JAK/STAT Pathway in Classical Hodgkin Lymphoma: From Pathogenic Mechanisms to Therapies

Yaosen Hu*

Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430000, China

*Corresponding Author: wilsonh@hust.edu.cn

Abstract. The JAK/STAT pathway is the primary mechanism for cytokine signaling and plays a pivotal role in classical Hodgkin lymphoma (cHL). The JAK/STAT pathway's abnormal activation contributes to the development and maintenance of tumors. Both intracellular aberrant gene mutations and extracellular cytokine stimulation can continuously activate JAK/STAT pathway, promoting the proliferation, survival and immune evasion of Hodgkin Reed-Sternberg (HRS) cells, the tumor cells of cHL. Moreover, JAK/STAT pathway mediates the formation of an inhibitory tumor micro-environment (TME), as it can regulates the recruitment, differentiation, proliferation and function of various immune cells in the tumor micro-environment (TME) of cHL, including immune effector cells such as CD4+ Th cells, CD8+ T cells, NK cells and immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), with cytokines binding to corresponding receptors on the surfaces of these cells. Blocking the JAK/STAT pathway can impede the growth of HRS cells and modulate the overall activity of immune cells within the TME of cHL, suggesting that JAK/STAT inhibition might be a viable treatment option for cHL.This review will summarize the performance of JAK/STAT pathway in the pathogenesis of cHL, its effect on immune cells in TME, and the performance of JAK/STAT inhibition in clinical trials, while highlighting potential future directions for JAK/STAT inhibition in cHL treatment.

Keywords: Classic Hodgkin lymphoma; JAK/STAT pathway; tumor microenvironment; immune evasion; combination therapy.

1. Introduction

Classical Hodgkin lymphoma (cHL) is a rare but curable B-cell hematologic malignancy, with the majority of newly diagnosed cHL patients across all stages can be cured with combination chemotherapy. N-AVD is the preferred regimen for low-risk and elderly patients, while BrECADD is recommended as the first-line choice for those with multiple adverse prognostic factors. However, A subset of cHL patients fail to respond to initial therapy, while those initially cured exhibit high relapse rates. Although salvage strategies such as high-dose chemotherapy followed by autologous stem cell transplantation (HDCT/ASCT) or immune checkpoint inhibitors can be employed, their efficacy remains suboptimal [1]. Therefore, more durable and effective therapeutic approaches are needed to refine the management of cHL.

The JAK/STAT pathway, which is structurally made up of transmembrane receptors, Janus kinases (JAKs), and signal transducers and activators of transcription (STATs), facilitates diverse cytokine signaling to control cellular differentiation, metabolic reprogramming, and immune regulatory functions [2]. At the molecular scale, extracellular signaling molecules attach to their specific transmembrane receptors, prompting JAKs to start the phosphorylation of receptor tyrosines, which forms a docking site for STATs. Once recruited, STATs are phosphorylated by JAKs into pSTATs, detach from the receptor complex, and then dimerize. These activated dimers move into the nucleus, where they attach to the promoter regions of target genes to control transcriptional activity. The JAK/STAT pathway is meticulously regulated by inherent negative protein regulators, which include: 1) Suppressors of Cytokine Signaling (SOCSs), 2) Protein Tyrosine Phosphatases (PTPs), and 3) Protein Inhibitors of Activated STATs (PIASs) [2]. Both overexpression and hyperphosphorylation of JAKs or STATs and impairment of negative regulators contribute to aberrant activation of the pathway.

In cHL, the JAK/STAT pathway is crucial for the functioning of both tumor cells and the immune cells that make up the tumor microenvironment (TME). Consequently, inhibiting JAK/STAT signaling might offer a novel therapeutic strategy for treating cHL. In this review, the author will summarize the mechanistic involvement of JAK/STAT in cHL pathogenesis and immune evasion, as well as clinical applications of JAK/STAT inhibition, aiming to indicate future directions of JAK/STAT inhibition in cHL treatment.

2. JAK/STAT Pathway in the Pathogenesis of cHL

A hallmark of cHL is the constitutive activation of the JAK/STAT pathway. In HRS cells, this pathological process induces hyperphosphorylation of STAT proteins, which in turn causes overexpression of multiple cancer-related genes such as the proto-oncogene MYC, immune checkpoint ligand PD-L1, and various cytokine genes, thereby driving tumorigenesis and maintenance. The following discussion will summarize the key factors contributing to constitutive JAK/STAT pathway activation in HRS cells and examine the biological impacts of this hyperactivated signaling pathway on HRS cells.

