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REVIEW

JAK-STAT Signaling in Autoimmunity and Cancer

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Abstract: The JAK-STAT pathway is an essential cell survival signaling that regulates gene expressions related to inflammation, immunity and cancer. Cytokine receptors, signal transducer and activator of transcription (STAT) proteins, and Janus kinases (JAKs) are the critical component of this signaling cascade. When JAKs are stimulated by cytokines, STAT phosphorylation, dimerization, and nuclear translocation occur, which eventually impacts gene transcription. Dysregulation of JAK-STAT signaling is linked with various autoimmune diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. This pathway is constitutively activated in human malignancies and leads to tumor cell survival, proliferation, and immune evasion. Oncogenic mutations in the JAK and STAT genes have been found in solid tumors, leukemia, and lymphoma. Targeting the JAK-STAT pathway is a viable and promising therapeutic strategy for the treatment of autoimmune diseases and cancers.

Keywords: JAK-STAT pathway, inflammation, autoimmune diseases, cancer

Introduction

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is a fundamental regulatory network that plays a central role in cellular communication and function. It is crucial in various physiological and pathophysiological processes, including cellular growth, differentiation, proliferation, immune responses, and tumorigenesis.[1,2] This pathway is activated by various signaling molecules such as cytokines, interferons (IFNs), interleukins (ILs), colony-stimulating factors, and growth factors (GF).[3] Over 60 cytokines and growth factors have been identified as activators within the pathway.[4,5] The downstream effects of JAK/STAT signaling are diverse and include regulation of hematopoiesis, immune system homeostasis, tissue repair, inflammation, apoptosis, and adipogenesis.[6] Dysregulation or mutations in any of the JAK/STAT components have been implicated in numerous human diseases.

JAKs are noncovalently bound to cytokine receptors, mediating the tyrosine phosphorylation of these receptors and subsequently recruiting one or more STAT proteins. Upon phosphorylation, STATs dimerize and translocate to the nucleus, where they regulate specific gene expression (Figure 1). Although several cytokines can activate the JAK/STAT pathway, each STAT protein has distinct and non-redundant biological effects.[7] This pathway has significantly advanced our understanding of human health and disease, particularly in the context of malignancies and autoimmune disorders.[8–13] As a result, targeting the JAK/STAT pathway has become a promising therapeutic approach for treating a variety of diseases, including cancer.

Numerous JAK inhibitors have demonstrated clinical efficacy across multiple settings, and ongoing research is focused on developing additional therapeutic agents.[14] This review aims to provide an in-depth and updated perspective on the JAK/STAT signaling pathway at the cellular, molecular, and genomic levels. It will also explore the relationship between JAK/STAT signaling and diseases such as autoimmunity and cancer, focusing on clinically approved and investigational therapies designed to target this pathway.

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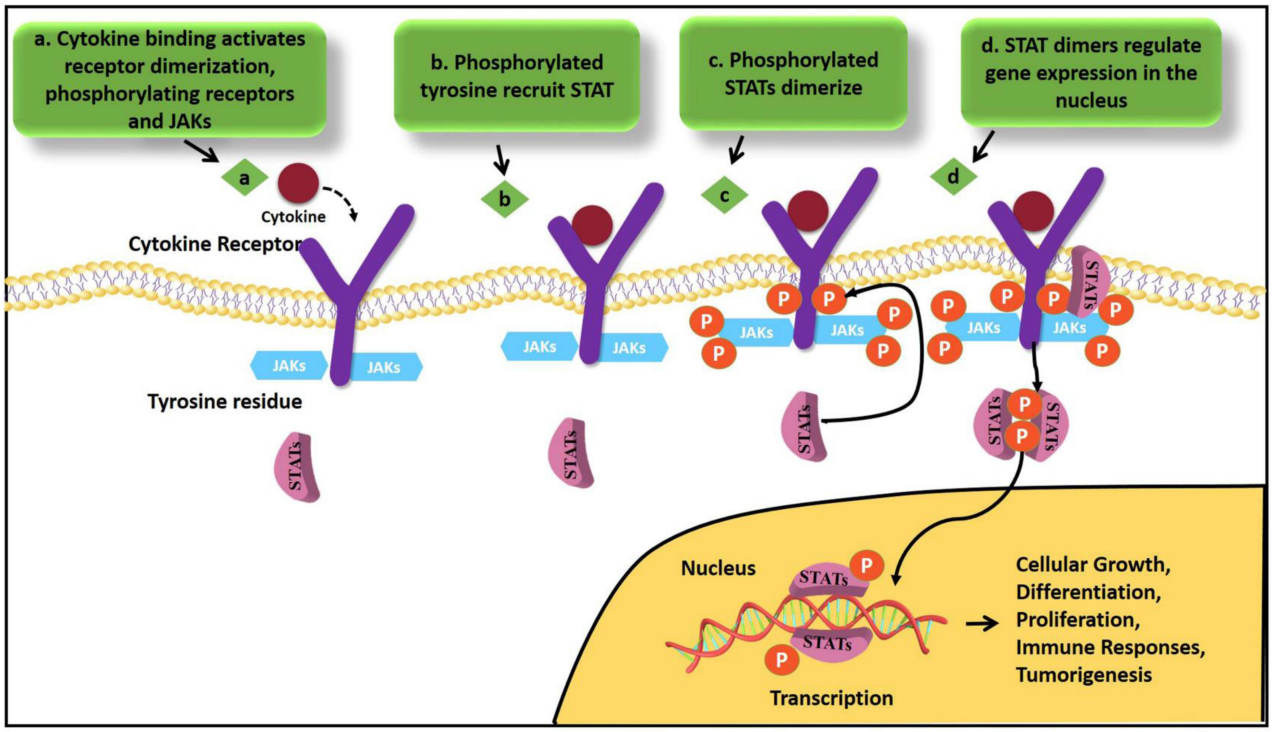

Figure 1 Shows the four phases by which JAK/STAT controls nuclear communication and transmembrane receptors. (**a**) When cytokines attach to receptors, the receptor molecules dimerize, activating and phosphorylating both the intracellular tail of the receptors and JAKs. (**b**) These phosphorylated tyrosine sites create a docking site, which attracts the STAT protein. (**c**) The STATs can dimerize because they are phosphorylated and active. (**d**) The STAT-STAT Dimers move into the nucleus and control gene expression.

Exploration of the JAK-STAT Signaling Pathway

The identification of the JAK-STAT signaling pathway originated from the fundamental question: how do cells react to interferons (IFN)? During the late 1980s and early 1990s, in the pre-genomic era, researchers faced the challenge of elucidating the mechanisms that regulate gene expression in response to various environmental signals. At this time, biochemistry, molecular biology, and cell biology were employed to study receptor-mediated signal transduction via G protein-coupled receptors (GPCR) and receptor tyrosine kinases (RTKs). This research was concurrent with the identification of DNA-binding proteins and a variety of transcription factors.[15] Despite these advances, the pathways connecting signal transduction to transcriptional activation, and the mechanisms by which membrane-bound receptors initiate gene transcription, remained unclear.

The finding of oncogenic serine/threonine and tyrosine kinases (TYKs) and their discovery of reversible protein phosphorylation sparked a rush to find novel TYKs. A unique family of TYKs was discovered by using the relatively new method of degenerate polymerase chain reaction to build protein kinase libraries. This family contained JAK-I, JAK-II, and TYK-II Because of the distinct structure of this kinase family which consists of an amino-terminal kinase domain followed by a regulatory pseudo-kinase domain the name “JAK” was inspired by the two-faced Roman god Janus. However, the alternative interpretation of JAK as “just another kinase” was also appropriate because the exact role of the JAK kinases was still unknown.[16–19]

In 1988, STAT proteins were identified as factors that bind to interferon-stimulated response elements in DNA to promote the transcription of type I IFNs.[20] The JAK/STAT signaling pathway was further elucidated through studies investigating how IFNs activate transcription factors.[21] In 1990, the transcriptional activator interferon-stimulated gene factor 3 (ISGF3), which is responsive to IFN-α, was discovered to be a complex made up of several interacting polypeptide chains weighing 48, 84, 91, and 113 kDa.[21] In 1992, Fu further elucidated that the ISGF3α proteins 113, 91, and 84 kDa contained conserved SH2 and SH3 domains. Additionally, a specific cytoplasmic tyrosine kinase induced by IFN-α was shown to phosphorylate and activate ISGF3α. Based on these findings, Fu proposed a direct effector model

for signal transduction induced by IFN-α, which helped outline the signaling mechanism of the JAK/STAT pathway.[22,23] Subsequent studies revealed that ISGF3 is composed of the proteins STAT-I, STAT-II, and IRF9.[24] Between 1993 and 1995, other STAT proteins, including STAT-III, STAT-IV, STAT-Va, STAT-Vb, and STAT-VI, were identified by various research groups.[25–28]

The discovery of the JAK proteins occurred from 1989 to 1994. In 1989, Wilks et al identified a tyrosine kinase with a recognizable kinase domain and a pseudokinase domain, which they named JAK-I. In 1991, a second tyrosine kinase with similar features was identified and named JAK-II.[19,29] The discovery of the remaining two JAKs, tyrosine kinase 2 (TYK-II) and JAK-III took place in 1990 and 1994, respectively.[17] The connection between JAKs and STATs was established in 1992 when Velazquez et al demonstrated that TYK-II is a critical protein in the IFN-α/β signaling pathway.[30] Further, in 1993, Müller et al found that JAKs are essential for IFN-dependent signaling by phosphorylating STATs.[31]

By the early 1990s, the major components and general structure of the JAK/STAT signaling pathway had been mapped out. Since then, research into additional proteins and the broader functions of this signaling pathway has continued, significantly enriching the current understanding of JAK/STAT signalling.

Components of the JAK/STAT Pathway

The JAK/STAT signaling pathway is a highly conserved mechanism in evolution, consisting of three main components, ie tyrosine kinase-associated receptor, JAK, and STATs.[32] Various cytokines and growth factors transmit signals through the JAK/STAT signaling pathway, including interleukin 2 ~ 7 (IL-2 ~ 7), GH, EGF, GM-CSF, PDGF, and IFNs.[8] The JAK family comprises four distinct members: JAK-I, JAK-II, JAK-III, and TYK-II with over 1000 amino acids and a molecular weight of between 120 and 140 kDa while the STAT family consists of seven members: STAT-I, STAT-II, STAT-III, STAT-IV, STAT-Va, STAT-Vb, and STAT-VI with molecular weights range from 79 to 113 kDa.[33,34] The structure and function of these family members are fundamental to their roles in various cellular processes.

The JAK Family

The JAK family is composed of non-receptor tyrosine protein kinases that play a crucial role in transmitting intracellular signals following cytokine binding to their respective receptors. Upon receptor activation, JAK kinases become phosphorylated and relay signals that regulate numerous cellular functions. The four main members of the JAK family, JAK-I, JAK-II, JAK-III, and TYK-II, have diverse tissue-specific expressions. Notably, JAK-III is predominantly expressed in the bone marrow, lymphatic system, endothelial cells, and vascular smooth muscle cells, while the other members are ubiquitously present across various tissues. Each JAK kinase contains seven homologous domains (JH), which are critical for their functional roles.[18,19,29,35–40]

The domains of JAK kinases include JH1, which represents the kinase domain (or conserved PTK domain ie located at the C-terminus) composed of approximately 250–300 amino acids and is responsible for substrate phosphorylation; JH2, the central Pseudokinase domain, shares structural similarities with the kinase domain but lacks kinase activity. JH2 primarily regulates the activity of JH1. The Src homology 2 (SH2) domain is formed by JH3 and a portion of JH4. The SH2 domain contains approximately 100 residues that bind to phosphotyrosine residues. The role of SH2 domain is the activation and dimerization of STATs. The N-terminal FERM domain formed by JH4, JH5, JH6, and JH7, are essential for mediating interactions between JAKs and cytokine receptors, specifically their membrane-proximal regions. These domains collectively influence JAK activation and receptor binding, regulating the overall signaling cascade (Figure 2). [19,37,41–43]

The STAT Family

The STAT family of transcription factors includes seven members: STAT-I, STAT-II, STAT-III, STAT-IV, STAT-Va, STAT-Vb, and STAT-VI. These proteins range from 750 to 900 amino acids in length and contain multiple functional domains. The domains, arranged from the N-terminus to the C-terminus, include the Unique N-terminal domain, coiled-coil domain, DNA binding domain, linker domain, SH2 domain, and transcription activation domain. Each domain has specific roles in STAT function and regulation (Figure 2). [22,25,26,28,44,45]

