of cardiomyocytes, a process during which oxidative stress levels are significantly elevated.

The JAK/STAT signaling pathway, as a key component in the regulation of oxidative stress post-MI, plays an essential role[31]. The JAK/STAT signaling pathway actively participates in the construction of antioxidant defense mechanisms, enhancing the overall antioxidant capacity of cardiac tissue by upregulating the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase[32]. It is noteworthy that scientific research has further uncovered the therapeutic potential of specific compounds, such as hypericin (Hyp), in the treatment of MI. Hyp not only improves electrocardiographic outcomes and enhances cardiac function, reducing the infarct size, but also significantly lowers myocardial fibrosis and oxidative stress levels. One of its mechanisms involves reducing the accumulation of reactive ROS within cardiomyocytes, combating apoptosis induced by oxygen-glucose deprivation (OGD), and this protective effect is partly attributed to the activation of the JAK2/STAT3 signaling pathway[33]. These studies suggest that a deeper understanding and effective intervention in the mechanisms by which the JAK/STAT signaling pathway participates in the oxidative stress response following MI could pave the way for new approaches and strategies in the treatment of MI.

## 3.4 Angiogenesis

Angiogenesis, the formation of new blood vessels from existing vasculature, is essential for growth, tissue repair, and disease progression, particularly in MI. In MI-induced ischemic regions, new blood vessels are urgently needed to restore oxygen and nutrient supply, which is critical for cardiomyocyte survival and cardiac function recovery. During cardiac repair and remodeling, angiogenesis reduces infarct fibrosis and promotes cardiomyocyte regeneration, thereby facilitating overall heart function recovery.

In MI, the JAK/STAT signaling pathway, particularly STAT3, is crucial for promoting myocardial angiogenesis and functional recovery. Experimental studies, as described by Denise et al.,[34] have shown that rats with cardiomyocyte-specific Stat3 knockout exhibit reduced myocardial capillary density and improved interstitial fibrosis, further confirming the necessity of Stat3 in promoting angiogenesis. In a mouse model with STAT3 gene knockout, although the expression of Vascular Endothelial Growth Factor (VEGF) does not change significantly, the levels of VEGF inhibitors such as Thrombospondin-1 (TSP-1), as well as proteins related to the formation of the extracellular matrix, such as Osteopontin (OPN) and Plasminogen Activator Inhibitor-1 (PAI-1), are elevated, collectively creating a cardiac environment that is less conducive to angiogenesis and more inclined towards fibrosis. On the other hand, research by Kang H et al.[35] has revealed that Granulocyte Colony-Stimulating Factor (G-CSF) and Erythropoietin stimulate angiogenesis and improve cardiac function following MI in a dose-dependent manner by activating the JAK2/STAT signaling pathway. These studies underscore the significant role of the JAK/STAT pathway in cardiac remodeling, particularly through its regulation of angiogenesis.

## 3.5 Apoptosis

Apoptosis, or programmed cell death, is a controlled process where cells are instructed to die as part of normal body functions[36]. The JAK/STAT pathway regulates apoptosis in cardiomyocytes, with particular significance attributed to STAT1 and STAT3[37]. For instance ,research has shown that Zhu J et al.[38], through experimentation, confirmed that factors released from necrotic primary cardiomyocytes (Necrotic-S) can activate the JAK1-STAT1 signaling pathway, promoting the nuclear translocation of c-Fos and NF-κBp65 after simulating a microenvironment of MI, leading to apoptosis in hypoxic cardiomyocytes. Notably, when the gene expression of STAT1 is inhibited, the apoptosis of cardiomyocytes induced by Necrotic-S is significantly reduced. This indicates that STAT1 plays a pro-apoptotic role in MI[39]. Additionally,

Neo1, a multifunctional transmembrane receptor, has been found to potentially exacerbate the impact of myocardial cell apoptosis by activating the STAT1 signaling pathway[40].

