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Review

Janus Kinase 3 (JAK3): A Critical Conserved Node in Immunity Disrupted in Immune Cell Cancer and Immunodeficiency

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Abstract: The Janus kinase (JAK) family is a small group of protein tyrosine kinases that represent a central component of intracellular signaling downstream from a myriad of cytokine receptors. The JAK3 family member performs a particularly important role in facilitating signal transduction for a key set of cytokine receptors that are essential for immune cell development and function. Mutations that impact JAK3 activity have been identified in a number of human diseases, including somatic gain-of-function (GOF) mutations associated with immune cell malignancies and germline loss-of-function (LOF) mutations associated with immunodeficiency. The structure, function and impacts of both GOF and LOF mutations of JAK3 are highly conserved, making animal models highly informative. This review details the biology of JAK3 and the impact of its perturbation in immune cell-related diseases, including relevant animal studies.

Keywords: cytokine; cytokine receptor; immunity; immunodeficiency; JAK3; leukemia

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1. Introduction

Cytokine receptor signaling represents a pivotal mode of cell-to-cell regulation that substantially impacts immune cell development and function [1]. Expressed on the surface of specific immune cell subsets, the activation of specific cytokine receptors by their respective cytokine can mediate an array of cellular responses, which can include lineage commitment, differentiation, proliferation, survival or functional activation [2]. Critical for transducing cytokine binding into the appropriate intracellular signals are protein tyrosine kinases (PTKs) called Janus kinases (JAKs) that are bound to the cytoplasmic domain of relevant cytokine receptors. Amongst these, the JAK3 protein is exclusive to a specific family of cytokine receptors that play multiple pivotal roles in immunity. Not surprisingly, therefore, mutations in JAK3 have been associated with a number of important immune cell diseases, with somatic gain-of-function (GOF) mutations identified in various immune cell malignancies and germline loss-of-function (LOF) mutations causative for severe combined immunodeficiency (SCID) [3]. This review describes the underlying biology of JAK proteins, and specifically the role of JAK3 in immune cell development and function. It then details how the JAK3 protein is disrupted by various mutations to mediate relevant immune cell diseases, including its cross-species conservation.

2. JAK Biology

2.1. Structure

The JAK protein family consists of four members in mammals: JAK1, JAK2, JAK3 and the alternatively named tyrosine kinase 2 (TYK2) [4]. Each of the JAK family members consists of the same unique structural architecture comprising four domains. At the N-terminus is a so-called four-point-one, ezrin, radixin, moesin (FERM) domain that lies in juxtaposition with a modified SRC homology 2 (SH2) domain that collectively facilitate

binding of the JAK protein to the cytoplasmic domain of relevant cytokine receptors. Adjacent to this lies a central pseudo-protein tyrosine kinase (pseudo-PTK) domain, which shows considerable homology to PTK domains but possesses no enzymatic activity and instead exerts a regulatory function on the protein. At the C-terminus, in contrast, is a classical PTK domain that provides the critical catalytic function for each JAK protein [5] (Figure 1A). This identical domain structure, with a high level of conservation at the amino acid level, is found in JAK proteins across a myriad of higher vertebrates [6].