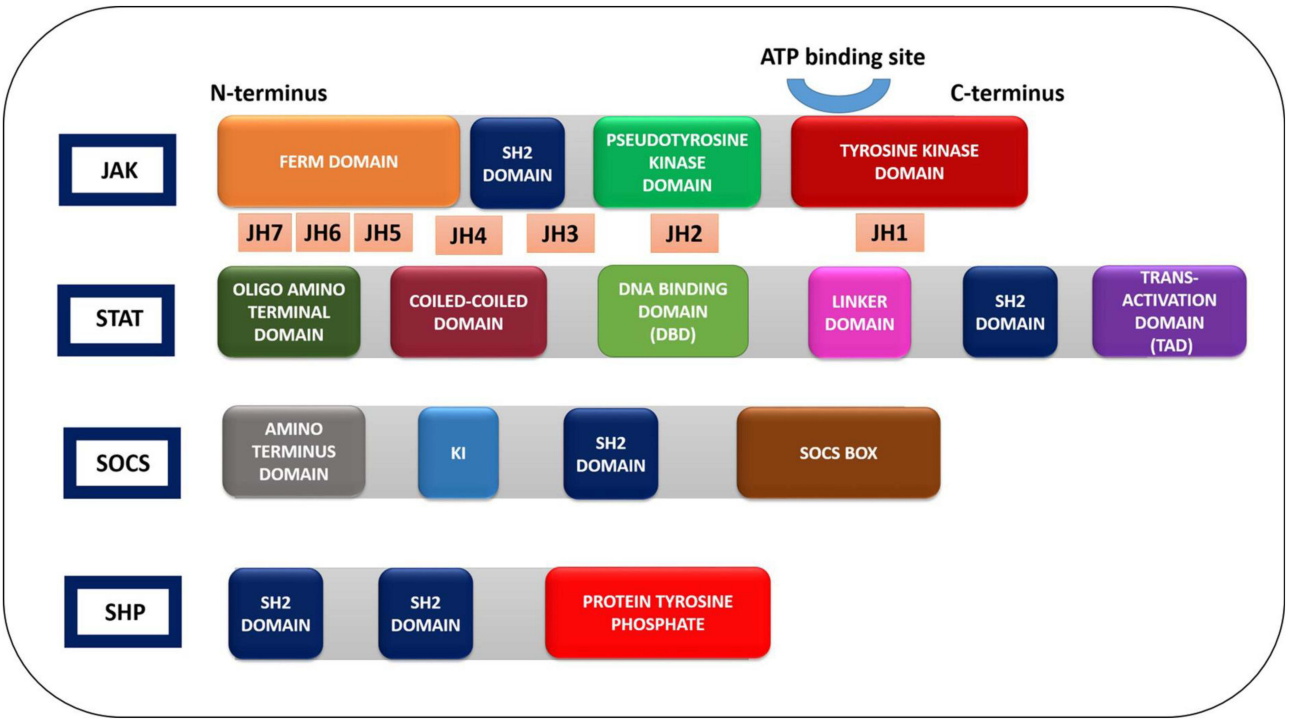

Figure 2 Domain architecture of essential proteins in the JAK-STAT signaling pathways. The figure illustrates the various domains represented in JAK (Janus Kinase), STAT (Signal Transducer and Activator of Transcription), SOCS (Suppressor of Cytokine Signaling), PIAS (Protein Inhibitors of Activated STATs), and SHP (SH2 domain-containing protein tyrosine phosphatase) proteins.

a. The Unique N-terminal domain, comprising approximately the first 100 amino acids, is significantly conserved across STAT family members and is essential for nuclear translocation and deactivation. Research with chimeric STATs has demonstrated that the N-terminus delivers a signal crucial for nuclear translocation and subsequent deactivation. It also facilitates the dimerization of STAT proteins, allowing interaction with transcription factors. It has been demonstrated to enhance interactions with co-activators, including the PIAS family, and affect nuclear translocation.[46–50]
b. The coiled-coil domain, characterized by a four-helix bundle, is involved in regulating nuclear import and export. It interacts with various regulatory proteins, including StlP, c-Jun, Nmi, and p48/IRF9 and plays a key role in controlling these processes.[46,51–56]
c. The linker domain connects the DNA binding and SH2 domains, contributing to the transcriptional regulation of STAT-I and other members.[53,57]
d. The DNA binding domain is responsible for recognizing specific DNA sequences in the regulatory regions of target genes, also aiding in the regulation of nuclear import and export.
e. The SH2 domain, highly conserved across the STAT family, is crucial for recognizing phosphotyrosine motifs in cytokine receptors. This domain facilitates the formation of homodimers or heterodimers by mediating interactions between phosphorylated STAT monomers.[58–61]
f. The transcriptional activation domain is vital for promoting gene transcription by recruiting co-activators, with a conserved serine phosphorylation site that regulates transcriptional activity. Additionally, this domain plays a role in protein stability, as STAT-IV, STAT-V, and STAT-VI are more susceptible to ubiquitin-mediated degradation, while STAT-I, STAT-II, and STAT-III exhibit greater stability.[22,26,28,44,45]

Various biological activities that JAK/STATs can mediate and the ligands that can activate them are listed in Table 1.

Table 1 The Ligands That Activate JAK/STATs and Modulate Biological Events

JAK/ STATs	Ligands	Biological Events	Role in Cancer and Autoimmune Diseases
JAK-I	All interferons (INFα/β, INFγ), IL-2, 4, 6, 7,9, 10, 15,21 family cytokines	ALL, AML, solid-organ malignancies[8]	Role in cytokine signaling essential for immune function, while its dysregulation is implicated in oncogenesis.
JAK-II	IFNγ, IL-3, 5, GM-CSF, GF, G-CSF	PV, PMF, ET, hypercoagulable state, acute and chronic hematologic malignancies[8]	Mutations contribute to autoimmune diseases and are also strongly linked to myeloproliferative neoplasms and hematological malignancies.
TYK-II	IFNα/β, IL-12, 23 family cytokines	Primary immunodeficiency[8]	Essential for lymphocyte development and immune function, with activating mutations contributing to leukemias and lymphomas.
JAK-III	IL-2, 4, 7, 9, 15, 21 family cytokines	SCID[8]	Regulates immune responses through cytokine signaling, and its mutations are linked to inflammatory diseases and cancer progression.
STAT-I	All interferons (INFα/β, INFγ)	Anti-virus and anti-bacteria response; Cell growth; Cell apoptosis; Oncogenesis[62,63]	Involved in antiviral and immune responses, while its dysregulation can contribute to tumor immune evasion.
STAT-II	Type I IFNs (INFα/β)	Anti-virus response; Oncogenesis[62,64]	Plays a key role in antiviral immunity, but its direct association with cancer is not well-defined.
STAT-III	IL-6 family members and Growth factors: EGF and HGF.	AD-HIES, LGL, Cell mitogenesis; Cell apoptosis; Oncogenesis; Cell proliferation; Th17 differentiation[62,65]	Mediates immune tolerance and inflammation, with hyperactivation promoting tumor growth and immune evasion in various cancers.
STAT-IV	IL-12, IL-23, type I interferons	Th1 development, RA and SLE[47,62]	Regulates Th1 immune responses, while its overexpression is linked to certain cancers, including leukemia.
STAT-Va	Prolactin, IL-2, GM-CSF, erythropoietin, and other hormone-like cytokines.	Prolactin signaling; Treg cells differentiation, autoimmunity, bleeding diathesis, immunodeficiency[62,66]	Essential for immune cell development and cytokine signaling, with persistent activation driving oncogenesis in hematological malignancies.
STAT-Vb	GH, IL-2 and other hormone-like cytokines.	Autoimmunity, bleeding diathesis, immunodeficiency, Growth hormone signaling[62,67]	Functions in immune regulation and cell proliferation, with its aberrant activation contributing to leukemia and prostate cancer.
STAT-VI	IL-4/13.	Th2 development, asthma, atopy, increased levels of IgE[62]	Regulates allergic inflammation and Th2 immune responses, while its involvement in cancer remains less understood.

Abbreviations: ILs, Interleukins; ALL, Acute lymphocytic leukemia; AML, Acute myeloid leukemia; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GF, growth factors; G-CSF, Granulocyte colony-stimulating factor; PV, Polycythemia vera; PMF, Primary myelofibrosis; ET, Essential thrombocytosis; SCID, Severe combined immunodeficiency; INFα/β, Interferon alpha/beta; INFγ, Interferon-gamma; EGF, Epidermal Growth Factor; HGF, Hepatocyte growth factor; AD-HIES, Autosomal dominant hyperimmunoglobulin E syndrome; LGL, Large granular Lymphocytic Leukemia; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; GH, Growth hormone; IgE, Immunoglobulin E.

Cytokine Receptor Family

Cytokine receptors are essential transmembrane proteins that mediate cytokine effects by initiating intracellular signaling cascades, including the JAK/STAT pathway. These receptors are categorized into two main families: the hematopoietin and immunoglobulin-like receptor families. Upon ligand binding, cytokine receptors undergo conformational changes that activate associated JAK kinases, triggering downstream signalling pathways.[68]

These receptors are distinguished by extracellular domains for ligand binding, a single transmembrane helix, and intracellular domains that interact with JAKs. The intracellular region often contains conserved motifs, such as Box1 and

Box2, which are crucial for recruiting JAKs and initiating signaling. Based on structure and function, they are classified as Type I and Type II cytokine receptors. Type I receptors typically involve JAK-I and JAK-III, while Type II receptors are associated with JAK-II and TYK-II.[69]

Cytokine receptors play a critical role in numerous physiological processes, including metabolism regulation, neural stem cell activation, inflammatory responses, bone development, and the growth of blood and immune cells. They also contribute to reproduction, lactation, postnatal growth, and body composition. Their defining feature is the activation of JAK tyrosine kinases, which initiate these signaling cascades. Some cytokine receptors, such as those for GH, PRL, and LEP, act as hormones and directly influence the endocrine system.

The receptors are divided into two classes based on sequence homology and structural characteristics. The class I cytokine receptor family, which includes more than 30 members like EPO, PRL, GH, TPO, and others, predominantly participates in signaling related to hematopoiesis and metabolic functions.[70] The class II receptor family, initially comprising interferon and IL-10 receptors, has expanded to include receptors for other cytokines like IL-19, IL-20, IL-22, IL-24, IL-26, and IL-29.[71,72]

Negative Regulation of JAK/STAT Signaling

Various regulatory factors hinder the activation of the JAK-STAT signaling pathway. The regulators can be classified into three primary categories: suppressors of cytokine signaling (SOCSs), protein inhibitors of activated STATs (PIASs), and protein tyrosine phosphatases.[73–77] The SOCS family comprises the principal signaling molecules that inhibit the JAK-STAT pathway, including CIS, SOCS-I, SOCS-II, SOCS-III, SOCS-IV, SOCS-V, SOCS-VI, and SOCS-VII.[78] All members of the SOCS family possess a structural composition that includes an SH2 domain and a SOCS box. Cytokines including IL-2, IL-3, and IFN-γ can stimulate SOCS proteins. Upon activation, STATs go to the nucleus, facilitating the transcription of SOCS genes.[79,80] These SOCSs negatively regulate JAK-STAT signaling by obstructing STAT-receptor binding, inactivating JAKs via the N-terminal kinase inhibitory domain, or binding to and ubiquitinating JAKs or STATs, resulting in their proteasomal destruction. This procedure creates a negative feedback loop initiated by STAT activation, subsequently increasing SOCS transcription.[81] The PIAS family (Figure 2), comprising PIAS1, PIAS3, PIASx, and PIASy, can disrupt STAT function by either obstructing STAT dimerization or impeding the attachment of STAT dimers to DNA.[4,82,83] Moreover, protein tyrosine phosphatases can dephosphorylate JAKs at receptor locations or directly dephosphorylate STAT dimers, thus suppressing JAK-STAT signaling.[84–86]

Cytokine receptor dysregulation, such as mutations or overexpression, is associated with various diseases, including autoimmune disorders, cancers, and chronic inflammation. As a result, they are key therapeutic targets for drug development aimed at modulating immune responses and treating related conditions.

Initiation and Regulation of JAK/STAT Signaling Pathways

Regulation of JAK/STAT Signaling Pathways are mainly focused on two signaling pathways first canonical and another non-canonical signaling. Current studies have mostly focused on the canonical pathways. However, some studies have shown that non-canonical pathways also play an important role in this pathway.

