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Review Article

The JAK/STAT Signaling Pathway in Lung Cancer: Mechanisms, Clinical Implications, and Therapeutic Opportunities

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide, with persistently poor survival outcomes despite advances in targeted therapies and immunotherapy. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway have emerged as a central regulator of lung cancer pathogenesis, integrating extracellular cytokine and growth factor signals into transcriptional programs that drive tumor progression. This review provides a comprehensive overview of the molecular mechanisms underlying JAK/STAT activation and dysregulation in lung cancer, with particular emphasis on the dominant oncogenic role of STAT3. Aberrant pathway activation arises through multiple converging mechanisms, including cytokine-driven stimulation from the tumor microenvironment, oncogenic receptor signaling, and epigenetic silencing of negative regulators. Functionally, JAK/STAT signaling promotes tumor cell proliferation, survival, epithelial–mesenchymal transition (EMT), metastasis, and immune evasion, notably through upregulation of programmed death-ligand 1 (PD-L1) and modulation of the tumor immune microenvironment. Therapeutically, targeting the JAK/STAT axis has shown promise in preclinical models, particularly in overcoming resistance to tyrosine kinase inhibitors and enhancing immunotherapy responses. Early-phase clinical studies highlight the potential of combination strategies, including JAK inhibitors with immune checkpoint blockade, demonstrating encouraging response rates and durable clinical benefit in selected patient populations. However, clinical translation remains challenged by pathway complexity, limited efficacy of monotherapies, and safety concerns. Future directions should focus on the development of isoform-selective inhibitors, identification of predictive biomarkers, and rational combination regimens to optimize therapeutic outcomes. Overall, the JAK/STAT pathway represents a critical and actionable target in lung cancer, with significant potential to advance precision oncology.

Keywords: Lung cancer, JAK/STAT pathway, STAT3, tumor microenvironment, immune evasion, targeted therapy, immunotherapy

1. Introduction

Lung cancer remains the most frequently diagnosed malignancy and the foremost cause of cancer-related mortality globally. According to GLOBOCAN 2022 estimates, approximately 2.48 million new cases were recorded, representing 12.4% of all incident cancers, while 1.82 million deaths were attributed to the disease, accounting for nearly one in five cancer deaths worldwide (Ji et al. 2025). Incidence and mortality rates differ substantially by sex and geography, with male-to-female ratios in age-standardized rates approximately twofold globally, though these gaps are narrowing in several high-income countries as tobacco exposure patterns evolve among women. Five-year net survival remains high, ranging between 10% and 20% across most nations, underscoring the continued urgency of

identifying novel therapeutic targets (Ji et al. 2025).

Histologically, lung cancer is broadly classified into non-small cell lung cancer (NSCLC), which constitutes approximately 85% of all cases and encompasses adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, and small cell lung cancer (SCLC), accounting for roughly 13% of diagnoses. The molecular landscape of NSCLC is characterized by recurrent variations in epidermal growth factor receptor (*EGFR)*, *KRAS*, *ALK*, *TP53*, and *RB*, among others, with each aberration influencing disease behaviour, therapeutic responsiveness, and prognosis (Smolarz et al. 2025).

Central to this oncogenic framework is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway which has emerged as a critical mediator of tumor progression. The pathway is activated by more than 50 cytokines, interferons, and growth factors, transmitting extracellular signals through four JAK family members (JAK1, JAK2, JAK3, and TYK2) to six principal STAT transcription factors (STAT1–STAT6) that govern proliferation, survival, differentiation, and immune regulation (Hu et al. 2023). Aberrant, constitutive activation of this pathway, particularly of STAT3, is documented in 30–70% of NSCLC cases depending on histological subtype, where it drives persistent oncogenic signaling and transcriptional dysregulation, and has been implicated in therapy resistance, immune evasion, and metastatic dissemination (Huang et al. 2025).

This review comprehensively examines the molecular mechanisms underlying JAK/STAT dysregulation in lung cancer, outlines its biological consequences across hallmark oncogenic processes, and critically evaluates preclinical and clinical evidence supporting pharmacological targeting of this pathway, with emphasis on rational combination strategies and future directions in precision oncology.

2. Overview of the JAK/STAT Pathway

2.1. Canonical Signaling

The JAK/STAT pathway constitutes one of the most evolutionarily conserved and functionally versatile intracellular signaling cascades, transducing extracellular cytokine and growth factor signals into transcriptional responses with remarkable speed and specificity. In mammals, the pathway encompasses four JAK family members (JAK1, JAK2, JAK3, and TYK2) and seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). While JAK1, JAK2, and TYK2 are ubiquitously expressed, JAK3 is predominantly restricted to hematopoietic tissues, where it governs immune cell development and homeostasis (Hu et al. 2021).

