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Review article

Janus kinases in inflammatory bowel disease: Four kinases for multiple purposes

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ABSTRACT

Inflammatory bowel disease (IBD) comprises mainly Crohn's disease and ulcerative colitis. These pathologies are characterized by inflammation of the gut and destruction of its epithelium. Many cytokines play key roles in this pathology. They are generally involved in the inflammatory process but also display anti-inflammatory activities and some regulate the gut epithelium homeostasis, constituting therapeutic targets for IBD. Many of these cytokines signal through the JAK/STAT pathway and thus, JAKs represent also very promising therapeutic targets and selective or non-selective inhibitors of these kinases have already been assayed in clinical trials with various success. The existence of four JAKs and six STAT factors that are used in combination make these pathways complex enough to generate various responses. Here we summarize the role of the JAKs in some cytokines involved in IBD. The multifunctional role they play through the various functions of the cytokines they signal for makes difficult the anticipation of the effective beneficial role that JAK inhibitors may have.

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Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a class of intestinal disease characterized by chronic and relapsing inflammation of the gastrointestinal (GI) tract. It is a growing worldwide health-care problem with a continually increasing incidence [1]. The exact etiology of UC and CD is still unknown, but it is considered that the origin of the disease involves a combination of genetic and environmental factors, immune dysregulation, barrier dysfunction and changes in the intestinal microbiome. The current consensus on the pathogenesis of IBD is that the disease develops and gradually evolves to a chronic state as a consequence of an inappropriate response of the immune system to the microbiome in genetically predisposed individuals exposed to particular environmental factors [2]. While being part of the same class of pathologies, UC and CD display remarkable differences at the level of signs and symptoms. CD affects any part of the GI tract, from mouth to rectum in a non-continuous manner and generally causes transmural inflammation. It is frequently associated with complications such as strictures, fistulas and abscesses [3]. In contrast, UC is characterized by a mucosal inflammation which is limited to the colon [4].

The essential role of inflammation in the development of UC and CD is extensively supported by the efficacy of treatments that impact the immune system. This however must not mask the importance of the integrity of the epithelial barrier that separates microbiome and the sentinels of the immune system. Of interest, many cytokines play a key role in the pathophysiology of IBD by their pro-inflammatory or anti-inflammatory roles, some of which also impact the integrity or defence of the epithelial barrier [5]. The Janus kinases (JAK) play a key role in the signaling of several of these cytokines and therefore constitute attractive potential therapeutic targets. As little direct evidence of JAK-related effects in IBD is known, the importance of JAKS in IBD will be indirectly analyzed based on the role of several cytokines in the IBD pathogenesis, thereby highlighting the multifaceted roles these kinases can fulfill.

The links between JAKs and IBD

JAK mode of action

The JAKs are tyrosine kinases that constitute a family of four proteins, JAK1, JAK2, JAK3 and TYK2. While JAK3 is mainly expressed in myeloid and hematopoietic cells, the three other JAKs are widely expressed. They function as pairs, as a relay between the receptors for cytokines of growth factors and the STAT (Signal Transducer and Activator of Transcription) factors. Upon direct phosphorylation by the JAKs, STATs migrate to the nucleus as dimers to stimulate transcription of the target genes of the signaling pathway. The STATs also belong to a large family of proteins encoded by 7 genes STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6 [6]. The combination of two JAKs activating two STATs allows specific patterns of response making a simple pathway complex enough to generate specific responses to many different stimuli.

The JAK/STAT pathways in IBD

Because of the multiple combinations that exist in the use of JAKs and STATs in cytokine signaling as well as the spread in expression of their cognate receptors on different target cells, the different cytokines and growth factors involved in IBD display specific effects that characterize very well the complexity of these diseases.

Interleukin-6

Interleukin-6 (IL-6) is one of the key pro-inflammatory cytokines. Although initially identified as signaling through JAK1, JAK2 and TYK2, recent studies have highlighted the essential role displayed by JAK1 [7]. IL-6 signals through the IL-6R and the glycoprotein 130 (gp130) receptor, the former being expressed only on the membrane of a few cell types (macrophages, hepatocytes), while the latter ubiquitously expressed. However, under inflammatory conditions, the membrane IL-6R is shed to produce the soluble form of IL-6R (sIL-6R) that allows IL-6 signaling in most cell types [8,9]. IL-6 concentration is increased in the plasma of IBD patients and several studies even found an association between the amount of IL-6 expression and disease activity in both CD and UC patients [10,11]. In IBD patients, IL-6 is produced by mononuclear cells of the lamina propria as well as by the intestinal epithelial cells (IECs) [12,13].

One of the key actions of IL-6 is the activation of STAT3 on T-cells of the lamina propria of IBD patients, increasing their survival and proliferation, and this role has been demonstrated in several mouse models of IBD where its inhibition with an IL-6-blocking antibody led to the induction of T cell apoptosis and the reduced production of pro-inflammatory cytokines, such as IFNγ, TNF and IL·1β [14–16]. The use of a blocking anti-IL-6R antibody allowed Yamamoto et al. [17] to demonstrate that IL-6 is required for the development of colitis mediated by T_H1 cells. In addition, IL-6 is an important stimulator of T_H17 polarization, regulating the balance between T_H17 and Treg cells, a critical equilibrium in IBD [18–20]. Finally, IL-6 has been demonstrated as a key inducer of recruitment and activation of macrophages and neutrophils to the lamina propria during the acute phase of the disease in mouse experimental models of IBD [21]. All together, these data identify IL-6 and the JAK1/STAT3 pathway as a major actor in the initiation and development of inflammation in IBD and point to the potential of JAK inhibitors for the treatment of this disease.

In parallel to these pro-inflammatory effects, IL-6 also affects the homeostasis of the epithelial barrier. Indeed, Al-Sadi et al. [22] have brought evidence that IL-6 increases intestinal epithelial tight junction permeability by activating the JAK pathway leading to an increased expression of the Claudin-2 gene. However, several reports highlight the protective effects of this cytokine on the intestinal epithelium. IL>-6 has been shown to be an important regulator of host defence against gavage-mediated *Citrobacter rodentium* infection by protecting the intestinal mucosa against infection-induced apoptosis in the colonic epithelium that leads to ulcerations [23]. This protective role toward the intestinal epithelium has also been demonstrated by Kuhn et al. [24] who showed that IL-6, produced mainly by intraepithelial lymphocytes at the onset of an inflammatory injury, is an important factor for epithelial proliferation and wound repair. Noteworthy, through Yes-associated protein (YAP) and Notch but independently of STAT3, intestinal gp130 signaling stimulates epithelial cell proliferation, causes aberrant differentiation and confers resistance to mucosal erosion. However, the proliferative and anti-apoptotic effect of the IL-6/STAT3 pathway is also crucial for the development of colitis-associated cancer (CAC) observed in some long-term IBD patients [25]. Collectively, these data may explain the mixed data obtained in patients with moderate to severe active UC treated with tocilizumab, a humanized monoclonal antibody against IL-6 receptor [26].

Interleukin-12/Interleukin-23

Interleukin-12 (IL-12) is a heterodimeric cytokine, composed of two covalent subunits (p40 and p35) binding the IL-12 receptors IL-12Rβ1 and IL-12Rβ2, and is produced by CD14-expressing monocytes/macrophages and dendritic cells, mostly in response to bacterial stimulation [27]. IL-12 promotes T_H1 cell polarization