INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 12, Issue 12- 2025

Review Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2025.12.12.005

The Role of JAK2 in the Hematopoietic Stem Cell Niche of Pediatric Leukemia: Mechanisms and Therapeutic Implications

***Emmanuel Ifeanyi Obeagu, PhD**
Division of Haematology, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.
*Corresponding author: Emmanuel Ifeanyi Obeagu, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe, *emmanuelobeagu@yahoo.com*,
ORCID: 0000-0002-4538-0161

Abstract

Janus kinase 2 (JAK2) is a central regulator of hematopoietic stem cell (HSC) function, mediating signals that control proliferation, differentiation, and survival. In pediatric leukemia, aberrant JAK2 activation disrupts the HSC niche, promoting leukemic stem cell expansion, chemoresistance, and relapse. Leukemic blasts remodel the bone marrow microenvironment, enhancing cytokine-mediated JAK2 signaling and suppressing normal hematopoiesis. Targeted inhibition of JAK2 offers a promising therapeutic strategy, particularly when integrated with conventional chemotherapy or immune-based approaches. This review synthesizes current understanding of JAK2's role in the pediatric HSC niche, its contribution to leukemogenesis, and implications for niche-directed and precision therapies.

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

Introduction

Hematopoietic stem cells (HSCs) are rare, multipotent cells residing in specialized microenvironments within the bone marrow, collectively referred to as the hematopoietic stem cell niche. These niches regulate HSC quiescence, self-renewal, and lineage commitment through a complex interplay of cellular and molecular cues, including stromal cells, osteoblasts, endothelial cells, extracellular matrix components, and a variety of cytokines and growth factors. The maintenance of HSC homeostasis is critical for lifelong hematopoiesis, and disruptions in niche signaling can predispose to malignant transformation [1].Janus kinase 2 (JAK2), a non-receptor tyrosine kinase, is a key mediator of cytokine receptor signaling in hematopoiesis. Through activation of the JAK-STAT pathway, JAK2 regulates essential processes such as proliferation, differentiation, and survival of HSCs. In normal physiology, JAK2 signaling is tightly controlled by receptor availability, cytokine concentration, and negative feedback regulators. However, in pediatric leukemia, dysregulation of JAK2 activity—whether via point mutations, translocations, or upstream cytokine receptor aberrations—leads to pathological proliferation of leukemic progenitors and perturbation of the bone marrow niche [2-3].

Pediatric leukemia, particularly acute lymphoblastic leukemia (ALL) and, less frequently, myeloid leukemias, is characterized by abnormal expansion of immature hematopoietic cells. Emerging evidence suggests that the bone marrow niche not only provides a sanctuary for leukemic stem cells (LSCs) but also actively contributes to disease progression and therapy resistance. Leukemic blasts can remodel the niche, altering stromal composition, extracellular matrix dynamics, and cytokine gradients, thereby creating a microenvironment that preferentially supports malignant cells while suppressing normal hematopoiesis [4].

Molecular Basis of JAK2 Signaling in the Hematopoietic Stem Cell Niche

Janus kinase 2 (JAK2) is a non-receptor tyrosine kinase that occupies a central position in cytokine-mediated signal transduction within hematopoietic stem cells (HSCs). It is intimately 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 are critical for HSC proliferation, lineage specification, and survival. Upon ligand binding, receptor dimerization induces JAK2 autophosphorylation, which in turn phosphorylates receptor-associated tyrosine residues. These phosphorylated residues serve as docking sites for downstream effectors, most prominently the signal transducer and activator of transcription (STAT) family [5].Activation of STAT proteins—particularly STAT5 in the hematopoietic context—leads to their translocation into the nucleus, where they modulate transcription of genes governing cell cycle progression, anti-apoptotic pathways, and differentiation programs. In the quiescent HSC niche, tightly regulated JAK2-STAT signaling ensures a delicate balance between self-renewal and differentiation, preventing both stem cell exhaustion and uncontrolled proliferation. Additionally, JAK2 interfaces with other signaling cascades, including PI3K-AKT, RAS-MAPK, and SOCS-mediated negative feedback loops, creating a highly interconnected network that integrates external cytokine cues with intrinsic HSC programs [6].

