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Review Article

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Therapeutic Potential of JAK2 Inhibitors in Pediatric Leukemia: Mechanisms, Challenges, and Clinical Prospects

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Abstract

Aberrant Janus kinase 2 (JAK2) signaling is a central driver of leukemic stem cell proliferation, survival, and therapy resistance in pediatric leukemia. Dysregulation arises from mutations, cytokine receptor fusions, or overactive upstream ligands, disrupting hematopoietic stem cell (HSC) niche homeostasis and promoting disease progression. JAK2 inhibitors, including ruxolitinib and emerging next-generation agents, offer targeted suppression of these pathways, reducing leukemic proliferation and enhancing sensitivity to chemotherapy and immunotherapy. Combination strategies targeting both leukemic cells and the bone marrow microenvironment show promise in overcoming resistance and preventing relapse. This review synthesizes the molecular mechanisms of JAK2 signaling, therapeutic evidence, resistance challenges, and clinical implications, highlighting the potential of JAK2-directed precision therapies to improve outcomes in children with high-risk or relapsed leukemia.

Keywords: JAK2 inhibitors, pediatric leukemia, hematopoietic stem cells, bone marrow niche, targeted therapy

Introduction

Pediatric leukemia, encompassing acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), is the most common malignancy in children, accounting for significant morbidity and mortality worldwide. Despite advances in chemotherapy and supportive care, relapse and refractory disease remain critical clinical challenges. Recent research has increasingly highlighted the role of dysregulated signaling pathways in leukemogenesis, particularly the Janus kinase 2 (JAK2) pathway, which plays a central role in the regulation of hematopoietic stem cells (HSCs) and their bone marrow niche [1]. Hematopoietic stem cells reside in specialized microenvironments within the bone marrow, where interactions with stromal cells, endothelial cells, osteoblasts, and extracellular matrix components regulate quiescence, self-renewal, and differentiation. Cytokines such as erythropoietin, thrombopoietin, and interleukins bind to their respective receptors on HSCs, activating intracellular signaling cascades that coordinate hematopoietic homeostasis. JAK2, a non-receptor tyrosine kinase, is a key mediator of these signals, phosphorylating STAT proteins and other downstream effectors to control proliferation, survival, and lineage commitment [2].

In pediatric leukemia, aberrant JAK2 signaling—whether through point mutations, cytokine receptor fusions, or excessive ligand stimulation—disrupts normal HSC-niche interactions, promoting leukemic stem cell survival, proliferation, and resistance to therapy. Leukemic blasts can remodel the bone marrow microenvironment, altering cytokine gradients, extracellular matrix composition, and stromal cell behavior to create a niche that favors malignant over normal hematopoiesis. This dynamic interplay between leukemic cells and the HSC niche amplifies oncogenic JAK2 signaling, contributing to disease progression and therapeutic failure [3-4]. Targeting JAK2 with small-molecule inhibitors represents a rational and promising therapeutic strategy in pediatric leukemia. By selectively suppressing aberrant signaling, these agents aim to reduce leukemic proliferation, restore niche homeostasis, and enhance sensitivity to conventional chemotherapy and immunotherapy. Understanding the molecular mechanisms underlying JAK2 activation, the pathological remodeling of the HSC niche, and the potential for therapeutic intervention is critical for developing precision medicine strategies that improve outcomes in children with high-risk or relapsed leukemia [5].

Molecular Basis of JAK2 Signaling in Hematopoietic Stem Cells

Janus kinase 2 (JAK2) is a non-receptor tyrosine kinase that occupies a central role in the regulation of hematopoietic stem cell (HSC) function. It is primarily associated with type I and type II cytokine receptors, including the erythropoietin receptor (EPOR), thrombopoietin receptor (MPL), and interleukin receptors such as IL-3R and IL-7R, which orchestrate HSC proliferation, differentiation, and survival. Upon ligand binding, receptor dimerization triggers autophosphorylation of JAK2, which in turn phosphorylates specific tyrosine residues on the receptor. These phosphorylated residues serve as docking sites for downstream effectors, most prominently the signal transducer and activator of transcription (STAT) family [6-7]. STAT proteins, once phosphorylated by JAK2, translocate into the nucleus and modulate the transcription of genes that regulate cell cycle progression, anti-apoptotic pathways, and lineage-specific differentiation. In the context of the bone marrow niche, JAK2 signaling is tightly regulated by cytokine concentrations, receptor availability, and negative feedback mechanisms, including suppressors of cytokine signaling (SOCS) proteins and phosphatases. These regulatory networks maintain a fine balance between HSC quiescence and proliferation, ensuring long-term hematopoietic homeostasis [8].

