

Differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn's disease

Friederike Cordes, Dirk Foell, John Nik Ding, Georg Varga, Dominik Bettenworth

ORCID number: Friederike Cordes 0000-0002-0376-0764; Dirk Foell 0000-0002-1946-3916; John Nik Ding 0000-0002-6232-1948; Georg Varga 0000-0002-1547-8766; Dominik Bettenworth 0000-0002-1435-4825.

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Friederike Cordes, Dominik Bettenworth, Department of Medicine B, Gastroenterology and Hepatology, University Hospital Münster, Münster D-48149, Germany

Dirk Foell, Georg Varga, Department of Pediatric Rheumatology and Immunology, University Children's Hospital Münster, Münster D-48149, Germany

John Nik Ding, Department of Gastroenterology, St. Vincent's Hospital, Melbourne 3002, Australia

John Nik Ding, Department of Medicine, University of Melbourne, East Melbourne 3002, Australia

Corresponding author: Friederike Cordes, MD, Doctor, Department of Medicine B, Gastroenterology and Hepatology, University Hospital Münster, Albert-Schweitzer-Campus 1, Münster D-48149, Germany. annafriederike.cordes@ukmuenster.de

Abstract

In 2018, the pan-Janus kinase (JAK) inhibitor tofacitinib was launched for the treatment of ulcerative colitis (UC). Although tofacitinib has proven efficacious in patients with active UC, it failed in patients with Crohn's disease (CD). This finding strongly hints at a different contribution of JAK signaling in both entities. Here, we review the current knowledge on the interplay between the JAK/signal transducer and activator of transcription (STAT) pathway and inflammatory bowel diseases (IBD). In particular, we provide a detailed overview of the differences and similarities of JAK/STAT-signaling in UC and CD, highlight the impact of the JAK/STAT pathway in experimental colitis models and summarize the published evidence on JAK/STAT-signaling in immune cells of IBD as well as the genetic association between the JAK/STAT pathway and IBD. Finally, we describe novel treatment strategies targeting JAK/STAT inhibition in UC and CD and comment on the limitations and challenges of the new drug class.

Key words: Janus kinase; Signal transducer and activator of transcription; JAK/STAT pathway; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; JAK/STAT inhibition; Tofacitinib

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Core tip: The pan-Janus kinase (JAK)-inhibitor tofacitinib is efficacious in patients with active ulcerative colitis (UC) but not Crohn's disease (CD), which hints at different contributions of JAK-signaling in both entities. In this review, available data on differential JAK/signal transducer and activator of transcription (STAT)-signaling in UC and CD were analyzed. The literature review identified differential cell-subset specific JAK/STAT-signaling including increased T-cell-associated STAT1 signaling in CD and STAT6 signaling in UC, while in myeloid cells inflammatory STAT1 was increased in UC compared with CD indicating a less inflammatory role of myeloid cells in CD. Development of JAK/STAT-inhibitors with specific targeting of associated inflammatory pathways might further improve the efficacy and safety profiles of this drug class.

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INTRODUCTION

Inflammatory bowel diseases (IBD) comprise the entities ulcerative colitis (UC) and Crohn's disease (CD) as well as unclassified IBD, which are chronic remitting diseases characterized by intestinal inflammation and the risk of uncontrolled disease activity which may lead to severe complications such as fistulas and strictures in CD, and colorectal neoplasia in both entities^[1-5]. Despite the plethora of available medical treatment options for IBD, treatment of patients is still complex and often challenging due to loss of response as well as adverse events including opportunistic infections^[6-8]. Population based studies report that 46% of patients with CD and 14% of patients with UC are still being treated with systemic corticosteroids for more than 6 months to achieve remission^[9,10].

The introduction of biological therapy has improved the spectrum of anti-inflammatory treatment. Nevertheless, the induction and maintenance of remission can still be challenging due to primary non response and secondary loss of response to biological therapy. Indeed, approximately one third of patients with CD and UC were classified as primary non-responders, and up to 50% of patients with IBD had a secondary loss of response to biological therapy or had to stop treatment due to severe side effects^[6,11]. Anti-tumor necrosis factor (TNF) therapy has the risk of immunogenicity including provocation of an immune response with occurrence of neutralizing antibodies towards anti-TNF α resulting in secondary loss of response. These observations clearly underline the need for new therapeutic agents with improvement of tolerability and long-term efficacy^[12].

Targeting cytokine signaling is already a proven therapeutic strategy as blockade of TNF α has been shown to have good efficacy in the treatment of IBD. However, aside from TNF α , a wide range of cytokines are crucially involved in maintaining intestinal inflammation and reveal a major role in the pathogenesis of IBD^[13]. Thus, modulation of several IBD-associated cytokines simultaneously appears to be a promising therapeutic target in IBD^[14-16]. Janus kinases (JAKs) mediate intracellular signaling of various cytokines and growth factors^[17-20].

The JAK/STAT pathway

JAKs are potent therapeutic targets and blockade can potentially interfere with more than 50 cytokines^[17,18]. JAKs are constitutively bound to cytokine receptors and are crucial in biological responses, mediating signals *via* signal transducers and activators of transcription (STATs)^[21-23]. Four different JAK molecules (JAK1, JAK2, JAK3 and tyrosine kinase (TYK) 2) and seven members of the STAT family (STAT1, 2, 3, 4, 5a, 5b, 6) are known^[18,24-27]. STAT5a and STAT5b represent two proteins with almost identical amino acids but are encoded by different genes^[28]. Binding of cytokines to their receptors mainly activates specific JAKs and subsequent STATs as final initiators of JAK signaling and can lead to specific cellular responses^[29-31]. The general mechanisms of JAK/STAT-signaling are summarized in **Figure 1**. Due to the fact that JAK/STAT-signaling is utilized by various cytokines, these pathways have become prominent targets for simultaneous inhibition of multiple pro-inflammatory cytokines^[32-34].