Canonical signaling is initiated when a ligand such as interleukin-6 (IL-6), IL-2, and interferon-gamma (IFN-γ), or a hematopoietic growth factor binds to its cognate cell-surface receptor, inducing receptor dimerization or conformational rearrangement (Figure 1). This structural change brings receptor-associated JAKs into proximity, enabling their transphosphorylation and catalytic activation (O'Shea et al. 2015). Activated JAKs subsequently phosphorylate specific tyrosine residues within the intracellular receptor domains, generating docking sites that recruit cytoplasmic STAT proteins via their Src homology 2 (SH2) domains. Once docked, STATs are phosphorylated at a conserved C-terminal tyrosine residue most notably Tyr705 in STAT3 and dissociate from the receptor complex. Phosphorylated STATs dimerize through reciprocal SH2–phosphotyrosine interactions, forming homo- or heterodimers that translocate into the nucleus and bind promoter response elements to modulate the transcription of target genes governing proliferation, survival, differentiation, and

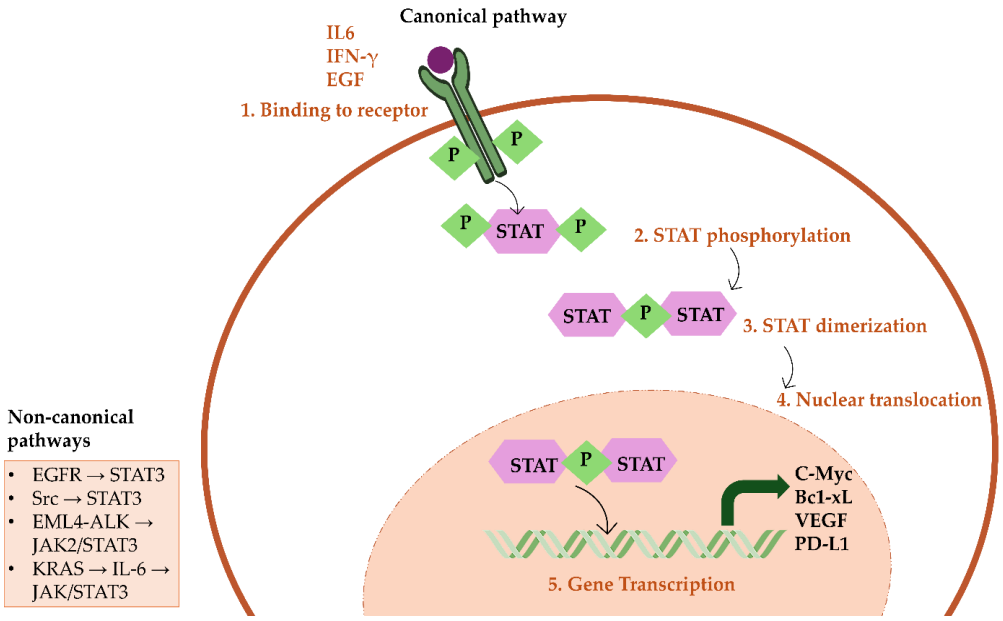

Figure 1: Canonical and non-canonical JAK/STAT signaling pathway in lung cancer. Canonical activation begins when extracellular ligands (IL-6, IFN-γ, EGF) bind their cell-surface receptors, inducing JAK transphosphorylation and STAT3 recruitment and phosphorylation at Tyr705 (Steps 1–2). Phosphorylated STATs dimerize (Step 3), translocate into the nucleus (Step 4), and drive transcription of target genes including *C-Myc*, *Bcl-xL*, *VEGF*, and programmed death-ligand 1 (*PD-L1*) (Step 5). IL-6, interleukin-6; IFN-γ, interferon-gamma; EGF, epidermal growth factor; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; C-Myc, cellular myelocytomatosis oncogene; Bcl-xL, B-cell lymphoma-extra large; VEGF, vascular endothelial growth factor; PD-L1.

immune function (Yu et al. 2009; Böhmer and Friedrich 2014; Fahrenkamp et al. 2015). STAT3, for instance, directly regulates a broad transcriptional program encompassing *VEGF*, *c-Myc*, *Bcl-xL*, *Mcl-1*, *HIF-1α*, cyclin E1, and MMPs, among others (Bromberg et al. 1999). Beyond tyrosine phosphorylation, full transcriptional activation of certain STATs also requires serine phosphorylation at Ser727, mediated by MAP kinases including extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38 MAPK), as well as protein kinase C and cyclin-dependent kinase 5 (Decker and Kovarik 2000). Reversible lysine acetylation, particularly at Lys685 in STAT3, further modulates dimerization efficiency by stabilizing STAT3 dimers, thereby enhancing its transcriptional activity, promoting retention and has linked to epigenetic silencing of tumor suppressor gene promoters through subsequent recruitment of the methylation machinery (Fu et al. 2004).

