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Commentary

Multifacet role of JAKs in chronic myeloid leukemia

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Abstract: The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is an essential cell signaling system that plays a significant role in the production of blood cells and regulates the growth, differentiation, and function of immune cells. Numerous hematological disorders can result from mutations that target this system, which can cause an excess of these cell types. This commentary perspectives JAKs in leukemia and also in chronic myeloid leukemia. This commentary also covers the relevant mutations and drug-targets for JAKs as well as the current therapeutic strategies for preventing constitutive, cytokine-independent pathway activation.

Keywords: JAKs; leukemia; chronic myeloid leukemia (CML)

1. Introduction

Janus kinases (JAKs) are essential modulators of immunological responses, gene expression, cell proliferation, and differentiation that transduce signals from hundreds of extracellular cytokines. Many human diseases, such as different forms of leukemia, other cancers, and autoimmune disorders, are mostly caused by the dysregulation of JAK/STAT signaling. All four JAKs (JAK1, JAK2, JAK3, and TYK2) have genomic abnormalities in various leukemia types; these abnormalities are primarily activating somatic mutations and, less frequently, translocations that result in constitutively active JAK fusion proteins[1-8]. The FDA has already approved six JAK inhibitors for the treatment of autoimmune disorders and hematological malignancies, demonstrating the importance of JAKs as therapeutic targets. Nevertheless, the existing medications' effectiveness is subpar, and JAK modulators' full potential in leukemia has not yet been realized. Discussing JAK inhibitors used in clinics and in clinical development, as well as the dysregulation of JAK-STAT signaling that underlies the etiology of leukemia—that is, mutations and other causes generating hyperactive cytokine signaling—may be of interest.

Cytokine signaling maintains the balance of various cell types in normal and stress conditions and controls the growth, development, and maintenance of cells throughout hematopoiesis. Janus kinase (JAK) is used by the majority of cytokine receptors that regulate hematopoiesis to initiate downstream cellular signaling. Signal transducers and activators of transcription (STAT) (STAT1-6) transcription factors, cytokine-specific gene responses, and receptor-associated JAKs are all activated when ligands bind to cytokine receptors. In addition to hematopoiesis, the JAK-STAT pathway is involved in a number of important biological processes, including tissue and immunological development, inflammatory responses, and embryogenesis. To guarantee both low tyrosine kinase activity in the absence of cytokines and effective and brief activation following extracellular cytokine stimulation, the JAK-STAT pathway needs to be strictly regulated. Numerous autoimmune disorders and cancers have been linked to abnormal JAK/STAT pathway regulation. As of right now, over 100 distinct JAK mutations have been connected to various forms of leukemia, proving the involvement of JAKs in leukemogenesis and offering support for therapeutic targeting of these proteins[6, 7, 9-12].

Two of the six JAK inhibitors currently licensed for clinical use—ruxolitinib and fedratinib—have indications for myeloproliferative neoplasms. With the ultimate goal of creating disease-specific inhibitors, the continuous development of novel JAK inhibitors aims for increased compound selectivity and potency. The development of next-generation JAK inhibitors requires a better knowledge of JAK regulation and its functions in immune response and cancer. JAKs are non-receptor tyrosine kinases that mediate signaling from about 60 cytokines and hormones by constitutively attaching to the cytoplasmic area of cytokine receptors. With the exception of JAK3, which is mostly expressed in hematopoietic cells, all four of the mammalian JAKs (JAK1–JAK3 and TYK2) are widely distributed. The four domains that make up the JAKs are the pseudokinase domain (JAK homology-2 [JH2]), the C-terminal kinase domain (JH1), the SH2-like domain, and the N-terminal FERM (4.1 protein, ezrin, radixin, and moesin) domain. JAKs are connected to the cytokine receptor juxtamembrane Box1 and Box2 sections by the FERM and SH2 domains. The JH2 domain is a crucial regulatory domain that binds ATP but has little to no catalytic activity. The active tyrosine kinase domain that

phosphorylates substrates is the JH1 domain. The properties of the interacting cytokine receptor dictate the function and downstream signaling cascades that are triggered by distinct JAKs. The cytokine receptors can form heterodimers (different subunits, such as receptors for interleukin 12 [IL12Rβ1, IL12Rβ2] and interferon γ [IFNGR1 and IFNGR2]) or homodimers (same receptor subunits, such as receptors for erythropoietin [EPOR] and growth hormone [GHR], etc.). Whereas homodimeric receptors exclusively bind JAK2, heterodimeric receptors contain two distinct JAK family members (e.g., JAK2 and TYK2). A cytokine's binding to the cytokine receptor's extracellular region starts signal transduction, which causes the receptor to rearrange and/or dimerize. The corresponding JAKs also change conformation, which causes the kinase domains to become transphosphorylated and kinase activity to be stimulated[1, 2, 4, 12-21].

