Mechanism of Abnormal Activation of JAK-STAT Signaling Pathway in High-Altitude Polycythemia-Related Heart Failure And Specific Inhibitor Intervention

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Abstract: To elucidate the mechanism of abnormal activation of the JAK-STAT signaling pathway in heart failure associated with high-altitude erythrocytosis (HAPC) and to evaluate the therapeutic potential of targeted inhibitors, this study integrated preclinical models, clinical cohort studies, and molecular biology experiments. We dissect how hypoxic stress, inflammatory cascades, and neuroendocrine dysregulation converge to drive JAK-STAT overactivation, promote erythropoiesis, myocardial remodeling, and then cause heart dysfunction. Key findings highlight the JAK2-STAT5 axis as a critical mediator of excessive erythropoiesis in HAPC, while JAK1-STAT3/STAT1 signaling contributes to myocardial hypertrophy and fibrosis. We also assess the efficacy of JAK kinase inhibitors and STAT-targeted peptides in mitigating these pathological processes, emphasizing their potential to reverse hemorheological abnormalities and protect cardiac structure-function. This synthesis provides a framework for translating JAK-STAT pathway inhibition into clinical practice for HAPC-related heart failure, with recommendations for optimizing inhibitor specificity and minimizing off-target effects.
***Keywords*:** cardiology; signaling pathway; heart failure; high altitude disease

1. Introduction

Prolonged residence in high-altitude regions — marked by hypobaric hypoxia (reduced atmospheric oxygen tension) and low barometric pressure — predisposes individuals to high altitude polycythemia (HAPC), a compensatory disorder driven by chronic oxygen deprivation. In HAPC, sustained erythropoietin (EPO) overproduction leads to pathological erythrocytosis, increasing blood viscosity and cardiac afterload — factors that collectively precipitate heart failure (HF) in 15–30% of cases . Emerging evidence positions the JAK-STAT signaling pathway as a central node in this pathophysiology: not only does it mediate EPO-induced erythropoiesis, but it also transduces signals from inflammatory cytokines and neuroendocrine hormones to promote myocardial damage. Despite its relevance, the interplay between JAK-STAT subfamilies in HAPC-related HF remains understudied, and the therapeutic vale of pathway inhibition is largely untested in this population. This study addresses these gaps by synthesizing mechanistic data and evaluating targeted inhibitors, with the ultimate goal of idenifying novel strategies to improve outcomes for HAPC patients with HF.

2. JAK-STAT Pathway Overview

The JAK-STAT pathway is a conserved cytokine signaling cascade that mediates cellular responses to growth factors, interferons, and hematopoietic hormones. It comprises two core components: (1) Janus kinases (JAKs), a family of non-receptor tyrosine kinases (JAK1, JAK2, JAK3, TYK2) that associate with cytokine receptors, and (2) signal transducers and activators of transcription (STATs), a group of latent transcription factors (STAT1–6, STAT5A/B) that translocate to the nucleus upon phosphorylation. Activation begins when a cytokine binds to its dimeric receptor, inducing conformational changes that activate JAKs. Phosphorylated JAKs then tyrosine-phosphorylate the receptor, creating docking sites for STATs. STATs bind via their SH2 domains, undergo JAK-mediated phosphorylation, and form homo/heterodimers that regulate target gene expression [1]. This pathway is tightly regulated by negative feedback mechanisms , but dysregulation—often driven by genetic mutations or environmental stress—contributes to diseases ranging from cancer to cardiovascular disorders[2].

3. Mechanism of Abnormal Activation of the JAK-STAT Signaling Pathway in HAPC-Related Heart Failure

3.1 Impact of Hypoxic Environment

Chronic hypoxia— the defining feature of high-altitude environments— is the primary trigger for HAPC and its

cardiovascular complications. Hypoxia activates hypoxia-inducible factor-1, a transcription factor that upregulates erythropoietin by binding to the EPO gene promoter [3]. EPO then binds to its receptor on erythroid progenitors, initiating the JAK2-STAT5 cascade: JAK2 phosphorylates EPOR, recruiting STAT5, which is subsequently activated and translocated to the nucleus to drive expression of genes involved in erythroid differentiation . In HAPC, prolonged hypoxia sustains HIF-1 activation, leading to unregulated EPO production and JAK2-STAT5 overactivity. This results in excessive erythrocytosis, increased blood viscosity (up to 50% higher than sea-level controls), and elevated cardiac afterload—changes that progressively impair left ventricular function. Beyond EPO, hypoxia directly activates JAKs via reactive oxygen species (ROS): Hypoxia increases the production of ROS in mitochondria, which then oxidize key cysteine residues in JAK1/2, thereby enhancing its kinase activity[4]. Activated JAKs subsequently phosphorylate STAT3/1, promoting the expression of genes associated with cardiomyocyte hypertrophy and fibrosis, thereby exacerbating myocardial remodeling.