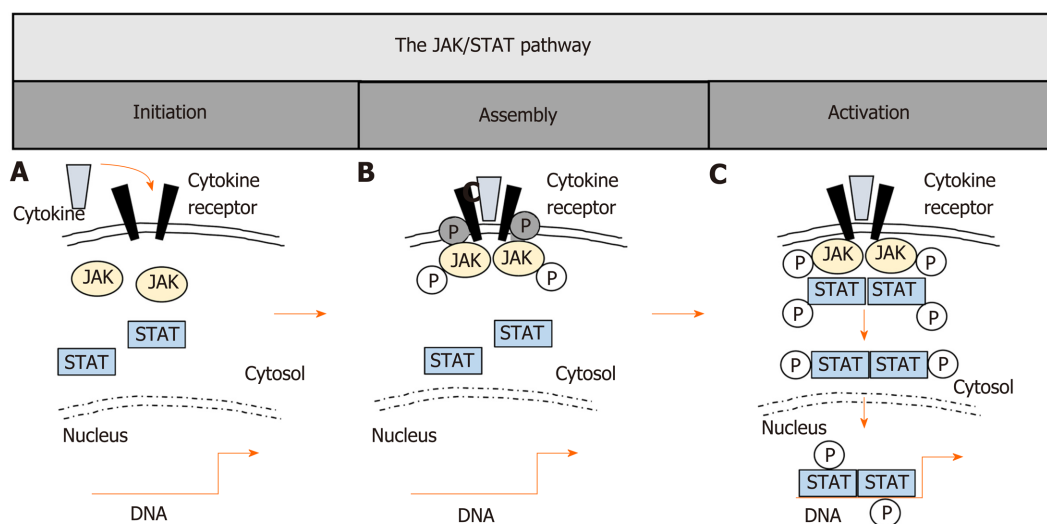


Figure 1 The JAK/STAT pathway. A: Canonical Janus kinase (JAK)/signal transducer and activator of transcription (STAT)-signaling initiates with the association of cytokines and their corresponding transmembrane receptors; B: Cytokine binding brings JAKs in proximity to the receptor, leading to phosphorylation of both the JAKs themselves and the cytoplasmic tails of the receptors, thereby creating docking sites for STAT monomers; C: STAT tyrosine phosphorylation (p-Tyr) is the major activating event, leading to dimerization of STATs, translocation to the nucleus, DNA binding of STAT dimers and subsequent target gene induction. JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

Nevertheless, targeting JAK/STAT-signaling is highly complex as overlapping JAK/STAT activation by various cytokines with induction of more than one specific downstream signaling pathway is known^[35-37]. In detail, similar JAK/STAT components can be activated by varying cytokines of related receptor families, which include cytokines of the interferon (IFN) receptor family *i.e.*, type I/II/III IFNs, IL-10, IL-19, IL-20, IL-22, the common γ -chain receptor family (*i.e.*, IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), the gp130 receptor family (*i.e.*, IL-6, IL-11, IL-12, IL-23), the common β -chain receptors (*i.e.*, GM-CSF, IL-3, IL-5) and the single chain receptor family (*i.e.*, Epo, GH)^[29,30,38]. Besides these classical canonical pathways, which include subsequent JAK/STAT activation, non-canonical pathways with independent activation of either JAKs or STATs for signal transduction have been described^[39-41]. Furthermore, JAKs can also activate other downstream targets separate to the classical STATs^[42]. It is incompletely understood how specific signaling can be achieved regarding the complexity of JAK/STAT activation, but a cell subtype-associated specificity of JAK/STAT-signaling has been suggested^[31] as activation of the same STATs can lead to partially opposing effects in cells of the innate compared to the adaptive immune system. For instance, STAT3 mediates regulatory signaling in epithelial or myeloid cells^[43], while in lymphocytes, STAT3 activation results in predominantly pro-inflammatory responses such as Th17 differentiation and inhibition of regulatory T-cells^[44-46], which further underlines the great plasticity and complexity of JAK/STAT-signaling in regulatory or inflammatory responses of different cell compartments.

Clinical efficacy of JAK inhibition in RA and IBD

The JAK/STAT pathway has been associated with several immune-mediated diseases besides its important impact in cellular signaling^[47-50]. The pan-JAK inhibitor tofacitinib results in predominant inhibition of JAK1/JAK3 at adequate dosage^[51,52], leading to inhibited JAK-associated intracellular signaling of various cytokines and growth factors^[17,18] and was first developed and approved as a synthetic disease-modifying anti-rheumatic drug (DMARD)^[53-56] for the treatment of moderate to severe rheumatoid arthritis (RA) in 2017 throughout Europe^[53-55,57]. Due to its clinical efficacy in RA, tofacitinib was subsequently investigated as a treatment option for IBD^[58-61].

In a recently published phase III RCT, tofacitinib demonstrated efficacy for induction and maintenance of remission in patients with UC^[61], which led to its approval for treatment of moderate-to-severe UC^[62]. More specifically, 40.6% of patients treated with 10 mg tofacitinib twice daily achieved remission at week 52 as the primary endpoint as compared to 11.1% of patients treated with placebo^[61]. Of note, in patients with CD, tofacitinib did not reach its primary endpoints including clinical response or remission at week 26 of maintenance in a phase IIb clinical trial^[58]. In detail, clinical response or remission rates for treatment with 10 mg twice daily were

55.8% compared to 38.1% with placebo treatment, which was not significantly different. The lack of clinical response to tofacitinib treatment in patients with CD was further confirmed by the observation of worsening disease activity in 19.3% of patients treated with 10 mg twice daily in an open-label 48-week extension phase II clinical trial^[63] which led to premature termination of the trial. However, in the phase IIb trial, biomarkers of inflammation such as C-reactive protein were different in both cohorts with increasing levels in the placebo group and stable levels in the treatment group indicating a likely treatment effect of tofacitinib even in patients with CD^[58]. There is ongoing debate regarding the possibility of lack of therapeutic efficacy being explained by an unusually high placebo rate and the small sample size of the study. On the other hand, the lack of superiority of tofacitinib over placebo in patients with CD in clinical trials might also reflect different pathogenic roles of JAK/STAT-signaling in UC and CD^[64,65].

Previous data from our own group demonstrated that a more regulatory monocyte phenotype was induced by tofacitinib at adequate dosage under inflammatory conditions^[66]. In line with the observations from clinical trials, the regulatory impact of tofacitinib was stronger in monocytes derived from patients with UC as compared to CD^[66]. These observations led to the hypothesis that the JAK/STAT pathway might be differentially activated in UC, mediating stronger inflammatory responses compared to CD. Therefore, we summarize and discuss the available evidence on JAK/STAT-signaling in patients with UC and CD in different cell compartments as well as the genetic association and further discuss the clinical implications.