2.2. Negative Regulators

Given the potency of JAK/STAT signaling, multiple feedback mechanisms operate to prevent aberrant or sustained activation. The suppressors of cytokine signaling (SOCS) family represent the primary negative feedback system. STAT activation directly induces SOCS gene transcription, and the resulting SOCS proteins bind phosphorylated JAKs or cytokine receptors via their SH2 domains, blocking kinase activity and competing with STAT recruitment (Liang et al. 2024; Yoshimura and Yasukawa 2012). Protein tyrosine phosphatases (PTPs), including SHP-1, SHP-2, and TC-PTP, dephosphorylate

activated JAKs and STATs at multiple nodes, effectively terminating signaling complexes and ensuring temporal restraint of the response (Xue et al. 2023). A third regulatory tier is provided by the protein inhibitors of activated STATs (PIAS) family, which acts in the nucleus to inhibit STAT–DNA binding or recruit transcriptional co-repressors, thereby attenuating gene expression independently of phosphorylation status (Shuai 2006). Additionally, a naturally occurring truncated isoform of STAT3 lacking the transactivation domain functions as a dominant-negative inhibitor, and proteasome-mediated ubiquitination of STAT3 represents a further degradative regulatory mechanism (Seif et al. 2017).

2.3. Non-Canonical Signaling and Oncogenic Crosstalk

Beyond the classical cytoplasmic signaling cascade, JAK/STAT components participate in several non-canonical modes of signal transduction with direct relevance to oncogenesis (Figure 1). Unphosphorylated STAT3 can localize to the nucleus and regulate heterochromatin stability in association with heterochromatin protein-1 (HP1), independently of tyrosine phosphorylation (Shi et al. 2008; Dutta et al. 2020). STATs have also been detected in mitochondria, where they promote oxidative phosphorylation and modulate membrane permeability, and STAT3 has been reported to confer resistance to oxidative stress induced apoptosis through endoplasmic reticulum localization (Lahiri et al. 2021).

Among these with relevance to lung cancer is the extensive crosstalk between JAK/STAT and other oncogenic signaling networks. The EGFR can directly phosphorylate STAT1, STAT3, and STAT5 independently of JAKs, while receptor tyrosine kinases (RTKs) such as c-Src constitutively activate STAT3 in tumor cells (Mohrherr et al. 2019). Oncogenic KRAS sustains STAT3 activation through paracrine IL-6 secretion from cancer-associated fibroblasts and autocrine feedback loops within the tumor microenvironment (TME) (Mohrherr et al. 2019). Bidirectional interactions with NF-κB amplify inflammatory gene expression and survival signaling, while convergence with the PI3K/AKT pathway reinforces anti-apoptotic programs and metabolic reprogramming (Li et al. 2013). A summary of key JAK/STAT pathway components, their activating ligands, and their functional roles in lung cancer is provided in Table 1.

3. Activation and Dysregulation of JAK/STAT in Lung Cancer

The JAK/STAT signaling pathway is subject to stringent regulatory control under physiological conditions, with STAT activation being transient and tightly linked to extracellular stimuli. In lung cancer, however, this temporal constraint is fundamentally impacted, resulting in constitutive pathway activation that sustains oncogenic transcriptional programs. Aberrant JAK/STAT signaling has been documented in 30–70% of NSCLC cases, with the exact prevalence varying according to histological subtype and the specific STAT isoform examined (Huang et al. 2025). Multiple convergent mechanisms underlie this dysregulation, and their interplay with the broader molecular landscape of lung cancer defines both the biological consequences and therapeutic vulnerabilities of pathway activation.