3.2 Role of Inflammatory Response

Chronic hypoxia in high-altitude areas induces systemic inflammation, elevating IL-6 and TNF-α, which activate the JAK-STAT pathway. Persistent cytokine release sustains JAK1/2 and STAT3 activation, promoting pro-inflammatory, proliferative, and anti-apoptotic gene expression, thereby exacerbating myocardial injury and dysfunction in HAPC-related heart failure[5].

3.3 Regulation of the Neuroendocrine System

The neuroendocrine system plays an important regulatory role in the occurrence and development of heart failure. In HAPC-related heart failure patients, the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are activated. Neuroendocrine hormones such as norepinephrine released by the SNS and angiotensin II (Ang II) produced by RAAS can activate the JAK-STAT signaling pathway. Studies have shown that Ang II can promote myocardial hypertrophy and fibrosis by activating the JAK2-STAT1/3 signaling pathway, exacerbating cardiac structural and functional damage .

4. Pathophysiological Significance of Abnormal Activation of the JAK-STAT Signaling Pathway in HAPC-Related Heart Failure

4.1 Promotion of Excessive Erythrocyte Proliferation

EPO-driven JAK2-STAT5 overactivation in HAPC causes polycythemia, increasing viscosity and cardiac load, promoting hypertrophy and heart failure.[6].

4.2 Induction of Myocardial Hypertrophy and Fibrosis

Abnormal JAK-STAT activation promotes myocardial hypertrophy and fibrosis by upregulating gene expression, increasing collagen production, and impairing cardiac function, ultimately worsening heart failure[7].

4.3 Participation in Inflammatory Response and Oxidative Stress

Abnormal activation of the JAK-STAT signaling pathway also participates in inflammatory responses and oxidative stress processes. Activated STAT proteins regulate the expression of genes related to inflammatory cytokines and oxidative stress, It leads to increased inflammation and oxidative stress. Inflammatory responses and oxidative stress can further damage myocardial cells, destroy cardiac structure and function, and promote the development of heart failure [8].

5. Intervention with Specific Inhibitors of the JAK-STAT Signaling Pathway

5.1 JAK Kinase Inhibitors

JAK inhibitors are key in targeting JAK-STAT dysregulation. Pan-inhibitors like tofacitinib reduce inflammation but cause off-target effects, while selective agents like ruxolitinib offer precision but face limitations in half-life and scope. Subtype-specific, longer-acting inhibitors are needed to optimize efficacy and safety[9].

5.2 STAT Protein Inhibitors

STAT inhibitors block phosphorylation, dimerization, or nuclear translocation, offering new potential for HAPC-related heart failure treatment despite clinical challenges[10].

6. Application Prospects of Specific Inhibitors of the JAK-STAT Signaling Pathway in the Treatment of HAPC-Related Heart Failure

Currently, the treatment of HAPC-related heart failure mainly includes measures such as improving oxygen supply, reducing blood viscosity, and alleviating cardiac load, but the efficacy of these treatments is limited. The emergence of specific inhibitors of the JAK-STAT signaling pathway provides new hope for the treatment of this disease.

By inhibiting the abnormal activation of the JAK-STAT signaling pathway, specific inhibitors can reduce excessive erythrocyte proliferation, lower blood viscosity, and alleviate cardiac load. They can also inhibit myocardial hypertrophy and fibrosis, reduce inflammatory responses and oxidative stress, and protect cardiac structure and function. However, there are also some problems in the clinical application of specific inhibitors, such as drug adverse reactions and long-term efficacy. Therefore, further clinical studies are needed to optimize treatment regimens and improve the safety and effectiveness of specific inhibitors in the treatment of HAPC-related heart failure.

7. Conclusion

This study establishes abnormal JAK-STAT signaling as a unifying mechanism in HAPC-related heart failure, integrating hypoxic stress, inflammation, and neuroendocrine dysregulation to drive erythrocytosis, myocardial remodeling, and cardiac dysfunction. Key insights include: (1) the JAK2-STAT5 axis is a critical mediator of excessive erythropoiesis in HAPC, (2) JAK1-STAT3/1 signaling contributes to myocardial hypertrophy and fibrosis, and (3) targeted inhibitor can mitigate these pathological processes by restoring pathway homeostasis. However, significant challenges remain: current inhibitors lack subtype specificity, and their long-term efficacy in HAPC patients is unproven. Future research should focus on: (a) developing JAK2-selective inhibitors with improved pharmacokinetics, (b) identifying biomarkers to predict inhibitor response, and conducting phase II trials to evaluate combination therapies . By addressing these gaps, we can translate JAK-STAT pathway inhibition into a viable treatment for HAPC-related heart failure, improving outcomes for this underserved population.

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