Canonical JAK/STAT Signaling

The canonical JAK/STAT signaling pathway is a critical mechanism for transmitting extracellular signals directly to the nucleus, regulating gene expression without the need for second messengers.[13] This evolutionarily conserved pathway plays a crucial role in various cellular processes, including immune regulation, cell growth, differentiation, and apoptosis.[6,87] The canonical JAK/STAT signaling pathway operates as follows: the ligand binds to its receptor, initiating receptor dimerization. Certain receptors, including EpoR, IL-17R, IL-10R, gp130, TNF-R1, and the GH receptor, can form inactive receptor dimers without ligand binding.[88–94] This pre-formation may facilitate the rapid assembly of the receptor complex upon ligand binding, leading to subsequent signal transduction. Ligand binding induces the trans phosphorylation of Janus kinases (JAKs), which then phosphorylate the receptor on tyrosine residues, creating docking sites for signal transducer and activator of transcription proteins (STATs). At these sites, JAKs phosphorylate STATs, causing them to dissociate from the receptor and form homodimers or heterodimers through SH2-domain

phosphotyrosine interactions.[8,75] These dimers subsequently translocate to the promoters of target genes, where they regulate transcription.

STATs influence gene expression in various ways: (1) they directly bind to DNA targets to initiate transcription; (2) they enhance STAT-driven transcription by complexing with non-STAT transcription factors; (3) they work with non-STAT DNA-binding elements to support STAT-mediated transcription; (4) they combine with other transcription factors to stimulate transcription by binding to different DNA locations; (5) PDGFR, EGFR, and FGFR can activate STATs independently or dependently on JAKs. It is true that EGFR kinases improve STAT signaling the most when EGF is stimulated, but JAK- and Src-mediated constitutive STAT-III activation happens even when EGF is not stimulated; (6) G-protein-coupled receptors, such as chemokine receptors, activate STATs after binding a ligand; (7) Non-receptor tyrosine kinases, such as SFK, can keep STATs active all the time. SFKs like c-Src, Blk, Fgr, Fyn, and others are involved in signaling pathways. Protein-tyrosine kinase, integrin, and G-protein-coupled receptors interact with Src, which activates at Tyr419 and inactivates at Tyr530. Activated Src directly phosphorylates and activates STATs.[62,95–98]

Non-Canonical JAK/STAT Signaling Pathway

Recent studies have revealed that JAK/STAT signaling also participates in non-canonical forms of signal transduction, which exhibit greater complexity. Non-canonical STAT signaling pathways include preassembled receptor complexes, preformed STAT dimers, unphosphorylated STATs (U-STATs), and non-canonical functions such as microtubule regulation, mitochondrial modulation, and heterochromatin stabilization.[99] For instance, unphosphorylated STAT-III has been shown to promote the expression of multiple target genes independently of phosphorylation at S727. Additionally, Lys-685 acetylation and NF-κB contribute to this process. STAT proteins can be activated not only in the cytoplasm but also in mitochondria, where all STATs except STAT-IV facilitate oxidative phosphorylation and regulate membrane permeability. STAT-III also localizes to the endoplasmic reticulum, where it plays a role in mitigating apoptosis induced by oxidative stress.[100] A fraction of the unphosphorylated STAT pool is associated with heterochromatin, particularly in relation to the allelic autosomal gene heterochromatin protein-1 (HP1) in the nucleus. When STAT is activated by JAK or other kinases, HP1 dissociates from heterochromatin, allowing phosphorylated STAT to bind to specific sites on autosomes and regulate gene transcription. This atypical form of JAK/STAT signaling is vital for the maintenance of heterochromatin stability.[101–103] Studies in Drosophila have shown that STAT phosphorylation can lead to the dissociation of HP1 from heterochromatin, disrupting its stability and potentially contributing to tumorigenesis.[103–106] Similar atypical JAK/STAT signaling patterns have been observed in mammals. For example, IFN-induced activation of STAT-I leads to higher-order chromosomal remodeling of MHC, and JAK-III-STAT-V activation induces chromatin remodeling at the Ifng locus during Th1 cell differentiation.[107,108] Notably, JAK proteins can also be activated by tumorigenic tyrosine kinases, independently of cytokine receptors.[109] For example, the proto-oncogene v-Abl of the Abelson murine leukemia virus constitutively activates the JAK/STAT pathway by modulating the interaction between suppressors of cytokine signaling (SOCS)-1 and JAK.[110] Likewise, the oncogenic fusion protein nucleophosmin-anaplastic lymphoma kinase inactivates SH2-containing protein tyrosine phosphatase-1 (SHP-1), inhibiting JAK-III degradation and enhancing JAK-III-STAT-III signaling, potentially contributing to the development of anaplastic large cell lymphoma.[111] The BCR-ABL fusion gene exerts anti-apoptotic effects, with BCR-ABL synergizing with hematopoietic growth factors through low-level constitutive phosphorylation of JAK proteins, thereby modulating STAT activation.[112] Additionally, STAT can be activated by other non-receptor tyrosine kinases or directly by receptors independent of JAK. For example, c-Src tyrosine kinase constitutively activates STAT-III, increasing the likelihood of STAT signaling regulating tumor-related gene expression.[113] The epidermal growth factor receptor can directly activate STAT-I, STAT-III, and STAT-V, while the platelet-derived growth factor receptor can directly activate STAT-V.[114–116]

The STAT Signaling Pathways in Autoimmune Disorders

The JAK-STAT signaling pathway is essential for immune system function, hematopoiesis, and cellular proliferation. The dysregulation of JAK signaling is associated with inflammatory conditions, multiple autoimmune diseases, and specific

hematological malignancies.[117] Consequently, the development of small-molecule inhibitors targeting JAKs has emerged as a promising avenue in the quest for more precise and effective therapies.

Cytokines are essential for the pathogenesis of immune-mediated diseases, each of which exhibits characteristic cytokine profile. Accelerated research in autoimmune diseases has demonstrated successful treatment results from targeting the JAK/STAT system in type I and type II cytokine signaling. We give brief information related to diseases that are known to be affected caused by changes in the JAK/STAT pathways:

Rheumatoid Arthritis (RA)

RA is a chronic and progressive autoimmune disorder, primarily marked by inflammation and pain in synovial joints.[118,119] Persistent activation of the JAK-STAT signaling pathway is a critical aspect of the pathogenesis and progression of RA, driven by various pro-inflammatory cytokines, or "immunokines", including IL-6, IL-15, IL-23, and IFN-γ, which are significant in disease development. Several cytokines play important roles in the pathogenesis of RA, including IL-1, IL-6, TNF-α, IL-7, IL-15, IL-12, IL-23, and GM-CSF.[120] The gp130 signaling component of the IL-6/IL-6Rα complex is closely associated with the continuation of inflammation in synovial joints affected by RA.[121] Pre-B cell colony-enhancing factor (PBEF) is recognized as a significant regulator. Research conducted by Nowell et al indicates that IL-6-mediated trans-signaling, specifically JAK-STAT activation through soluble IL-6R, influences PBEF in a manner dependent on STAT-III. The JAK-STAT signaling pathway, influenced by PBEF, is linked to arthritis severity and elevated PBEF levels in synovial tissue in murine models of antigen-induced arthritis.[122] The increased production of IL-17 via JAK-STAT signaling is pivotal in the advancement of RA pathology, as it facilitates the differentiation of TH17 cells from naïve lymphocytes.[123] This indicates that inhibiting IL-6/gp130 may serve as a therapeutic approach to diminish TH17 cell production.[124]

Vasculitis

The term "vasculitis" describes a collection of many systemic inflammatory diseases characterized by vascular wall inflammation, which results in intramural vascularization, thickening of the outer membrane, and intimal hyperplasia. This leads to poor tissue perfusion, vascular integrity degradation, and eventually organ damage.[125] The pathophysiology of vasculitis is significantly influenced by the activation of the JAK/STAT signaling system, which is closely associated with the synthesis of several cytokines, including type I and type II cytokines. IL-1, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, IL-17, IL-21, IL-23, IFN-γ, type I IFN, TNF-α, and GM-CSF are among the cytokines that are elevated in this disease.[126] By attaching to their respective receptors on the surface of immune cells, these elevated cytokines trigger the JAK/STAT pathway, which in turn controls the immune response at the subcellular level. When immune cells, such as T cells and macrophages, are activated, they release a variety of cytokines that encourage T cell differentiation into distinct subtypes, which in turn causes the cells to infiltrate the vascular wall and, eventually, cause vasculitis. Positive feedback mechanisms also serve to further activate these cells. T-helper (Th) cells 1 and Th17 are among the T cells that infiltrate the vascular wall of vasculitis patients.[125,127] The increased cytokine levels in vasculitis cause these ligands to attach to immune cell surface receptors, including T cells, which causes JAK to dimerize. Following its activation, this receptor-associated JAK phosphorylates the tyrosine residue in the receptor's tail, creating p-JAK. Tyrosine phosphorylation and activation of STAT to create p-STAT occur when STAT docks at these phosphorylation sites and binds via its SH2 domain. Although heterodimers like STAT-I/2 can exist, the majority of STAT proteins form homodimers. As a result, STAT dimers go from the cytoplasm to the nucleus, where they act as transcription factors to control the expression of certain genes. When immune cells are activated in vasculitis, they release a variety of cytokines that affect the differentiation of naïve T cells into Th1, Th17, TFH, and TRM cells. These T cells contribute to intramural vascularization, thickening of the outer membrane, and intimal hyperplasia in addition to secreting different cytokines to stimulate immune cells. Vascular wall thickening causes the vascular lumen to constrict, tissue blood circulation to be insufficient, and ultimately organ injury.[128]

According to preclinical research, in mice with inflammatory human arteries, inhibiting the JAK/STAT system successfully reduces tissue-resident memory T cells and blocks important vasculogenic effector pathways.[127] Furthermore, the JAK/STAT pathway can be used to modify the Th1 (IL-12, IFN-γ) and Th17 (IL-6, IL-23) signaling

pathways, which are implicated in Vasculitis.[129] These results suggest that JAK inhibitors may be used therapeutically to treat systemic vasculitis.

Systemic Lupus Erythematosus

The complicated pathophysiology of systemic lupus erythematosus (SLE), a chronic systemic autoimmune disease, involves hormone molecules, environmental triggers, hereditary variables, and an excess of several cytokines. A loss of self-tolerance and an excess of autoantibodies occurred under these circumstances. The pathophysiology of SLE involves significant functions for both the innate and adaptive immune systems.[130] SLE patients, who previously received high-dose corticosteroids and hydroxychloroquine have seen significant improvements in treatment and life expectancy.[131] Early investigations into lupus pathophysiology focused on faulty T cell apoptosis as a putative mechanism of immunological tolerance failure in SLE.[132] The FasL/Fas signaling pathway was initially believed to be the key player in this process. However, investigations indicated that Fas-mediated apoptosis was not faulty in monocytes from SLE patients, leading a move towards examining alternative important signaling pathways.[133,134] Recent genome-wide association studies have demonstrated that polymorphisms in the STAT-IV gene are related with the development of human SLE.[135] Furthermore, enhanced STAT-I mRNA and total STAT-I levels in SLE T and B cells imply a main mechanism behind increased STAT-I response to interferon (IFN). This was verified by Kawasaki et al, who reported that IFN-regulated genes and those linked with the IFN signature were enhanced in active SLE due to altered JAK-STAT system activation.[136]

In addition to STAT-I, other components of the JAK-STAT pathway, such as STAT-III and STAT-VB, have also been implicated in SLE. These proteins are crucial for the function of TH17 and T regulatory (Treg) cells, and an imbalance between activated STAT-V and STAT-III in SLE has been linked to reduced IL-10 expression.[135] Moreover, the production of autoantibodies by SLE B cells appears to be STAT-III-dependent. In vitro investigations have demonstrated that enhanced autoantibody synthesis can be reduced by the JAK inhibitor ruxolitinib or the STAT inhibitor BStattic.[137] Clinical research by Meshaal et al, shown a positive connection between pSTAT-V levels and the systemic lupus activity measure (SLAM), as well as with other clinical symptoms in SLE patients.[138]

Pre-clinical research in animal models of SLE further suggest the involvement of JAK-STAT signaling in the disease. B cell activation factor (BAFF), a tumor necrosis factor family member is crucial in the pathogenesis of SLE.[139] This discovery led to the development of belimumab, a human IgG1λ monoclonal antibody which is now an important treatment option for SLE.[140–143] Immunoreceptor tyrosine-based activation motif (ITAM)-coupled receptors, which modulate macrophage responses to Toll-like receptor and cytokine receptor stimulation, have been identified as key regulators in SLE pathogenesis.[144] In murine lupus nephritis models, treatment with the highly selective JAK-II inhibitor CEP33779 resulted in clinical improvement, prolonged survival, and reduced levels of IL-12, IL-17A, IFN-α, IL-1β, TNF-α, anti-nuclear antibodies, and autoantigen-specific antibody-secreting cells.[145,146] Additionally, treatment with the tyrosine kinase inhibitor tyrphostin (AG-490) inhibited JAK-II activation and STAT-I phosphorylation, leading to a reduction in renal inflammation in MRL/lpr mice (murine model of Lupus), includes "SLE".[147] These findings emphasize the potential of targeting JAK-II/STAT-I activation as a therapeutic method, presenting hope for broadening lupus therapy techniques, particularly in lupus nephritis.