JAK/STAT-SIGNALING IN IBD: T-CELLS

The JAK/STAT pathway has a crucial impact on the regulation of T-cell differentiation. Additionally, dysregulated JAK/STAT-signaling leading to aberrant T-cell differentiation as well as defective regulatory T-cell activity has been suggested as important in IBD pathogenesis^[43,67-70]. Excessive T-cell activation and infiltration of the colonic mucosa has been observed in both CD and UC^[70,71], but the precise role of T-cells in both phenotypes is still a matter of debate. Historically, aberrant Th1 differentiation and associated cytokines (like IFN γ and IL-2) were predominantly associated with the pathogenesis of CD^[72] and Th2-cell-associated cytokines with UC^[73]. However, this concept has partially been abandoned as the contribution of different T-cell subsets infiltrating the intestinal mucosa is far more complex and has been demonstrated as a core player in the pathogenesis of both entities^[69,74,75]. Differences in the JAK/STAT-signaling in T-cells obtained from UC and CD have also been described, which may lead to similar but incongruent T-cell differentiation in both entities.

Most studies assess STAT-signaling as a surrogate marker for JAKs. Before we focus on IBD-related aberrant STAT-signaling in the T-cell compartment, we summarize the impact of JAK/STAT-signaling on T-cells in experimental colitis. Available data on T-cell attributed STAT expression/activation in UC and CD has also been summarized in [Figure 2](#).

Experimental colitis

T-cell-associated IFN γ induced a reduction in epithelial integrity and Paneth cells in mouse crypt enteroids, and led to exacerbation of radiation colitis^[76]. This effect could be abolished by JAK1,2 inhibition indicating the important impact of the JAK/STAT pathway in T-cell-mediated impairment of the intestinal barrier. Furthermore, several anti-inflammatory molecules ameliorating disease activity in experimental colitis are associated with modulation of JAK/STAT-signaling in lymphocytes. In detail, decreased expression or activation of JAK1 and JAK2^[77], STAT1^[77], STAT3^[77-79] and STAT4^[77,79] as well as enhancement of STAT5^[78] phosphorylation in T-cells, have been linked to effective pharmacological treatment of DSS-induced murine colitis and TNBS-induced rat colitis. Additionally, inflammatory activity was reduced by general STAT1 knockout in DSS-treated STAT1-null mice^[80] and by specific inhibition of STAT1 in T-cells in TNBS-induced colitis^[81]. Furthermore, knockdown of TYK2 ameliorated DSS-induced and TNBS-induced murine colitis possibly due to reduced Th1 and Th17 activity^[82]. In addition, in murine colitis, STAT6/Th2-linked cytokine IL-4 is associated with reduced Treg induction^[83,84]. In contrast to this, STAT6-deficient mice were shown to be protected against experimental colitis, partially due to reduced Th2 cytokines^[85].

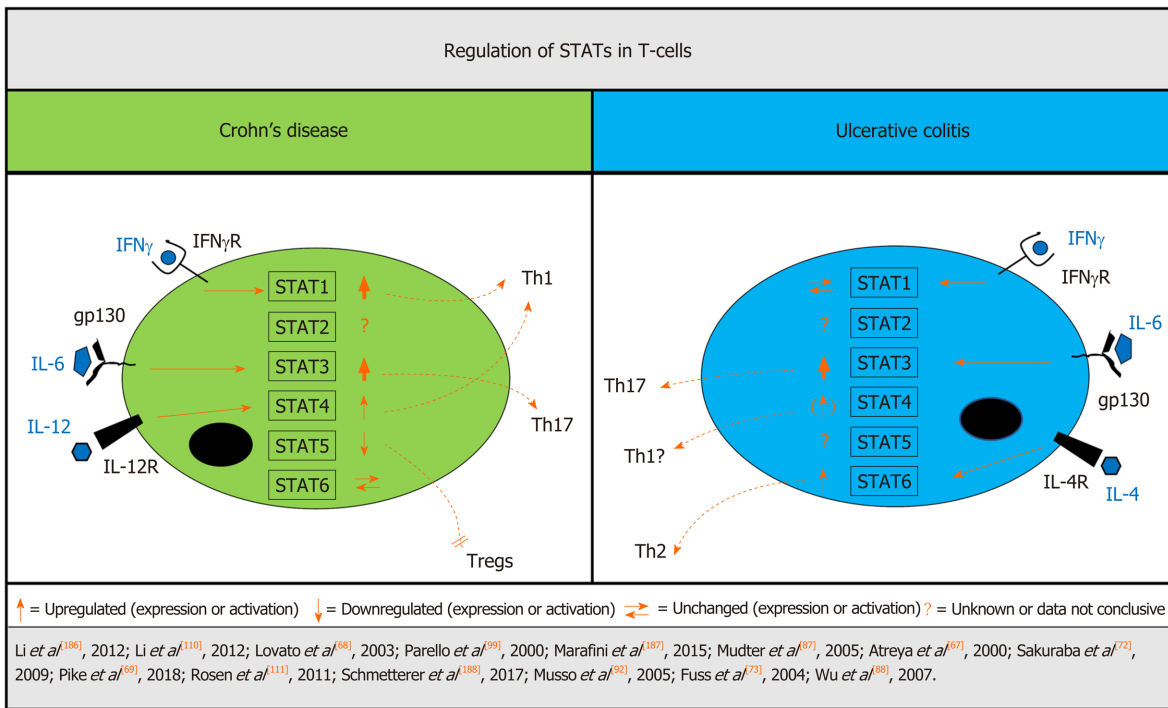


Figure 2 Differentially regulated STATs in T-cells from patients with inflammatory bowel disease. In T-cells, signal transducer and activator of transcription (STAT)1 signaling is increased in Crohn's disease (CD) but not ulcerative colitis (UC), while STAT3 is associated with a critical role in both UC and CD pathogenesis and overactivation is linked to increased intestinal inflammation. There is stronger evidence of STAT4 signaling in CD but STAT4 induction is also apparent in UC, while the STAT6 pathway seems to be more affected in UC. Down-regulation of STAT5 in CD leads to inhibition of regulatory T-cells. Strength of arrows indicates available supporting data. CD: Crohn's disease; IFN: Interferon; IFN γ -R: Interferon γ receptor; IL: Interleukin; IL4R: Interleukin 4 receptor; IL12R: Interleukin 12 receptor; STAT: Signal transducer and activator of transcription; Th: T-helper cell; Treg: Regulatory T-cell; UC: Ulcerative colitis.