3.1. Cytokine-Driven Activation from the Tumor Microenvironment

One of the most clinically significant mechanisms of aberrant JAK/STAT activation in lung cancer is the sustained paracrine and autocrine secretion of cytokines within the TME, promoting phosphorylation of STAT. IL-6 is known as potent activator of JAK1/2 and STAT3

Table 1: JAK/STAT Pathway Components and Their Roles in Lung Cancer

Member	Family	Primary Activating Ligands	Role in Lung Cancer	Key Target Genes in Lung Cancer	References
JAK1	JAK kinase	IL-6, IL-2, IL-4, IFN-α/β, IFN-γ	Mediates cytokine-driven STAT3/STAT1 activation; supports tumor cell survival	VEGF, Bcl-xL, c-Myc, PD-L1	(Mathew et al. 2024).
JAK2	JAK kinase	IL-6, IFN-γ, EPO, GM-CSF	Central mediator of STAT3 and STAT5 activation	STAT3 targets, PD-L1, HIF-1α	(Sumimoto et al. 2016)
JAK3	JAK kinase	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	Regulates immune cell infiltration into TME	Immune regulatory genes	(Hu et al. 2021).
STAT1	STAT protein	IFN-α/β, IFN-γ	Context-dependent: classically tumor suppressive via pro-apoptotic and immune	PD-L1, IRF1, CXCL9, CXCL10, MHC-I	(Mohrherr et al. 2019).
STAT2	STAT protein	IFN-α/β	Mediates antiviral type I interferon responses	ISGs	(Dutta et al. 2020)
STAT3	STAT protein	IL-6, OSM, LIF, EGF, EGFR, Src	Master oncogenic transcription factor; drives proliferation, survival	c-Myc, Bcl-xL, survivin, VEGF, MMP2, PD-L1, HIF-1α	(Huang et al. 2025).

Note: TME, tumor microenvironment; ISG, interferon-stimulated gene; IFN, interferon; EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; OSM, oncostatin M; LIF, leukemia inhibitory factor.

and is overexpressed in approximately 40% of lung cancer patients and functions as a central driver of persistent STAT3 phosphorylation (Dutta et al. 2014). Binding of IL-6 to the gp130 receptor subunit triggers persistent JAK2 activation, which maintains STAT3 in a constantly phosphorylated state. This creates a self-sustaining feed-forward loop where STAT3 further upregulates IL-6 expression, promoting tumor cell survival and a pro-tumorigenic inflammatory niche (Johnson et al. 2018). In KRAS-mutant lung adenocarcinoma, oncogenic KRAS further amplifies this paracrine circuit by promoting IL-6 secretion, linking two of the most frequently mutated oncogenic drivers in NSCLC to constitutive JAK/STAT activation (Sumimoto et al. 2016).

3.2. Receptor Alterations and Molecular Crosstalk

Beyond cytokine stimulation, dysregulation is often secondary to alterations in upstream RTKs. In NSCLC, the EGFR/JAK2/STAT3 signaling node is critical. EGFR is overexpressed in a substantial proportion of NSCLC tumors and activating kinase domain mutations (Tasdemir et al. 2017). Oncogenic mutations in EGFR provide a continuous stimulus that bypasses normal regulatory checks, activating STAT3 either through JAK2 or directly via Src family kinases. Additionally, mesenchymal-epithelial transition factor (MET)-oncogenic alterations induce STAT signaling through AKT-dependent pathways, further diversifying the mechanisms of activation. Notably, while direct mutations in JAK2 are rare in lung cancer compared to myeloproliferative neoplasms, they do occur and can lead to a complete loss of responsiveness to exogenous signals like IFN-γ, subsequently resulting in immune evasion (Saigi et al. 2018).

3.3. Loss of Negative Regulatory Mechanisms

Epigenetic silencing of negative regulators constitutes a critical and underappreciated mechanism of constitutive JAK/STAT activation

in lung cancer. SOCS1 and SOCS3, the principal feedback inhibitors of JAK kinase activity, undergo promoter hypermethylation and transcriptional silencing in a substantial proportion of NSCLC cases, effecting the primary brake on cytokine-driven signaling (Yoshimura and Yasukawa 2012). Similarly, reduced expression or functional impairment of the PTP, SHP-1 and SHP-2 prevents dephosphorylation of activated JAKs and STATs, prolonging signaling duration. Naturally occurring gain-of-function mutations within STAT coding sequences have also been reported, though these occur at low frequency relative to epigenetic and upstream mechanisms (Li et al. 2013).