Inflammatory Bowel Disease (IBD)

IBD includes immune-mediated intestinal illnesses of indeterminate origin, marked by cytokine dysregulation and a typical mucosal responses.[148,149] A robust correlation between JAK-STAT activity and inflammatory bowel disease (IBD) has been established.[2,9,148] Sanchez-Muñoz et al, noted heightened levels of IL-6 and STAT-III in individuals with IBD,[149] whereas West et al, identified augmented expression of oncostatin M (OSM) and its receptor in inflamed tissues, corresponding with disease severity.[150] Moreover, abnormalities in the interaction between STAT and SOCS proteins were seen in patients with IBD.[151–153] accompanied by higher serum soluble IL-6R levels, signifying active IL-6 transsignaling.[154]

Clinical trials and experimental investigations have investigated JAK-STAT targets for alleviating inflammation in inflammatory bowel illness, specifically in ulcerative colitis and Crohn's disease.[148,155–158] Research on natural products also focuses on JAK-STAT in experimental colitis, with curcumin demonstrated to inhibit dendritic cell activation by

modulating JAK-STAT and SOCS interactions.[159] In murine models, the expression of Krüppel-like factor-5 (KLF5) diminished the severity of colitis, possibly by regulation of the JAK-STAT signaling pathway.[160] Regulating STAT-III activation by targeting SOCS-III has been suggested as a method to mitigate experimental colitis.[161] Dysfunction of immune cells associated with changes in JAK-STAT signaling contributes to the pathophysiology of IBD. Nieminen et al, discovered reduced STAT phosphorylation in plasmacytoid dendritic cells from Crohn's disease patients, despite high IL-6 levels, indicating that abnormalities in JAK-STAT signaling contribute to immunological dysfunction.[162] Furthermore, CD2-facilitated T cell activation through STAT transcription factors is crucial in IBD, especially in modulating IFN-γ production in the gastrointestinal tract.[163–167] Modifications in CD2 activity correlate with diminished lymphocyte populations in ulcerative colitis and irregular IL-10 secretion in Crohn's disease.[168,169]

Dermatomyositis

Dermatomyositis is a rare, devastating autoimmune disease characterized by inflammation of both muscle and skin, leading to muscle weakness and skin rashes in the majority of affected individuals. In severe cases, systemic involvement, including inflammation of the lungs, joints, gastrointestinal tract, and heart, may occur, resulting in a poor prognosis. Traditional treatments, such as glucocorticoids and disease-modifying antirheumatic drugs (DMARDs), have shown limited efficacy, particularly in patients with systemic involvement.[170,171] Analysis of muscle and skin samples from dermatomyositis patients has revealed elevated inducible transcript and protein levels associated with type I interferon signaling. Notably, the IFN1 and IFN2 pathways are differentially activated in various forms of myositis.[172]

Psoriasis and Psoriatic Arthritis

Psoriasis, a chronic, T cell-mediated skin ailment, is often accompanied with comorbidities,[157] including Psoriatic Arthritis (PsA),[9] which causes synovitis and tissue and bone damage.[173] Two investigations revived interest in signal transduction, particularly JAK-STAT signaling, in psoriasis etiology three years ago. In psoriasis lesions, Hald et al, found higher STAT-I mRNA and protein levels. In addition, psoriatic lesions have higher STAT-I activity at the Tyr701 and Ser727 phosphorylation sites than non-lesions.[174] Studying normal human keratinocytes activated with IFN-α or IFN-γ in vitro revealed elevated STAT-I levels, linking IFN signaling to STAT activation in dysregulated cells. IFN-α and IFN-γ produced STAT-I phosphorylation at Ser727 and Tyr701 activation, respectively, requiring PKC and p38 MAPK activity. The latter was dependent on PKCδ activity. Psoriasis pathogenesis may depend on STAT-I activity, according to these findings.

In cultured normal human keratinocytes subjected to tetradecanoylphorbol-13-acetate and UVB irradiation, Andrés et al, verified and extended these findings by revealing that ERK1/2 and p38 MAPK pathways phosphorylated STAT-III at Ser727.[175] This suggested that STAT-III activation may contribute to psoriasis.[176] According to Johansen et al, psoriasis sufferers' lesional skin has higher STAT-II levels than non-lesional skin.[177] The chemokines CXCL11 and CCL5, which are common in psoriasis, were connected with STAT-II-dependent activation, which was likewise impacted by IRF9. STAT-I and STAT-VI were not. Findings suggest no association between CXCL11 or CCL5 expression and IL-17A, suggesting STAT-II may be a potential target for limiting IFN-γ-producing immune cell migration to the skin, where psoriatic plaques form.

PsA, originating from psoriatic skin lesions, is linked to T cell signaling via JAK-I/STAT-III/STAT-I and PKCδ activation. In clinically active PsA, Fiocco et al, found that this signaling pathway increases CD4+ (IL17A-F and CD4+ IL-23R+) TH17 T effector cells.[178] Based on these findings, JAK inhibition was suggested a treatment for psoriasis and PsA. Several studies have evaluated the clinical efficacy of JAK inhibitors, including tofacitinib, baricitinib, and ruxolitinib for PsA treatment.

Multiple Sclerosis

MS is an autoimmune central nervous system condition that causes neural cell demyelination and death. CD4+ T and myeloid cells may be key players in MS development.[179] MS contributes to elevated levels of pro-inflammatory cytokines, including IL-2, IL-6, IL-12, IL-18, IL-21, IL-23, GM-CSF, and IFN-γ.[179–181] MS may potentially include the IL-7 receptor (IL-7R). Downregulation of IL-7R promotes JAK-STAT signaling, causing oligodendrocyte death in adult transgenic zebrafish. Despite being conducted in an animal model, this study may help us understand how IL-7R causes MS demyelination. These findings support JAK-STAT signaling in MS, considering its pro-inflammatory cytokine profile.[182,183] Hatami et al found that relapsing-remitting MS patients' blood cells had lower STAT-VA expression and higher STAT-VI expression than healthy

controls. High STAT-VI levels were linked to the Kurtzke Expanded Disability Status Scale (EDSS), a measure of physical impairment in MS patients.[184] These findings indicate that STAT-VA and STAT-VI dysregulation may contribute to MS's immunological responses that transition from TH1 to TH2 cytokine production. Other research is needed to determine if these findings can be used to develop new MS treatments targeting JAK-STAT signaling.

Other Autoimmune Diseases

Dysregulation of JAK-STAT signaling has been implicated in various other autoimmune and inflammatory diseases. Many of these diseases are Sjögren's Syndrome (SS), Systemic sclerosis (SSc), Graft-versus-Host Disease (GVHD), Multiple Sclerosis (MS), Juvenile Idiopathic Arthritis (JIA), Allergic Rhinitis, Idiopathic Pulmonary Fibrosis (IPF), and Celiac Disease. For example, Primary Sjögren's syndrome (SS) is a systemic autoimmune disease marked by inflammation of the exocrine glands, which leads to sicca symptoms in people with the condition. In mouse models treated with filgotinib exhibited increased salivary flow rates, indicating that JAK inhibitors may provide a new therapeutic strategy for primary SS.[185] Systemic sclerosis (SSc), another autoimmune condition causing inflammation in the connective tissues of the skin and internal organs, leads to fibrosis and vasculopathy.[186] Similar to SLE and other connective tissue diseases, patients with SSc showed overexpression of IFNα, suggesting a direct pathogenetic role in the disease's development.[187] Importantly, The IFN signature is detectable at early stages of the disease, indicating that IFN upregulation occurs early and may play a significant role in disease pathogenesis.[188] The another main players in the field of SSc pathogenesis are the IL-6 and IL-6 cytokine families. IL-6 plays a significant role in the pathogenesis of SSc by contributing to vasculopathy and promoting fibrotic processes. It is associated with disease activity and the degree of skin thickening.[189] Reports have indicated that tofacitinib may improve polyarthritis in SSc patients, pointing to the potential of JAK inhibitors as therapeutic options for arthropathy, scleroderma, and vasculopathy in SSc. This pathway has received considerable attention in immunology and autoimmunity because to its crucial role in several immunological diseases. Dysregulated activation of JAK/STAT signaling is associated with the pathogenesis of numerous autoimmune diseases, such as RA, psoriasis, SLE, and IBD etc. The intricacy has prompted a growing number of research investigations focused on elucidating the specific mechanisms by which JAK/STAT signaling contributes to these diseases and identifying possible therapeutic targets within this pathway (Figure 3).

The JAK/STAT Signaling Pathways and Cancer

The influence of the JAK-STAT pathway on disease progression is complex. Cellular plasticity enables cells to assume novel phenotypes in reaction to environmental alterations, and cancer cells utilize this plasticity to promote tumor heterogeneity, metastasis, and therapeutic resistance.[190–194] A notable instance of lineage plasticity in cancer is the histological transition of lung malignancies with EGFR mutations, wherein tumors evolve from adenocarcinoma to aggressive neuroendocrine carcinoma.[195,196] Numerous evidences demonstrate a robust association between JAK-STAT signaling, lineage flexibility, and resistance, especially via the regulation of stem cell self-renewal and multilineage differentiation.[197–199] A significant instance is the involvement of activated JAK-STAT signaling in the lineage change of prostate cancer from adenocarcinoma to neuroendocrine carcinoma.[200] In liver cancer, JAK-STAT-III is involved in the RAS-induced trans-differentiation of hepatocytes into intrahepatic cholangiocarcinoma cells, a process linked to malignancy.[201] The stimulation of the IL-6-JAK-STAT pathway by WNT5A is recognized to facilitate epithelial-mesenchymal transition (EMT) in keloid scarring.[194] A comprehensive understanding of the impact of JAK-STAT signaling on lineage plasticity may establish a biological basis for the creation of innovative therapeutic approaches for malignant conditions.[202]

The substantial success of JAK inhibitors in clinical applications has led to the development of innovative strategies for targeting the JAK/STAT signaling pathway in immune-mediated diseases.[9] The tumor microenvironment comprises various elements surrounding a tumor, including blood vessels, immune cells, fibroblasts, signaling molecules, and the extracellular matrix.[203] A pioneering treatment approach utilizing checkpoint inhibitors to overcome the limitations of traditional chemotherapy highlights the considerable potential of immunotherapy as an effective cancer treatment.[204] The JAK/STAT pathway regulates complex cytokine signaling networks as well as the differentiation and activation of immune cells. Consequently, an increasing number of studies have focused on the role of the JAK/STAT pathway in the pathogenesis of various tumors.