STATs

STAT1 is closely linked to IFN γ -receptor signaling and has an important involvement in Th1 differentiation^[86]. Mudter *et al.*^[87] found increased IFN γ -induced STAT1 but not phospho-STAT1 in lamina propria T-cells of CD compared to patients with UC. Similarly, elevated gene expression of STAT1 as well as that of other IFN γ -Th1-related genes was detected by Wu *et al.*^[88] in colonic biopsies of patients with CD but not UC. Of note, the latter study did not provide cell specific investigations or analysis of STAT1 on protein level. Taken together, these data confirm an important role for STAT1-associated Th1 response in CD.

STAT2 is associated with type I IFN signaling^[89]. So far, only a trend towards decreased STAT2 gene expression in lamina propria mononuclear cells (LPMC) from patients with active UC and CD has been reported^[87] without further available data on STAT2 signaling in IBD.

In contrast, the impact of STAT3 in T-cell differentiation has been widely investigated. JAK1, JAK2 and TYK2 are involved in the activation of STAT3^[29] and increased STAT3 activation and signaling contributes to pathogenic Th17 differentiation and promotion of inflammation^[45], and is involved in the pathogenesis of UC and CD^[74,75]. However, STAT3 has also been linked to IL-10-dependent regulatory features of Tregs^[90,91] and the definitive role of STAT3 in T-cell regulation and its contribution to IBD has not been finally elucidated. Various studies on T-cell-associated STAT3 signaling have demonstrated increased levels of STAT3 and phospho-STAT3 in mucosal tissue samples from patients with UC and CD^[67,68,87,92]. Furthermore, Jin *et al.*^[93] performed transcriptomic and proteomic analyses of colonic biopsies and demonstrated that the inflammatory response of the IL-6-JAK/STAT3 signaling pathway was positively enriched in CD and UC samples. T-cells represent a large population of immune cells in the intestinal mucosa^[94] but whether these data could be attributed to only T-cells is not clear, as no cell compartment specific analysis was performed. Specific analyses of STAT3 signaling in CD-derived intestinal T-cells revealed constitutive STAT3 activation^[68] with IL-6-attributed induction of downstream anti-apoptotic genes^[67]. Furthermore, impaired STAT3-regulating mechanism has been identified in IBD. In a healthy environment, the phosphatase DUSP2 is induced by activation of T-cells and inhibits STAT3. Impaired DUSP2

expression is associated with enhanced STAT3 signaling and Th17 induction^[45]. It is noteworthy that DUSP2 has been demonstrated to be decreased in peripheral blood samples derived from patients with UC and active disease flare^[45]. However, no direct comparison with CD patients has been performed to date and no studies have investigated the role of DUSP2 in CD to date. Another STAT3-regulating factor is the protein tyrosine phosphatase PTPN2, which is linked to prevention of auto-reactivity in the context of T-cell homeostasis by STAT3 dephosphorylation^[95]. Deficiency of PTPN2 is associated with autoimmunity by increased lymphocyte activation^[96] and PTPN2 genetic risk locus with loss of function has been linked to CD^[95]. Taken together, impaired direct or indirect STAT3 regulation leading to increased STAT3 activation seems to be involved in both UC and CD pathogenesis, even though underlying mechanisms might partially differ.

The role of STAT4 in T-cells has been well described and various studies demonstrated an IL-12-triggered STAT4-dependent development of IFN γ -secreting Th1-cells^[97,98]. Available data on STAT4 in colonic tissue samples from patients with IBD are controversial; while increased IL-12-dependent expression and activation of STAT4 in T-cells from colonic mucosa was found in CD^[68] associated with IL-12-dependent Th1 polarization^[99], no increased T-cell-associated STAT4 signaling was detected in patients with UC^[99]. In contrast to these studies, increased STAT4 was found in the mucosa of adult^[100] and pediatric patients with UC but not in patients with CD^[101]. However, subtype analyses of intestinal cells were not performed in the latter studies, thus data can only speculatively be linked to STAT4 signaling in T-cells. In summary, published evidence of increased T-cell-associated STAT4 signaling in CD is strong, emphasizing the important role of Th1 response in CD pathogenesis. In UC, increased STAT4 signaling was also detected, but direct linkage to T-cells was not investigated: Thus, Th1 response may also play a distinct role in intestinal inflammation in UC but still remains a matter of debate.

STAT5 is mainly linked to induction of regulatory FoxP3⁺T-cells (Tregs)^[102] and limitation of Th17 differentiation *via* IL-2^[103], while Treg development is negatively controlled by STAT3^[104] and thus disruption of the STAT3/STAT5 balance might shift T-cell differentiation towards Th17 development^[46]. Tregs can limit autoimmunity, but in IBD, Tregs are not able to control inflammation due to increased induction and differentiation of effector T-cells^[105,106]. Direct data on STAT5 in IBD T-cells are scarce. In CD, $\alpha 4\beta 7^+$ CD4⁺cells, which are strongly associated with gut-homing lymphocytes, show decreased induction of pSTAT5 in response to IL-2, while pSTAT3⁺cells were increased after specific stimulation^[107]. However, data on T-cell-associated STAT5 signaling in UC are still missing.

STAT6 is associated with Th2 differentiation^[108,109]. Although Mudter *et al*^[87] found no increased STAT6 expression in LPMCs in IBD patients, there was increased activation of STAT6 in colonic tissue of inactive UC^[110] as well as specifically in LPMCs in UC, in contrast to lower levels in CD^[111]. It is noteworthy that T-cells represent the largest immune cell population of LPMCs; however, no specific T-cell analysis was performed. Nevertheless, both studies point to the overactivation of STAT6 in UC, which further underlines the importance of the Th2 response in UC pathogenesis, while in CD the role of STAT6 remains unclear.