Beyond the canonical JAK-STAT pathway, JAK2 interacts with other intracellular signaling cascades, including PI3K-AKT, RAS-MAPK, and

mTOR pathways, integrating multiple environmental cues to coordinate HSC fate decisions. The bone marrow niche itself contributes to this regulation by providing spatially and temporally controlled cytokine gradients, adhesion-mediated signals, and metabolic cues that collectively modulate JAK2 activity. Stromal cells, osteoblasts, and endothelial cells dynamically influence JAK2-mediated signaling, maintaining HSC self-renewal under homeostatic conditions and promoting controlled differentiation in response to hematopoietic demand [9]. In pediatric leukemia, these regulatory mechanisms are frequently disrupted. Constitutive JAK2 activation—whether through point mutations, receptor fusions, or overexpression of upstream ligands—leads to sustained STAT-driven transcription, favoring leukemic stem cell self-renewal and survival. The pathological activation of JAK2 also reshapes the bone marrow niche, altering stromal cell function, extracellular matrix composition, and cytokine profiles. This remodeling creates a microenvironment that preferentially supports malignant cells while suppressing normal hematopoiesis, amplifying disease progression and therapy resistance [10].

JAK2 Alterations in Pediatric Leukemia

While JAK2 mutations such as V617F are hallmark drivers in adult myeloproliferative neoplasms, their incidence in pediatric leukemia is relatively low. Nevertheless, aberrant JAK2 signaling is a recurrent feature in high-risk pediatric acute lymphoblastic leukemia (ALL) and, less commonly, acute myeloid leukemia (AML). In children, JAK2 activation most frequently arises through alternative mechanisms, including cytokine receptor rearrangements, gene fusions, and dysregulated expression of upstream ligands. Rearrangements of CRLF2, IL7R fusions, and aberrant TSLP signaling create constitutively active receptor-JAK2 complexes, leading to persistent STAT phosphorylation and transcriptional activation of genes that drive leukemic stem cell (LSC) proliferation and survival [11]. These alterations have profound biological and clinical consequences.

Constitutively activated JAK2 enhances LSC self-renewal, promotes evasion of apoptosis, and supports the maintenance of minimal residual disease. Leukemic cells exploit JAK2-driven signaling to remodel the bone marrow niche, altering stromal cell behavior, extracellular matrix composition, and cytokine gradients, thereby creating a microenvironment that preferentially supports malignant over normal hematopoiesis. Such remodeling reinforces leukemic dominance and contributes to therapy resistance [12].

Beyond genetic alterations, epigenetic dysregulation and loss of negative regulatory mechanisms, such as suppressor of cytokine signaling (SOCS) proteins, further potentiate JAK2 activity. These molecular perturbations are often associated with high-risk disease phenotypes, early relapse, and refractory responses to standard chemotherapy, emphasizing the need for targeted interventions [13]. The identification of JAK2 pathway dysregulation in pediatric leukemia has translational significance. Molecular profiling of JAK2 alterations, CRLF2 rearrangements, and STAT5 phosphorylation can inform risk stratification, guide therapeutic selection, and identify patients likely to benefit from JAK2-directed therapies. Understanding the diverse mechanisms of JAK2 activation highlights the importance of a precision medicine approach that addresses both leukemic cell-intrinsic abnormalities and the supportive microenvironment that drives disease persistence and progression [14].

Therapeutic Potential of JAK2 Inhibitors

The recognition of aberrant JAK2 signaling in pediatric leukemia has provided a strong rationale for the development and clinical evaluation of JAK2-directed therapies. Small-molecule JAK2 inhibitors, such as ruxolitinib, pacritinib, and fedratinib, act by competitively binding to the ATP-binding pocket of the kinase, preventing phosphorylation of downstream effectors, including STAT proteins. By suppressing constitutive JAK2 activity, these agents reduce leukemic stem cell (LSC) proliferation, impair survival pathways, and partially restore normal

hematopoietic stem cell function within the bone marrow niche [15]. Preclinical studies have demonstrated that JAK2 inhibition can disrupt the protective microenvironment that leukemic cells exploit. By reducing STAT-mediated transcription of anti-apoptotic and self-renewal genes, these inhibitors sensitize malignant cells to conventional chemotherapy and emerging immunotherapies. Combination strategies, integrating JAK2 inhibitors with cytotoxic agents, BCL-2 inhibitors, or chimeric antigen receptor (CAR) T-cell therapies, have shown synergistic effects in preclinical models, highlighting the potential for multi-modal treatment approaches that target both leukemic cells and their supportive niche [16]. Next-generation JAK2 inhibitors are being developed to improve selectivity, reduce toxicity, and overcome resistance mechanisms. These agents, combined with strategies targeting the bone marrow niche or downstream effectors, hold promise for improving survival and reducing relapse in high-risk pediatric leukemia. Overall, the therapeutic potential of JAK2 inhibitors underscores a shift toward precision medicine in pediatric leukemia, moving beyond broadly cytotoxic regimens to targeted interventions that address both leukemic cells and the microenvironment that sustains them [17].