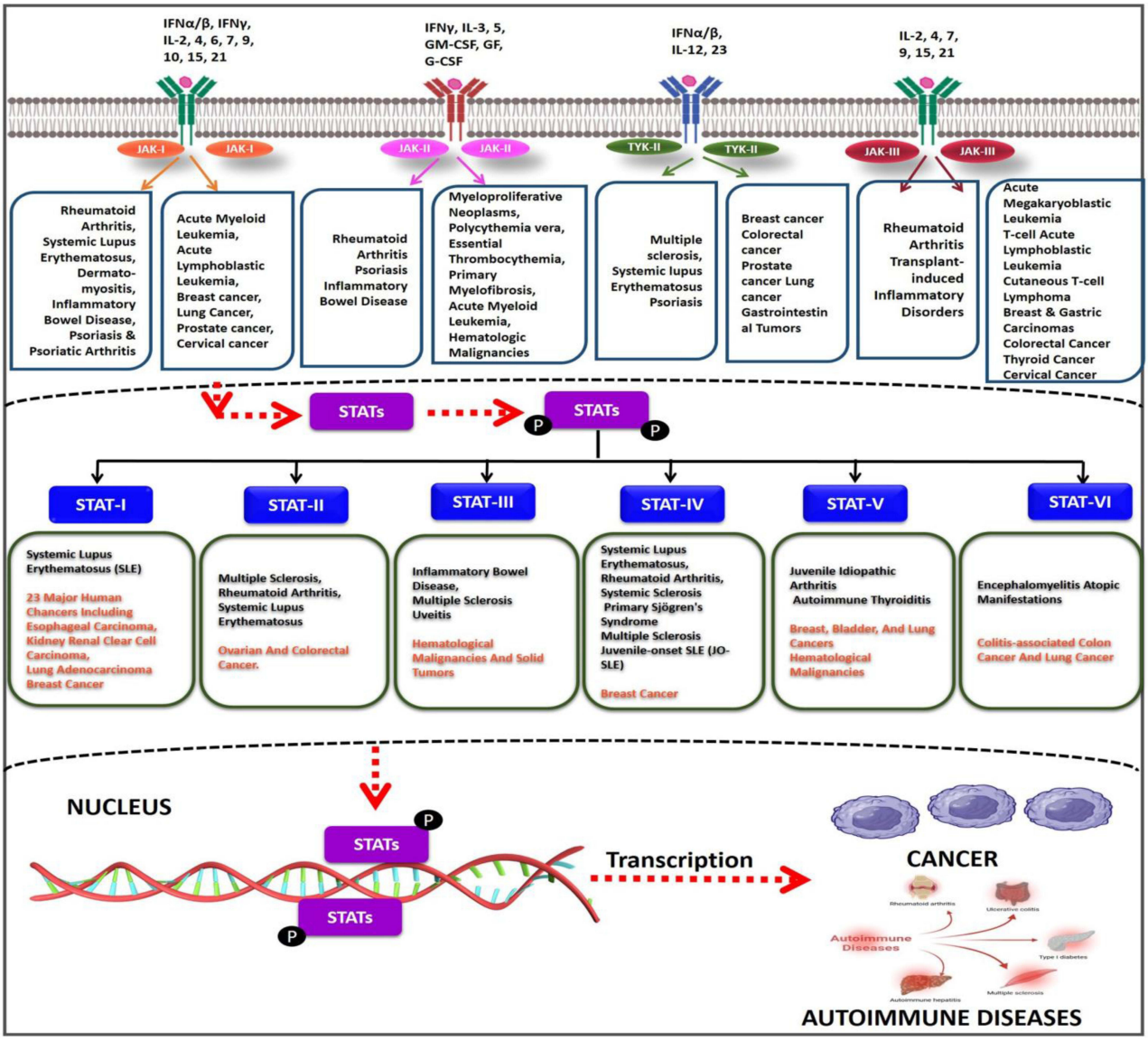

Figure 3 This figure illustrates the involvement of JAK-STAT signaling in autoimmunity and cancer. The pathway is activated by cytokines (IFNs, ILs, GM-CSF, etc.) and growth factors, leading to phosphorylation of JAKs and STATs. Different STATs (I–VI) then dimerize and translocate to the nucleus, where they regulate gene transcription, influencing the development of cancer and autoimmune diseases. The figure also lists specific diseases associated with the activation of each STAT, such as rheumatoid arthritis, leukemia, multiple sclerosis, and various cancers.

Hematologic Malignancies

The JAK-STAT signaling pathway plays a crucial role in the development and progression of hematologic malignancies, which encompass hematologic malignancies including leukemia, lymphoma, and multiple myeloma.[205,206] This pathway regulates essential processes such as cell proliferation, differentiation, survival, and immune response modulation. Dysregulation in these tumors often results in uncontrolled cell growth and immune evasion.[207] Hematological malignancies, including myeloproliferative neoplasms (MPNs) such as polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), have been shown to aberrantly activate the JAK-STAT pathway.[81]

Dysregulated JAK/STAT signaling in these conditions is often due to activating mutations in JAK-II, especially the V617F mutation, which results in the substitution of valine with phenylalanine at position 617 of the JAK-II protein.[208,209] The discovery of the JAK-IIV617F mutation led to the development of JAK-II inhibitors as targeted therapy for MPNs.[210] Activated JAK-STAT signaling is a common feature across different MPN phenotypes, regardless of the specific driver mutation.[210,211] This mutation plays a key role in the development of the PV phenotype in mouse

models.[212,213] Approximately 80% of PV patients carry the homozygous JAK-IIV617F mutation, underscoring the role of JAK-II activation in the development and progression of this hematological disorder.[214] This pathway is involved in clonal proliferation of mature myeloid cells and upregulation of downstream transcription and gene expression in MPNs.[211] Interestingly, while JAK inhibitors have shown clinical efficacy in MPNs, they are not clonally selective for JAK-IIV617F-mutant cells and have limited ability to reduce disease burden or reverse myelofibrosis.[209,210] Recent studies have identified additional mechanisms contributing to MPN pathogenesis, including alterations in gene regulation through differential enhancer utilization and activation of NF-κB signaling. Combined JAK/BET inhibition has shown promise in reducing inflammatory cytokines, disease burden, and bone marrow fibrosis in vivo.[209] STAT-V acts as a crucial adaptor in transducing signaling mediated by activated JAK-IIV617F in MPNs.[215,216] Constitutive activation of STAT-V is associated with the progression of hematologic malignancies, including myelofibrosis.[217] Targeting STAT-V by reducing its phosphorylation inhibits MPN cell growth, highlighting the therapeutic potential of disrupting JAK/STAT signaling in these diseases.[218] Emerging therapies are focusing on multiple biological levels, including JAK-II-mutant MPN stem cells, non-JAK signaling pathways, and the inflammatory bone marrow microenvironment.[219]

Furthermore, mutations affecting the JAK/STAT pathway have been identified in plasmablastic lymphoma (PBL), a malignant B-cell lymphoma, as well as in T-cell acute lymphoblastic leukemia (T-ALL). In T-ALL, activating mutations in the IL-7R-mediated JAK/STAT pathway, along with the loss of function of the polycomb repressor complex 2 (PRC2), have been linked to poor responses to prednisone-based therapies.[220] Mutations in the JH2 domain of JAK-I, which enhance kinase activity, have also been found in patients with ALL and T-cell prolymphocytic leukemia (T-PLL).[221,222] Recent studies have reported upregulation of JAK-II signaling and increased cell cycle progression in primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (pcAECyTCL).[223]

Additionally, constitutive activation of the JAK-STAT pathway has been reported in various types of leukemias, including acute myelogenous leukemia, T-LGL leukemia (T-cell large granular lymphocytic leukemia), and multiple myeloma.[207] In chronic myelogenous leukemia (CML), the BCR-ABL fusion protein induces persistent activation of JAK/STAT signaling, particularly STAT-V, promoting survival and proliferation of leukemia cells.[224] The importance of JAK-STAT signaling in hematologic malignancies is further emphasized by the fact that STAT proteins, particularly STAT-III, regulate the expression of numerous critical mediators of tumor formation and metastatic progression.[225] STAT-III and STAT-V activation in hematologic malignancies can modulate the immune microenvironment by promoting immunosuppressive cytokine production (eg, IL-10, TGF-β) and inhibiting the activity of immune cells such as T cells and natural killer (NK) cells.[226]

Inhibition of aberrant STAT-III activation has shown promise in abrogating cancer growth in preclinical models, suggesting that targeting this pathway may have therapeutic potential in hematological malignancies[87,207] In conclusion, the JAK-STAT pathway serves as a critical mediator of malignant transformation and progression in hematologic malignancies. Understanding the consequences of JAK-STAT pathway mutations and aberrant activation is integral to developing targeted therapies for hematological malignancies. Ongoing research and clinical investigations are focused on JAK and STAT inhibitors as potential therapeutic strategies for these cancers.[87,207,227,228]

Solid Tumors

The initial information indicating the activation of JAK/STAT signaling in solid tumors was obtained from cancer cell lines. Substantial evidence indicates tyrosine phosphorylation and nuclear localization of STATs, signifying STAT activity, in tumor tissue obtained from numerous patients across various tumor types.[81] A correlation between JAK/STAT activity and prognosis has been established in numerous tumor types. Typically, the activation of STAT-III or STAT-V correlates with a poorer prognosis; however, in breast cancer and certain studies including colorectal cancer and head and neck squamous cell carcinoma, it seems to be linked to more favorable results. The association in breast cancer aligns with the function of pSTAT-V in normal physiology; persistent phosphorylation of STAT-V characterizes normal breast epithelial cells, where it is believed to facilitate differentiation.[229] Variations in the methodologies employed to measure STAT phosphorylation across different tumor types may explain the seemingly contradictory relationships between STAT phosphorylation and tumor outcomes, Notably, data indicates that in MPNs (Myeloproliferative Neoplasms), STAT-III may counteract malignant growth,[230,231] implying that this phenomenon may also manifest in specific contexts inside solid tumors. Conversely, the activation of STAT-I, is typically linked to improved outcomes in all tumor types. Despite the observation of STAT activation across several tumor types, the mechanisms behind this

activation remain poorly elucidated in many instances. These investigations primarily delineate relationships between JAK/STAT activation and outcomes, although they do not establish whether the observed JAK/STAT activation plays a causative role in the disorders. Additional research is required to confirm this, particularly in relation to the JAK/STAT pathway as a potential therapeutic target.[81]

Point mutations affecting JAK activity have also been observed in solid tumors. Some patients with JAK-I mutations exhibit upregulated JAK-I and STAT-III phosphorylation, facilitating cell growth independent of cytokine expression, particularly in hepatitis B-associated hepatocellular carcinoma.[232] Amplification of the JAK-II gene locus in gastric adenocarcinoma, corresponding to increased JAK-II transcript levels, suggests enhanced JAK-dependent pathway activity.[233] Although mutations in the STAT locus are rare, approximately 40% of patients with large granular lymphocytic leukemia harbor STAT-III mutations, leading to stable dimer formation of the STAT protein and enhanced expression of its downstream genes.[234] High levels of STAT-III expression are associated with poor prognosis in various cancers, including gastric cancer, lung cancer, gliomas, liver cancer, osteosarcoma, and pancreatic cancer.[235] Increased STAT-VA/B expression is linked to nuclear accumulation of STAT-V in prostate cancer, and the activation of STAT-III and STAT-V drives tumor progression by regulating genes involved in cell cycle, inflammation, and stemness. Cyclin D, a major target gene of STAT-III and STAT-V, is stabilized by acetylation of STAT-III by p300 acetyltransferase, promoting cell cycle progression.[236,237] Additionally, the STAT-III-p300-CD44 complex regulates survival genes such as c-MYC, BCL2, BCL-XL, and surviving.[238]

The engagement of cytokines or growth factors activates the JAK/STAT pathway, increasing phosphorylation of STAT-III and contributing to tumor progression. The common γ chain in cytokine receptors is essential for receiving signals from various cytokines (eg, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), which regulate immune cell proliferation, activation, and differentiation.[68] Other cytokines such as IL-6, IL-11, IL-13, and IL-31 activate downstream signaling partners through JAK-I- and JAK-II-dependent mechanisms. TYK-II mediates signaling triggered by IL-10 family members (eg, IL-10, IL-19, IL-22).[74] IL-6 stimulation induces constitutive activation of STAT-III in head and neck squamous cell carcinoma, while granulocyte colony-stimulating factor (G-CSF)-induced JAK-II-STAT-III activation promotes ovarian cancer growth.[239,240] In basal-like breast cancers, inflammatory response genes are closely associated with STAT-III activation. Several proinflammatory molecules in addition to IL-6, such as IL-17, TNF-α and IFN-γ, can also exert biological functions through STAT-III and NF-κB and drive cancer associated inflammation to promote cancer development (Figure 3).[241,242]

Role of JAK/STAT Signaling in the Induction of Epithelial-Mesenchymal Transition (EMT)