JAK/STAT-SIGNALING IN IBD: MONOCYTES AND MONOCYTE-DERIVED CELLS

Monocytes are central to our health as uncontrolled and sustained inflammation can lead to auto-inflammatory syndromes and sometimes to autoimmune diseases. Monocytes can be a driving force in such diseases when their ability to also contribute to the resolution of inflammation is impaired. Therefore, anti-inflammatory mechanisms of monocytes, are of vast importance for downregulation and resolution of inflammation^[112-115]. As an example, we recently demonstrated that GM-CSF-activated monocytes also have regulatory capabilities such as in the induction of Tregs from naïve T-cells in *in vitro* co-cultures thus leading to amelioration of experimental colitis in mice *in vivo*^[116,117]. Furthermore, in IBD, monocytes are key players and function as effectors of inflammation^[118-120], presumably because most intestinal macrophages are replenished by peripheral monocytes from the circulation^[121,122]. In the intestine, recruited monocytes immediately adapt to the local environment. When they replenish intestinal monocytes during homeostasis, they become tolerogenic, but they differentiate into inflammatory drivers in the presence of intestinal inflammation^[123] which turns monocytes into important targets for treatment.

JAK/STAT-signaling does play decisive roles in monocyte-differentiation and regulation of monocyte-activation^[66,124]. For example, de Vries *et al*^[124] demonstrated that JAK1/STAT1 inhibition resulted in a prominent switch of macrophages from pro-inflammatory M1-like to a more regulatory M2-like phenotype, which leads to an enhanced recovery in acute rescue DSS-colitis. Similarly, JAK1/3 inhibition dose-dependently leads to a predominant M2-like phenotype shift of human monocytes derived from healthy volunteers and patients with IBD accompanied by an increased anti-inflammatory potential reflected by enhanced Treg induction^[66].

JAK/STAT

In monocytes, STAT1 activation *via i.e.*, IFN γ R is believed to be strongly inflammatory^[125,126]. Schreiber *et al*^[127] showed that patients with active UC had significantly higher levels of STAT1 expression and activation in colonic tissue compared to active CD, which could be predominantly attributed to infiltrating peripheral neutrophils and monocytes/macrophages. Among other regulatory mechanisms, STAT activation is inhibited by proteins of the suppressor of cytokine signaling (SOCS) family^[128-131] and SOCS3 and SOCS1 are involved in STAT1 regulation. Indeed, Schreiber and colleagues^[127] further detected that increased STAT1 activation was associated with distinctly lower mucosal SOCS3 protein levels in UC compared to patients with CD. In contrast, Soendergaard *et al*^[132] found SOCS1 and SOCS3 mucosal RNA level to be upregulated in an inflammation-dependent manner in UC compared to controls; however, no patients with CD were included in this study and direct comparison is missing.

Opposite to STAT1, STAT3 is associated with a more protective role in myeloid cells against inflammation and seems to be important for mucosal homeostasis^[43,133,134]. In their mouse study, Takeda *et al*^[43] genetically disrupted STAT3 in macrophages and neutrophils resulting in chronic enterocolitis induced by high levels of pro-inflammatory cytokines. Furthermore, the suppressive effects of IL-10 on macrophages and neutrophils were completely abolished in mice lacking STAT3 in these cells, further emphasizing the importance of STAT3 signaling in the regulation of inflammation^[43]. Depending on the environmental stimuli, monocytes, when leaving the bloodstream, can differentiate into macrophages and dendritic cells (DCs). An analysis of STAT activation in subsets of DCs from patients with CD revealed enhanced IL-10-induced STAT3-signaling in myeloid DCs^[135]. The study did not include patients with UC, so the role of STAT3 in UC-derived DCs remains unclear. Monocyte-specific expression of other STAT members including STAT2, STAT4, STAT5 and STAT6 has not yet been studied in IBD in detail. Available data on STAT expression/activation in monocytes and -derived cells in UC and CD are summarized in [Figure 3](#).

Taken together, the contribution of JAK/STAT in IBD-derived myeloid cells in driving inflammation cannot be elucidated yet due to the scarcity of available data. However, STAT1 seems to be particularly increased in monocytes/macrophages in UC but not CD, which is possibly linked to an insufficient mechanism to regulate STAT1 signaling, and hints at a more pro-inflammatory phenotype of monocytes/macrophages in UC compared to CD.

GENETIC ASSOCIATION OF IBD AND THE JAK/STAT PATHWAY

For IBD, more than 250 genome susceptibility loci could be specified, of which some reveal an association with the JAK/STAT pathway^[136-139]. However, systematic analysis and comparison of the JAK/STAT components and associated genetic risk loci in UC and CD are scarce. We therefore summarize the available studies on JAK/STAT-associated susceptibility genes in IBD and elucidate the similarities and differences in UC *vs* CD in the next paragraphs and in [Table 1](#)^[136,138-158].

JAKs

To date, the genetic risk loci associated with JAK1 have not been identified in IBD. This appears reasonable, as JAK1-deficient mice are non-viable^[159,160], which underlines the fundamental involvement of JAK1 in cell signaling as essential for survival^[160,161]. Similarly, JAK3-linked genetic risk loci have not been detected in IBD so far. Patients suffering from genetic defects in JAK3 develop severe combined immunodeficiency without specificity for IBD^[161,162].

In contrast, an association of JAK2 gene variants with both UC and CD has been clearly shown in various studies^[136,138,140]. Especially the IBD risk locus rs10758669

Table 1 Genetic association between JAK/STAT-signaling and the development of inflammatory bowel disease