Mutations in JAK or STAT genes (or both) represent the most direct molecular mechanism underlying constitutive JAK/STAT pathway activation in cHL. While persistent JAK/STAT signaling is commonly observed in Hodgkin-Reed-Sternberg (HRS) cells, genetic alterations directly affecting JAK genes occur relatively infrequently. Among these genetic abnormalities, the most extensively studied is the amplification of JAK2 located on chromosomal region 9p24.1. A whole-exome sequencing analysis of HRS cells from 23 treatment-naïve cHL patients revealed copy number gains at 9p24.1 in approximately 13% of cases [3]. Interestingly, the 9p24.1 locus harbors not only JAK2 but also the immune checkpoint genes PD-L1/PD-L2. Consequently, chromosomal amplification of this region leads to dual oncogenic effects: enhanced JAK2 signaling and upregulated PD-L1/PD-L2 expression on tumor cells. Furthermore, hyperphosphorylated STAT6 can transcriptionally activate these immune checkpoint genes, creating a synergistic mechanism that amplifies expression of PD-L1/PD-L2 and potentiates immune escape - a hallmark of HRS cell pathogenesis. Another study reveals that a subset of cHL cases harbor the t(4;9)(q21;p24) translocation in HRS cells, generating a novel SEC31A-JAK2 fusion transcript, which could drive aberrant JAK2 overexpression. In contrast, STAT mutations demonstrate higher prevalence in cHL, with documented alterations affecting STAT6, STAT3, and STAT5B. The most frequently observed variants occur in STAT6's DNA-binding domain (11/34 cases) [4]. Functional loss of negative regulators (SOCS/PTPN genes) can also induce constitutive JAK/STAT activation through impaired protein function, correlating with adverse clinical outcomes in patients [5].

Other factors that may contribute to constitutive JAK/STAT pathway activation include genetic alterations in GNA13 and XPO1, as well as Epstein-Barr virus (EBV) infection. Genomic analyses reveal a significant co-occurrence between GNA13 and STAT6 mutations in cHL (7 of 11 cases), though the underlying mechanistic linkage remains elusive [3]. The nuclear export protein XPO1 facilitates nuclear translocation of macromolecules including STATs, suggesting its potential regulatory role in JAK/STAT signaling. In cases of cHL, the E571K mutation of XPO1 is associated with adverse clinical outcomes [6].

The cytokine-rich tumor microenvironment in cHL provides persistent activation signals for the JAK/STAT pathway, sustaining elevated STAT protein levels in HRS cells. Multiple immune mediators—including various ILs, TNF-α, and LTA—derived from both paracrine (tumor-infiltrating immune cells) and autocrine (HRS cells themselves) sources collectively contribute to this pathogenic signaling milieu. Beyond JAK/STAT activation, cytokines orchestrate a multifaceted regulatory network in HRS cells through alternative signaling pathways. This induces secretion of diverse cytokines/chemokines that recruit immune cell infiltrates, ultimately shaping an immunologically complex microenvironment with intricate, self-regulating cellular crosstalk around HRS cells.

The JAK/STAT pathway is essencial for the proliferation and survival of tumor cells. Accumulating evidence identifies STAT3 as a master regulator in HRS pathophysiology, transcriptionally controlling key oncogenic targets including Bcl-xL and Myc that govern cell cycle progression and apoptotic resistance. Pharmacological inhibition of JAK kinases or STAT3, as well as genetic upregulation of SOCS1/SOCS3, can effectively induce apoptosis. The JAK/STAT pathway regulates cytokine production in HRS cells as well. JAK inhibition (e.g., ruxolitinib) significantly downregulates multiple cytokine networks in these malignant cells—spanning IL-1, IL-4, IL-13, and IL-17. Furthermore, as previously discussed, STAT6-mediated PD-L1 induction represents a critical immune evasion mechanism in this malignancy.