STAT proteins are involved in cancer carcinogenesis in a context-dependent manner. While STAT-I is recognized for promoting anti-tumor immunity, other members of the STAT family, such as STAT-III, STAT-V, and STAT-VI, primarily contribute to cancer progression. STAT-III has received much focus as a pivotal intrinsic transcription factor in the initiation of EMT and the development of cancer.[243] The activation of the JAK/STAT signaling pathway promotes metastasis by inducing EMT through the upregulation of EMT-inducing transcription factors (EMT-TFs) such as Snail, Zeb1, JUNB, and Twist-1, and by enhancing cell motility via the activation of focal adhesion kinase (FAK).[244–247] In prostate cancer, paracrine signaling through JAK/STAT initiates an autocrine IL-6 loop, whereas the stimulation of insulin-like growth factor receptor (IGF-IR) by IL-6 and IGF promotes EMT via the STAT-III/NANOG/Slug pathway.[248,249] STAT-III acts as a transcriptional activator by associating with the promoter regions of target genes in a way dependent on tyrosine phosphorylation.[61] Once active, STAT-III interacts with the estrogen receptor (ER) to bind the LIV-1 promoter, resulting in the activation of LIV-1 expression. This is succeeded by proteolytic cleavage of the N-terminal of LIV-1 protein and its subsequent translocation to the plasma membrane, where it stabilizes Snail by inactivating GSK3β.[250–252] Furthermore, RANKL (Receptor activator of nuclear factor kappa-B ligand) is recognized for facilitating EMT in prostate cancer through the STAT-III/LIV-1 pathway.[253] Furthermore, IL-8-induced synthesis of IL-6 and TGF-β1 promotes STAT-III association with the AUF-1 promoter, resulting in the activation of breast stromal fibroblasts via the downregulation of p16, p21, and p53 in a paracrine fashion. Increased AUF-1 levels subsequently facilitate EMT by augmenting the expression of SDF-1, α-SMA, TGF-β1, and IL-6, due to AUF-1's interaction with their respective promoters.[254,255] Moreover, the STAT-III-mediated enhancement of Fra-1 and PTTG1 expression via promoter binding facilitates tumor invasion and leads to resistance against androgen deprivation therapy (AR). The increased expression of RTVP-1 by

the concurrent binding of C/EBPβ and STAT-III to the RTVP-1 promoter maintains the stemness of glioblastoma cells and is associated with unfavorable clinical outcomes.[256–258] Furthermore, STAT-III enhances UHRF1 expression by directly interacting with its promoter. The PHD and SRA domains of UHRF1 play a crucial role in the silence of tumor suppressor genes in colorectal cancer (CRC) cells, which is particularly significant in cancer biology.[259] The characteristics of cancer, regulated by STAT-III-dependent transcriptional control of target proteins, directly affect cellular responses that promote tumor growth.[260] Activation of JAK/STAT protein stimulated by IL-6 up-regulates MMP-2 and SNAIL expression, which results in EMT.[261,262] However, the JAK-II/STAT-III inhibitor WP1066 prevents IL-6– induced activation of the JAK-II/STAT-III pathway and EMT.[263] Furthermore, Ovatodiolide effectively suppresses nasopharyngeal cancer development through the induction of apoptosis and inhibition of EMT, aligning with the repression of the JAK/STAT signaling pathway. The IL-6-mediated JAK/STAT signaling pathway promotes cancer progression by inhibiting autophagy.[264,265] Recent studies have shown that resveratrol inhibits the IL-6–mediated JAK/STAT signaling pathway, causing autophagy and prevents ovarian cancer cell migration, according to recent studies. In primary effusion lymphoma, quercetin inhibits STAT-III to induce autophagy. Docetaxel-mediated autophagy inhibited STAT-III to reduce castration-resistant prostate cancer (CRPC) cell survival and metastasis.[266–269] Another study on Head and neck squamous cell carcinomas revealed that Inhibition of either IL-6R or ERK effectively reverses EMT and re-sensitizes cells to ionizing radiation. According to Niu et al, the hyaluronan-mediated motility receptor (HMMR) responsible for cell mitosis and proliferation might be implicated in the proliferation and metastasis of clear cell renal cell carcinoma (ccRCC) through EMT and JAK-I/STAT-I signaling pathways.[260,270,271] Hence, many pathways like autophagy activators might be used to hinder EMT by suppressing JAK/STAT signaling (Figure 4).

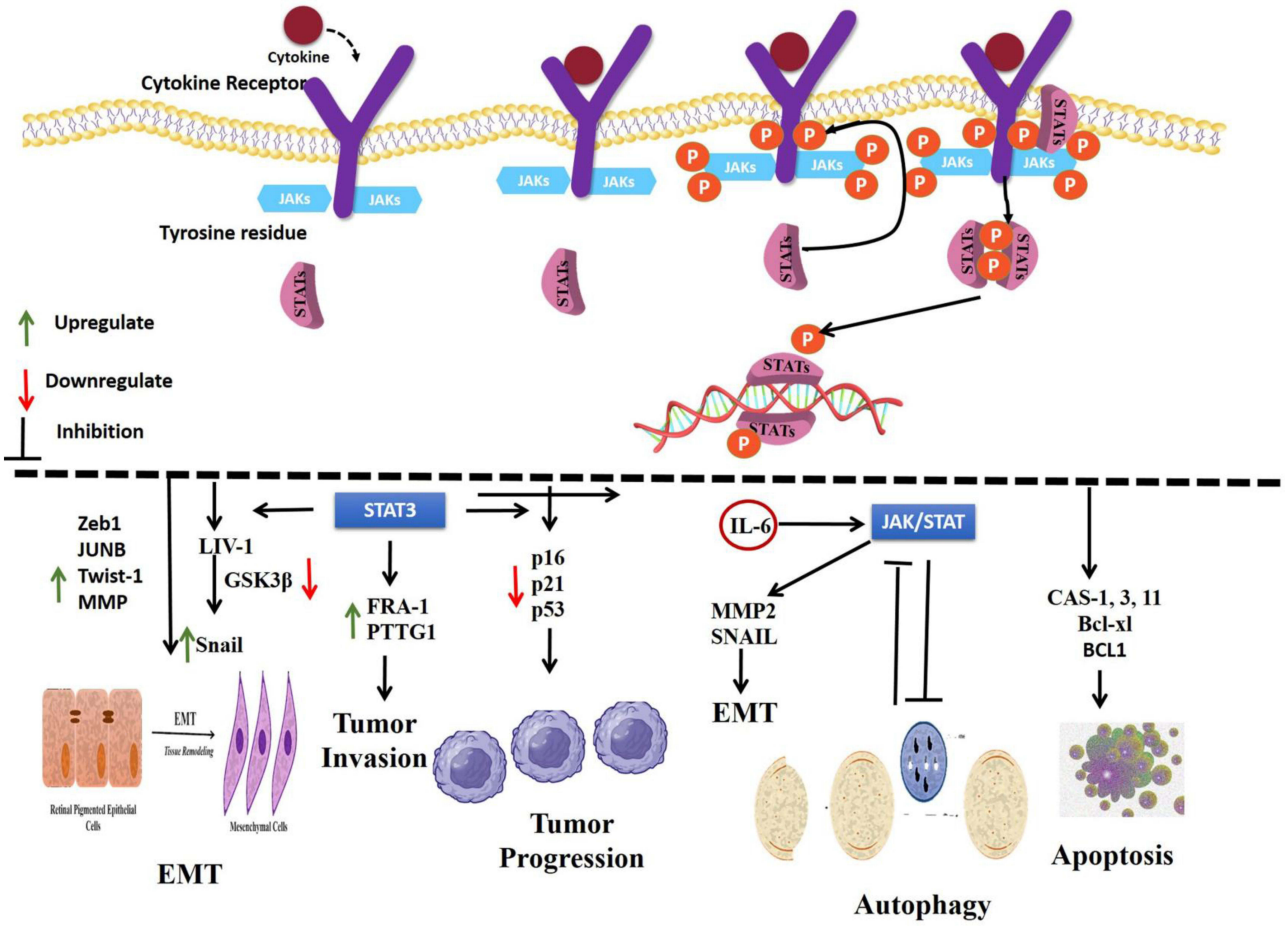

Figure 4 The figure illustrates the JAK/STAT signaling pathway and its role in cancer progression, highlighting its influence on tumor invasion, progression, autophagy, and apoptosis. This pathway promotes tumor invasion by regulating factors like ZEB1, JUNB, TWIST-1, and MMP, and supports EMT via IL-6 and SNAIL. The JAK/STAT pathway also inhibits autophagy and apoptosis, contributing to tumor survival and progression. Key factors like p16, p21, p53, and Bcl-xl are involved in these processes.

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JAK Inhibitors (Jakinibs) as a Therapeutic Approach

Janus kinase inhibitors (JAK inhibitors or JAKinibs) have emerged as a vital class of targeted biologic therapies, initially developed for autoimmune, inflammatory, and allergic diseases, and more recently extended to cancer treatment.[272] These drugs function by inhibiting type I/II cytokine receptors through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, a central mechanism in immune and inflammatory responses. The development of JAK inhibitors has progressed from non-selective first-generation drugs like baricitinib and tofacitinib to second-generation agents such as filgotinib and upadacitinib, which exhibit selective inhibitory activity against specific JAK family members JAK-I, JAK-II, JAK-III, and TYK-II.[273] This evolution in selectivity has been associated with differences in safety and efficacy profiles. Additionally, JAKinibs can be classified based on their binding mode into reversible (competitive) and irreversible (covalent) inhibitors, further diversifying their potential applications. JAK inhibitors have demonstrated substantial efficacy in treating chronic inflammatory conditions such as rheumatoid arthritis and psoriatic arthritis (PsA).[274] Their potential extends to other diseases, including ankylosing spondylitis (AS), where polymorphisms in JAK-II and STAT-III genes have been linked to disease susceptibility. The role of the JAK/STAT pathway in the IL-23/IL-17 axis, which is critical in PsA and spondyloarthropathies, underscores the importance of JAKinibs in addressing these conditions. In cancer therapy, acquired genetic mutations like JAK-II V617F, K607N, and T875N activate JAK-II signaling, providing a strong rationale for targeting this pathway. Beyond oncology, JAK inhibitors are being investigated for hyperinflammatory conditions such as COVID-19, where modulation of the JAK-STAT pathway could mitigate severe immune responses.[275] For example, the combination of baricitinib with methotrexate (MTX) has produced remarkable clinical outcomes, suggesting that such combinations could be effective strategies for managing complex inflammatory diseases. Despite their promising therapeutic potential, JAK inhibitors come with challenges, particularly the increased risk of infections due to blocking the JAK-STAT pathway.[276] Additionally, their efficacy and safety profiles do not always align with predictions based on selectivity, necessitating long-term studies and rigorous post-marketing surveillance to establish comprehensive risk profiles. The relative risk across different JAK inhibitors and their dose-dependent effects remain areas requiring further investigation. The continued development of more selective and safer JAK inhibitors is expected to expand their clinical applications. Combining JAKinibs with other therapies, such as antiviral agents or novel anti-inflammatory drugs, represents a promising avenue for tackling diseases with complex pathophysiology.[151] The integration of these agents into treatment paradigms will depend on ongoing innovation and a careful balance between efficacy and safety to maximize their therapeutic potential.

