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Janus kinase inhibitors and fields of usage

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ABSTRACT

Jak regions have been identified on chromosome 1, 9, and 19. Cytokines and receptors in the janus kinase/signal transducers and activators of transcription pathway are involved in cell signaling. In order to treat damages in the Jak pathway, molecules called inhibitors have been studied and used for treatment.

Keywords: Inhibitor, janus kinase, chromosome, signal path.

JANUS KINASE (JAK) MECHANISM

The differentiation, growth, and longevity of hematopoietic cells are controlled by a group of growth factors known as cytokines. Cytokines bind to their receptors, resulting in the activation of Janus Kinase receptor-related tyrosine kinases and thus intracellular signal transmission.[1,2]

The JAK family is the name given to a group of tyrosine kinases (without intracellular receptors) that play a role in cytokine-mediated signal transduction. This is known as the JAK-STAT (Signal Transducers and Activators of Transcription) pathway. Transcription factors in this pathway are called STATs. The JAK-STAT pathway is crucial in hematopoiesis as it regulates hematopoietic cells in terms of division, differentiation, and apoptosis. It also plays a role in embryonic development and inflammation.[3,4]

The JAK family consists of four members: JAK1, JAK2, JAK3, and Tyrosine Kinase 2 (TYK2). These proteins do not work alone. In 1989, it was established that amino acid sequences in the catalytic regions of all known tyrosine kinases of hematopoietic cell lines were similar and identified as such.[5,6]

JAK family members have different chromosomal locations. JAK1 is found at 1p31.3, JAK2 at 9p24; JAK3 at 19p13.1, and TYK at 19p13.1 (Figures 1, 2).[7,8] As JAKs are large proteins, they contain over a thousand amino acids. There are seven different JAK homology regions that make up the structural portion of JAK members.[9,10] While JAK1, JAK2, and TYK2 are expressed by almost every cell in mammals, JAK3 is primarily expressed in hematopoietic and lymphoid tissues.[11] Mutation of the JAK2 gene, which encodes tyrosine kinase, a protein involved in the JAK/STAT signaling pathway, was identified as the guanine nucleotide of the 14th exon and 1849th position changed with thymine (G1849T), leading to the V617F mutation, in which phenylalanine is coded instead of valine at the 617th position in the synthesized protein.[12-14]

JAK3 is the only JAK kinase that binds to the common signal transduction subunit γc (gamma) of the receptor complex of several cytokines (IL2, IL4, IL7, IL9, IL15, and IL21). Hereditary

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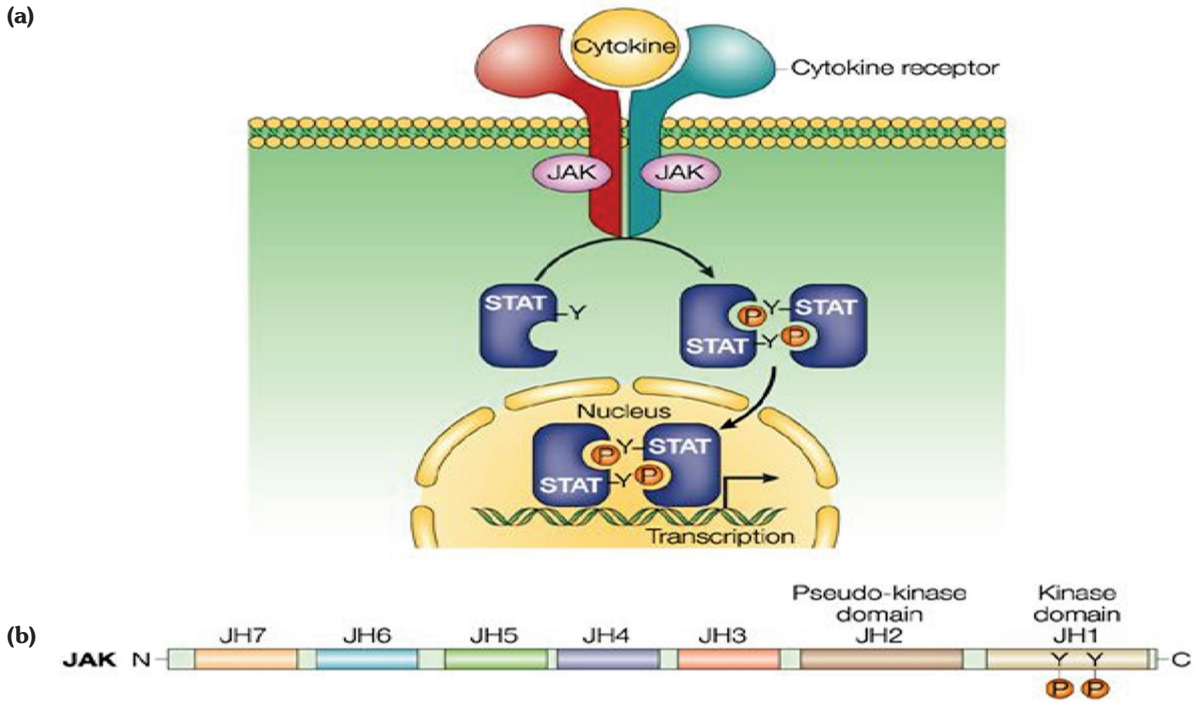