3.4. STAT Family Member Hierarchy in Lung Cancer

Among the seven STAT family members, STAT3 occupies a dominant oncogenic role in lung cancer, with constitutive activation serving as both a driver of tumor initiation and a mediator of therapeutic resistance. Experimentally, an engineered constitutively dimerizing form of STAT3 (STAT3-C) induces malignant transformation of immortalized fibroblasts and, when overexpressed in murine alveolar type II epithelial cells, drives spontaneous bronchoalveolar adenocarcinoma (Dutta et al. 2020). STAT5 represents a secondary contributor, particularly in growth factor–rich contexts and in tumors with activated JAK2 signaling. STAT1, by contrast, exhibits a more context-dependent role while classically considered anti-tumorigenic through its mediation of IFN-γ–driven immune surveillance and pro-apoptotic gene expression, STAT1 has been shown in some NSCLC models to facilitate AIM2 inflammasome–driven programmed death-ligand 1 (PD-L1) upregulation and promote metastatic behavior, illustrating that the functional outcome of STAT1 activation is shaped by the molecular context of the tumor (Carmo et al. 2011). STAT2 and STAT4 have received comparatively little investigation in lung cancer, while STAT6 has been implicated in IL-4 and IL-13 driven immunosuppressive polarization within the TME (Dutta et al. 2020).

4. Biological Roles of JAK/STAT in Lung Cancer Progression

The constitutive activation of JAK/STAT signaling particularly through STAT3 exerts broad and multiple effects on lung cancer biology, influencing virtually every sign and process of malignant progression (Figure 2).

4.1. Cell Proliferation and Survival

STAT3 functions as a master transcriptional activator of proliferative and pro-survival gene programs in lung cancer cells. Through direct promoter binding, STAT3 induces expression of *c-Myc*, a central regulator of the G1-to-S phase transition and an inducer of *cdc25A*, which governs cyclin-dependent kinase activity (Bowman et al. 2000). STAT3 also upregulates cyclin D1 at the transcriptional level and interacts with Pim-1 kinase to accelerate cell cycle progression (Bowman et al. 2001). In parallel, STAT3 suppresses apoptosis through transcriptional induction of the anti-apoptotic proteins Bcl-xL and Mcl-1, which prevent mitochondrial cytochrome c release, as well as survivin, which directly inhibits caspase-9 activity (Bhatt et al. 2012). Experimental blockade of STAT3 in multiple NSCLC cell lines consistently induces apoptosis and growth arrest, validating its non-redundant role in tumor cell viability (Haura et al. 2005).

The EML4-ALK fusion oncoprotein, present in approximately 5% of NSCLC cases and more prevalent among non-smokers and women with adenocarcinoma, has been shown to constitutively activate JAK2 and drive phosphorylation of STAT1, STAT3, STAT5, and STAT6 simultaneously (Christopoulos et al.

2018). Transcriptomic profiling of EML4-ALK-positive cells identified broad upregulation of STAT target genes governing viability and proliferation, and ALK-specific inhibitors suppress this signaling axis while inducing apoptosis, mechanistically linking EML4-ALK–driven tumorigenesis to JAK2-STAT pathway engagement. The IL-6/JAK2/STAT3 axis additionally promotes the self-renewal and tumor-initiating capacity of lung CSCs through DNMT1-mediated epigenetic suppression of *p53* and *p21*, reinforcing a stem-like phenotype capable of driving disease recurrence (Liu et al. 2015).

4.2. Invasion, Metastasis, and Epithelial-Mesenchymal Transition

Beyond proliferative control, STAT3 plays an active role in promoting the invasive and metastatic properties of lung cancer cells. STAT3 transcriptionally induces *VEGF*, *HGF*, *HIF-1α*, and multiple matrix metalloproteinases, collectively facilitating extracellular matrix remodeling, tumor angiogenesis, and stromal invasion (Dutta et al. 2020). A key mechanism linking STAT3 to metastasis is its regulation of epithelial-mesenchymal transition (EMT). STAT3 upregulates *Lin-28*, a microRNA (miRNA) processing factor that suppresses the let-7 family of tumor-suppressive miRNAs, resulting in increased expression of HMGA2 and acquisition of a mesenchymal gene expression program (Jin 2020). TGF-β, a canonical EMT inducer in the lung cancer TME, activates the JAK2/STAT3 axis in tumor cells and establishes a positive feedback loop with tumor-associated macrophages (TAMs) that further amplifies mesenchymal transition and invasive capacity (Shi et al. 2017). STAT3-induced miR-92a additionally targets RECK which is a matrix metalloproteinase inhibitor reducing its expression and thereby promoting matrix degradation, augmenting the tumor invasiveness in NSCLC cells (Lin et al. 2013).