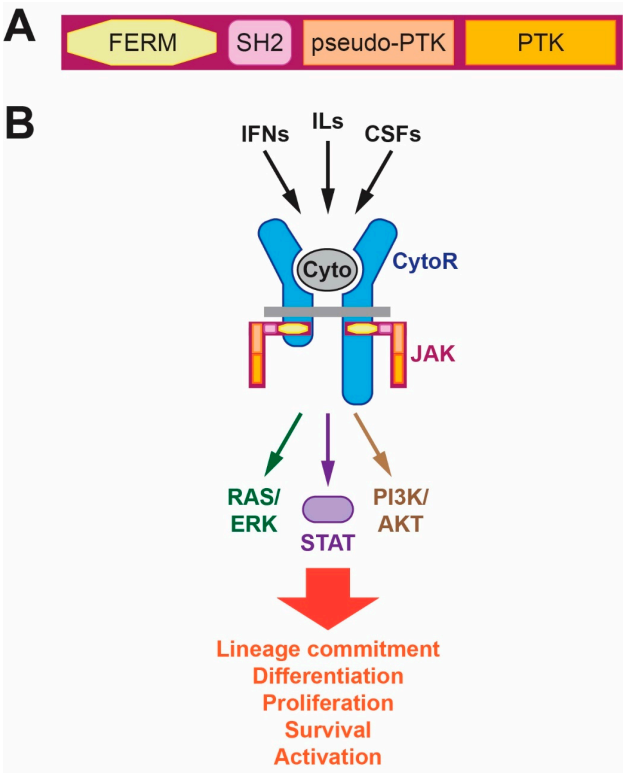

Figure 1. Structure and function of the JAK proteins. (**A**) Diagram of a JAK protein showing the four domains common in all family members: FERM (yellow), SH2 (pink), pseudo-PTK (fawn) and PTK (orange). (**B**) Schematic representation of major cytokine receptor signaling pathways, highlighting the key role for JAK proteins. Various cytokines (Cyto) bind to their specific cytokine receptor complex (CytoR) to activate associated JAK proteins that mediate extensive tyrosine phosphorylation that initiates multiple intracellular signaling pathways to facilitate a variety of cellular impacts. Abbreviations: AKT: Ak strain transforming; CSF: colony-stimulating factor; ERK: extracellular-regulated kinase; FERM: four-point-one, ezrin, radixin, moesin; IFN: interferon; IL: interleukin; PI3K: phosphatidyl inositol 3′-kinase; PTK: protein tyrosine kinase; RAS: rat sarcoma; SH2: SRC homology 2; STAT: signal transducer and activator of transcription.

2.2. Function

Cytokine receptor signaling plays a number of pivotal roles in development and homeostasis but with particularly important functions in the generation and function of blood and immune cells. The majority of these signal through JAK kinases associated with the membrane-proximal region of their cytoplasmic domains, which activate a variety of intracellular signaling pathways. These notably include the latent signal transducer and activator of transcription (STAT transcription factors but also include those involving the rat sarcoma/extracellular-regulated kinase (RAS/ERK) and phosphatidyl inositol 3-kinase/Ak strain transforming (PI3K/AKT) pathways [7–9]. Collectively, these pathways elicit the full gamut of cellular responses following cytokine receptor activation from lineage commitment and differentiation to cell proliferation and survival to functional activation (Figure 1B).

3. JAK3 and Its Role in Immune Development

3.1. Gene Expression

The human *JAK3* gene, located at 19p13.11, is unique amongst the four *JAK* genes in having restricted expression in hematopoietic cells, particularly within those belonging to the lymphoid compartment, although this also extends to certain myeloid cell populations [10,11]. The mouse *Jak3* gene similarly displays its highest expression in the thymus and spleen, which is elevated in double-negative thymocytes [12]. Zebrafish *jak3* has also been shown to be expressed in the embryonic thymus as well as adult hematopoietic and lymphoid tissues [13].

3.2. Role in Cytokine Receptor Signaling

The development and function of the various lymphoid lineages is largely driven by cytokines that act via the interleukin 2 receptor (IL-2R) cytokine receptor family, of which IL-2R, IL-4R type I, IL-7R, IL-9R, IL-15R and IL-21R are members [14]. Each of these cytokine receptor complexes possesses a unique ligand-specific chain, but shares a common signal transducing chain, called IL-2R gamma common (IL-2Rγc), and in some cases a third IL-2R beta (IL-2Rβ) chain [15,16]. JAK3 exclusively associates with the IL-2Rγc chain, whereas JAK1 associates with an alternate chain [17] (Figure 1B). JAK1 has been demonstrated to exert a dominant function over JAK3 with respect to signaling from these cytokine receptor complexes [18,19] with JAK3 playing a secondary but still important role. Collectively, these two JAKs activate multiple intracellular signaling pathways to mediate the appropriate cellular responses for each cytokine receptor. These include signal transducer and activator of transcription (STAT) proteins, principally STAT5 downstream of IL-2R, IL-7R, IL-9R and IL-15R, STAT6 downstream of IL-4R type I and STAT3 downstream of IL-21R, which in concert with other pathways [7–9] impacts specific cell lineages (Figure 2).

