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Review article

The promise of Janus kinase inhibitors in the treatment of hematological malignancies

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ABSTRACT

The Janus kinases (JAK) are a family of kinases that play an essential role in cytokine signaling and are implicated in the pathogenesis of autoimmune diseases and hematological malignancies. As a result, the JAKs have become attractive therapeutic targets. The discovery of a JAK2 point mutation (JAK2 V617F) as the main cause of polycythemia vera lead to the development and FDA approval of a JAK1/2 inhibitor, ruxolitinib, in 2011. This review focuses on the various JAK and associated components aberrations implicated in myeloproliferative neoplasms, leukemias, and lymphomas. In addition to ruxolitinib, other JAK inhibitors are currently being evaluated in clinical trials for treating hematological malignancies. The use of JAK inhibitors alone or in combination therapy should be considered as a way to deliver targeted therapy to patients.

Contents

1. Introduction

The differentiation, proliferation, survival, and immune functions of hematopoietic cells are regulated by cytokines which bind to their appropriate cell surface receptor. Some important cytokine receptors, however, lack intrinsic kinase activity and thus rely on a family of tyrosine kinases called Janus Kinases (comprised of 4 members JAK1, JAK2, JAK3, and TYK2) that associate with the cytoplasmic tail of the receptor [1,2]. Following the binding of a cytokine to its receptor, JAKs autophosphorylate and transphosphorylate other proteins. JAKs phosphorylate sites on the cytokine receptor cytoplasmic tails, which create docking sites for signaling

Abbreviations: JAK, Janus kinase; STAT, signal transducers and activators of transcription; EPOR, erythropoietin receptor; TPOR, thrombopoietin receptor; G-CSFR, granulocyte colony stimulating factor receptor; γc, common gamma chain; SCID, severe combined immunodeficiency; ALL, acute lymphoblastic leukemia; AML, acute myeloleukemia; RA, rheumatoid arthritis; TNFα, tumor necrosis factor alpha; MPN, myeloproliferative neoplasm; PV, polycythemia vera; PMF, primary myelofibrosis; ET, essential thrombocythemia; CML, chronic myelogenous leukemia; ETP, early T cell precursor ALL; Ph, Philadelphia chromosome; CRLF2, cytokine receptor-like factor 2; TSLP, thymic stromal lymphopoietin; IgH, immunoglobulin heavy chain; DS-ALL, Down's Syndrome ALL; ML-DS, Down's Syndrome ALL; PMBL, primary mediastinal B-cell lymphoma; HL, Hodgkin's Lymphoma; PDX, patient derived xenograft.

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effectors, principally the signal transducers and activators of transcription (STATs). The STATs are then phosphorylated, resulting in nuclear translocation. The STAT family of proteins play critical roles in regulating gene expression. JAKs play important roles in erythroid, myeloid and lymphoid cells. In the erythroid lineage, JAK2 associates with the erythropoietin receptor (EPOR), and in the myeloid lineage with the thrombopoietin receptor (TPOR) and granulocyte colony stimulating factor receptor (G-CSFR). In lymphoid cells, JAK1 mainly associates with the cytokine chain (IL2, IL4, IL7, IL9, IL15, IL21), and JAK3 associates with the common gamma chain (γc) to result in a fully functional cytokine receptor heterodimer [3].

The significance of JAKs in hematopoietic function is clear when these kinases are deleted. JAK1 and JAK2 deletions have been shown to be embryonic lethal; loss of JAK1 results in defective neural and lymphoid development, while the loss of JAK2 effects erythropoiesis [4]. JAK3 mutations cause severe combined immunodeficiency (SCID), resulting in patients who lack T cells and NK cells, largely due to IL-7 and IL-15 receptor loss of function [2,5,6].

The finding that loss of JAK3 results in SCID highlights the necessity of this kinase in immune function. However, while cytokine signaling is critical for immune cell function, their aberrant function is also implicated in the pathogenesis of autoimmune diseases and hematopoietic malignancies. Since JAK3 is immediately downstream of many cytokine receptors, this kinase became an attractive therapeutic target for treating autoimmune and organ transplant patients. Furthermore, since JAK3 is only expressed in a few cell types, inhibiting or downregulating its expression had the potential to be less toxic than other broad immunosuppressants [4]. The interest in using JAK inhibitors to treat hematological malignancies originated with the discovery that the underlying cause of polycythemia vera in over 95% of patients is due to a single point mutation in JAK2 (JAK2 V617F) which renders the enzyme hyperactive and cytokine-independent. Since then, mutations in components of the JAK/STAT pathway (IL7R, CRLF2, JAK1, JAK2, or JAK3) have been discovered in other hematological malignancies such as acute lymphoblastic leukemia (ALL), acute myeloleukemia (AML), and lymphomas (Table 1). Due to these discoveries, the idea of using JAK inhibitors as a monotherapy or in combination with other chemotherapies is becoming an attractive option in this era of precision medicine. Using a targeted therapy approach could hopefully cure patients with various mutations that historically have a poor prognosis. This review will aim to highlight common JAK/STAT pathway mutations in hematological malignancies, where a JAK inhibitor may be useful in the treatment regimen.