Within the bone marrow niche, stromal cells, osteoblasts, and endothelial cells provide a rich array of cytokines and adhesion-mediated signals that modulate JAK2 activity. For instance, stromal cell–derived thrombopoietin engages MPL-JAK2-STAT5 signaling to maintain long-term HSC quiescence, while IL-3 and GM-CSF act through JAK2-dependent pathways to promote proliferation of committed progenitors under stress or demand. Importantly, these signals are spatially and temporally regulated within the niche; localized gradients of cytokines and the

physical architecture of the extracellular matrix ensure that HSCs receive context-specific instructions, maintaining homeostasis [7].In pediatric leukemia, this finely tuned molecular system is perturbed. Genetic alterations such as JAK2 point mutations, chromosomal translocations involving cytokine receptors, or overexpression of upstream ligands lead to constitutive JAK2 activation. The result is a persistent STAT-driven transcriptional program that favors leukemic stem cell (LSC) self-renewal and survival while disrupting normal HSC-niche interactions. Leukemic cells exploit this dysregulated signaling to outcompete healthy HSCs, remodel the niche, and create a microenvironment conducive to malignant persistence [3].Thus, the molecular basis of JAK2 signaling within the HSC niche is not merely a linear cascade but a dynamic network influenced by niche-derived cues, intracellular regulatory circuits, and pathological alterations in leukemia. Understanding these mechanisms provides a critical foundation for targeting JAK2 therapeutically, aiming to restore niche balance, suppress leukemic expansion, and enhance responsiveness to conventional and targeted therapies in pediatric patients [8].

JAK2 Alterations in Pediatric Leukemia

While JAK2 mutations are classically associated with myeloproliferative neoplasms in adults, their role in pediatric leukemia is increasingly recognized, particularly in high-risk subsets of acute lymphoblastic leukemia (ALL) and, less commonly, acute myeloid leukemia (AML). In children, direct point mutations in JAK2, such as the canonical V617F mutation, are rare; however, aberrant activation of JAK2 signaling frequently arises through alternative mechanisms, including cytokine receptor rearrangements, gene fusions, or overexpression of upstream ligands. Notably, rearrangements of CRLF2 and fusions involving IL7R and other cytokine receptors create constitutively active signaling complexes that engage JAK2, promoting downstream STAT activation and leukemic proliferation [9].These alterations are clinically significant because they confer both a proliferative advantage and resistance to apoptosis. Constitutively active JAK2 signaling drives leukemic stem cell (LSC) expansion, sustains self-renewal, and enhances survival within the bone marrow niche. Leukemic cells harboring JAK2 aberrations can remodel the microenvironment by altering stromal cell behavior, extracellular matrix composition, and cytokine gradients, creating a niche that favors malignant over normal hematopoiesis. This remodeling amplifies leukemic dominance and establishes a protective environment against chemotherapeutic stress [10].

Beyond structural genetic changes, epigenetic modulation and post-translational modifications can further influence JAK2 activity in pediatric leukemia. For example, dysregulation of negative regulators such as SOCS (suppressor of cytokine signaling) proteins or phosphatases can prolong JAK2 activation, reinforcing aberrant signaling loops. Such alterations are often associated with high-risk disease phenotypes, early relapse, and minimal residual disease persistence [11].The identification of JAK2 pathway dysregulation in pediatric leukemia has profound translational implications. Molecular profiling can stratify patients into risk categories, guide the use of targeted therapies such as JAK inhibitors, and inform clinical trial design. Furthermore, understanding the diverse mechanisms of JAK2 activation underscores the importance of evaluating both genetic and microenvironmental contributors to leukemogenesis, highlighting that therapeutic strategies must address not only leukemic cells but also the niche that supports their survival [12].