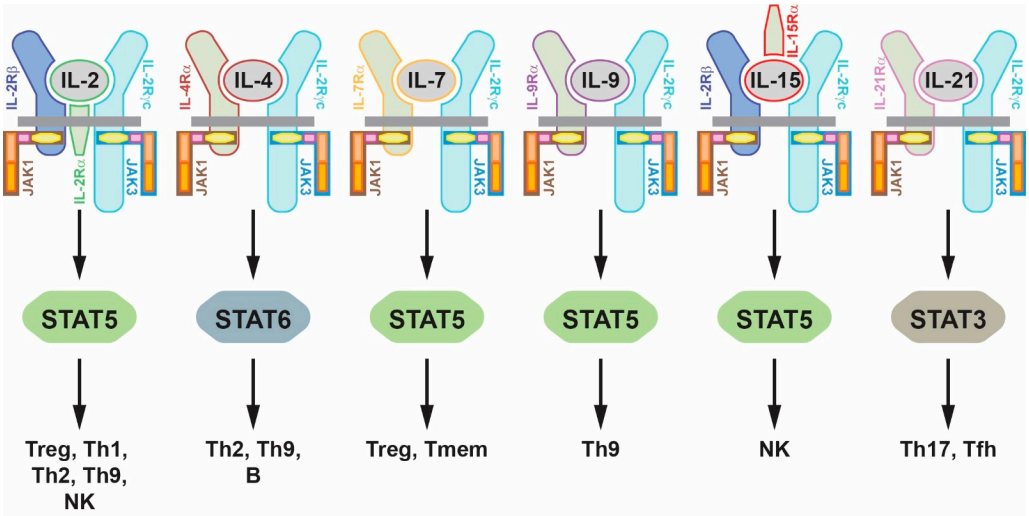

Figure 2. Central role for JAK3 in signaling via the interleukin 2 cytokine receptor family. Schematic representation of the cytokine receptor signaling complexes for the interleukin 2 (IL-2) family of cytokines (gray ellipses), including IL-2 (green edge), IL-4 (brown edge), IL-7 (orange edge), IL-9 (purple edge), IL-15 (red edge) and IL-21 (pink edge), with their respective ligand-specific chains (green, matching edges), the shared IL-2 receptor gamma common (IL-2Rγc) signaling chain (light blue), with an additional shared IL-2 receptor beta (IL-2Rβ) chain (dark blue) in two cases. Associated with the IL-2Rγc chain is JAK3 (blue edge) and associated with one of the alternative chains is JAK1 (brown edge). These cytokine receptor complexes activate multiple signaling pathways but particularly the indicated STAT proteins, STAT3 (brown), STAT5 (green) and STAT6 (blue). Below this is indicated the major cell lineage impacted by each cytokine receptor signaling complex. Abbreviations: IL: interleukin; NK: natural killer; Tfh: follicular helper T cell; Th: helper T cell; Tmem: memory T cell; Treg: regulatory T cell.

IL-2R stimulates T cell proliferation and is critical for regulatory T cell (Treg) development, promoting differentiation of the helper T cell (Th) populations Th1, Th2 and Th9 but antagonizing differentiation of Th17 and follicular helper T cell (Tfh) populations as well as mediating natural killer (NK) cell proliferation and enhancing B cell function. IL-4R type I also promotes Th2 and Th9 differentiation, but it additionally plays a major role in B cell differentiation, including immunoglobulin (Ig) switching, and macrophage differentiation. IL-7R stimulates the generation of Treg and memory T cell (Tmem) populations and contributes to overall T cell homeostasis. IL-9R is a major promoter of Th9 differentiation and also facilitates mast cell proliferation and mucus production. IL-15R is the principal mediator of NK cell development, proliferation and survival but also contributes to Tmem differentiation while antagonizing Th17 differentiation. Finally, IL-21R promotes Th17 and Tfh development and enhances the antitumor actions of lymphoid cells but antagonizes Th9 and B cell differentiation and Ig production [14,20].

