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JAK/STAT disruption induces immuno-deficiency: Rationale for the development of JAK inhibitors as immunosuppressive drugs

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ABSTRACT

Cytokines are mediating immune cells responses through the activation of the JAK/STAT signaling pathway. Being critical for immune cells, a defective JAK/STAT signaling leads to various immune disorders, such as immunodeficiency. In contrast, hyperactivation of JAK/STAT signaling is linked to autoimmunity and cancer. Targeting the JAK/STAT proteins by small protein inhibitors impedes immune cell function by uncoupling cells from cytokine effects and by interfering with functional immune cell hallmarks, such as cell migration. This review will explore immune syndromes driven by JAK/STAT deregulation and discuss the emerging role of JAK inhibitors as immunosuppressive drugs used in autoimmunity and transplantation medicine.

The highly conserved JAK/STAT signaling pathway is critical for our immune system to defend our body against pathogens and tumor cells but also to avoid autoimmunity by maintaining immune tolerance. In order to sense and transfer external cytokine-mediated signals to the nucleus and subsequently induce target gene expression, receptors of the type I and II cytokine-receptor superfamily recognize different ligands such as interferons (IFN-γ, -β and α), interleukins (but not IL-1 and IL-8), growth factors, erythropoietin (EPO), thrombopoietin (TPO), prolactin and leptin. Upon binding of the aforementioned cytokines to their corresponding receptor, the two transmembrane receptor chains come to close proximity, allow the transactivation and phosphorylation of the JAKs that are bound to their cytoplasmic tails as well as the phosphorylation of the cytoplasmic tail itself. From the four JAKs (JAK1, JAK2, JAK3 and the non-receptor tyrosine-protein kinase TYK2), only JAK3 always binds to the same subunit, namely the common interleukin-2Rγ chain (γc), while the other JAKs can be linked to different cytokine-receptor subunits. Once the cytoplasmic tail of the receptor is phosphorylated, it creates a docking site for one of the 7 Signal Transducer and Activator of Transcription (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) proteins, that also get in turn phosphorylated. Consecutively, phosphorylated STATs dimerize and migrate to the nucleus to regulate target gene expression, as shown in Fig. 1. The final response to a specific cytokine by JAK/STAT signaling is subtly tuned by the fact that one cytokine can activate different STATs, that STAT activation can also be JAK independent and that STATs are competing for the same binding sites in the genome thereby giving a fine tuning of gene regulation and expression (as reviewed in (Villarino et al., 2015)). In the current review, we will focus on immune disorders that are linked to dysregulation of JAK/STAT signaling and (as a logical consequence) on the clinical potential of JAK/STAT inhibitors as anti-inflammatory and immunosuppressive compounds in myeloproliferative neoplasia, GVHD, and autoimmune diseases.

1. Deregulated JAK/STAT signaling in immune disorders

As mediators of immune cell responses, cytokines are triggering the activation of JAK/STAT signaling and are highly relevant to regulate immune cell differentiation and activation. Not surprisingly, deregulation of JAK/STAT signaling pathway has been linked to various immune disorders such as primary immunodeficiency, autoimmunity or cancer. We here discuss mutations that either turn off or activate the JAK/STAT signaling in immune cells and their

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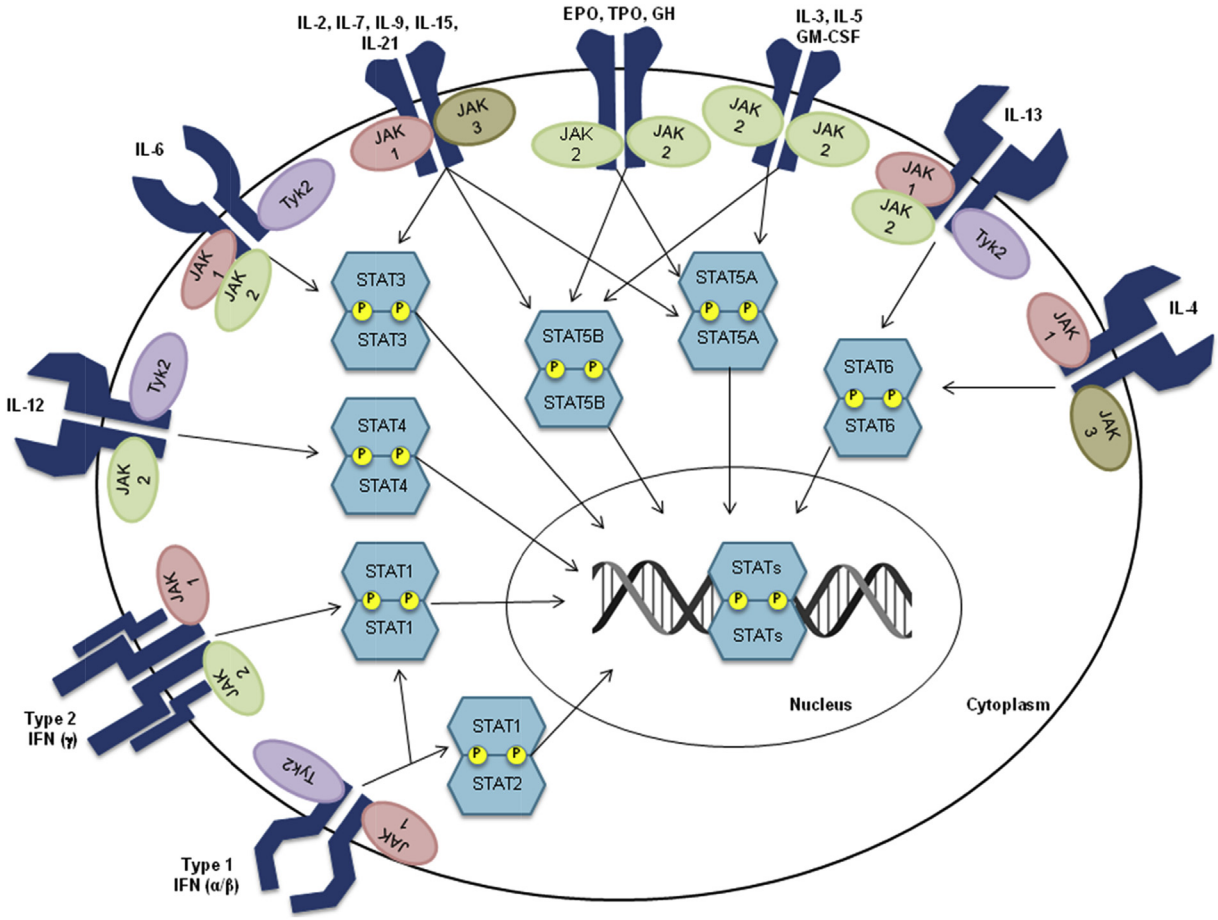