JAK2 in Relapse and Refractory Pediatric Leukemia

Relapse and refractory disease remain major challenges in pediatric leukemia, often representing the most critical determinants of morbidity and mortality. Accumulating evidence implicates aberrant JAK2 signaling as a central contributor to these adverse outcomes. Leukemic stem cells (LSCs) that survive initial chemotherapy frequently exhibit persistent activation of JAK2-dependent pathways, which

confer enhanced survival, proliferative potential, and resistance to apoptosis. These cells can exploit the protective features of the bone marrow niche, where paracrine cytokine signaling, hypoxic conditions, and stromal cell interactions synergize with intrinsic JAK2 activation to shield LSCs from cytotoxic agents [13].Mechanistically, constitutive JAK2-STAT signaling in relapsed or refractory leukemic cells sustains transcriptional programs that favor self-renewal, quiescence escape, and DNA damage tolerance. Additionally, aberrant JAK2 activity can modulate the immune microenvironment, suppressing anti-leukemic immune responses and promoting the recruitment of niche-supportive stromal and endothelial elements. This niche remodeling not only enhances leukemic survival but also perpetuates a feedback loop in which JAK2 signaling and microenvironmental cues reinforce each other [14].

Clinical observations corroborate these molecular findings. Pediatric patients with JAK2-activated leukemias often exhibit early relapse, minimal residual disease persistence, and poor response to standard chemotherapy regimens. Moreover, the heterogeneity of JAK2 pathway alterations—including point mutations, cytokine receptor fusions, and upstream ligand dysregulation—contributes to variable therapeutic resistance profiles, complicating treatment strategies [15].The recognition of JAK2's role in relapse and refractory disease underscores the importance of targeted therapeutic interventions. JAK2 inhibitors, when combined with conventional chemotherapy or immunomodulatory approaches, have shown potential in preclinical models to eradicate resistant LSC populations and restore niche homeostasis. Ongoing research is focused on optimizing timing, dosing, and combination strategies to overcome resistance mechanisms and improve long-term outcomes in pediatric leukemia [16].

JAK2-Directed Targeted Therapies

The identification of aberrant JAK2 signaling in pediatric leukemia has catalyzed the development of targeted therapeutic strategies aimed at disrupting this central oncogenic pathway. JAK2-directed therapies primarily employ small-molecule inhibitors that competitively bind the ATP-binding pocket of the kinase, thereby preventing phosphorylation of downstream effectors such as STAT proteins. Among these, ruxolitinib, a selective JAK1/JAK2 inhibitor, has been the most extensively studied in both preclinical and early-phase clinical trials. In pediatric leukemia models, ruxolitinib effectively suppresses leukemic stem cell proliferation, reduces cytokine-driven survival signaling, and partially restores normal hematopoietic function within the bone marrow niche [3].Beyond monotherapy, combination strategies are emerging as a critical approach to enhance therapeutic efficacy and mitigate resistance. JAK2 inhibitors are being investigated alongside conventional chemotherapeutic regimens, targeted agents (e.g., BCL-2 inhibitors), and immunotherapies, including bispecific T-cell engagers and chimeric antigen receptor (CAR) T-cell therapies. Such combinations aim to simultaneously eradicate leukemic blasts and disrupt the protective signaling provided by the HSC niche. Preclinical studies suggest that targeted inhibition of JAK2 can sensitize leukemic cells to apoptosis, reduce minimal residual disease, and prevent niche-mediated survival signals that drive relapse [17].