4.3. Tumor Microenvironment Regulation and Immune Evasion

JAK/STAT signaling plays a central and mechanistically complex role in shaping the immunological character of the lung TME. STAT3 activation within tumor cells suppresses the production of pro-inflammatory cytokines and chemokines including IL-12, RANTES, and CXCL10, while promoting secretion of immunosuppressive mediators such as IL-10, which impairs dendritic cell maturation and induces STAT3 activation in infiltrating immune cells (Yu et al. 2007). This creates a self-reinforcing intercellular feed-forward loop between tumor cells and immune cells that sustains immunosuppression. STAT3 activation also promotes the local accumulation of regulatory T cells (Tregs), Th17 cells, and myeloid-derived suppressor cells (MDSCs), collectively fostering an immunologically tolerant TME (Yu et al. 2007).

PD-L1 upregulation represents one of the most clinically consequential immune evasion mechanisms downstream of JAK/STAT signaling in NSCLC. The IL-6/JAK/STAT3 axis drives transcriptional induction of *CD274* (encoding PD-L1), and this mechanism is operative in EGFR-mutant tumors as well as in EML4-ALK–rearranged tumors, where PD-L1 upregulation occurs through both STAT3 and HIF-1α binding to the PD-L1 promoter (Carmo et al. 2011). Conversely, JAK2 inactivating mutations, occasionally observed in SCLC, disrupt IFN-γ–induced PD-L1 upregulation, revealing a biologically distinct mode (Carmo et al. 2011).

5. Therapeutic Targeting of JAK/STAT in Lung Cancer

5.1. Preclinical Evidence

The preclinical rationale for targeting the JAK/STAT pathway in lung cancer has been established through multiple lines of evidence

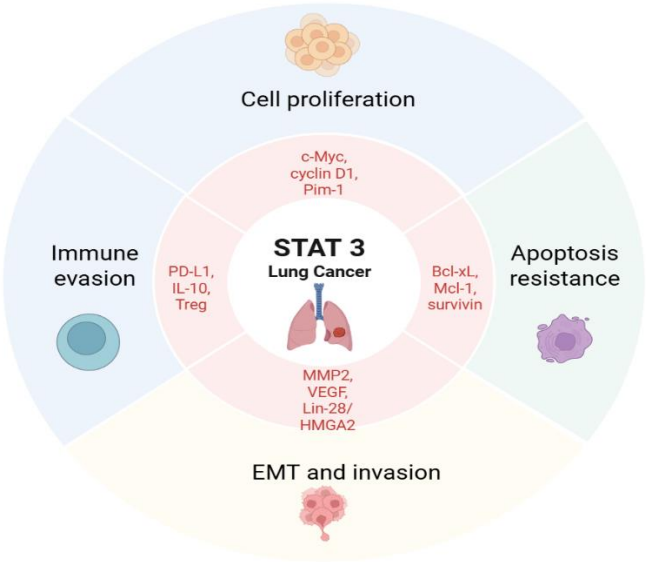

Figure 2: Biological consequences of constitutive STAT3 activation in lung cancer. STAT3 functions as a central oncogenic hub driving four hallmark processes in lung cancer. Cell proliferation is promoted via c-Myc, cyclin D1, and Pim-1. Apoptosis resistance is conferred through Bcl-xL, Mcl-1, and survivin upregulation. EMT and invasion are facilitated by MMP2, VEGF, and the Lin-28/HMGA2 axis. Immune evasion is mediated through PD-L1 and IL-10 induction alongside regulatory T cell accumulation.

converging on JAK kinases and STAT transcription factors as actionable therapeutic nodes. Ruxolitinib is a potent JAK1/2 inhibitor, has been evaluated in combination with erlotinib in EGFR-mutant NSCLC preclinical models, where co-treatment suppressed STAT3 activation that erlotinib alone failed to inhibit, and the combination reduced tumor growth in EGFR-mutant xenografts more effectively than erlotinib monotherapy. The basis for this approach derives from the observation that EGFR- tyrosine kinase inhibitors (TKI) treatment paradoxically elevates pSTAT3 levels in EGFR-mutant cell lines, and that RNA interference-mediated knockdown of STAT3 increases apoptosis and enhances erlotinib sensitivity, while constitutive STAT3 activation confers erlotinib resistance (Wang et al. 2026).