3. JAK/STAT Pathway in TME of cHL

The tumor microenvironment (TME) constitutes a fundamental component of classical Hodgkin lymphoma (cHL), playing indispensable roles in disease pathogenesis and progression. Characteristically, the cHL TME exhibits sparse malignant cells enveloped by abundant non-neoplastic immune cells—a heterogeneous mix of immunosuppressive populations and effector immune subsets. Given the typically low proliferative activity of HRS cells, their survival critically depends on immune evasion strategies. Through sophisticated cytokine networks, HRS cells orchestrate both recruitment and functional polarization of immune cells toward immunosuppressive phenotypes, thereby establishing their unique permissive niche. The JAK/STAT pathway serves as a critical mediator of cytokine communication that profoundly shapes the Hodgkin lymphoma microenvironment. This essential pathway contributes to the formation, maintenance, and functional coordination of cellular interactions within the cHL tumor niche. The following discussion explores how JAK/STAT signaling influences the specialized functions of various immune cell populations that characterize the cHL tumor microenvironment.

3.1. Tumor-Infiltrating Lymphocytes (TILs)

Lymphocytes represent the predominant cellular constituency within the cHL tumor microenvironment, with CD8+ T cells, CD4+ T cell subsets, and natural killer (NK) cells exhibiting distinct functional specializations. Despite their frequent histological presence in cHL-involved lymph nodes, B lymphocytes demonstrate minimal functional involvement in antitumor immunity and thus will be excluded from subsequent analysis.

3.1.1 CD4+ T cells

Within the cHL ecological niche, CD4+ T cells represent the most prevalent lymphocyte group, consisting of six distinct functional groups, covering Th1, Th2, Th17, and regulatory T cells (Tregs). The current analysis will focus on the pathophysiologically pivotal Th1, Th2, and Treg subpopulations.

HRS cells create a cytokine-enriched microenvironment that persistently activates JAK/STAT signaling and directs CD4+ T cell differentiation. The IFN-γ/STAT1 and IL-12/STAT4 are collaboratively responsible for promoting Th1 polarization through T-bet upregulation, while IL-4 signaling via JAK1/JAK3/STAT6 induces GATA3 expression to drive Th2 differentiation. Notably, IL-2 further potentiates Th2 bias through dual mechanisms: STAT5A/B phosphorylation and IL-4 receptor induction [7]. Parallel to these processes, the IL-2/STAT5 axis facilitates regulatory T cell development by inducing FOXP3 expression.

Functionally distinct CD4+ T cell subsets exert divergent modulatory effects within the tumor microenvironment. Th1 cells secrete effector cytokines including IL-2 and IFN-γ that potentiate CD8+ cytotoxic T cell activation while driving M1 polarization of tumor-associated macrophages. Th2 cells secrete cytokines including IL-4, IL-5, IL-9, and IL-13, mediating key processes such as M2 polarization and Th2 differentiation. This paradoxical observation suggests potential antitumor functions of Th2 cells in cHL that warrant further investigation. Tregs are classically defined as immunosuppressive populations due to their characteristic expression of inhibitory substances

including IL-10, IL-2, and CTLA-4. Notably, cHL exhibits a unique immunosuppressive landscape featuring type 1 regulatory T cells (Tr1) - a distinct subset absent in normal lymph node physiology. These Tr1 cells demonstrate potent immunomodulatory capacity through IL-10 secretion, effectively suppressing the cytotoxic functions of both CD8+ T lymphocytes and NK cells. In fact, CD4+ T cells could exhibit cytotoxic potential under specific conditions [8].

Intriguingly, CD4+ T cells can surround HRS cells through TCR/CD4/MHC class II and CD2/CD58-mediated interactions, forming rosetting CD4+ T cells. These rosetting CD4+ T cells exhibit further functional suppression via PD-L1+ HRS cells and M2 macrophages, collectively establishing the tumor niche of cHL, which physically enhance immune evasion of malignant cells.

3.1.2 CD8+ T cells

CD8+ cytotoxic T lymphocytes (CTLs) demonstrate functional suppression in cHL. This impaired cytotoxic activity primarily stems from the common lack of MHC I presentation on HRS cells, which prevents proper antigen recognition and subsequent activation of MHC I-restricted CD8+ T cells. Nevertheless, emerging evidence suggests a potential correlation between CD8+ T cell infiltration (both in peripheral blood and TME) and clinical outcomes in cHL patients, warranting further mechanistic investigation [9, 10].

STAT5 and STAT3 play regulatory roles in CD8+ T cell biology. Cytokines including IL-15, IL-2, and IL-7 activate STAT5 signaling to drive cellular proliferation and differentiation. Conversely, STAT3 activation by IL-10 and IL-21 mediates dual immunomodulatory effects: inhibition of CD8+ effector T cell activity and facilitation of memory T cell differentiation.