However, the functions of STAT3 are distinctly different from those of STAT1. Recent research advancements have highlighted the positive role of STAT3 in promoting the proliferation and survival of cardiomyocytes, thereby revealing its potential in cardiac regeneration after MI[41,42]. The activation of STAT3 not only helps to reduce apoptosis but also supports cell survival by upregulating anti-apoptotic proteins and maintaining mitochondrial function, which is crucial for protecting cardiac tissue under ischemic conditions[43]. Furthermore, STAT3 can promote the proliferation of cardiomyocytes, thereby accelerating the repair and recovery of cardiac tissue after MI[44,45]. The research by Nakao et al.[45] confirms the role of STAT3 in promoting the proliferation of cardiomyocytes derived from primitive stem cells and participates in cardiac regeneration by promoting the dedifferentiation and proliferation of cardiomyocytes. These research results indicate that therapeutic strategies targeting the activation of STAT3 can promote cardiac regeneration, providing a feasible approach to improve the prognosis of patients with MI. In addition, non-coding RNAs (microRNAs, miR) also participate in the regulation of STAT3 activity. Inhibition of miR-206 can target STAT3 to prevent cardiomyocyte apoptosis, thereby protecting the myocardium after MI[42].

In summary, the JAK/STAT pathway plays a critical role in MI by regulating the activity of STAT1 and STAT3, which respectively act as pro-apoptotic and anti-apoptotic factors, thereby influencing cardiomyocyte apoptosis and repair. This provides a new perspective for improving the prognosis of MI.

# 4. JAK/STAT Targeting as a Potential Therapeutic Strategy in MI

The prominence of the JAK/STAT signaling pathway in the medical field continues to grow, with targeting the JAK/STAT pathway emerging as a promising therapeutic strategy for the treatment of MI. The pharmacological inhibitors designed to target this pathway are divided into three main categories: (1) receptor antibodies or cytokine antagonists; (2) JAK inhibitors; (3) STAT inhibitors.

## 4.1 Receptor antibodies or cytokine antagonists

In the JAK/STAT signaling pathway, cytokines play an essential role by activating the pathway, triggering the phosphorylation and activation of STAT proteins, and subsequently inducing these proteins to dimerize and translocate to the nucleus, where they precisely regulate the expression of specific genes. For instance, the newer generation of anti-IL-6 and anti-IL-6R monoclonal antibodies, such as sirukumab and olamkicept, are being evaluated in multiple clinical trials for their therapeutic efficacy in various diseases, owing to their enhanced binding affinity, high specificity, and reduced toxicity[46]. It is noteworthy that studies have shown that olamkicept can significantly reduce arterial wall inflammation in patients without affecting lipoprotein metabolism, and no significant clinical or laboratory side effects have been observed during or after treatment[47]. This not only highlights the significant potential of olamkicept in treating cardiovascular diseases, but also suggests that it may play a role in balancing the metabolic regulation of the cardiovascular system.

## 4.2 JAK inhibitors

JAK inhibitors effectively block STAT protein phosphorylation and activation but have a broad action that may disrupt other signaling pathways, causing adverse reactions such as infections, hyperlipidemia, and cytopenias. Tofacitinib, a first-generation JAK inhibitor selective for JAK1 and JAK3, has revolutionized the treatment of rheumatoid arthritis and other immune-mediated diseases. However, its use in rheumatoid arthritis patients is linked to an increased risk of MI and cardiovascular mortality. Other JAK inhibitors, such as baricitinib and upadacitinib, while offering targeted inhibition of specific JAK isoforms, are similarly associated with side effects that may limit their use in cardiovascular contexts[48]. The non-specific JAK inhibition by these drugs may be unsuitable for patients at high cardiovascular risk. Given the lack of direct comparative studies on JAK inhibitors' efficacy in MI treatment, future drug development should focus on targeting STAT or downstream pathways to enhance specificity, reduce off-target effects, and minimize adverse reactions. This approach aims to optimize drug safety while maintaining efficacy. Additionally, research into selective JAK/STAT modulators or partial inhibitors could provide a balanced therapeutic strategy, preserving benefits without extensive immune suppression.