Hematopoietic stem cells (HSCs) undergo a multi-step process of differentiation into various blood cell types driven by cytokines. The majority of hematopoietic cytokines use JAK-mediated signaling to control the survival, maintenance, differentiation, and proliferation of hematopoietic cells, however signaling during hematopoiesis involves a number of receptor tyrosine kinases, including c-Kit, CSF-1R, and FLT-3. Blood cells must be continuously regenerated due to their limited lifespan. Hematopoiesis is therefore our body's most active biological activity. The differentiation of pluripotent HSCs in bone marrow initiates the process. Conditional JAK2 knockout mice exhibit a rapid loss of HSCs, resulting in bone marrow failure and death, demonstrating the critical role that JAK2 plays in the maintenance and function of HSCs. JAK2 is linked to the thrombopoietin receptor (TPOR or MPL) and plays a role in the control of megakaryocytes in platelet formation as well as early hematopoiesis[2, 22-25]. JAK2 is the primary signaling mediator in the differentiation of cells of the myeloid lineage since it is also linked to EPOR, granulocyte/macrophage colony-stimulating factor receptor (GM-CSFR), granulocyte colony-stimulating factor receptor (G-CSFR), IL-3R, and IL-5R. Different interleukins direct the development of the lymphoid lineage, and their signaling mostly happens through the so-called common γc chain receptors for IL-2, IL-4, IL-7, IL-15, and IL-21, where JAK1 binds to the cytokine-specific receptor chain and JAK3 binds to the γc chain. Interferon (IFN) receptors with JAK1/JAK2 in IFN-γ and JAK1/TYK2 combos in IFN-α/β play a role in inflammation and immunological response, but they also help HSCs proliferate and self-renew. The exact function of JAKs linked to IFNα and IFNγ receptors in leukemia and hematopoiesis is yet unknown, though.

Given the critical role that JAKs play in the growth and operation of hematopoietic cells, it is not unexpected that leukemia frequently contains mutations in JAK1, JAK2, and JAK3. Leukemia may be caused by germline mutations in TYK2, despite the fact that somatic point mutations more rarely affect TYK2. Acute myeloid and lymphocytic leukemia (AML and ALL, respectively), chronic lymphocytic and myeloid leukemia (CLL and CML, respectively), myeloma, and lymphoma have all been associated with JAK mutations. The most prevalent childhood cancer, ALL, is the one where JAK mutations are most commonly detected. Either immature B cells or T cells undergo change to cause ALL. About 85% of ALL cases are B-ALL, which has a better prognosis than T-ALL, which has a worse prognosis, particularly in adults. While abnormal JAK2-signaling mostly impacts myeloid lineage, JAK1 and JAK3 are frequently associated with disorders of lymphoid origin (i.e., ALL). Myeloproliferative neoplasms (MPNs), a class of disorders marked by aberrant proliferation of hematopoietic progenitor cells in the bone marrow, are primarily caused by hyperactivating JAK2 mutations. MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF), which can develop into AML. CML is distinguished by the BCR-ABL1 translocation, also known as the Philadelphia chromosome. Myelofibrosis (MF) or, less commonly, myelodysplastic syndrome (MDS) can also develop from PV and ET[24, 26-32].

The discovery of the ETV6-JAK2 (t(9;12) translocation breakpoint, formerly known as the TEL-JAK2 fusion protein, in ALL and CML patients was the first evidence of aberrant JAK activation in human carcinogenesis. Lymphoid transformation can also be brought on by other, less common translocations between JAK2 and PCM1, SSBP2, STRN3, BCR, or PAX5. Patients with BCR-ABL1-like ALL, a subtype of the characteristic BCR-ABL1 translocation in adult ALL (and less frequently in CML), have been found to have these translocations. 15–30% of B-lineage ALL is caused by BCR-ABL1-like ALL. A significant number of juvenile BCR-ABL1-like ALL patients develop growth signal independence as a result of constitutive JAK-STAT pathway activation. Despite being identified in both myeloid and lymphoid leukemia, JAK2 translocations primarily impact myeloid cells and are frequently undetectable in a patient's lymphocyte population. Compared to T-ALL, B-ALL or leukemia of myeloid origin is less likely to have JAK1 mutations. Nonetheless, two AML patients had a JAK1 V623A mutation found in them, demonstrating how constitutively active JAK1 can promote different kinds of leukemia. Additionally, four B-ALL patients recently had a JAK1 S646P mutation discovered in them, which demonstrated a significant sensitivity to the JAK1/2 inhibitor ruxolitinib. Adult T-and B-ALL have been found to have the analogous mutation AK1 V658F, which is similar to JAK2 V617F and has been demonstrated to cause constitutive JAK1 activation in cell lines. Additionally, many mutations at the analogous JAK1 R724 location (specifically to His, Gln, or Ser) have been found in T- and B-ALL cohorts, and the JAK2 disease mutation R683G has a pathogenic parallel in JAK1.