3.1.3 Natural killer (NK) cells

NK cells, while numerically scarce in cHL, may assume heightened cytotoxic importance given the functional impairment of CD8+ T cells, potentially serving as a critical compensatory mechanism for tumor cell elimination. MHC I can bind to killer-cell immunoglobulin-like receptors (KIRs) located on the surfaces of NK cells, transmitting inhibitory signals that reduce cytotoxic activity. This regulatory mechanism serves as a critical safeguard, protecting healthy host cells from NK cell-mediated cytotoxicity. Despite the lack of MHC I expression on HRS cells—a condition that should theoretically trigger NK cell activation and tumor lysis—the cHL tumor microenvironment exhibits significantly reduced NK cell numbers and impaired functionality compared to normal tissues. This paradoxical suppression results from multiple coordinated mechanisms: 1) physical blockade by rosetting CD4+ T cells, 2) inhibitory cytokine signaling (IL-10/TGF-β), and 3) PD-1-mediated immune checkpoint engagement on NK cell surfaces [11].

The JAK/STAT pathway governs multiple facets of NK cell biology. In a manner akin to its function in CD8+ CTLs, STAT5 stands out as the key regulator overseeing the development, maturation, survival, and functional capability of NK cells, primarily induced by cytokines like IL-15, IL-2, and IL-7. Interferons (IFNs) induce STAT1 activation to regulate NK cell maturation and cytotoxic function. In contrast, STAT3 primarily mediates immunosuppressive effects, exemplified by IL-10-induced JAK1/STAT3 signaling that attenuates NK cell cytotoxicity.

3.2. Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs serve as major immunosuppressive mediators across various solid tumors. Emerging evidence indicates that MDSCs similarly mediate immunosuppressive effects in cHL.

MDSCs derive from bone marrow precursors and contain two functionally distinct subsets: monocytic MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs, alternatively termed granulocytic MDSCs [G-MDSCs]). These populations exhibit distinct anatomical distributions, with M-MDSCs predominantly localizing to tumor microenvironments, while PMN-MDSCs primarily circulate through peripheral lymphoid tissues and the vascular system. Distinct MDSC subsets employ divergent mechanisms to suppress immune responses, with M-MDSCs exhibiting significantly greater immunosuppressive potency than PMN-MDSCs. Consequently,

tumor-infiltrating MDSCs demonstrate markedly enhanced inhibitory capacity compared to their circulating counterparts [12].

The JAK/STAT pathway regulates the proliferation and immunosuppressive effects of MDSCs through the following specific mechanisms: (1) Tumor-derived factors such as G-CSF, GM-CSF, and VEGF activate the JAK/STAT pathway through their respective receptors, leading to upregulated expression of anti-apoptotic factors (c-Myc, Bcl-XL, survivin), thereby encouraging the growth of undeveloped cells while preventing cell death and maturation. (2) STAT3 directly enhances the expression of NADPH Oxidase-2 (NOX2) and arginase-1 (Arg1), which serve as essential enzymatic mediators of MDSC-inmmunosuppression. (3) STAT3 induces the overexpression of the pro-inflammatory protein S100A9, which attaches to CD33 on MDSCs and triggers the release of Arg1, ROS, as well as TGF-β and IL-10. Additionally, S100A9 itself acts as a chemokine to recruit more MDSCs [12].

Given the substantial heterogeneity of tumor microenvironments TMEs across malignancies, the immunomodulatory roles of MDSCs may vary significantly between different cancer models. While the immunosuppressive functions of MDSCs have been extensively characterized in various solid tumors, their contribution to immune evasion by malignant HRS cells remains preliminarily established. It has been observed that elevated frequencies of all MDSC subsets in PB of cHL patients relative to healthy controls, with particular clinical significance observed for CD34+ MDSC and PMN-MDSC populations - their increased levels demonstrate consistent correlation with adverse clinical outcomes [13]. A recent multiplex spatial profiling study identified peritumoral accumulation of M-MDSCs in proximity to malignant HRS cells as a novel biomarker of poor prognosis [14]. Recently, a clinical trial evaluating combined JAK/PD-1 inhibition in relapsed/refractory cHL demonstrated that treatment with ruxolitinib significantly reduced both circulating PMN-MDSC frequencies and surface immunosuppressive marker expression, correlating with improved patient outcomes. These findings provide clinical validation for the pivotal role of MDSCs in mediating immune evasion in cHL [15].