## 4.3 STAT inhibitors

STAT inhibitors, with higher specificity, are expected to reduce side effects compared to JAK inhibitors. However, their development faces challenges due to STAT proteins' lack of catalytic activity, making small molecule design difficult. Most research is preclinical, and high drug concentrations are often needed for efficacy. STAT3 is notable for its dual role as an oncogene and cardioprotective factor. Its inhibition benefits cancer treatment, while its activation is crucial for

cardiovascular protection by promoting angiogenesis, reducing apoptosis, and mitigating oxidative stress in myocardial cells. Thus, selective STAT3 activation is needed for cardiovascular therapy, with precise drug modulation of STAT3 activity being crucial. It is worth mentioning that sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), such as empagliflozin, originally developed for the treatment of type 2 diabetes, have been shown to improve the clinical outcomes of patients with MI. Although empagliflozin is not a direct inhibitor of the STAT pathway, it can exert its cardioprotective effects by modulating the STAT3 pathway and related signal transduction mechanisms[49,50], this has further expanded our understanding of the role of the JAK/STAT pathway in cardiovascular diseases.

### 4.4 Therapeutic challenges

While JAK and STAT inhibitors show therapeutic promise, their use is not without challenges. Off-target effects are a significant concern due to the wide-ranging roles of the JAK/STAT pathway in various tissues and physiological processes, leading to adverse reactions such as immunosuppression, hyperlipidemia, and cytopenias. The European Union (EU) recommends that measures be taken against JAK inhibitors for the treatment of chronic inflammatory diseases to reduce their serious side effects, such as cardiovascular disease, blood clots, cancer and serious infections. Long-term use of JAK inhibitors has been linked to the development of resistance, possibly through alternative pathway activation or mutations within the JAK/STAT pathway that reduce drug efficacy. Addressing these issues will require the development of more selective inhibitors and potentially combining therapies to minimize off-target actions while maintaining therapeutic effectiveness.

Although current evidence for the use of JAK/STAT pathway-targeted in MI is not yet sufficient, scientists have never stopped exploring this field. In the future, through in-depth research and innovative strategies, we hope to develop new drugs that can both protect the myocardium from further damage and effectively promote recovery after MI. In this process, precise control of the activation process of the JAK/STAT signaling pathway will be crucial to ensure that it maximizes its positive effects while avoiding potential adverse effects.

## 5. Conclusion and perspectives

The JAK/STAT signaling pathway is deeply involved in the complex pathophysiology of MI, influencing key processes such as inflammation, immune cell differentiation, cardiomyocyte survival, and fibrosis. In the acute phase of MI, JAK/STAT signaling promotes inflammatory responses and macrophage recruitment, which are essential for clearing necrotic tissue, yet also risk exacerbating tissue damage if unregulated. In the subacute and chronic phases, the pathway's role shifts toward tissue repair, fibrosis, and remodeling, with both protective and potentially harmful outcomes depending on activation patterns and duration.

JAK and STAT inhibitors show promise in managing inflammation but raise concerns about off-target effects, immunosuppression, and adverse reactions like hyperlipidemia and cytopenias. Resistance development also highlights the need for alternative or complementary therapies. STAT3 has a dual role as an oncogene and a cardioprotector. In early MI, STAT3 activation reduces cardiomyocyte apoptosis and preserves cardiac function. However, in later stages, sustained STAT3 activation may worsen fibrosis and impair cardiac self-repair. Thus, therapies should precisely regulate STAT3 activity: promoting it in acute MI to reduce apoptosis and inhibiting it in chronic MI to mitigate fibrosis.

Looking ahead, the therapeutic horizon for MI is promising, particularly in the realm of JAK/STAT signaling pathway research. The specific prospects can be summarized as follows:

### 5.1 Precision regulation and targeted therapy

Targeted therapies based on JAK/STAT could prevent and treat MI more effectively. Future research will develop selective JAK inhibitors to reduce off-target effects, enhancing cardiac repair and regeneration while minimizing inflammation and fibrosis.

### 5.2 Personalized therapies in MI

Customizing MI treatment based on individual traits improves outcomes. JAK/STAT pathway insights need solid clinical trial frameworks. Trials should evaluate JAK/STAT therapies across MI groups, noting effects on high-risk, comorbid, and elderly patients. Monitoring outcomes like infarct size and ventricular remodeling is vital. Tailoring strategies for recurrent MI and elderly patients, considering polypharmacy and frailty, will optimize treatment efficacy and safety.

### 5.3 Exploration of combination therapies

In pursuit of a more comprehensive therapeutic effect, the modulation of the JAK/STAT signaling pathway will be combined with other treatment modalities to form combination therapies. These will work synergistically to address the

complex pathological processes of MI.