Ruxolitinib has also been evaluated in combination with oncolytic virotherapy. Vesicular stomatitis virus expressing IFNβ (VSV-IFNβ) exploits defective interferon signaling in cancer cells to achieve selective tumor cell killing, but some NSCLC cells retain intact or partially intact IFN signaling, conferring resistance to this approach. Across five human and two murine NSCLC cell lines, the addition of ruxolitinib to VSV-IFNβ enhanced cytotoxic activity in both resistant and sensitive cell lines. Mechanistically, ruxolitinib suppressed STAT1 phosphorylation and, to a lesser extent, STAT3 phosphorylation, and prevented virotherapy-induced PD-L1 upregulation in NSCLC cells. In an immunocompetent murine NSCLC model, the combination trended toward improved survival, providing preclinical support for further clinical evaluation of JAK/STAT inhibition alongside virotherapy (Ghonime and Cassady 2018).

Direct pharmacological targeting of STAT3 has

been done through several mechanistic strategies. Napabucasin (BBI-608), a first-in-class cancer stemness inhibitor targeting the DNA-binding domain of STAT3, is the first STAT3 inhibitor to advance into phase III clinical trials. Preclinical studies demonstrated that napabucasin inhibits stemness gene expression, depletes cancer stem cells (CSCs), and overcomes cisplatin resistance in NSCLC. Phase I/II studies confirmed its tolerability and preliminary antitumor activity across multiple malignancies (Wang et al. 2026).

Targeting the SH2 domain of STAT3 which is responsible for receptor recruitment, phosphorylation, and dimerization has yielded several investigational agents including OPB-31121, OPB-51602, and C188-9, all of which are currently undergoing clinical evaluation. OPB-51602, a direct inhibitor of STAT3 phosphorylation at Tyr705, demonstrated objective responses in lung cancer patients in early-phase studies, with EGFR-mutant cases comprising the majority of responders (Wang et al. 2026).

5.2. Clinical Trials Evidence

The first clinical study combining EGFR and JAK inhibition enrolled 22 patients with EGFR-mutant NSCLC who had developed acquired resistance to erlotinib, a population in which resistance is not mediated by EGFR T790M mutation in approximately 40% of cases. In the phase 1, the combination of erlotinib 150 mg daily and ruxolitinib 20 mg twice daily was established as the maximum tolerated dose without dose-limiting toxicities. The most frequently observed adverse events of any grade were anaemia, diarrhoea, and elevation of liver function tests. Despite acceptable tolerability, the phase 2 component demonstrated very limited efficacy where a single partial response was observed (5%; 95% CI: 0–13%), and median progression-free survival was only 2.2 months (95% CI: 1.4–4.1 months), indicating that dual EGFR-JAK blockade was insufficient to overcome the broader resistance landscape in refractory population (Schoenfeld et al. 2018).

More promising results emerged from a phase 2 trial evaluating pembrolizumab followed by delayed addition of itacitinib which is a selective JAK1 inhibitor in treatment-naive metastatic NSCLC patients with tumor PD-L1 expression ≥50%. A total of 21 evaluable patients received two initial cycles of pembrolizumab, followed by two cycles of combined pembrolizumab and itacitinib, after which pembrolizumab was continued as monotherapy. The 12-week objective response rate was 62%, and the best overall response rate with extended follow-up reached 67%, with only one patient experiencing disease progression as best overall response. After a median follow-up of 27.6 months, the median progression-free survival was 23.8 months (95% CI: 4.9 months to not reached), and the median duration of response had not been reached at the time of reporting. Notably, eight patients who failed to respond or experienced tumor growth following initial pembrolizumab alone subsequently achieved objective responses after itacitinib addition, demonstrating that JAK inhibition can rescue anti-programmed cell death protein 1 (PD-1) refractory responses. Furthermore, none of the nine analysable patients who fell below the established 1.5-fold Ki67+ CD8 T cell proliferative threshold after pembrolizumab a biomarker predictive of progression in approximately 71% of anti-PD-1 monotherapy patients experienced disease progression following itacitinib addition ($p= 0.009$), suggesting that delayed JAK inhibition induces a secondary CD8 T cell proliferative burst capable of sustaining durable anti-tumor immunity (Mathew et al. 2024).

5.3. Limitations and Safety Considerations

Despite the tolerability established in the erlotinib-ruxolitinib phase 1/2 trial, the absence of meaningful clinical activity in that population

underscores the challenge of overcoming the molecular complexity of EGFR-TKI resistance through JAK inhibition alone. With respect to tofacitinib, post-hoc analysis of the randomized controlled trial designed to evaluate cardiovascular and cancer safety of tofacitinib versus TNF inhibitors in rheumatoid arthritis patients aged over 50 years with additional cardiovascular risk factors identified a higher incidence of lung cancer among patients receiving tofacitinib 10 mg twice daily compared to controls. Lung cancer was the most common malignancy observed. However, a large cohort study of rheumatoid arthritis patients in routine clinical care found no increased malignancy risk associated with tofacitinib compared to anti-TNF therapy, highlighting the heterogeneity of available safety evidence and the need for careful patient selection when considering JAK inhibitors in oncological applications (Bezzio et al. 2023).