However, several challenges limit the widespread application of JAK2 inhibitors in pediatric populations. These include dose-limiting hematologic toxicities, off-target inhibition of related kinases, and the emergence of compensatory signaling pathways that bypass JAK2 blockade. Additionally, the heterogeneity of JAK2 activation mechanisms—ranging from point mutations to cytokine receptor fusions—necessitates precise patient stratification to identify those most likely to benefit from therapy. Biomarker-driven selection, including detection of CRLF2 rearrangements or elevated phosphorylated STAT5 levels, is therefore essential for optimizing treatment outcomes [18].Emerging next-generation inhibitors are being designed to improve selectivity for aberrantly activated JAK2 while sparing normal

hematopoietic function. These agents, combined with strategies that modulate the bone marrow niche or target downstream effectors, hold promise for overcoming resistance and achieving durable remissions. Ultimately, JAK2-directed therapies represent a paradigm shift in pediatric leukemia management, moving from broadly cytotoxic approaches toward precision-targeted interventions that address both leukemic cells and their supportive microenvironment [19].

Clinical Implications

The recognition of JAK2 as a central regulator of hematopoietic stem cell (HSC) function and leukemic progression carries significant clinical ramifications for pediatric leukemia. Aberrant JAK2 signaling influences disease onset, progression, therapeutic response, and relapse, making it a critical biomarker for risk stratification and treatment planning. Molecular profiling to detect JAK2 mutations, cytokine receptor fusions, or evidence of pathway hyperactivation allows clinicians to identify patients who may benefit from targeted interventions, improving precision in therapeutic decision-making [20].Integration of JAK2-directed therapies into existing treatment regimens has the potential to enhance outcomes, particularly in high-risk or relapsed cases. Targeted inhibition of JAK2 not only reduces leukemic stem cell proliferation but also modulates the bone marrow niche, disrupting the supportive microenvironment that contributes to chemoresistance. Such strategies may complement conventional chemotherapy, immunotherapies, or emerging niche-modulating agents, offering a multi-pronged approach to disease eradication [21].Monitoring of JAK2 signaling and niche interactions also has prognostic value. Elevated JAK2-STAT activity, persistent phosphorylated STAT5 expression, or aberrant niche remodeling may indicate minimal residual disease or early risk of relapse, guiding closer surveillance and timely intervention. Furthermore, the heterogeneity of JAK2 alterations necessitates individualized therapeutic approaches; patient selection based on molecular and microenvironmental profiles is essential to maximize efficacy while minimizing toxicity [22].

Conclusion

JAK2 is a central orchestrator of hematopoietic stem cell (HSC) function and niche dynamics, with profound implications in pediatric leukemia. Dysregulated JAK2 signaling—arising from mutations, cytokine receptor fusions, or upstream ligand abnormalities—disrupts the delicate balance of the bone marrow microenvironment, promoting leukemic stem cell survival, proliferation, and therapy resistance. This pathological interplay between leukemic cells and the niche contributes to disease progression, relapse, and refractory phenotypes, underscoring the importance of targeting both intrinsic cellular mechanisms and extrinsic microenvironmental support.Therapeutic strategies directed against JAK2, including selective inhibitors and combination regimens, offer a promising avenue to restore niche homeostasis, reduce leukemic burden, and enhance treatment response. Precision medicine approaches, guided by molecular profiling and biomarker detection, are essential to identify patients most likely to benefit from these interventions while minimizing toxicity.Future research should focus on elucidating the complex molecular networks linking JAK2 to niche remodeling, developing next-generation inhibitors with improved specificity, and integrating JAK2-targeted therapies into multi-modal treatment strategies. By addressing both leukemic cells and their supportive microenvironment, such approaches have the potential to improve survival, reduce relapse rates, and transform the clinical management of pediatric leukemia.