4. JAK3 GOF Mutations in Immune Cell Cancers

4.1. Human Disease Specificity

Somatic JAK3 GOF mutations have been identified in the context of a diverse spread of human immune cell cancers. These mutations are most significant across a range of T cell malignancies, notably including T cell acute lymphoblastic leukemia (T-ALL) [21–23], cutaneous T cell lymphoma (CTCL) [7,24], early T cell precursor acute lymphoblastic leukemia (ETP-ALL) [25], NK/T cell lymphoma (NKTCL) [26], T cell prolymphocytic leukemia (T-PLL) [27,28] and enteropathy-associated T cell lymphoma (EATL) [29]. Germline JAK3 GOF mutations have also been identified in the context of familial chronic lymphoproliferative disorder of NK cells (CLPD-NKs) [30]. JAK3 has further been observed to be constitutively activated in a range of lymphoid malignancies even when not mutated, such as a cohort of peripheral T cell lymphoma (PTCL) patients positive for ALK [31], underpinning its central role in T cell malignancies.

Somatic JAK3 GOF mutations have also been identified in cancers affecting other hematopoietic cell lineages, such as acute megakaryoblastic leukemia (AMKL) [32–34], juvenile myelomonocytic leukemia (JMML) [35] and B cell precursor acute lymphoblastic leukemia (BCP-ALL) [36]. A large number of JAK3 mutations have additionally been found in a variety of solid tumors, most notably including lung cancer [37] and high-grade serous ovarian cancer [38]. Analysis of TCGA Research Network data additionally revealed the mutations in solid tumors to be a mix of GOF, LOF and likely benign. *JAK3* copy number changes were also evident with copy number gain most prevalent in adenoma/adenocarcinoma, ovarian cancer and glioblastoma, while copy number loss was highest in cancers of the bronchus and lungs.

4.2. Mode of Action

A large number of mutations in JAK3 have been identified in immune cell cancers, the majority being within the pseudo-PTK and PTK domains, with the most common being M511I, A573V and R657A in the pseudo-PTK domain, although no clear correlation of specific mutations with cancer type has been identified [39] (Figure 3). A JAK3–INSL3 fusion transcript has also been reported in CTCL [40]. JAK3 GOF mutations have been collectively found to result in constitutive tyrosine-phosphorylation and the ability to elicit factor-independent growth of relevant cell lines [26,32,41]. As such, these mutations are typically thought of as bypassing normal control mechanisms leading to the chronic activation of pathways normally activated downstream of those cytokine receptor complexes with which JAK3 typically interacts [41,42]. However, so-called 'non-canonical' mechanisms have also been identified with JAK3 GOF proteins found in the nucleus of CTCL cells where they could phosphorylate histone H3 and interact with RNA polymerase III [43].

4.3. Animal Models

The transplantation of mouse bone marrow cells overexpressing human JAK3 A572V into lethally irradiated mice produced a lymphoproliferative disorder with megakaryocytic hyperplasia [7]. Both this and another pseudo-PTK domain mutant, JAK3 M511I, were also shown to induce a transplantable T-ALL-like disease with long latency, which was characterized by the ligand-independent proliferation of T cells, while the PTK domain mutant L857Q displayed splenomegaly and lymphadenopathy without the peripheral increase in T cells [41]. A mouse knock-in model that expressed an A572V mutant of mouse Jak3 from its native promoter exhibited a much milder disease with CD8+ T cells expanding over time and evidence of minor skin pathology [17]. A zebrafish Jak3 A573V knock-in mutant also showed enhanced lymphopoiesis over the lifespan, with a sustained elevation of T and NK cells, but not B cells [44]. No evidence of malignancy was identified in either study [17,44], consistent with JAK3 GOF mutations being able to cause a mild lymphoproliferative disorder rather than overt leukemia, which requires additional genetic events.

