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Review

JAKs in pathology: Role of Janus kinases in hematopoietic malignancies and immunodeficiencies

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ABSTRACT

The four mammalian Janus kinase (JAK) family members, JAK1, JAK2, JAK3 and TYK2, are non-receptor protein tyrosine kinases (PTKs) that are crucial for cytokine receptor signaling in blood formation and immune responses. Mutations and translocations in the *JAK* genes leading to constitutively active JAK proteins are associated with a variety of hematopoietic malignancies, including the myeloproliferative disorders (JAK2), acute lymphoblastic leukemia (JAK2), acute myeloid leukemia (JAK2, JAK1), acute megakaryoblastic leukemia (JAK2, JAK3) and T-cell precursor acute lymphoblastic leukemia (JAK1). In contrast, loss-of-function mutations of JAK3 and TYK2 lead to immunodeficiency. The role of JAKs as therapeutic targets is starting to expand, as more insights into their structure and activation mechanisms become available.

Contents

1. Introduction

Janus kinases were initially discovered by a polymerase chain reaction (PCR)-based screen of kinases using degenerate oligonucleotide primers corresponding to sequences in the catalytic domain of protein tyrosine kinases (PTKs). JAK1 and JAK2 were two new kinases isolated among a large number of others and were initially termed "Just Another Kinase" [1]. Because JAKs possess two nearly identical phosphate-transferring domains, an active kinase domain and a catalytically inactive pseudokinase domain, their name was changed to Janus kinase, Janus being the name of a roman God having two faces [2,3]. TYK2 was discovered in a T-cell cDNA library screened with a probe covering the c-fms tyrosine kinase domain [4] and was shown to play a major role in the interferon α/β signaling pathway by acting as a liaison between the receptor and downstream transcription factors regulating target genes [5]. JAK3 was also cloned using a PCR-based strategy and was shown to be activated in response to IL-2 and IL-4 in myeloid and T cells [6–8].

The cytokine receptor superfamily comprises single span membrane proteins that are devoid of enzymatic activity in their cytosolic domain. These receptors bind members of the Janus kinase fam-

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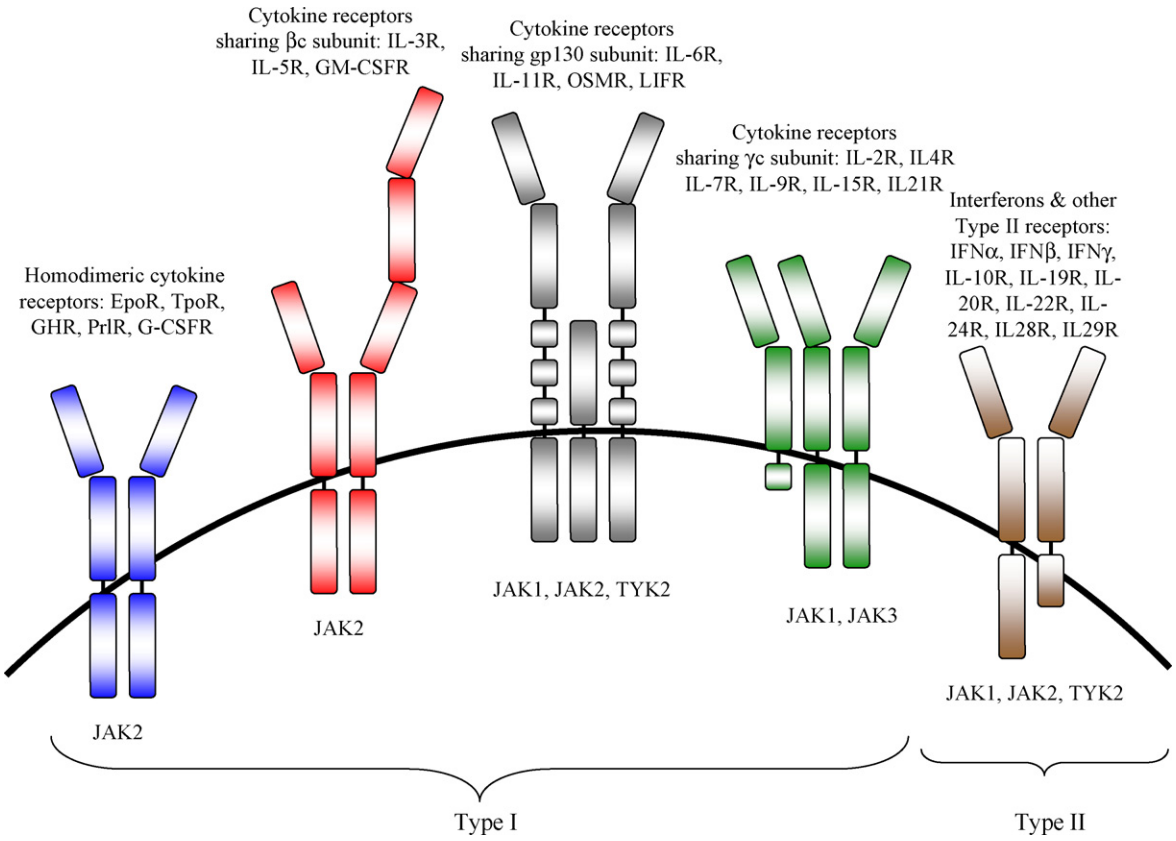