	Ulcerative colitis	Crohn's disease
JAK1	No association found to date	No association found to date
JAK2	Yang <i>et al</i> ^[140] , 2011 Barrett <i>et al</i> ^[136] , 2008 Wellcome trust case control Consortium ^[138] , 2007 Anderson <i>et al</i> ^[141] , 2009 Zhang <i>et al</i> ^[142] , 2014 Hedl <i>et al</i> ^[143] , 2016 Cleynen <i>et al</i> ^[144] , 2013: N/A Ferguson <i>et al</i> ^[145] , 2010: N/A Prager <i>et al</i> ^[146] , 2014: No association	Yang <i>et al</i> ^[140] , 2011 Barrett <i>et al</i> ^[136] , 2008 Wellcome trust case control Consortium ^[138] , 2007 Anderson <i>et al</i> ^[141] , 2009 Zhang <i>et al</i> ^[142] , 2014 Hedl <i>et al</i> ^[143] , 2016: N/A Cleynen <i>et al</i> ^[144] , 2013 Ferguson <i>et al</i> ^[145] , 2010 Prager <i>et al</i> ^[146] , 2014
JAK3	No association found to date	No association found to date
TYK2	Can <i>et al</i> ^[147] , 2015 Lian <i>et al</i> ^[148] , 2013 Sato <i>et al</i> ^[149] , 2009: No association	Can <i>et al</i> ^[147] , 2015 Lian <i>et al</i> ^[148] , 2013: No association Sato <i>et al</i> ^[149] , 2009
STAT1	No association found to date	No association found to date
STAT2	No association found to date	No association found to date
STAT3	Barrett <i>et al</i> ^[136] , 2008 Wellcome Trust Case Control Consortium ^[138] , 2007 Anderson <i>et al</i> ^[150] , 2011 Willson <i>et al</i> ^[151] , 2012: N/A Zhang <i>et al</i> ^[142] , 2014 Prager <i>et al</i> ^[146] , 2014: No association	Barrett <i>et al</i> ^[136] , 2008 Wellcome Trust Case Control Consortium ^[138] , 2007 Anderson <i>et al</i> ^[150] , 2011 Willson <i>et al</i> ^[151] , 2012 (pediatric patients) Zhang <i>et al</i> ^[142] , 2014 Prager <i>et al</i> ^[146] , 2014
STAT4	Glas <i>et al</i> ^[152] , 2010: No association Diaz-Gallo <i>et al</i> ^[153] , 2010 Liu <i>et al</i> ^[139] , 2015	Glas <i>et al</i> ^[152] , 2010 Diaz-Gallo <i>et al</i> ^[153] , 2010: No association Liu <i>et al</i> ^[139] , 2015: No association
STAT5	Huang <i>et al</i> ^[154] , 2015 (STAT5A/STAT3 haplotypes): No association	Huang <i>et al</i> ^[154] , 2015 (STAT5A/STAT3 haplotypes)
STAT6	Klein <i>et al</i> ^[155] , 2015: No association Xia <i>et al</i> ^[156] , 2003: No association Chua <i>et al</i> ^[157] , 2016: No association de Jong <i>et al</i> ^[158] , 2003: No association	Klein <i>et al</i> ^[155] , 2015 Xia <i>et al</i> ^[156] , 2003: No association Chua <i>et al</i> ^[157] , 2016: No association de Jong <i>et al</i> ^[158] , 2003: No association

JAK: Janus kinase; N/A: Not investigated in this cohort; STAT: Signal transducer and activator of transcription.

within the JAK2 region has been widely investigated. Alongside associations with both UC and CD^[136,141,142], gain of function of this gene variant including increased JAK2 signaling in macrophages of patients with UC and healthy donors carrying the rs10758669 CC genotype was shown^[143]. Furthermore, in CD, the JAK2 variant rs10758669 was associated with a more complicated disease course and shorter time interval to stenosis occurrence^[144,145]. Increased intestinal permeability was detected in patients with CD with the C risk allele within this JAK2 variant, which might hint at JAK2 being involved in increasing permeability in IBD as a possible pathomechanism^[146].

The available data of TYK2 gene polymorphism and IBD association are rare and

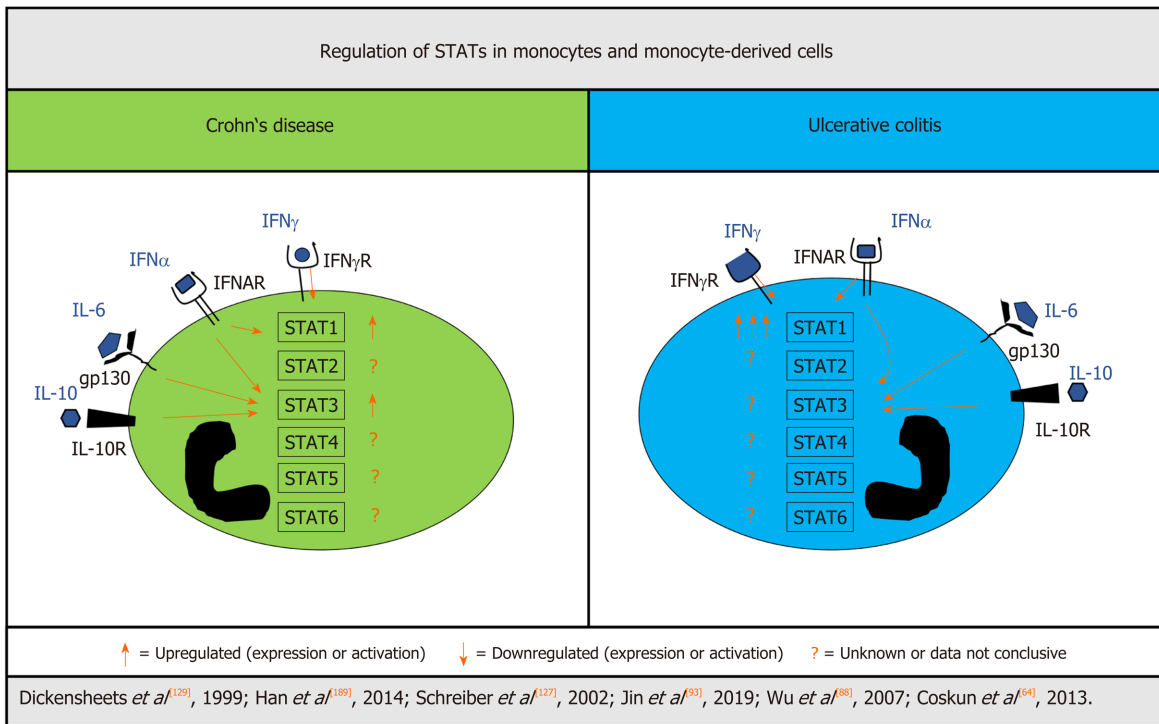


Figure 3 Differentially regulated STATs in monocytes and monocyte-derived cells from patients with inflammatory bowel disease. Signal transducer and activator of transcription (STAT)1 activation seems to be different in myeloid cells of patients with Crohn's disease (CD) and ulcerative colitis (UC). Although induced in CD, STAT1 is greatly elevated in monocytes and monocyte-derived cells from UC. There is evidence for increased STAT3 signaling in CD, while UC was not investigated. For STAT2, STAT4, STAT5, and STAT6 there are no solid data available from patients with IBD. Count of arrows indicates strength of increase in a direct comparison of UC and CD. CD: Crohn's disease; IFN: Interferon; IFNAR: Interferon α receptor; IFNγ-R: Interferon γ receptor; IL: Interleukin; IL10R: Interleukin 10 receptor; STAT: Signal transducer and activator of transcription; UC: Ulcerative colitis.