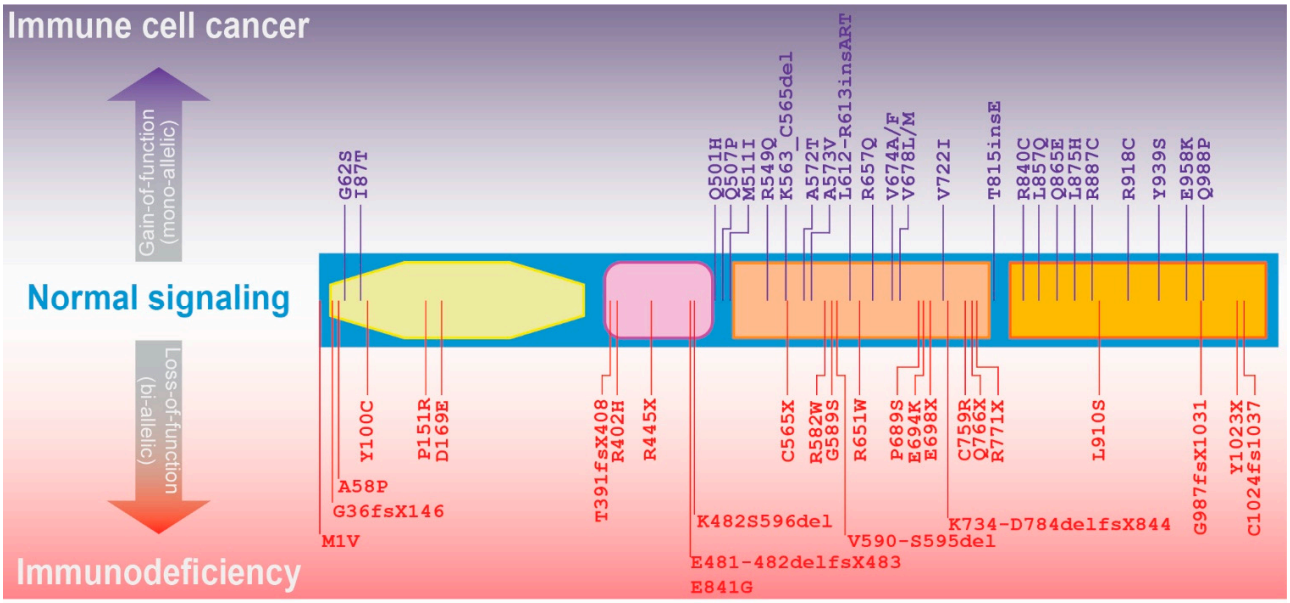

Figure 3. JAK3 mutations associated with immune cell diseases. Schematic of the JAK3 protein and its constituent FERM (yellow), SH2 (pink), pseudo-PTK (fawn), and PTK (orange) domains, showing representative gain-of-function mutations (purple, above), typically mono-allelic and somatic, associated with immune cell cancers, and loss-of-function (red, below) mutations, typically bi-allelic and germline, associated with immunodeficiency [45–58].

4.4. Interactions with Other Genes and Mutations

JAK3 GOF mutations typically do not act autonomously, with other signaling components critically needed to facilitate their cellular effects. Amongst these, the IL-2Rγc chain has been shown to be required for both downstream signaling and factor-independent growth mediated by JAK3 GOF mutants [59], with both IL-2Rγc and JAK1 needed for the maximal activation of downstream signaling proteins, including STAT5 phosphorylation [19,41,42]. The kinase activity of JAK1 has been demonstrated to be essential to facilitate this [18,19,42] with JAK1 proteins being constitutively activated in the presence of JAK3 mutants [42,47]. STAT5 proteins have also been shown to be constitutively activated by JAK3 GOF mutants [42,47]. Genetic analyses in animal models have confirmed the importance of these other pathway components. Thus, both IL-2Rγc and JAK1 were found to be essential for zebrafish Jak3 A573V to mediate embryonic T cell expansion [44] with a similar result observed for IL-2Rγc in the context of the mouse Jak3 A572V knock-in

model [17]. Zebrafish Jak3 A573V also caused an overactivation of the Stat5.1 protein, which contributed to the increase in embryonic T cells [44]. It has been suggested that the presence of wild-type JAK3 suppresses the effects of JAK3 GOF mutants, explaining why patients are often homozygous or compound heterozygous for JAK3 mutations [47,60]. However, zebrafish carrying two copies of the Jak3 A573V allele displayed similar impacts on lymphopoiesis as those with a single copy, although homozygote mutants did exhibit reduced survival [44]. Importantly, some JAK3 mutants, particularly those involving the PTK domain such as L857P and Q988P, did not show dependence on JAK1 [41,49].