Fig. 1. JAK/STAT signaling.
Each cytokine receptor chain is associated with a particular JAK protein (JAK1, JAK2, JAK3 or TYK2). Upon binding of hormones or cytokines on their respective receptors, 2 receptor chains get into close vicinity, JAKs phosphorylate each other and mediate signaling by phosphorylating and activating one or more specific STATs. The latter dimerize upon phosphorylation and can then get into the nucleus to regulate gene expression. Phosphorylated STATs are indicated by the "P" in yellow circle.

biological consequences in terms of immune responses.

1.1. Loss of function mutations and immunodeficiencies

By genetically complementing the human cell line 11.1 to restore IFNα responsiveness, TYK2 sharing similar domains with JAK1 was discovered (Velazquez et al., 1992) and subsequently the link between JAKs and cytokine signaling was defined (Ihle, 1995). Shortly thereafter, the essential and specific role of JAKs in cytokine signaling could be validated by the establishment of genetically modified mice deficient for either *JAK1* (Rodig et al., 1998), *JAK2* (Neubauer et al., 1998; Parganas et al., 1998), *JAK3* (Thomis et al., 1995; Nosaka et al., 1995; Park et al., 1995) or *TYK2* (Karaghiosoff et al., 2000). The critical role of JAK1 and JAK2 for cytokine-dependent organ development is exemplified by the life threatening phenotype of the respective knock-out (KO) mice. Indeed, because JAK1 and JAK2 are associated to different cytokine receptors, *JAK1* KO mice die shortly after birth and *JAK2* KO mice die *in utero* (E12.5) due to impaired erythropoiesis. In contrast, *JAK3*- and *TYK2*-deficient mice are viable but show either a severe immunodeficiency or a modest susceptibility to viral infections coupled to an impaired IL-12 and IFN type I response, respectively.

In humans, different primary immunodeficiency syndromes are linked to mutations involving JAK3, TYK2 or the associated cytokine receptors. Severe combined immunodeficiency (SCID), a rare inherited disorder, affects lymphocyte development and function. Because of severe recurrent infections, infants are at high risk of mortality in the first two years of age and quickly necessitate hematopoietic stem cell transplantation to replace the defective immune system (Cirillo et al., 2015). Approximately half of the SCID cases carry mutations in the common interleukin-2Rγ chain (γc), thereby blocking the signal transduction induced by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 in lymphocytes. As a consequence, T and NK cell development is impaired and B cells are present but poorly activated. Because JAK3 exclusively binds to the γc chain, mutations in the *JAK3* gene might also lead to SCID in patients and have the same deleterious effect on lymphocyte populations. However, in SCID patients, mutations in the *IL7Rα* receptor that also dimerizes with the γc chain only affects T cell development and B cell function, since NK cell development mainly depends on IL-15 binding to another receptor (Cirillo et al., 2015). Moreover, by analyzing transplanted SCID patients with *IL-2Rγ* or *JAK3* mutations and therefore showing chimerism in B cell population, the authors could demonstrate a critical role for IL-21 in B cell function (Recher et al., 2011).

Another primary immunodeficiency in humans results from autosomal recessive mutations in the *TYK2* gene leading to mycobacterial and/or viral infections with or without Hyper-immunoglobulin E syndrome (HIES). By analyzing the immune response of 7 patients who are deficient for *TYK2*, a recent study could show that the main characteristics of *TYK2* deficiency are an impaired response to IL-12 and IFNα/β. Moreover, by genetically