divergent. Although TYK2 has been identified as a susceptibility gene for both UC and CD in the Turkish population^[147], in Malaysian patients no association between CD and TYK2 genes has been detected^[148]. Conversely, in the Japanese population, a strong association of TYK2 with CD, but not UC was found^[149].

STATs

Contrary to STAT1/STAT2, for which no genetic association for UC or CD has been found to date, STAT3 gene variants have been distinctly associated with susceptibility for both, CD and UC^[136,138,150,163]. Willson *et al*^[151] analyzed STAT3 genetic variant rs744166 and demonstrated that pediatric patients with CD carrying STAT3 "A" risk allele revealed enhanced STAT3 activation in intestinal tissue and increased signaling linked to intestinal leukocyte homing. A meta-analysis including 10298 patients with CD and 4244 patients with UC, which further evaluated this STAT3 variant, confirmed the (A) allele to increase susceptibility for both UC and CD^[164]. Of note, Caucasian carriers of the (A) allele were more susceptible to UC and CD as compared to other ethnicities^[164].

Available data on STAT4 genetic variants linked with UC or CD are divergent. Jostins *et al*^[137] detected an increased association of STAT4 polymorphisms with IBD in general without specific association with either UC or CD. Glas *et al*^[152] investigated STAT4 genetic variant rs7574865 and found an association with colonic disease manifestation and early onset of disease in CD without increased UC susceptibility. Conversely, two studies identified an association of rs7574865 with increased risk for UC but not CD^[139,153].

Specific polymorphisms in the STAT5 gene locus have not been detected for IBD to date. However, Huang and colleagues^[154] identified that STAT5A/STAT3 haplotypes were generally linked to IBD and to CD.

The data on STAT6 genetic variants and IBD susceptibility are also rare: In a small study, comprising 243 patients with CD and 100 patients with UC, Klein *et al*^[155] detected a link between STAT6 gene risk locus G2964A (rs324015) and the subgroup of patients with CD, which revealed no variation in the CARD15 gene. However, the association of CD with STAT6 polymorphism rs324015 could not be confirmed by other studies^[156-158], which suggests that STAT6 gene variants may not have an

important involvement in IBD susceptibility.

JAK/STAT-associated signaling and regulation

A distinct genetic association has been shown for specific protein tyrosine phosphatases (PTPs) which are involved in regulation of JAK/STAT-signaling. Among those, PTPN22, which is linked to the regulation of STAT1 and Th1^[69,165-167], has been detected as a risk gene for CD susceptibility without an association to UC^[137,150]. Surprisingly, PTPN22 variant rs33996649 was identified as protective against CD, while it is associated with an increased risk for other autoimmune diseases^[136,153,168]. Similarly, genetic variants of PTPN2, which is associated with regulation of STAT1 and STAT3 phosphorylation, were found to be linked to CD but not UC^[138]. In detail, patients with CD carrying PTPN2 loss-of-function variant rs1893217 showed increased Th1- and Th17-related transcription factors and cytokines. Similarly, STAT1/3 activation, which is associated with Th1 and Th17 differentiation, was increased in PTPN2-/-CD4 T-cells^[95]. However, in a large meta-analysis, associations between PTPN2 gene polymorphisms and both CD and UC were found, which emphasizes the importance of PTPN2 and associated regulation of STAT1/3-linked Th1 and Th17 differentiation in both entities^[169]. For PTPN11, regulating STAT1 signaling^[81,170], a genetic association with UC but not CD was found^[171]. Furthermore, in DSS-induced colitis, conditional PTPN11 knockout in T-cells increased colitis severity^[172] stressing the important role of PTPN11 in colitis pathogenesis. Additionally, several studies have identified a marked association between the cytokine receptor IL-23R and IL-12R genes, which are both linked to Th17 differentiation, in both UC and CD^[137,141,150,173]. The relevance of IL-23 and IL-12 signaling on IBD pathogenesis is further confirmed by the therapeutic efficacy of the IL-12/IL-23 blocker ustekinumab in both entities.

CLINICAL IMPLICATIONS

Regarding the summarized data, it becomes evident that aberrant signaling of various direct and indirect components of the JAK/STAT pathway are critically involved in initiation and/or perpetuation of inflammation in both UC and CD. Dysregulated JAK/STAT-signaling is possibly linked to specific JAK/STAT-associated genetic predispositions and is partially cell subset specific with different signaling aberrations in the innate *vs* adaptive immunity. With the regulatory drug approval of the pan-JAK inhibitor tofacitinib, therapeutic inhibition of the JAK/STAT pathway is available for the clinical management of patients with UC. While the OCTAVE study program has proven the efficacy of tofacitinib for UC, some questions regarding its safety in terms of herpes zoster infection^[61] and pulmonary embolism have occurred recently as severe adverse events in patients treated twice daily with 10 mg tofacitinib were observed^[174]. Furthermore, tofacitinib revealed no effective response in CD compared to placebo in a phase II RCT^[58]. These data underline that adequate selection of patients with UC for tofacitinib treatment is key.