References

1. Pinho, S., & Zhao, M. (2023). Hematopoietic Stem Cells and Their Bone Marrow Niches. *Advances in experimental medicine and biology*, *1442*, 17–28. https://doi.org/10.1007/978-981-99-7471-9_2
2. Staerk, J., & Constantinescu, S. N. (2012). The JAK-STAT pathway and hematopoietic

stem cells from the JAK2 V617F perspective. *JAK-STAT*, *1*(3), 184–190. https://doi.org/10.4161/jkst.22071

3. Obeagu E. I. (2025). JAK2 in pediatric leukemia: mechanisms of pathogenesis and drug development - a narrative review. *Annals of medicine and surgery (2012)*, *87*(6), 3410–3423. https://doi.org/10.1097/MS9.0000000000003180
4. Long, N. A., Golla, U., Sharma, A., & Claxton, D. F. (2022). Acute Myeloid Leukemia Stem Cells: Origin, Characteristics, and Clinical Implications. *Stem cell reviews and reports*, *18*(4), 1211–1226. https://doi.org/10.1007/s12015-021-10308-6
5. Yamaoka, K., Saharinen, P., Pesu, M., Holt, V. E., 3rd, Silvennoinen, O., & O'Shea, J. J. (2004). The Janus kinases (Jaks). *Genome biology*, *5*(12), 253. https://doi.org/10.1186/gb-2004-5-12-253
6. Wang, Z., & Bunting, K. D. (2013). STAT5 in hematopoietic stem cell biology and transplantation. *JAK-STAT*, *2*(4), e27159. https://doi.org/10.4161/jkst.27159
7. Prummel, K. D., Woods, K., Kholmatov, M., Schmitt, E. C., Vlachou, E. P., Labyadh, M., Wehner, R., Poschmann, G., Stühler, K., Winter, S., Oelschlaegel, U., Wobus, M., Schwartz, L. S., Moura, P. L., Hellström-Lindberg, E., Rajalingam, K., Theobald, M., Trowbridge, J. J., Carron, C., Jaffredo, T., … Guezguez, B. (2025). Inflammatory stromal and T cells mediate human bone marrow niche remodeling in clonal hematopoiesis and myelodysplasia. *Nature communications*, *16*(1), 10042. https://doi.org/10.1038/s41467-025-65803-y
8. Mascarenhas, M. I., Bacon, W. A., Kapeni, C., Fitch, S. R., Kimber, G., Cheng, S. W., Li, J., Green, A. R., &Ottersbach, K. (2016). Analysis of Jak2 signaling reveals resistance of mouse embryonic hematopoietic stem cells to myeloproliferative disease mutation. *Blood*, *127*(19), 2298–2309. https://doi.org/10.1182/blood-2015-08-664631
9. Passamonti, F., Maffioli, M., Caramazza, D., &Cazzola, M. (2011). Myeloproliferative neoplasms: from JAK2 mutations discovery to JAK2 inhibitor therapies. *Oncotarget*, *2*(6), 485–490. https://doi.org/10.18632/oncotarget.281
10. Cook, A. M., Li, L., Ho, Y., Lin, A., Li, L., Stein, A., Forman, S., Perrotti, D., Jove, R., & Bhatia, R. (2014). Role of altered growth factor receptor-mediated JAK2 signaling in growth and maintenance of human acute myeloid leukemia stem cells. *Blood*, *123*(18), 2826–2837. https://doi.org/10.1182/blood-2013-05-505735
11. Gnanasambandan, K., &Sayeski, P. P. (2011). A structure-function perspective of Jak2 mutations and implications for alternate drug design strategies: the road not taken. *Current medicinal chemistry*, *18*(30), 4659–4673. https://doi.org/10.2174/092986711797379267
12. Downes, C. E., McClure, B. J., McDougal, D. P., Heatley, S. L., Bruning, J. B., Thomas, D., Yeung, D. T., & White, D. L. (2022). *JAK2* Alterations in Acute Lymphoblastic Leukemia: Molecular Insights for Superior Precision Medicine Strategies. *Frontiers in cell and developmental biology*, *10*, 942053. https://doi.org/10.3389/fcell.2022.942053
13. Martin, A., Morgan, E., &Hijiya, N. (2012). Relapsed or refractory pediatric acute lymphoblastic leukemia: current and emerging treatments. *Paediatric drugs*, *14*(6), 377–387. https://doi.org/10.2165/11598430-000000000-00000
14. Ruchatz, H., Coluccia, A. M., Stano, P., Marchesi, E., &Gambacorti-Passerini, C. (2003). Constitutive activation of Jak2 contributes to proliferation and resistance to apoptosis in NPM/ALK-transformed cells. *Experimental hematology*, *31*(4), 309–315. https://doi.org/10.1016/s0301-472x(03)00007-9
15. Hu, M., Liu, R., Li, J., Zhang, L., Cao, J., Yue, M., Zhong, D., & Tang, R. (2023). Clinical features and prognosis of pediatric acute lymphocytic leukemia with JAK-STAT pathway genetic abnormalities: a case series. *Annals of hematology*, *102*(9), 2445–2457. https://doi.org/10.1007/s00277-023-05245-y