In terms of their role in the etiology of human immune cell cancers, evidence suggests that JAK3 GOF mutations act as 'disease driver' mutations within the context of T cell malignancies, with 'co-operating' mutations essential for JAK3-mediated leukemic transformation [22,27,41]. A number of classes of co-operating mutations have been identified, which include transcription factors, epigenetic regulators and other signaling components as well as chromosomal aberrations that likely impact multiple genes (Table 1).

Table 1. Examples of JAK3 co-operating gene mutations.

Functional Class	Protein	Mutation Type	Disease	References
Transcription factor	RUNX1	LOF	ETP-ALL	[61]
	HOXA9	GOF	T-ALL	[62]
Epigenetic modifier	PHF6	LOF	T-ALL	[63]
	SUZ12	LOF	T-ALL	[64]
Signaling component	JAK1	GOF	T-PLL	[27,65]
	STAT5B	GOF	T-ALL, EATL	[29,60]
Multiple	Various on chromosome 21	↑ copy no. (trisomy)	CTCL	[17]

Abbreviations: CTCL: cutaneous T cell lymphoma; EATL: enteropathy-associated T cell lymphoma; ETP-ALL: early T cell precursor acute lymphoblastic leukemia; GOF: gain of function; LOF: loss of function; T-ALL: T cell acute lymphoblastic leukemia; T-PLL: T cell prolymphocytic leukemia; ↑: increased.

Several hematopoietic transcription factors have been found to co-operate with JAK3 GOF mutations across a range of leukemia types. These commonly include RUNX1 LOF mutations [61] and HOXA gene overexpression [62]. Thus, around one-quarter of T-ALL patients harboring JAK3 GOF mutations also possessed RUNX1 LOF mutations, with co-mutation enriched in the ETP-ALL cohort, while JAK3 GOF and RUNX LOF mutations synergized in a murine T-ALL model [61]. In contrast, the overexpression of *HOXA* genes, particularly *HOXA9*, has been observed concurrently with JAK3 GOF mutations in T-ALL with *HOXA9* overexpression co-operating with the JAK3 M511I mutation to elicit a short latency, aggressive leukemia in mice [66]. This correlated with enhanced STAT5 transcriptional activity and the co-occupation of similar genomic loci with HOXA9 [66]. JAK3 GOF mutations are also associated with LOF mutations of epigenetic regulators, such as PHF6 [63] and SUZ12 [64]. In T-ALL, over 40% of patients with JAK3 GOF mutations also possessed PHF6 LOF mutations, with this cohort showing reduced survival, while PHF6 inactivation in mice accelerated cell transformation mediated by JAK3 M511I, inducing an aggressive form of leukemia [63]. SUZ12 LOF mutations have also been associated with JAK3 in T-ALL with an ablation of SUZ12 co-operating with JAK3 M511I to drive transformation in a mouse pro-T cell ex vivo model [64]. Mutations in other signaling components additionally co-operate with JAK3 GOF mutations. Principal amongst these are concurrent JAK1 GOF mutations observed in several T cell malignancies [22,23,26,27,29,39]. JAK1 GOF and JAK3 GOF mutations have been shown to synergize in vitro [18] with concurrent mutations increasing downstream STAT5 activation [65]. STAT5B GOF mutations have also been identified concurrently with JAK3 GOF mutations in ALL [23,60] and EATL [29]. Concurrent GOF mutations in other signaling proteins, such as IL-7RA [22] and RAS pathway components [29], may also be important. However, such associations exhibit cell lineage

specificity, with mutations in JAK3, JAK1 and STAT5B reported to be mutually exclusive in T-PLL, for example [28,48]. Finally, JAK3 GOF mutations were initially identified in the context of Down syndrome-associated AMKL [32,33]. Subsequent experiments in a mouse Jak3 A572V knock-in line have demonstrated that partial trisomy 21 enhanced the aggressiveness of cutaneous T-cell lymphoma (CTCL)-like phenotypes, making it a fully penetrant, lethal disease [17].