Figure 1. (a) JAK-STAT Pathway. **(b)** Regions on the JAK gene.[7]

JAK3 and γc mutations lead to severe combined immunodeficiency (SCID). Patients with TYK2 function loss also develop immune deficiency. Therefore, JAK3 and TYK2 inhibition requires the most caution when using JAK inhibitors.[15]

Janus kinases regulate signal production of cytokine receptors. Janus kinases enzymes that bind to cytokine receptors on the cell surface, upon binding to the cytokine receptor gland, become phosphorylated and the receptor undergoes dimerization. When JAK is phosphorylated, it becomes activated. Activated JAK-receptor complex becomes phosphorylated and activates STATs which are substrate molecules and transcription factors. Activated STAT dimers move towards the nucleus, binding to the special DNA sequences at the promotor region of the relevant gene that is responsive to the cytokine, and activate gene transcription.[16,17]

JAK INHIBITORS

Tofacitinib

Tofacitinib is an orally available, small-molecule JAK-family inhibitor of JAK1, JAK2, JAK3, and TYK2 that competitively binds to the active region of adenosine triphosphate kinase and prevents activation of signal transduction.[17,18]

Baricitinib

Another JAK inhibitor, Baricitinib, received approval for RA treatment in February 2017 and mainly shows minimal binding to JAK1, JAK2, as well as JAK3. Therefore, it inhibits many cytokines by blocking the signal through the γc chain, β common chain (IL-3, IL-5, and GM-CSF), gp130 (IL-6 family), interferons, and interleukins (IL-12, IL-23, IL-27).[19]

Ruxolitinib

Ruxolitinib (INCB018424) is a strong, selective JAK1 and JAK2 inhibitor. Its main effect is to prevent cell division and induce apoptosis by inhibiting JAK from phosphorylating STAT.[20] Ruxolitinib (INCB018424) is the first tyrosine kinase inhibitory agent to be used in myelofibrosis treatment.[21]

Peficitinib

Peficitinib is an oral JAK1, JAK2, and JAK3 inhibitor that has 6-7 times greater *in vitro* potential for JAK3 compared to JAK1 and JAK2.[22]