Resistance Mechanisms to JAK2 Inhibition

Despite the therapeutic promise of JAK2 inhibitors in pediatric leukemia, resistance remains a significant clinical challenge. Resistance can arise through intrinsic, acquired, or microenvironment-mediated mechanisms, all of which compromise the efficacy of targeted therapy. One well-characterized mechanism involves secondary mutations within the JAK2 kinase domain, which reduce inhibitor binding and allow persistent activation of downstream STAT signaling. These mutations may emerge during therapy or be present in minor subclones prior to treatment, contributing to relapse [18]. Parallel signaling pathways also play a critical role in mediating resistance. Activation of compensatory pathways such as PI3K-AKT, RAS-MAPK, or mTOR can bypass JAK2 blockade, sustaining leukemic proliferation and survival. Additionally, loss of negative regulators of cytokine signaling, including SOCS proteins or phosphatases, can amplify residual JAK2 activity despite inhibitor therapy, further promoting therapeutic escape [19]. Microenvironmental factors within the bone marrow niche are particularly important in pediatric leukemia. Stromal and endothelial cells can secrete cytokines such as IL-7, TSLP, or GM-CSF, which activate alternative survival pathways in leukemic stem cells, effectively bypassing JAK2 inhibition. Hypoxic conditions and direct cell-cell interactions in the niche further enhance leukemic stem cell quiescence and resistance to therapy [20].

Clinical Implications

The elucidation of JAK2 signaling dysregulation in pediatric leukemia has important clinical ramifications, influencing diagnosis, risk stratification, and therapeutic decision-making. Aberrant JAK2 activity not only drives leukemic stem cell proliferation and survival but also remodels the bone marrow niche, creating a microenvironment that protects malignant cells from conventional therapies. Recognizing these molecular and microenvironmental contributions is critical for optimizing patient management [21]. Molecular profiling to detect JAK2 mutations, cytokine receptor fusions, or downstream STAT activation allows clinicians to identify patients who may benefit from JAK2-targeted therapies. Incorporating JAK2 inhibitors into treatment regimens, either as monotherapy in high-risk cases or in combination with chemotherapy, immunotherapy, or niche-modulating agents, has the potential to improve therapeutic response and reduce relapse. Such strategies aim to eradicate leukemic cells while restoring normal hematopoietic function and disrupting the protective niche [22]. Monitoring biomarkers of JAK2 activation, such as phosphorylated STAT5 or CRLF2 rearrangements, can inform treatment efficacy, detect minimal residual disease, and guide early intervention in patients at risk of relapse. Furthermore, understanding resistance mechanisms highlights the need for combination

therapies and personalized treatment plans, emphasizing the role of precision medicine in pediatric leukemia [3].

Conclusion

Aberrant JAK2 signaling plays a central role in the pathogenesis of pediatric leukemia by driving leukemic stem cell proliferation, survival, and resistance to therapy. Dysregulated JAK2 activity disrupts hematopoietic stem cell (HSC) niche homeostasis, remodels the bone marrow microenvironment, and reinforces a protective niche that favors malignant cells. These mechanisms contribute to disease progression, relapse, and refractory phenotypes, underscoring the importance of targeted therapeutic interventions. JAK2 inhibitors represent a promising strategy to address these challenges, offering the potential to suppress leukemic proliferation, restore niche balance, and enhance sensitivity to conventional chemotherapy and emerging immunotherapies. However, resistance—mediated by secondary mutations, compensatory signaling pathways, and niche-dependent survival cues—remains a key obstacle, highlighting the need for combination strategies and precision medicine approaches. Future research should focus on elucidating the complex molecular networks linking JAK2 to the HSC niche, optimizing next-generation inhibitors, and integrating targeted therapy into multi-modal treatment strategies. By addressing both leukemic cells and their supportive microenvironment, JAK2-directed therapies hold promise for improving survival and long-term outcomes in children with high-risk or relapsed leukemia.

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