In the context of other malignancies, JAK3 GOF mutations are believed to represent co-operating mutations. Thus, in B cell malignancies, they act in concert with alternative disease driver mutations, including PAX5 fusions [67], SPI1 deletions [68] and IRF4 deficiency [36]. In JMML, they also act in concert with alternative disease driver mutations to contribute to disease progression, being associated with poor clinical outcomes [35].

4.5. Therapeutic Approaches

A variety of small molecule inhibitors targeting JAK proteins have been developed that are applicable to JAK3 GOF-mediated disease [69,70], although the viability of JAK3-specific inhibitors has been questioned due to the dominant role played by JAK1 in signal transduction [18], and so attention has focused on pan-JAK inhibitors. Ruxolitinib, which targets only JAK1 and JAK2 and is approved for use in myeloproliferative neoplasms [71], has displayed effectiveness against JAK3 pseudo-PTK domain GOF mutations [72]. However, it has proven less effective in PTK domain mutants, such as Q988P, which are more sensitive to JAK3-specific inhibitors [42,49]. Moreover, the use of Ruxolitinib to treat JAK1 GOF mutations has been shown to expand clones containing JAK3 mutations [39]. Tofacitib, which targets JAK3 as well as both JAK1 and JAK2, and is approved for use in rheumatoid and psoriatic arthritis and ulcerative colitis [71], has been shown to be highly effective in cell line models of various JAK3 GOF mutations [26,42,73,74]. Notably, phosphoproteome analysis revealed that STAT5 phosphorylation was the most impacted by both Tofacitib and Ruxolitinib, but this was highest for Tofacitib [74]. Tofacitib was also impactful in lymphocyte expansion in both mouse Jak3 A572V [17] and zebrafish Jak3 A573V [44] models. Furthermore, efficacy for this drug has been demonstrated in relevant human clinical trials [75]. A JAK3 inhibitor, PRN371, was shown to be effective in NKTL cell lines and mouse models [76]. The JAK3/TEC-selective inhibitor PF-06651600, being trialed for several inflammatory bowel and dermatological diseases [71], also has potential. JAK3 inhibitors have also proven effective in cases of PTCL in which JAK3 is constitutively activated but not mutated [31]. Of note, co-operating JAK1 and JAK3 mutations are associated with enhanced resistance to JAK inhibitors generally [65], suggesting the need for alternative strategies. Of relevance, potential synergy has been noted between JAK inhibitors and inhibitors of other pathways, including MEK and BCL2 [47].

5. JAK3 LOF Mutations in Immunodeficiency

5.1. Human Disease Specificity

JAK3 LOF mutations cause an autosomal-recessive form of severe combined immune deficiency (SCID), comprising approximately 5% of total SCID [77]. SCID is associated with defects in T cell differentiation leading to low numbers of mature T cells, being defined as $<0.05 \times 10^9$ autologous T cells/L [78]. This results in disease symptoms characterized by recurrent respiratory tract infections, pneumonia meningitis and failure to thrive with patients typically presenting with hypogammaglobulinemia [79]. There is an extremely high risk of severe, disseminated infections following live-attenuated vaccine inoculation that often proves fatal, particular the Bacille Camette–Guerin (BCG) vaccine based on *Mycobacterium bovis* [80].

5.2. Mode of Action

Close to 100 different SCID-causing JAK3 mutations have been identified, most of which directly impact the coding region [77,78], although rare mutations impacting splicing have also been described [81]. These can affect all domains of the JAK3 protein but

particularly in the pseudo-PTK domain, including a large number that lead to truncations of the encoded protein (Figure 3). These JAK3 LOF mutations impair signaling from the suite of IL-2Rγc-utilizing receptors, which results in the severe impacts across all lymphoid lineages [51,82]. Moreover, patients harboring these mutations present with lymphoid tissue hypoplasia as a consequence of severely reduced T and NK cells, and while B cells are generated, their functionality is compromised [83,84]. Patients with hypomorphic mutations, such as the missense E481G mutation with the SH2 domain, typically harbor a milder SCID phenotype [85]. Somatic JAK3 mutations have also been identified in cases of NK cell enteropathy [57].