Similar outcomes to those of mutant JAKs may result from altered cytokine receptor or STAT function. Activating somatic STAT3 mutations have been identified in T and B cell lymphomas and chronic lymphoproliferative diseases of NK cells, while STAT3 and (to a lesser extent) STAT5 mutations have been reported to be often leukemogenic in adults with large granular lymphocyte leukemia. The induction of BCR-ABL-driven ALL and CML is significantly influenced by STAT5. Together with the known mutations in IL7R, JAK1, and JAK3, the fact that STAT5 mutations are frequent in T-ALL further emphasizes the significance of the IL7R/JAK/STAT5 axis in T-cell formation and function in both health and disease.

Two JAKs must engage and then be transphosphorylated for JAK activation to take place. This can happen through two JAK2s in homodimeric receptors or between two distinct JAKs in heterodimeric receptors. JAK2 causes STAT3 and STAT5 activation, cell proliferation, differentiation, and survival in myeloid cells by binding to TPOR/MPL, (EPOR), and G-CSFR. Growth hormone (GH) and prolactin (PRL) receptors are examples of other homodimeric JAK2 systems. JAK1 binds to IL7Rα, which can combine with the γc and cytokine receptor-like factor 2 (CRLF2) in the thymic stromal lymphopoietin (TSLP) receptor to form a heterodimeric complex. Deletions or mutations of the Ikaros transcription factor IKZF1 are linked to activating mutations in JAK1 and JAK2, and CRLF2 increases B-cell leukemogenesis. B-ALL, which has a gene-expression profile similar to BCR-ABL1 ALL and a poor prognosis, is correlated with elevated CRLF2 expression and its interaction with JAK2.

The development of JAK inhibitors has been prompted by the discovery of somatic mutations in MPNs and the pivotal role that JAKs play in immune response modulation. Since then, a number of clinical-stage JAK inhibitors have been created by combining structure-guided optimization with high-throughput screening. Two JAK inhibitors are now approved for myeloid malignancies: fedratinib (JAK2 inhibitor) for PMF and rufolitinib (JAK1/JAK2 inhibitor) for primary and secondary MF and hydroxyurea-resistant PV. Treatment with ruxolitinib reduces spleen size and improves symptoms in people with MF. Ruxolitinib was the first JAK inhibitor authorized for clinical use against MPNs. Some disease-modifying effects of roxolitinib medication include slowed bone marrow fibrosis progression. However, because ruxolitinib monotherapy does not appreciably lower the load of mutant alleles, molecular remission is unlikely. A JAK2 selective inhibitor called fedratinib was authorized for the management of PMF. Fedratinib treatment exhibits notable symptom relief and spleen size reduction, much like ruxolitinib. In patients with myelofibrosis who were either ruxolitinib-resistant or ruxolitinib-intolerant, fedratinib also shown therapeutic effectiveness. A number of additional JAK inhibitors, besides fedratinib and ruxolitinib, are presently undergoing clinical studies to treat hematological disorders.

Conclusions and future perspectives: Hematopoiesis and immunology are regulated by JAKs, and leukemia etiology is significantly influenced by abnormal JAK activation. Numerous mutations that cause JAK activation through different pathways have been identified, including leukemogenic JAK. First-generation type I JAK inhibitors have been approved for clinical usage against MPNs, and further indications are being assessed. JAK inhibitors are currently being tested in clinical trials against leukemia. However, new therapeutic strategies, such as combination therapy, are needed because the existing medications are not curative. The development of next-generation JAK inhibitors with improved potency and selectivity will be facilitated by the disclosure of the molecular aspects of the physiologic and pathologic regulation of JAK signaling.

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