### 5.4 New uses for existing medications

Exploring new applications for existing medications, such as empagliflozin, in improving cardiovascular function, will not only facilitate faster clinical application but also benefit the joint management of cardiovascular diseases and other chronic conditions.

### 5.5 Enhancement of antioxidant capacity

By modulating the expression of antioxidant enzymes, the antioxidant capacity of cardiac tissue can be enhanced to mitigate the damage caused by oxidative stress to the myocardium, thereby improving the prognosis of patients with MI.

### 5.6 JAK/STAT and other pathways in MI regulation

This study emphasizes JAK/STAT's role in MI, alongside other vital pathways. MAPK regulates cardiomyocyte inflammation and apoptosis, PI3K/Akt supports survival under hypoxia, and NF-κB manages post-MI immune responses. These pathways interact, creating a complex network that governs MI pathophysiology. Further research into their interplay could deepen our understanding of MI's molecular network and inform multi-targeted therapies.

## 6. Conclusion

The future research should focus on developing selective modulators that target specific components of the JAK/STAT pathway or downstream effectors, as well as identifying the optimal timing and patient populations for intervention. Combining JAK/STAT inhibitors with other targeted therapies might also mitigate adverse effects while maximizing therapeutic efficacy.

## References


[1] Bavia L, Lidani K C F, Andrade F A, et al. Complement activation in acute myocardial infarction: An early marker of inflammation and tissue injury? [J]. Immunol. Lett., 2018, 200: 18-25.

[2] Bergmark B A, Mathenge N, Merlini P A, et al. Acute coronary syndromes [J]. Lancet, 2022, 399(10332): 1347-1358.

[3] Doenst T, Haverich A, Serruys P, et al. PCI and CABG for Treating Stable Coronary Artery Disease: JACC Review Topic of the Week [J]. J Am Coll Cardiol, 2019, 73(8): 964-976.

[4] Philips R L, Wang Y, Cheon H, et al. The JAK-STAT pathway at 30: Much learned, much more to do [J]. Cell, 2022, 185(21): 3857-3876.

[5] Raychaudhuri S, Cheema K S, Raychaudhuri S K, et al. Janus kinase–signal transducers and activators of transcription cell signaling in Spondyloarthritis: rationale and evidence for JAK inhibition [J]. Current Opinion in Rheumatology, 2021, 33(4): 348-355.

[6] Banerjee S, Biehl A, Gadina M, et al. JAK–STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects [J]. Drugs, 2017, 77(5): 521-546.

[7] Liu J, Wang F, Luo F. The Role of JAK/STAT Pathway in Fibrotic Diseases: Molecular and Cellular Mechanisms [J]. Biomolecules, 2023, 13(1): 119.

[8] Liu Y, Wang W, Zhang J, et al. JAK/STAT signaling in diabetic kidney disease [J]. Frontiers in Cell and Developmental Biology, 2023, 11.

[9] Swiatek-Machado K, Kaminska B. STAT Signaling in Glioma Cells [Z]. Advances in Experimental Medicine and Biology. Springer International Publishing. 2020: 203-222.10.1007/978-3-030-30651-9_10

[10] Yu H, Jove R. The STATs of cancer — new molecular targets come of age [J]. Nature Reviews Cancer, 2004, 4(2): 97-105.

[11] Hu X, li J, Fu M, et al. The JAK/STAT signaling pathway: from bench to clinic [J]. Signal Transduction and Targeted Therapy, 2021, 6(1).

[12] Bejerano T, Etzion S, Elyagon S, et al. Nanoparticle Delivery of miRNA-21 Mimic to Cardiac Macrophages Improves Myocardial Remodeling after Myocardial Infarction [J]. Nano Letters, 2018, 18(9): 5885-5891.

[13] Hu Q, Bian Q, Rong D, et al. JAK/STAT pathway: Extracellular signals, diseases, immunity, and therapeutic regimens [J]. Frontiers in Bioengineering and Biotechnology, 2023, 11.

[14] Xia T, Zhang M, Lei W, et al. Advances in the role of STAT3 in macrophage polarization [J]. Frontiers in Immunology, 2023, 14.