Tofacitinib

Tofacitinib is an oral Janus kinase (JAK) inhibitor that selectively targets JAK-I and JAK-III, with moderate activity against JAK-II, disrupting the JAK-STAT signaling pathway to reduce inflammation and immune responses. Approved by the FDA in 2012 for the treatment of RA,[277] tofacitinib has since been approved for PsA in 2017, ulcerative colitis in 2018, juvenile idiopathic arthritis (JIA) in 2020, and ankylosing spondylitis (AS) in 2021.[278,279] Its mechanism of action involves inhibiting cytokine-mediated signaling pathways, particularly those utilizing the common γ chain family, effectively blocking interleukins such as IL-2, IL-7, and IL-6. This inhibition alleviates symptoms and slows disease progression.[280] Tofacitinib, the first JAK inhibitor aimed at JAK-I, JAK-II, and JAK-III, showed greater selectivity for JAK-I and JAK-III. It received approval from the US Food and Drug Administration (FDA) in November 2012 and from the European Medicines Agency (EMA) in March 2017 for moderate to severe active RA. Tofacitinib has been recommended as a second-line or subsequent therapy for RA by the European League against Rheumatism (EULAR) and the American College of Rheumatology (ACR).[278] Tofacitinib offers a convenient oral administration alternative to biologic therapies. Unlike biologics, it is rapidly absorbed after oral administration of the immediate-release tablet and maintains consistent plasma concentrations without susceptibility to immunogenicity or disease activity. Comprehensive safety evidence for tofacitinib has been gathered in Phase 1–3 clinical trials and long-term extension studies. However, it carries risks such as infections, including herpes zoster and cellulitis, as well as elevated liver enzymes, thromboembolic events, and cardiovascular issues.[278,280,281] Mechanistically, JAK inhibition by tofacitinib has been shown to reduce CD80/CD86 expression and T cell stimulatory capacity by suppressing type I IFN signaling in human dendritic cells. Consequently, it not only hinders the differentiation of plasmablasts and Th1 and Th17 cells but also modulates innate immune responses, thereby reducing autoimmune inflammation. Additionally, low-density lipoprotein and high-density lipoprotein levels increase, while

blood neutrophil levels decrease during treatment.[282] Despite these risks, tofacitinib remains a key option for patients unresponsive to other therapies, as demonstrated in short-term dose-ranging studies showing significant improvements in ACR20 response rates and surrogate markers of decreased disease progression within three months.[280] The OCTAVE trials highlighted the efficacy of tofacitinib in managing ulcerative colitis. While the rate of serious infections was higher during induction trials compared to placebo, it was similar across treatment groups during maintenance trials. In SLE, studies in murine lupus models have demonstrated that tofacitinib effectively decreases anti-dsDNA levels, reduces proteinuria, alleviates nephritis symptoms, and improves skin rashes. Case studies of SLE patients treated with tofacitinib have shown rapid improvement in arthritis symptoms and partial improvement of skin rashes, although its effects on serological parameters were limited.[283,284] In patients with RA and psoriasis, the drug has been associated with an increased risk of infections, particularly herpes zoster. Nevertheless, pharmacokinetic studies confirm its consistent efficacy without a decrease in plasma concentrations over time.[281] Tofacitinib has also been shown to mitigate the proinflammatory and profibrotic effects of T cells derived from amyopathic dermatomyositis-associated interstitial lung disease (ILD) in vitro.[285] In patients with anti-melanoma differentiation-associated gene 5 (MDA5)-positive dermatomyositis, who also have refractory and rapidly progressive ILD, combination therapy with tofacitinib has been associated with significantly improved survival.[286] Similar studies have demonstrated that tofacitinib improves survival following ILD onset and substantially enhances lung function, as assessed by high-resolution computed tomography.[287] Based on these findings, a phase 1 clinical trial evaluating the safety and efficacy of tofacitinib in adults with active, treatment-refractory dermatomyositis was initiated [NCT03002649]. Preclinical studies have shown the effectiveness of tofacitinib in T-ALL patients with JAK-I/JAK-III mutations. However, its use in autoimmune diseases (AIDs), which relies on immune suppression, raises concerns about tumorigenesis. Therapy with tofacitinib has been reported to increase the risk of malignancy compared to tumor necrosis factor (TNF) inhibitors.[288,289] JAK inhibition modifies the pro-inflammatory cytokine profile of psoriatic T cells, as tofacitinib dramatically inhibited IL-23, IL-17A, IL-17F, and IL-22 receptors in activated lymphocytes from psoriasis patients. In addition, tofacitinib reduced p-STAT-III, p-STAT-I, NF-κB p65, and increased SOCS-III and PIAS3 mRNA in PsA patients' fibroblast-like synoviocytes and synovial tissue explants.[290] Moreover, tofacitinib decreased spontaneous secretion of IL-6, IL-8, MMPs, and TIMP3, while without altering IP-10 or IL-10.[291] Despite these concerns, a meta-analysis of observational studies found no increased malignancy risk in RA patients treated with tofacitinib compared to those receiving conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) or TNF inhibitors.[292] This underscores the controversial nature of the association between tofacitinib and tumorigenesis. In conclusion, tofacitinib represents an important therapeutic option for autoimmune and inflammatory conditions, targeting a distinct biochemical pathway that differentiates it from available biologics. While it offers significant clinical benefits, its associated risks necessitate careful monitoring and patient selection to optimize outcomes.

Ruxolitinib

Ruxolitinib is a selective inhibitor of JAK-I and JAK-II, originally identified as INCB018424 or INC424. It was approved by the FDA in 2011 and the European Medicines Agency (EMA) in 2012 for the treatment of myelofibrosis (MF) and later for polycythemia vera (PV) in 2014 and acute and chronic graft-versus-host disease (GVHD) in 2021.[293] In addition to its established indications, ruxolitinib has shown potential applications in various malignancies and inflammatory disorders, highlighting its versatility in clinical practice. Ruxolitinib demonstrated significant clinical benefits in Applications in Myeloproliferative Neoplasms (MPNs), including reducing splenomegaly, alleviating constitutional symptoms, and improving patient conditions such as weight gain and general physical status. Mechanistically, it preferentially eliminated JAK-II$^{^{2}6i7M}$-mutant cells, reduced circulating inflammatory cytokines, and improved survival in a mouse model of JAK-II$^{^{2}6i7M}$-positive MPNs. The drug's effectiveness is highly dependent on the inflammatory milieu, suggesting its utility in conditions where cytokine dysregulation is central. Ruxolitinib has shown efficacy in autoimmune diseases such as SLE. In MRL/LPR murine models of SLE, it suppressed the development of cutaneous lesions, reduced autoantibody production, and downregulated cytokines such as CXCL10, CXCL9, and MxA, which are associated with cutaneous lupus erythematosus.[137,294–297] In PsA and plaque psoriasis, ruxolitinib modulates inflammatory cytokine profiles by targeting key pro-inflammatory mediators in the JAK/STAT pathway, offering therapeutic benefits in these chronic inflammatory conditions.[291] Ruxolitinib's immunomodulatory effects include inhibition of mast cell degranulation and cytokine production (eg, IL-6, TNF-α, MCP-1) in response to stimuli like codeine and substance P.[298] These findings suggest crosstalk between the JAK-II-STAT-V pathway and GPCRs, with potential

implications for neoplastic mast cells through interactions with the PI3K and STAT-V pathways. The JAK/STAT signaling pathway is pivotal in tumorigenesis and immune regulation within the tumor microenvironment. By inhibiting JAK-I and JAK-II, ruxolitinib disrupts cytokine-mediated tumor progression. Ruxolitinib has shown significant anti-tumor efficacy across various cancers by targeting the JAK/STAT signaling pathway. In T-ALL, ruxolitinib demonstrated anti-tumor activity in xenograft models, particularly in cases with JAK-I, JAK-III, or STAT-V mutations, which are present in 20–30% of patients. Synergistic effects were observed when combined with venetoclax, a BCL-2 inhibitor.[299] In pancreatic ductal adenocarcinoma (PDAC), ruxolitinib, when combined with MAPK/ERK inhibitors, enhances immune checkpoint therapy and helps overcome therapeutic resistance. In breast cancer, ruxolitinib exhibits synergistic effects in triple-negative and HER2-positive cancers when combined with calcitriol or SMO-GLI1/tGLI1 pathway inhibitors.[300,301] Additionally, ruxolitinib showed modest efficacy in advanced Hodgkin lymphoma (HL), with a well-tolerated safety profile, supporting its potential for use in combination therapies. Additionally, ruxolitinib demonstrates efficacy in metastatic lung cancer, non-small-cell lung cancer, and hepatocellular carcinoma, either as monotherapy or in combination with other agents.[302–304] Ruxolitinib's diverse applications, spanning autoimmune diseases, inflammatory conditions, and cancers, highlight its broad therapeutic potential.[151,305] Its ability to modulate cytokine production, inhibit mast cell activity, and target the JAK/STAT signaling pathway underscores its utility in addressing complex pathologies. Continued exploration of combination therapies and resistance mechanisms will be instrumental in expanding its clinical applications.

Baricitinib

Baricitinib is the second medication in its class and has been proven efficacious for the treatment of RA. Due to concerns about adverse effects associated with baricitinib, it is recommended for patients who have failed one or more tumor necrosis factor inhibitors (TNFis). Baricitinib functions by inhibiting the JAK-I and JAK-II proteins, which target the stimulation of cytokine and growth factor receptors, consequently diminishing downstream immune cell activity. Four trials have shown the efficacy of baricitinib, both alone and in combination with methotrexate, in patients who are naïve to disease-modifying antirheumatic drugs (DMARDs) as well as in those who have had an inadequate response to or intolerance of conventional and biological DMARDs.[306] Baricitinib (Olumiant™) is an oral small-molecule Janus kinase (JAK) inhibitor, developed by Eli Lilly and Incyte Corporation, for the treatment of RA, atopic dermatitis, and SLE. JAKs facilitate the transmission of intracellular signals from cell surface receptors for numerous cytokines and growth factors associated with inflammation and immune function, indicating that JAK inhibitors could offer therapeutic advantages in inflammatory disorders. Baricitinib has been recently approved for the treatment of specific autoimmune disorders. Through JAK-I/JAK-II inhibition, baricitinib is expected to demonstrate efficacy for SLE by impacting the release of pro-inflammatory cytokines such as IL-12, IL-6, and type I interferon, subsequently downregulating signal pathways associated with disease pathogenesis.[307] Baricitinib represents a small molecular weight reversible JAK inhibitor with excellent selectivity and potency for JAK-I and JAK-II. It can easily diffuse into cells and competitively inhibit this pathway, suppressing type-I interferon to modulate dendritic cells of the innate immune system. Additionally, it modulates B and T cells of adaptive immunity by blocking signals from IL-23, IL-2, IL-12, and type-I interferon. Blocking JAK prevents the production of several cytokine signaling pathways that are upregulated in SLE, explaining baricitinib's potential role in improving SLE-associated manifestations. Baricitinib was approved as a monotherapy for the treatment of RA in 2017 by the European Medicines Agency (EMA) and in 2018 by the FDA.[277,308] It is also approved for use in combination with methotrexate.[309] Furthermore, baricitinib was authorized as a treatment for COVID-19 under Emergency Use Authorization (EUA) in 2020 and received full FDA approval in 2022.[310] The efficacy of baricitinib as a cancer therapy has rarely been explored. One study reported that baricitinib did not induce apoptosis in T-ALL, while synergistic effects were observed when combined with docetaxel in androgen-receptor-negative prostate cancer cells. Potential effects on the risk of tumorigenesis have also been evaluated. While one study reported a high malignancy rate among RA patients treated with baricitinib, the rate was not significantly different from that of the general population or patients treated with TNF inhibitors.[311] Long-term safety data for baricitinib in RA patients indicate no increased risk of malignancy.[312] In summary, baricitinib is a selective Janus kinase inhibitor that has demonstrated efficacy in treating RA, SLE, and other autoimmune disorders. Despite its potential adverse effects, such as an increased risk of infections, its role in modulating inflammatory and immune pathways offers significant therapeutic benefits in autoimmune and inflammatory conditions. Apart from these, numerous other inhibitors have been developed, as outlined in Table 2.

Table 2 Provides a Comprehensive List of Clinically Approved JAK Inhibitors for Autoimmune Diseases and Cancer. (Www.clinicaltrials.com)

S. No.	Drug	Indications	IC50	Status
1.	Tofacitinib	Juvenile Rheumatoid arthritis, Psoriatic Arthritis, Rheumatoid arthritis, ulcerative colitis	JAK-I: 112 ηM JAK-II: 20 ηM JAK-III: 1 ηM	Approved (2012)
2.	Ruxolitinib	Vitiligo, Graft-versus-host disease (GVHD), Atopic Dermatitis (AD), Myelofibrosis (MF), Polycythemia vera	JAK-I: 3.3 ηM JAK-II: 2.8 ηM	Approved (2011)
3	Baricitinib	Rheumatoid arthritis	JAK-I: 5.9 ηM JAK-II: 5.7 ηM	Approved (2017)
4.	Pacritinib	Myelofibrosis	JAK-II: 23 ηM JAK-IIV617F: 19 ηM FLT3: 22 ηM FLT3D835Y: 6 ηM	Approved (2022)
5.	Fedratinib	Myelofibrosis	JAK-II and JAK-IIV617F: 3 ηM	Approved (2019)
6.	Delgocitinib	Atopic Dermatitis (AD)	JAK-I: 2.8 ηM JAK-II: 2.6 ηM JAK-III: 13 ηM TYK-II: 58 ηM	Approved (2020)
7.	Abrocitinib	Atopic Dermatitis (AD)	JAK-I: 29 ηM JAK-II: 803 ηM	Approved (2021)
8.	Ritlecitinib	Alopecia areata	JAK-III: 33.1 ηM	Approved (2023)
9.	Upadacitinib	Rheumatoid arthritis	JAK-I: 43 ηM	Approved (2019)
10.	Peficitinib	Rheumatoid arthritis	JAK-I: 3.9 ηM JAK-II: 5 ηM JAK-III: 0.7 ηM TYK-II: 4.8 ηM	Approved (2019)
11.	Filgotinib	Rheumatoid arthritis, Ulcerative colitis	JAK-I: 10 ηM JAK-II: 28 ηM JAK-III: 810 ηM TYK-II: 116 ηM	Approved (2020)
12.	Pacritinib	Myelofibrosis	JAK-II23 ηM JAK-IIV617F: 19 ηM FLT3: 22 ηM FLT3D835Y: 6 ηM	Approved (2022)
13.	Golidocitinib	Non-small cell lung cancer (NSCLC), cutaneous T-cell lymphoma (CTCL), and peripheral T-cell lymphoma (PTCL)	JAK-I: 73 ηM JAK-II: 14.7 μM JAK-III: 30 μM	Phase II clinical trials
14.	Zotiraciclib	Glioblastoma, brain cancer, gliosarcoma, and astrocytoma.	JAK-II: 73 ηM CDK2: 13 ηM FLT3: 56 ηM	Phase II clinical trials
15.	Brepocitinib	Dermatomyositis.	JAK-I: 17 ηM TYK-II: 23 ηM JAK-II: 77 ηM JAK-III: 6.49 μM	Phase III clinical trials

(*Continued*)

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Table 2 (Continued).