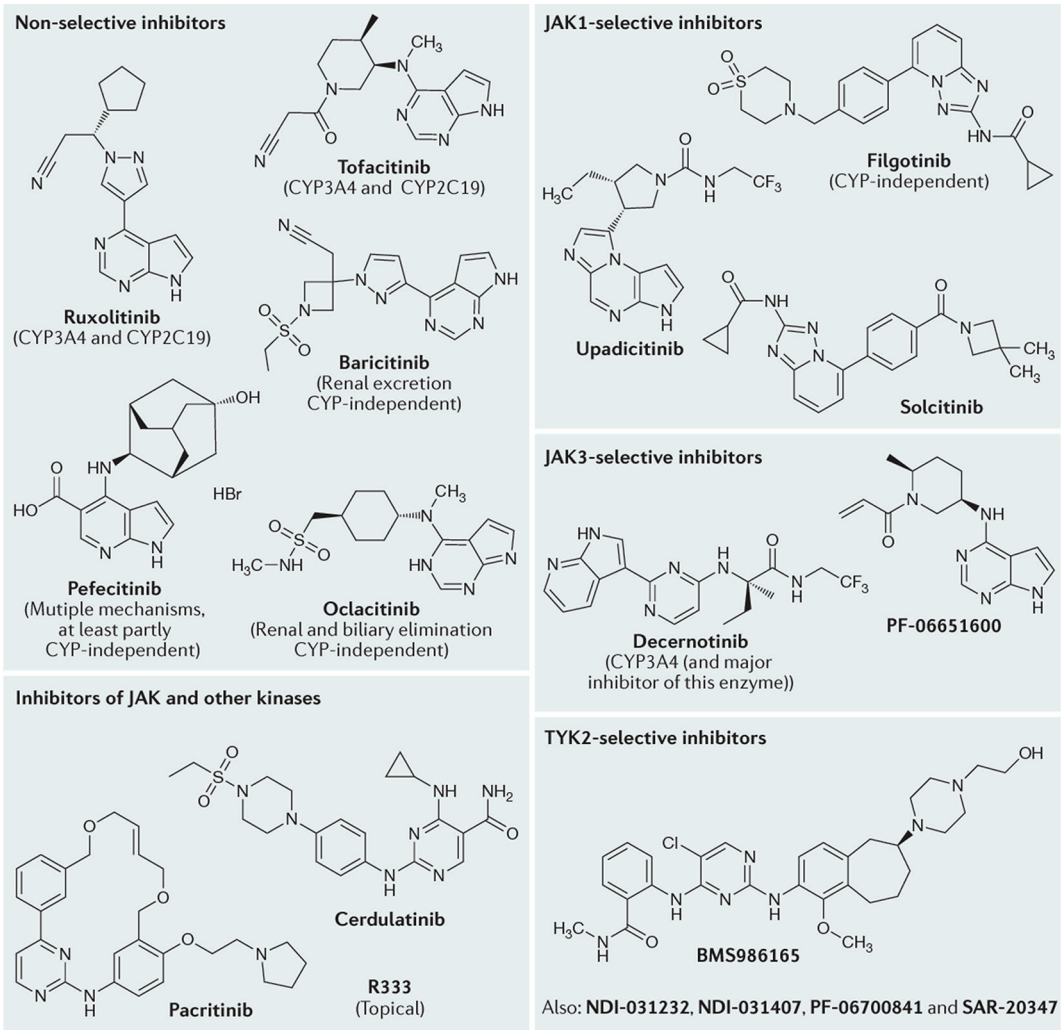

Figure 2. Types of janus kinase inhibitors and their chemical structures.[8]

Upadacitinib

Upadacitinib is a JAK1 inhibitor that was developed for the treatment of rheumatoid arthritis and other inflammatory diseases. Oral upadacitinib treatment is currently under study[23] but so far there are no conclusive results.[24]

Filgotinib

Filgotinib was the first JAK1 inhibitor and may provide limited toxicity. It is well tolerated and has no effect on JAK2 signaling.[25]

Momelotinib

Momelotinib is a selective JAK1 and JAK2 inhibitor that may be beneficial in improving anemia in myelofibrosis patients.[26]

Oclacitinib

Oclacitinib is a new JAK inhibitor that targets cytokine activity involved in dermatologic dog allergies. Oclacitinib is most effective in inhibiting JAK1.[27]

Decernotinib

Decernotinib is a relatively new JAK inhibitor which has roughly five times more selectivity over JAK3 compared to other JAKs (JAK1, JAK2, TYK2) based on *in vitro* kinase assays.[26] Studies on decernotinib have also shown an adverse reaction of lymphopenia, also known in tofacitinib. This could be associated with effects on JAK3 related cytokines such as IL-7 and IL-15.[28]

Fedratinib

Fedratinib is an orally available small molecule. It competes with the mutated form of AK2V617F as well as JAK2 for ATP binding, which may result in inhibition of JAK2 activity, JAK-STAT signaling pathway inhibition, and induction of tumor cell apoptosis. Its use was approved by the FDA on August 16, 2019.[29]

Pacritinib

Pacritinib is an orally available inhibitor of the JAK2 mutant JAK2V617F that has potential antineoplastic activity.[30]

Cerdulatinib

Cerdulatinib is a dual spleen tyrosine kinase (SYK) and JAK inhibitor which uniquely inhibits two key cell signaling pathways in certain hematological malignancies and autoimmune diseases. Both targets have been strongly shown to inhibit both SYK (B cell receptor pathway) and JAK (cytokine receptors) targets in B cell malignancies that have been shown to increase cancer cell growth and survival.[31]

Solcitinib

Solcitinib is a selective JAK1 inhibitor initially developed to treat systemic lupus erythematosus, psoriasis, and ulcerative chollitis.[32]

Diseases in which inhibitors are used

Skin diseases

Psoriasis, Lichen planus

Cutaneous lupus erythematosus

Pyoderma gangrenosum, atopic dermatitis

Alopecia areata, vitiligo, plaque psoriasis

Other diseases

Acute and chronic graft versus host disease,

Myeloproliferative neoplasms (MPN)

Rheumatoid arthritis (RA)

Severe combined immunodeficiency (SCID)

Ankylosing spondylitis (Low Back Rheumatism)

Juvenile idiopathic arthritis (Childhood Rheumatism)

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