[15] Li J, Shen D, Tang J, et al. IL33 attenuates ventricular remodeling after myocardial infarction through inducing alternatively activated macrophages ethical standards statement [J]. European Journal of Pharmacology, 2019, 854: 307-319.

[16] Wang N, Liu C, Wang X, et al. Hyaluronic Acid Oligosaccharides Improve Myocardial Function Reconstruction and Angiogenesis against Myocardial Infarction by Regulation of Macrophages [J]. Theranostics, 2019, 9(7): 1980-1992.
[17] Huang C-K, Chen Z, Zhou Z, et al. RNF149 Destabilizes IFNGR1 in Macrophages to Favor Post-Infarction Cardiac Repair [J]. Circulation Research, 2024.
[18] Niu X-H, Liu R-H, Lv X, et al. Activating α7nAChR helps post-myocardial infarction healing by regulating macrophage polarization via the STAT3 signaling pathway [J]. Inflammation Research, 2023, 72(4): 879-892.
[19] Wang J, Liu M, Wu Q, et al. Human Embryonic Stem Cell-Derived Cardiovascular Progenitors Repair Infarcted Hearts Through Modulation of Macrophages via Activation of Signal Transducer and Activator of Transcription 6 [J]. Antioxidants & Redox Signaling, 2019, 31(5): 369-386.
[20] Fan D, Takawale A, Lee J, et al. Cardiac fibroblasts, fibrosis and extracellular matrix remodeling in heart disease [J]. Fibrogenesis & Tissue Repair, 2012, 5(1).
[21] Pang Q, You L, Meng X, et al. Regulation of the JAK/STAT signaling pathway: The promising targets for cardiovascular disease [J]. Biochemical Pharmacology, 2023, 213: 115587.
[22] Liu J, Wang F, Luo F. The Role of JAK/STAT Pathway in Fibrotic Diseases: Molecular and Cellular Mechanisms [J/OL] 2023, 13(1):119
[23] Jiang H, Yang J, Li T, et al. JAK/STAT3 signaling in cardiac fibrosis: a promising therapeutic target [J]. Frontiers in Pharmacology, 2024, 15.
[24] Zhang Q, Wang L, Wang S, et al. Signaling pathways and targeted therapy for myocardial infarction [J]. Signal Transduction and Targeted Therapy, 2022, 7(1).
[25] Wang Y, Wang M, Samuel C S, et al. Preclinical rodent models of cardiac fibrosis [J]. British Journal of Pharmacology, 2021, 179(5): 882-899.
[26] Niu W, Zhu M, Wang M, et al. Discovery and development of benzene sulfonamide derivatives as anti-hepatic fibrosis agents [J]. Bioorg Med Chem Lett, 2023, 88: 129290.
[27] Di Martino J S, Nobre A R, Mondal C, et al. A tumor-derived type III collagen-rich ECM niche regulates tumor cell dormancy [J]. Nat Cancer, 2022, 3(1): 90-107.
[28] Ye L, Huang J, Liang X, et al. Jiawei Taohe Chengqi Decoction attenuates CCl(4) induced hepatic fibrosis by inhibiting HSCs activation via TGF-β1/CUGBP1 and IFN-γ/Smad7 pathway [J]. Phytomedicine, 2024, 133: 155916.
[29] He S, Chen X, Cheng Q, et al. [Tofacitinib inhibits the transformation of lung fibroblasts into myofibroblasts through JAK/STAT3 pathway] [J]. Beijing Da Xue Xue Bao Yi Xue Ban, 2024, 56(3): 505-511.
[30] Bao H, Wang X, Zhou H, et al. PCSK9 regulates myofibroblast transformation through the JAK2/STAT3 pathway to regulate fibrosis after myocardial infarction [J]. Biochem Pharmacol, 2024, 220: 115996.
[31] Wang Z, Li J, Xiao W, et al. The STAT3 inhibitor S3I-201 suppresses fibrogenesis and angiogenesis in liver fibrosis [J]. Lab Invest, 2018, 98(12): 1600-1613.
[32] Xia B, Ding J, Li Q, et al. Loganin protects against myocardial ischemia-reperfusion injury by modulating oxidative stress and cellular apoptosis via activation of JAK2/STAT3 signaling [J]. International Journal of Cardiology, 2024, 395: 131426.
[33] Rao T, Tong H, Li J, et al. Exploring the role and mechanism of hyperoside against cardiomyocyte injury in mice with myocardial infarction based on JAK2/STAT3 signaling pathway [J]. Phytomedicine, 2024, 128: 155319.
[34] Hilfiker-Kleiner D, Hilfiker A, Fuchs M, et al. Signal Transducer and Activator of Transcription 3 Is Required for Myocardial Capillary Growth, Control of Interstitial Matrix Deposition, and Heart Protection From Ischemic Injury [J]. Circulation Research, 2004, 95(2): 187-195.
[35] Kang H-J, Kim H-S. G-CSF- and erythropoietin-based cell therapy: a promising strategy for angiomyogenesis in myocardial infarction [J]. Expert Review of Cardiovascular Therapy, 2008, 6(5): 703-713.
[36] Ai Y, Meng Y, Yan B, et al. The biochemical pathways of apoptotic, necroptotic, pyroptotic, and ferroptotic cell death [J]. Molecular Cell, 2024, 84(1): 170-179.
[37] Barry S P, Townsend P A, Latchman D S, et al. Role of the JAK–STAT pathway in myocardial injury [J]. Trends in Molecular Medicine, 2007, 13(2): 82-89.
[38] Zhu J, Yao K, Guo J, et al. miR-181a and miR-150 regulate dendritic cell immune inflammatory responses and cardiomyocyte apoptosis via targeting JAK1-STAT1/c-Fos pathway [J]. J Cell Mol Med, 2017, 21(11): 2884-2895.
[39] Kim H S, Lee M-S. STAT1 as a key modulator of cell death [J]. Cellular Signalling, 2007, 19(3): 454-465.
[40] Zhang J, Xu Y, Wei C, et al. Macrophage neogenin deficiency exacerbates myocardial remodeling and inflammation after acute myocardial infarction through JAK1-STAT1 signaling [J]. Cellular and Molecular Life Sciences, 2023, 80(11).
[41] Wang W, Chen X K, Zhou L, et al. Chemokine CCL2 promotes cardiac regeneration and repair in myocardial infarction mice via activation of the JNK/STAT3 axis [J]. Acta Pharmacol Sin, 2024, 45(4): 728-737.
[42] Dong W, Chen J, Wang Y, et al. miR-206 alleviates LPS-induced inflammatory injury in cardiomyocytes via directly targeting USP33 to inhibit the JAK2/STAT3 signaling pathway [J]. Mol Cell Biochem, 2024, 479(4): 929-940.
[43] Kleinbongard P. Perspective: mitochondrial STAT3 in cardioprotection [J]. Basic Res Cardiol, 2023, 118(1): 32.