3.3. Tumor-Associated Macrophages (TAMs)

TAMs infiltrate the cHL microenvironment and predominantly exhibit immunosuppressive properties. Macrophages functionally polarize into two distinct subsets: M1-type (with demonstrated antitumor activity) and M2-type (which promote tumor progression). The cHL TME is characteristically enriched with pro-tumorigenic M2-polarized macrophages and the M2 counts correlate with adverse clinical outcomes. Mechanistically, M2-polarized macrophages exhibit abundant surface PD-L1 expression, functionally suppressing CD8+ and CD4+ T lymphocytes as well as NK cells. Furthermore, their interaction with rosetting CD4+ T cells surrounding tumor cells aids in the formation of an immunosuppressive barrier [11].

The JAK/STAT pathway critically governs macrophage polarization dynamics. IFN-mediated STAT1 phosphorylation drives transcriptional activation of genes encoding proteins of NOS2, MHC class II and IL-12, promoting M1-polarization. Conversely, arginase-1 and macrophage mannose receptor 1 (Mrc1) can be upregulated by IL-4/IL-13-initiated JAK-STAT6 signaling, steering differentiation toward the M2 phenotype. This polarization process is fundamentally regulated by the mutually antagonistic relationship between STAT1 and STAT6 pathways, where their signaling exclusivity dictates the functional fate of TAMs.

Given the ubiquitous involvement of the JAK/STAT pathway in regulating virtually all immune cell populations, its precise role within the cHL TME remains incompletely understood. Consequently, the actual impact of JAK/STAT inhibitors on the TME is currently unpredictable. These inhibitors simultaneously target both immunostimulatory and immunosuppressive cells, yet exert differential inhibitory effects across distinct cellular subsets. Thus, their net immunomodulatory outcome likely exhibits dose-dependent characteristics.

No clinical trials to date have conclusively demonstrated the immunomodulatory effects of JAK/STAT inhibitor monotherapy in cHL. However, a combination therapy trial utilizing JAK

inhibitors with PD-1 blockade demonstrated that in patients with PD-1 inhibitor-resistant relapsed/refractory cHL, precisely dosed JAK inhibition effectively suppressed MDSC activity while concurrently enhancing the functionality of T cells and NK cells. These findings indicate that at therapeutic concentrations, JAK inhibitors exhibit greater inhibitory potency against MDSCs compared to their effects on effector immune cells, resulting in an overall immunostimulatory outcome [15].

4. Clinical Application of JAK/STAT Inhibition in cHL

Although the JAK/STAT pathway represents a critical target for therapy in cHL, clinical trial data for related inhibitors remain limited. Currently, ruxolitinib—a selective JAK1/JAK2 inhibitor originally developed for treating myelofibrosis (MF)—stands as the only JAK/STAT-targeting agent under clinical investigation for cHL.

4.1. JAK Inhibitor Monotherapy

Clinical trials evaluating ruxolitinib monotherapy as a JAK inhibitor have demonstrated limited efficacy in cHL. In the phase II trial (NCT01877005) involving 33 advanced cHL patients (27 refractory cases), six cycles of ruxolitinib treatment yielded suboptimal clinical outcomes: a 9.4% (3/32 evaluable patients) overall response rate (ORR) and a 3.5-month median progression-free survival (PFS) [16]. The JeRiCHO phase II trial further corroborated these findings, reporting a final ORR of 16.7% (2/12 patients) and median PFS of 3.6 months in relapsed/refractory (r/r) cHL cohorts [17]. Comparatively, the NCT01965119 trial yielded more encouraging outcomes, with 7 of 13 HL patients achieving clinical responses (ORR 54%) [18].

However, preclinical studies utilizing cHL xenograft mouse models demonstrated significant tumor growth suppression with ruxolitinib treatment [19], revealing a discordance with clinical trial outcomes. This therapeutic discrepancy may be explained by several mechanisms: (1) The immunobiological effects of JAK inhibitors on neoplastic cells may differ between murine models and human pathophysiology. (2) JAK inhibitors exert dual effects on immune cell populations within the TME, requiring precise dose optimization to balance immunostimulatory and immunosuppressive responses. Iterative dose-escalation protocols may be necessary to establish therapeutic windows. (3) Genomic analyses revealed that clinical response correlates with 9p24.1 amplification status. Patients harboring this chromosomal alteration exhibited superior response rates to JAK inhibition (53.8% ORR), whereas those without amplification showed complete refractoriness [16, 18]. Notably, the 9p24.1 amplification occurs in only 13% of cHL patients [3], potentially explaining limited population-level efficacy.