S. No.	Drug	Indications	IC50	Status
16.	Momelotinib Dihydrochloride	Myelofibrosis	JAK-I: 11 ηM JAK-II:18 ηM JAK-III: 155 ηM	Approved (2022)
17.	Itacitinib	Graft-versus-host disease (GVHD)	JAK-I: 2 ηM	Phase III clinical trials
18.	Ivarmacitinib	Atopic Dermatitis (AD), Rheumatoid arthritis	JAK-I	Phase III clinical trials
19.	Lorpucitinib	Colorectal cancer (adenomatous polyposis, FAP),	STAT-III	Phase I clinical trials
20.	Gandotinib	Hematologic malignancies	JAK-II: 68 nM JAK-IIV617: 55 nM ηM	Phase II clinical trials
21.	Ilginatinib	Myelofibrosis	JAK-II: 0.72 ηM JAK-I: 33 ηM JAK-III: 39 ηM TYK-II: 22 ηM	Phase II clinical trials
22.	Nezulcitinib	Pneumonia and novel Coronavirus infection	pan-JAK inhibitor	Phase II clinical trials
23.	Izencitinib	Ulcerative colitis (UC)	JAK-I, JAK-II, JAK-III, and TYK-II	Phase III clinical trials
24.	Lestaurtinib	Leukemia, ALL, and precursor T-lymphoblastic lymphoma leukemia.	JAK-II, STAT-V, and STAT-III	Phase III clinical trials
25.	Povorcitinib	Hidradenitis suppurativa (HS).	JAK-I	Phase III clinical trials
s26	Decernotinib	Rheumatoid arthritis	JAK-III: 50–170 ηM	In-vivo
27	Solcitinib	Autoimmune diseases, including psoriasis and ulcerative colitis.	JAKs: 33–76 ηM	Phase III clinical trials
29	PF-04965842	Moderate-to-severe atopic dermatitis (eczema)	JAK-I: 29 ηM JAK-II: 803 ηM JAK-III: > 10,000 ηM	Approved (2022)
30	WHI-P131	Immunosuppressive effects.	JAK-III: 78 μM	Approved (2018)

Efficacy of Jakinibs in Autoimmune Diseases and Cancers

The efficacy and safety of Jakinibs (Janus kinase inhibitors) have been extensively studied, beginning with the FDA-approved tofacitinib and advancing to next-generation Jakinibs. These agents have transformed the management of autoimmune and inflammatory diseases, representing a significant advancement over earlier therapies.[310] Biologics, including monoclonal antibodies and recombinant proteins targeting cytokines such as TNF-α, IL-6, and IL-1, have been pivotal in this progress.[313] However, targeting a single cytokine often fails to fully address the complexity of autoimmune diseases for all patients. Moreover, issues such as reduced efficacy over time due to immunogenicity and the challenges of intravenous or subcutaneous administration present limitations to their widespread utility. Tofacitinib has demonstrated remarkable long-term efficacy in treating moderate to severe RA.[314] The ORAL Sequel study, involving over 4,000 patients, showed sustained clinical improvement over 48 months, as evidenced by key metrics such as ACR 20/50/70, DAS28-4-ESR, and HAQ-DI.[315] A long-term extension trial further reinforced these findings, highlighting improved

physical function and consistent relief of disease signs and symptoms in patients treated with tofacitinib. Advancements in Jakinibs continued with baricitinib, which progressed to Phase III studies and demonstrated significant efficacy in patients with RA unresponsive to methotrexate.[312] Phase IIb trials revealed dose-dependent benefits, with improvements in clinical symptoms and musculoskeletal MRI findings over 12 to 24 weeks. Subsequent Phase III trials solidified baricitinib's position as a superior treatment option, notably outperforming adalimumab in the RA-BEAM study, an achievement unmatched by other disease-modifying agents.[316] Long-term data from these studies highlighted its ability to prevent progressive joint damage and maintain clinical efficacy, while early response rates enabled better patient stratification and minimized unnecessary drug exposure for non-responders. Despite their success, first-generation Jakinibs like tofacitinib have been associated with adverse effects such as cytopenias due to their nonselective pan-JAK blockade.[317] This limitation has driven the development of next-generation Jakinibs with selective activity for specific JAK pathways, aiming to reduce side effects while retaining efficacy. However, increased selectivity can sometimes limit therapeutic effectiveness, given the diverse cytokines reliant on the JAK–STAT pathway.[318] The potential of Jakinibs extends beyond RA, with promising applications in diseases characterized by elevations in JAK-dependent cytokines. Conditions such as SLE, myositis, scleroderma, and primary Sjögren's syndrome are under investigation, alongside type I interferonopathies like SAVI, where baricitinib has shown efficacy.[319] These findings are complemented by emerging evidence supporting the use of Jakinibs in skin-related conditions such as alopecia and vitiligo, offering new hope for patients with limited treatment options. As Jakinibs are increasingly used to treat a wide array of diseases, understanding their mechanism of action within cytokine biology becomes crucial. Not all cytokines are JAK dependent, and while over 200 factors fall under the cytokine umbrella, only a subset engages the JAK–STAT pathway. This distinction is essential to optimize therapeutic strategies while mitigating potential side effects. The ongoing development of Jakinibs reflects the growing recognition of their therapeutic potential. By addressing both efficacy and safety considerations, these agents continue to redefine treatment paradigms for autoimmune diseases and cancers, offering the possibility of better outcomes for patients worldwide.

Conclusion and Future Prospective

The Signal Transducer and Activator of Transcription (STAT) and Janus kinase (JAK) pathways are essential signaling pathways that control a wide range of biological functions, such as hematopoiesis, immunological responses, cell survival, and proliferation. The scope of JAK/STAT pathways studies is varied and bright in several ways because of their pivotal function in cell signaling and their participation in numerous diseases, especially inflammatory conditions, autoimmune disorders, and cancers. Research on the JAK/STAT pathway has a bright future ahead of it, with potential uses in both diagnosis and treatment. JAK/STAT modulation may transform the treatment of numerous inflammatory, autoimmune, and oncological conditions as a result of growing knowledge of how these pathways govern healthy and diseased states and the ongoing development of targeted small molecule inhibitors, biologics, and combination therapies. Numerous JAK inhibitors, such as tofacitinib and baricitinib, have demonstrated considerable progress in the treatment of autoimmune disorders, including RA and ulcerative colitis. Future research should prioritize the development of next-generation JAK inhibitors that exhibit enhanced specificity and reduced side effects. The combination of JAK inhibitors with other immunomodulatory agents, including biologics (eg, TNF inhibitors, autophagy inhibitors, apoptosis inhibitors, and various signaling pathway inhibitors), may improve efficacy and expand treatment options for patients with complex autoimmune or inflammatory diseases. Analyzing the genetic profiles of patients alongside the specific abnormalities in the JAK/STAT pathway may facilitate personalized treatments, enhancing the efficacy of JAK inhibitors while minimizing adverse effects. The JAK/STAT pathway engages with various other signaling networks, such as the PI3K/Akt, NF-kB, and MAPK pathways. Comprehending the intricate interactions among these pathways could facilitate the creation of advanced therapeutic strategies that simultaneously target multiple molecular mechanisms. The JAK/STAT signaling system is integral to autoimmune disorders and cancer, rendering it a viable therapeutic target. JAK inhibitors (Jakinibs) have demonstrated considerable efficacy in autoimmune disorders.[9] Tofacitinib, the inaugural FDA-approved Jakinibs for rheumatoid arthritis, has facilitated the treatment of other autoimmune illnesses.[9] Multiple other Jakinibs are undergoing clinical trials for ailments including psoriasis and inflammatory bowel disease.[9] In cancer treatment, targeting the JAK/STAT pathway has emerged as a viable option due to its role in fostering aggressive tumor traits.[320] STAT3 has

been recognized as a viable target for molecular therapies in many solid cancers.[320] The inhibition of JAK/STAT signaling has demonstrated promise in gastric cancer, squamous cell carcinoma, and ovarian cancer.[320] Notably, certain JAK inhibitors originally approved for autoimmune disorders are being investigated for their anti-tumor properties.[302] These pharmaceuticals have exhibited efficacy in both hematological and solid neoplasms.[302] Nevertheless, it is crucial to acknowledge that although JAK/STAT inhibition demonstrates potential in both autoimmunity and oncology, meticulous evaluation is required due to the pathway's intricate involvement in immune regulation and its possible dualistic impact on cancer progression.[6,304] Future treatments that are customized to each patient's unique genetic and molecular profile are also suggested by the expanding field of precision medicine and new discoveries into the molecular pathways behind JAK/STAT signaling.

Abbreviation

AD-HIES, Autosomal dominant hyperimmunoglobulin E syndrome; ALL, Acute lymphocytic leukemia; alpha-SMA, Alpha smooth muscle actin; AML, Acute myeloid leukemia; AUF-1, AU-binding factor 1/ AU-rich element RNA-binding protein 1; Blk, B-lymphoid tyrosine kinase; CCL5, Chemokine (C-C motif) ligand 5; CIS, Cytokine-induced SH-2 protein; CXCL11, C-X-C Motif Chemokine Ligand 11; EGF, Epidermal Growth Factor; EPO, Erythropoietin; EpoR, Erythropoietin Receptor; ET, Essential thrombocytosis; Fgr, Feline Gardner-Rasheed sarcoma viral oncogene homolog; Fra-1, Fos-related antigen 1; Fyn, Fyn-related kinase; G-CSF, Granulocyte Colony-Stimulating Factor; GF, growth factors; GH, Growth hormone; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; Gp130, Glycoprotein 130; GPCR, G Protein-Coupled Receptors; GSK3B, Glycogen synthase kinase 3 beta; GVHD, Graft-versus-host disease; HGF, Hepatocyte growth factor; HP1, Heterochromatin protein-1; IFNs, Interferons; IFN-γ, Interferon-γ; IL-6, Interleukin-6; ILs, Interleukins; IRF9, interferon regulatory factor 9; IRF9, Interferon Regulatory Factor 9; ISGF3, Interferon-Stimulated Gene Factor 3; JAKs, Janus kinases; LGL, Large granular Lymphocytic Leukemia; LPE, Lysophosphatidylethanolamine; Nmi, N-myc-interactor; PDGF, Platelet-Derived Growth Factor; PIASs, Protein Inhibitors of Activated STATs; PKCδ, Protein kinase C delta type; PMF, Primary myelofibrosis; PRL, Prolactin; PTTG1 Pituitary tumor-transforming gene-1; PV, Polycythemia vera; RA, Rheumatoid Arthritis; RANKL, Receptor activator of nuclear factor kappa-B ligand; RTKs, Receptor Tyrosine Kinases; SCID, Severe combined immunodeficiency; SDF-1, Stromal cell-derived factor 1; SFK, Src family tyrosine kinase; SH2, Src homology 2; SLE, Systemic Lupus Erythematosus; SOCSs, Suppressors of Cytokine Signaling; STAT, Signal Transducer and Activator of Transcription; StlP, stomatin-like protein; T-ALL, T-cell acute lymphoblastic leukemia; TGF-beta 1, transforming growth factor beta 1; TNF-R1, Tumor necrosis factor receptor 1; TNF-α, Tumor necrosis factor alpha; TPO, Thrombopoietin; TYKs, Tyrosine Kinases.

Data Sharing Statement

Available on request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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