Table 1
Genetic aberrations affecting the JAK/STAT pathway in hematological malignancies.

Gene	Aberration	Disease	Refs.
IL7Rα	Gain-of-function amino acid insertions (containing cysteine and proline)	Pediatric T-ALL ETP B-ALL	[42,43,46]
IL7Rα	Gain-of-function mutations not containing cysteine	Pediatric ALL	[45]
CRLF2	IgH-CRLF2 translocation	B-ALL	[55–57,59]
CRLF2	P2RY8-CRLF2 translocation	B-ALL DS-ALL	[55,56,59]
CRLF2	F232C	B-ALL	[57,59]
JAK1	S703I, I631>RGI	ETP	[46]
JAK1	S512L, A634N, R724H, R879S, R879C, R879H	Adult T-ALL	[49]
JAK1	L624_R629>W, S646F, and V658F	B-ALL	[52]
JAK2	V617F	Polycythemia vera Essential thrombocythemia Primary myelofibrosis	[20–23]
JAK2	TEL-JAK2 translocation	Pediatric T-ALL	[41]
JAK2	R683G, R683S, I682F, QGinsR683 R683K, L681-I682ins, I628del	B-ALL DS-ALL	[52,61–63]
JAK2	V617F, L611S, R683S, R867Q	ML-DS	[76]
JAK2	Amplification of chromosome 9p24	Primary Mediastinal B cell lymphoma Hodgkin's Lymphoma	[78,79]
JAK3	M511I, A573V	ETP	[46]
JAK3	S197N, M511I, R657Q, P664L, L857P, K885E, E960A Frame shift deletion at 958	Adult T-ALL	[51]
JAK3	S789P	B-ALL	[52]
JAK3	A572V, A573V	Natural Killer/T cell lymphoma	[77]

2. Tofacitinib and Ruxolitinib-two FDA approved JAK inhibitors

The idea of creating JAK inhibitors to treat immune diseases was initiated for rheumatoid arthritis (RA) therapy. RA is generally treated with monoclonal antibodies, particularly anti-tumor necrosis factor (TNFα) antibodies that block cytokine and cytokine receptor activity. The possibility to treat autoimmune diseases with a JAK inhibitor was initially realized in 1995 [5,7]. The concept of targeting JAKs for the treatment of chronic autoimmune diseases had several advantages over other biologics such as monoclonal antibodies. TNF inhibitors are a popular therapeutic option for rheumatoid arthritis, psoriasis, and inflammatory bowel disease, but patients often need to take drugs for decades to control the disease. Many patients do not want to receive injections or intravenous therapy; research has shown that only 50% of rheumatoid arthritis patients are still receiving monoclonal antibody treatment after two years [8]. JAK inhibitors, on the other hand, are taken orally. Tofacitinib, a JAK1 and JAK3 inhibitor, was FDA approved in 2012 for the treatment of rheumatoid arthritis. Tofacitinib is currently being explored for use in alopecia areata, psoriasis, and ulcerative colitis. The use of tofacitinib to treat autoimmune disorders is outside the scope of this review and will not be discussed here.

The discovery of the JAK2 V617F mutation in myeloproliferative neoplasms (MPN) opened up new roles for JAK inhibitors, especially in the treatment of hematological malignancies. Ruxolitinib, a JAK1 and JAK2 inhibitor, was FDA approved in 2011 for the treatment of myelofibrosis. Ruxolitinib is a competitive inhibitor of the ATP binding site on kinase domain. In a first-in-human pharmacodynamics study, ruxolitinib was shown to inhibit STAT3 phosphorylation in a dose- and time-dependent manner; maximal inhibition of STAT3 occurred within 1–2 h following a single oral dose of the drug [9]. In a Phase I/II study with JAK2V617F positive and negative myelofibrosis (PMF) patients, the maximum tolerated dose was determined to be 25 mg twice a day or 100 mg once a day; the dose is limited by reversible thrombocytopenia [10]. Following a single oral 24 mg dose, ruxolitinib is rapidly and efficiently absorbed, reaching peak plasma concentrations within 2 h. The drug has a relatively short half-life of about 3 h. Healthy volunteers receiving a single dose of ruxolitinib excrete approximately 70% of metabolized compound within 24 h, mostly through the urine. After ten days of dosing, it was determined that very little of the parent compound or metabolites accumulate in the body [9,11]. Clinical efficacy of ruxolitinib in trials with myelofibrosis patients will be discussed below.

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