[44] Wei G, Li C, Jia X, et al. Extracellular vesicle-derived CircWhsc1 promotes cardiomyocyte proliferation and heart repair by activating TRIM59/STAT3/Cyclin B2 pathway [J]. J Adv Res, 2023, 53: 199-218.
[45] Nakao S, Tsukamoto T, Ueyama T, et al. STAT3 for Cardiac Regenerative Medicine: Involvement in Stem Cell Biology, Pathophysiology, and Bioengineering [J]. Int J Mol Sci, 2020, 21(6).
[46] Uciechowski P, Dempke W C M. Interleukin-6: A Masterplayer in the Cytokine Network [J]. Oncology, 2020, 98(3): 131-137.
[47] Schulte D M, Waetzig G H, Schuett H, et al. Case Report: Arterial Wall Inflammation in Atherosclerotic Cardiovascular Disease is Reduced by Olamkicept (sgp130Fc) [J]. Frontiers in Pharmacology, 2022, 13.
[48] Virtanen A, Spinelli F R, Telliez J B, et al. JAK inhibitor selectivity: new opportunities, better drugs? [J]. Nat Rev Rheumatol, 2024, 20(10): 649-665.
[49] Butler J, Jones W S, Udell J A, et al. Empagliflozin after Acute Myocardial Infarction [J]. New England Journal of Medicine, 2024, 390(16): 1455-1466.
[50] Hernandez A F, Udell J A, Jones W S, et al. Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction: Insights From the EMPACT-MI Trial [J]. Circulation, 2024, 149(21): 1627-1638.