5.3. Animal Models

Jak3 LOF mice also possessed severely reduced numbers of B and T cells [86] as well as specific innate lymphoid populations including NK cells [87]. They further exhibited impaired myelopoiesis that impacts the differentiation of both monocytes and neutrophils [88]. Zebrafish Jak3 LOF mutants displayed a severe reduction in T cells during embryonic hematopoiesis [13,89], while in adults both T and NK cells were decreased [13,90], with evidence of disrupted B cell development as well [13]. These Jak3 LOF mutants additionally developed an invasive lymphoid leukemia during adulthood suggesting that tumor immunity was abrogated, consistent with the reduced NK cells observed, and also showed perturbed neutrophil homeostasis with circulating numbers increased at the expense of those in the kidney [13].

5.4. Treatment of JAK3-Mediated SCID

Hematopoietic stem cell (HSC) transplantation is curative for SCID patients with JAK3 LOF and other related mutations [91], but while it represents an effective means to reconstitute T cell immunity but is less effective for B cells and NK cells [79]. Transplant recipients display defects in mucosal immunity with nasophyrangeal dysbiosis over the long term, although immunoglobulin replacement therapy can aid with these presentations [92]. Pre-transplant conditioning can improve outcomes, with patients exhibiting increased CD4+ T cells and B cells, obviating the need for IgG replacement therapy [93]. Gene therapy of HSC using induced pluripotent stem cell (iPSC) technology is an attractive alternative option, but a number of significant hurdles remain [94].

6. Wider Pathway Conservation

The conservation observed with respect to the JAK3 structure, function and role in pathogenesis also extends to other relevant cytokine receptor signaling components [2,6]. For example, patients with LOF mutations in the human IL2Rγc-chain presented with X-linked SCID (X-SCID) [95]. Il-2rγc knockout mice also developed SCID, albeit more severe with B cell numbers additionally decreased [86,96], whereas an ablation of Il-2rγc in zebrafish resulted in T−B+NK−SCID similar to humans [97]. Furthermore, patients harboring LOF mutations in the IL-7 receptor alpha (IL-7Rα) chain display a T-B+NK+ SCID phenotype [98,99]. Mice with IL-7Rα deficiency again possessed a more severe SCID that included B cell involvement [100,101]. Zebrafish carrying an inactivating mutation of Il-7rα exhibited reduced T cells, but unaffected B cells, again similar to humans, with NK cells not characterized in this study [89]. STAT5B-deficient humans also displayed immunodeficiency and growth defects [102], which closely resembled those observed in Zebrafish Stat5.1 LOF mutants [103]. In contrast, an activating zebrafish Stat5.1 N649H mutant impacted both lymphoid and myeloid lineages [104], replicating features of the STAT5B N649H-mediated disease observed in mice [105]. This high conservation makes animal models particularly suited to explore JAK3 biology, pathology and potential therapeutic strategies.

7. Conclusions

JAK proteins were named after the two-faced Roman god Janus based on structural considerations, since they possessed pseudo-kinase and kinase domains in juxtaposition, However, this eponym has also proven apt with respect to both its normal function and role in disease. For Janus is additionally the god of gates, with JAK3 representing the gatekeeper controlling the transition between inactive and active states for cytokine receptor signaling, but also the god of beginnings and ends, with JAK3 LOF mutations preventing cytokine receptor signaling from commencing, while JAK3 GOF mutations interfere with its termination. The conservation of this gatekeeper and those signaling components with which it interacts has allowed animal models to act as key platforms to understand JAK3 biology and pathology with considerable future promise for the development of treatment strategies for relevant diseases. For example, there are clear opportunities to use the zebrafish Jak3 LOF model to further understand the role of JAK3 in neutrophil homeostasis and susceptibility to lymphoid malignancy with the JAK3 GOF model amenable to investigating co-operation with other genes as well as pharmacological testing. Conversely, the zebrafish JAK3 LOF model can be applied as a xenotransplantation platform to examine JAK3 GOF-mediated cancers in a patient-specific manner, underpinning the development of patient-centered therapeutic approaches.

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