16. Kim, S., Ruminski, P., Singh, M., Staser, K., Ashami, K., Ritchey, J., Lim, S., DiPersio, J. F., & Choi, J. (2024). Novel JAK Inhibitors to Reduce Graft-Versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation in a Preclinical Mouse Model. Molecules, 29(8), 1801. https://doi.org/10.3390/molecules29081801
17. Peng, X., Tang, F., Li, Y., Bai, J., Li, L., & Zhang, L. (2024). Combination of BCL-2 inhibitors and immunotherapy: a promising therapeutic strategy for hematological malignancies. *Discover oncology*, *15*(1), 311. https://doi.org/10.1007/s12672-024-01161-3
18. Thaw, K., Harrison, C. N., &Sriskandarajah, P. (2024). JAK Inhibitors for Myelofibrosis: Strengths and Limitations. *Current hematologic malignancy reports*, *19*(6), 264–275. https://doi.org/10.1007/s11899-024-00744-9
19. Nair, P. C., Piehler, J., Tvorogov, D., Ross, D. M., Lopez, A. F., Gotlib, J., & Thomas, D. (2023). Next-Generation JAK2 Inhibitors for the Treatment of Myeloproliferative Neoplasms: Lessons from Structure-Based Drug Discovery Approaches. *Blood cancer discovery*, *4*(5), 352–364. https://doi.org/10.1158/2643-3230.BCD-22-0189
20. Liang, D., Wang, Q., Zhang, W., Tang, H., Song, C., Yan, Z., Liang, Y., & Wang, H. (2024). JAK/STAT in leukemia: a clinical update. *Molecular cancer*, *23*(1), 25. https://doi.org/10.1186/s12943-023-01929-1
21. Reddy, M. M., Deshpande, A., & Sattler, M. (2012). Targeting JAK2 in the therapy of myeloproliferative neoplasms. *Expert opinion on therapeutic targets*, *16*(3), 313–324. https://doi.org/10.1517/14728222.2012.662956
22. Al-Amrani, S., Al-Zadjali, F., Jeelani, Y., Al-Jabri, Z., Al-Bulushi, M., AlRawahi, M., Al Zaabi, A., AlShekaili, J., Al-Huneini, M., & Al-Khabori, M. (2024). Expression of JAK/STAT Signaling Proteins at Diagnosis and Remission in Patients with Acute Myeloid Leukemia. *Oman medical journal*, *39*(3), e633. https://doi.org/10.5001/omj.2024.80

Access this Article in Online	
Quick Response Code	Website: www.ijcrcps.com Subject: Oncology
DOI: 10.22192/ijcrcps.2025.12.12.005	

How to cite this article:
Emmanuel Ifeanyi Obeagu. (2025). The Role of JAK2 in the Hematopoietic Stem Cell Niche of Pediatric Leukemia: Mechanisms and Therapeutic Implications. Int. J. Curr. Res. Chem. Pharm. Sci. 12(12): 35-41.
DOI: http://dx.doi.org/10.22192/ijcrcps.2025.12.12.005