Fig. 1. Cytokine receptors have different preferences for the Janus kinases. The homodimeric receptors almost exclusively employ JAK2, as do the receptors sharing the β_c subunit. JAK3 is only activated by cytokine receptors containing the γ_c subunit. Receptors sharing the gp130 subunit, and the type II cytokine receptors utilize JAK1, JAK2 or TYK2 in various combinations.

ily via their cytosolic domains (Fig. 1) [9] The superfamily is divided into types I and II receptors, based on conserved motifs in the extracellular domains, and on loosely conserved motifs in the cytosolic domains [9]. Both types I and II cytokine receptors are activated when a ligand binds to their extracellular domains, imposes an active dimeric/oligomeric conformation of the chains and induces close apposition of JAKs, which then cross-phosphorylate and initiate signaling. Within the type I receptors, which share conserved cysteine residues and a WSXWS motif in the extracellular domain, there are several subfamilies, based on the architecture of the active complex: receptors activated as homodimers, such as receptors for erythropoietin (EpoR), thrombopoietin (TpoR) and growth hormone, receptors activated as heterodimers – sharing a common beta chain (β_c subunit) – that associates with the specific α chains for GM-CSF, IL-3, and IL-5, multimeric receptors for cytokines of the IL-6 family that contain the gp130 signaling chain and heteromeric receptors containing the common gamma chain (γ_c subunit) that is shared among IL-2, IL-4, IL-7, IL-9, IL-13, IL-15 and IL-21 (Fig. 1). For certain receptors, such as the EpoR, preformed dimeric complexes exist, that have been visualized for the extracellular domain by X-ray crystallography [10]. These dimeric complexes are inactive in the absence of ligand [11,12]. Ligand binding changes this inactive conformation into an active one, where the appended JAK proteins activate each other [13–15]. Such preformed dimers/oligomers also exist for other receptors, as they were also described for growth hormone receptor [16,17]. One or several of the four mammalian JAKs are associated with each receptor subunit. The interaction between JAKs and receptors is mediated by weakly conserved Box 1 (proline-rich) and Box 2 (hydrophobic and charged) sequences in the cytosolic domain of the type I receptors. For type II receptors (i.e. IFNα/β and γ receptors, IL-22, IL-24, IL-28, IL-29 receptors), which are activated in heteromeric manner by the corresponding ligands [18], intracellular domains sequences like Box 1 and Box 2 are less well defined, indicating that the mechanism of JAK association may differ [19]. JAK2 was shown to be directly involved in signaling by the growth hormone and erythropoietin receptors [20,21], while both JAK1 and JAK2 are involved in IFNγ signaling [22,23]. JAK3 is unique among the JAKs, in that it only binds to the γ_c receptor subunit of the receptor complexes for IL-2, IL-4, IL-7, IL-9, IL-13, IL-15 and IL-21 [24,25]; therefore, JAK3 is crucial for signaling of receptors that contain the γ_c receptor subunit [6–8].

2. Structure and the different domains of JAKs

JAKs have seven defined regions of homology, called JAK homology (JH) domains (JH1-7) [26]. The carboxyl terminus contains the kinase and pseudokinase domains, denoted JH1 and JH2, respectively (Fig. 2A). The JH1 domain contains all the features typical of a catalytic tyrosine kinase, including tyrosine residues in the activation loop region, the canonical GXGXXG motif in the nucleotide-binding loop and a conserved aspartic acid residue involved in the phosphotransfer reaction in the catalytic loop [27]. The sequence of the JH2 pseudokinase domain, also called kinase-like domain, is highly homologous to the kinase domain, but lacks characteristic residues of active tyrosine kinases, making it catalytically inactive [2]. It has been suggested that the exon–intron structure of the nucleotide sequence coding for the JAK3 pseudokinase domain resembles that of genes coding for Src kinases, while no homology with other known genes was detected for the kinase domain [28]. Thus, it seems unlikely that the pseudokinase domain