Given that patients with 9p24.1 chromosomal amplification mutations exhibit favorable response rates to ruxolitinib, ruxolitinib may be utilized for the treatment of this specific subtype of cHL, provided that the optimal dose must be established.

4.2. JAK Inhibitor in combination with Other Targeted Drugs

A recent phase I clinical trial investigating the combination of JAK inhibitor and PD-1 blockade for PD-1 blockade-resistant r/r cHL demonstrated promising results. Among 19 r/r cHL patients who received the JAK inhibitor ruxolitinib followed by anti-PD-1 therapy after checkpoint inhibitor failure, the ORR reached 53%. Analysis of post-treatment peripheral blood samples from responders revealed decreased PMN-MDSCs, increased CD4+ T cells, CD8+ T cells, NK cell populations, and enhanced T cell activation [15]. Notably, while JAK inhibitors broadly suppress immune cells in the TME, these findings suggest preferential inhibition of MDSCs over effector immune cells in r/r cHL, indicating JAK inhibitors may function as immunomodulators to synergize with targeted therapies. However, three critical issues require further investigation: (1) Observed peripheral blood alterations may not reflect TME modifications in affected lymph nodes, necessitating direct analysis of tumor-associated immune infiltrates. (2) Current data cannot exclude direct tumoricidal effects of JAK

inhibitors during combination therapy, requiring functional studies to delineate mechanism-of-action. (3) Systematic dose-escalation studies are needed to establish the therapeutic window for this combinatorial approach [20].

Apart from in combination with PD-1 blockade, preclinical studies have also investigated the combinatory potential of luxolitinib and brentuximab vedotin (BV) (CD30-targeted therapy) for classical Hodgkin lymphoma. In mouse models, co-administration of luxolitinib and BV induced sustained complete eradication of HDLM-2 cHL cell line-derived tumors [21]. However, no clinical trials have been initiated to assess the safety profile or therapeutic effect of this combination in humans.

5. Conclusion

Overall, the JAK/STAT pathway works as a critical role in the onset and ongoing presence of cHL. In cHL, the constitutive activation of the JAK/STAT pathway might serve as a vital oncogenic process that prompts the growth, proliferation, and survival of tumor cells. This constitutive activation JAK/STAT is typically caused by mutations in pathway-related protein genes, including well-characterized abnormalities such as 9p24.1 chromosomal amplification, SEC31A-JAK2 fusion mutation, STAT3/STAT6/STAT5B mutations, SOCS1/SOCS3 mutations, PTP1B mutations, and XPO1 mutations. Multiple cytokines in the tumor microenvironment can also act on tumor cells through the JAK/STAT pathway to facilitate tumor maintenance. Additionally, the JAK/STAT pathway influences HRS cell expression of various cytokines (e.g., IL-4, IL-13) and suppressive molecules (e.g., PD-1), thereby enhancing tumor immune evasion.

The tumor microenvironment of cHL contains diverse immune cells, including immune effector cells such as Th1, CTLs, and NK cells, alongside immunosuppressive cells like Tregs, MDSCs, and M2 macrophages. Cytokines regulate the functions of these cells through JAK/STAT signaling, establishing a comprehensive and finely-tuned immunosuppressive microenvironment around tumor cells. This mechanism protects tumor cells and supports their survival.

JAK/STAT inhibition suppresses the growth of tumor cells and promotes their apoptosis. However, its impact on the cHL tumor microenvironment remains uncertain, as the overall immune efficacy of the microenvironment depends on the balance between immunosuppressive cells and immune effector cells. Therefore, further studies are required to investigate the effects of JAK/STAT inhibitors on distinct immune cell populations within the same microenvironment and to determine whether these effects exhibit dose dependency.

The clinical application of JAK/STAT inhibitors for cHL remains limited. Monotherapy with the JAK inhibitor ruxolitinib in cHL clinical trials has shown suboptimal efficacy, though it may hold potential for treating specific cHL subtypes harboring 9p24.1 chromosomal amplification mutations. However, JAK inhibitors used as immunomodulators in combination with other targeted therapies for r/r cHL continue to demonstrate promising prospects.

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