6. Conclusions and Future Perspectives

The evidence from numerous studies suggests that the JAK/STAT signaling pathway as one of the most consequential molecular axes in lung cancer pathogenesis. Constitutive activation of this cascade driven by cytokine-rich tumor microenvironmental inputs, EGFR and ALK oncogenic crosstalk, epigenetic silencing of negative regulators, and autocrine IL-6 feed-forward loops sustains a broad transcriptional program that promotes tumor cell proliferation, survival, invasion, angiogenesis, and metastatic dissemination. Among STAT family members, STAT3 occupies a dominant oncogenic role, regulating anti-apoptotic proteins, cell cycle mediators, stemness programs, and immune checkpoint ligand expression, while STAT1 and STAT5 contribute context-dependent functions that shape both tumor-intrinsic biology and the immunological character of the TME. The pathway's extensive crosstalk with NF-κB, PI3K/AKT, MAPK, and epigenetic regulatory networks further amplifies its oncogenic impact and underlies its role as a central integrator of diverse pro-tumorigenic signals in both NSCLC and SCLC.

The most clinically compelling translational opportunity currently lies in rational combination regimens pairing JAK/STAT inhibition with immune checkpoint blockade or molecularly targeted therapies. Early-phase clinical evidence most notably the phase 2 trial demonstrates a 67% best overall response rate and a median progression-free survival of 23.8 months with delayed itacitinib added to pembrolizumab in PD-L1-high NSCLC establishes proof of concept that sequential JAK inhibition can rescue anti-PD-1 refractory immune states and sustain durable responses. Preclinical data further support combinations of JAK inhibitors with EGFR-TKIs to overcome STAT3-mediated acquired resistance, with radiotherapy to augment interferon-driven immune priming, and with ferroptosis-inducing agents and epigenetic modifiers to broaden the spectrum of therapeutic vulnerability (Mathew et al. 2024).

Despite this progress, several fundamental questions remain unresolved and must be addressed before JAK/STAT-directed therapy can be integrated into routine lung cancer management. The most important among these is the identification and prospective validation of reliable biomarkers of JAK/STAT pathway dependency, including STAT3 phosphorylation status, JAK2/PD-L1 co-amplification, interferon-stimulated gene expression signatures, and circulating IL-6 levels, that can stratify patients most likely to benefit from pathway inhibition. The development of isoform-selective inhibitors that suppress tumor-promoting STAT3 and JAK2 activity without extinguishing immunostimulatory STAT1 signaling or impairing cytotoxic T cell and Natural Killer

(NK) cell function represents a critical unmet pharmacological need. Defining the precise mechanisms of primary and acquired resistance to JAK/STAT inhibitors including compensatory pathway reactivation, epigenetic adaptation, and microenvironmental reprogramming will be equally essential for designing durable therapeutic strategies (Yao et al. 2025).

Several emerging technological and conceptual directions hold promises for advancing JAK/STAT-directed therapy in lung cancer. Proteolysis-targeting chimeras (PROTACs) designed to selectively degrade STAT3 protein such as SD-36, which achieved complete and durable tumor regression in xenograft models at well-tolerated doses offer a mechanistically distinct approach to overcoming the limitations of catalytic inhibitors and addressing previously non druggable aspects of STAT3 biology (Bai et al. 2019). Tissue-specific and tumor-targeted delivery platforms, including nanoparticle-encapsulated JAK inhibitors and locally administered oligonucleotide-based STAT3 suppressors such as AZD9150, may mitigate systemic immunosuppressive toxicities while achieving pharmacologically effective intratumoral concentrations (Hong et al. 2015). Prospective clinical trials that incorporate pharmacodynamic correlates, rigorous resistance profiling, and companion diagnostic development will ultimately determine whether the remarkable mechanistic insights accumulated over the past decade can be translated into meaningful and durable improvements in outcomes for patients with lung cancer.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA

Data Availability

All the raw data related to this study are available with the authors.

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Authors Contributions

MBA conceptualized and organized the study, MS did the literature search and analysis, MBA and MS wrote the initial manuscript, MBA wrote the final manuscript, and supervised the project.

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