Selective JAK/STAT-inhibition

Targeting JAK/STAT components more precisely rather than inhibiting the complete pathway appears promising to limit adverse events and potentially improve clinical response in CD. Various compounds associated with selective JAK inhibition, including filgotinib and upadacitinib as predominantly JAK1-selective inhibitors, are currently under clinical investigation for IBD, while upadacitinib has most recently been approved for the treatment of RA^[175,176]. Filgotinib has entered a phase III RCT due to promising results in moderate-to-severe CD including induction of clinical remission and mucosal healing^[177]. Results from the phase II RCT with upadacitinib also show dose-dependent favorable outcomes with 27% clinical remission rates in patients with CD treated with 6 mg twice daily^[178] and phase III studies in CD and UC are ongoing (NCT03006068, NCT03345836). Furthermore, the JAK3-selective inhibitor Pf-06651600 and dual JAK1/TYK2 inhibitor Pf-06700841 are currently being investigated in phase II RCTs for CD (NCT03395184) and UC (NCT02958865). Additionally, the agent BMS-986165 is a selective TYK2 inhibitor leading to blockade of IL-12-, IL-23-, and type I IFN signaling^[179] and is being investigated in moderate-to-severe CD in a phase II RCT (NCT03934216). The intestinally restricted pan-JAK inhibitor TD-1473 is also under investigation in a phase II RCT in CD (NCT03635112) and a phase II study is planned for UC (NCT03920254).

However, since all JAKs are involved in complex biological processes, which control a wide range of cellular responses, inhibition of a specific JAK may lead to imprecise

outcomes including both inhibition of regulatory and inflammatory pathways as well as unwanted side effects. Thus, specific inhibition of STATs as downstream effectors of JAK/STAT-signaling might be the next step in using the JAK/STAT pathway as a therapeutic target. However, therapeutic agents investigated in IBD still target JAKs and to our knowledge, no STAT inhibitor has been established for IBD treatment to date, which might be due to certain challenges: STATs lack catalytic activity and pharmacological targeting is complex compared to the kinase domains of JAK, which represent distinct targets for therapeutic inhibition^[31]. Nevertheless, STAT inhibitors are currently under investigation in several oncologic diseases such as acute myeloid leukemia or recurrent malignant glioma^[80]; thus, the investigation of pharmacological STAT targeting might also be prospectively possible in IBD.

Cell specific targeting

Of note, in considering JAK/STAT-signaling as a therapeutic target, one should take into account that STATs are associated with partially counter-directional functions in different cell compartments. Namely, STAT3 has different function in monocytes and monocyte-derived cells (innate immune system) with rather regulatory features *i.e.*, IL-10 release, while in T-cells (adaptive immune system) STAT3 is strongly pro-inflammatory involved in Th17 differentiation. It needs to be emphasized that an important regulatory impact of the innate immune system was suggested for CD^[43]. This is supported by the fact that in myeloid cells of patients with CD, STAT3 reveals strong activation^[35], while pro-inflammatory STAT1 is significantly lower in its expression and activation in myeloid cells of intestinal tissue of active CD compared to UC^[27]. Furthermore, our own observations demonstrate higher levels of pro-inflammatory cytokines including TNF α and IL-6 in a pro-inflammatory setting and a stronger susceptibility to regulatory tofacitinib treatment in UC compared to CD-derived monocytes^[66]. These data underline the suggestion of myeloid cells as part of the innate immune system which possibly plays a less inflammatory and more regulatory role in CD compared to UC. The pan-JAK inhibitor tofacitinib revealed no significant efficacy in CD and a possible explanation might be the broad JAK/STAT inhibition which targets T-cell associated inflammatory signaling^[7] but might simultaneously inhibit important regulatory responses in myeloid cells in CD. Indeed, the impact of JAK inhibition specifically on myeloid cells is controversial: Some studies describe an effective inhibition of pro-inflammatory responses by JAK blockade^[7,181], while conversely, upregulated pro-inflammatory signaling has also been described^[82,183]. During intestinal injury, peripheral monocyte recruitment to intestinal tissues is increased, which are pro-inflammatory and primed in an inflammatory environment to contribute to inflammatory outcomes^[66,184,185]. Thus, induction of pro-inflammatory myeloid cells by broad JAK inhibition might contribute to its sustained impact on intestinal inflammation. With regard to that, cell subset-specific JAK/STAT targeting has been suggested as a future therapeutic strategy in IBD to improve efficacy^[43], especially in CD.

Consideration of different genotypes

Last but not least, data on JAK/STAT components as genetic risk loci clearly indicate that patients with IBD reveal specific overlap and differences such as JAK2, STAT3 as common and STAT regulating PTP22 and PTPN11 as potential different genetic risk loci. In terms of an individualized therapy, genotypic adaptation of medical treatment or individualized drug dosing, which is already established for thiopurine treatment in patients with IBD by assessing TMPT genotypes, would be an elegant future clinical target for different JAK/STAT-associated genotypes. Hedl and coworker^[43] already demonstrated that monocyte-derived macrophages (MDMs) of patients with the JAK2 rs10758669 CC risk gene revealed enhanced JAK2 signaling and increased pro- and anti-inflammatory cytokines. In rs10758669 AA disease carrier-derived MDMs compared to C carrier-derived MDMs, lower doses of JAK2 inhibitor and tofacitinib changed decreasing to increasing inflammatory cytokines. These data further underline the need to adapt dosage or treatment to JAK-associated genotype. In addition to an improved individualized therapy, JAK-genotyping could be of use to anticipate disease course as was already shown for the JAK2 genetic variant rs10758669 and STAT4 genetic variant rs7574865, which were both associated with a complicated disease course in CD^[44,145,152].

SUMMARY

A clear assignment of JAK/STAT components to CD or UC pathogenesis is difficult due to pleiotropic and partially overlapping dysregulation of JAK/STAT molecules or its regulators. Nevertheless, some general conclusions can be drawn:

First, in T-cells, STAT3 is associated with a critical role in both UC and CD pathogenesis and over-activation is linked to increased Th17 response and intestinal inflammation. Aberrant T-cell linked STAT1 expression is predominantly detected in CD and STAT6 expression predominantly in UC, while there is evidence for dysregulation of STAT4 in both entities. These data indicate a partial confirmation of the Th1/CD and Th2/UC concept but also hint at a certain impact of Th1 in UC.

Secondly, the overlap of both UC and CD-associated risk genes STAT3, JAK2, IL23R and IL12R, all being involved in Th17-cell differentiation, further strongly underlines the contribution of dysregulated Th17 response to both UC and CD. Furthermore, risk loci of genes associated with Th1 differentiation were found in both UC and CD such as STAT4 in both entities and STAT1-regulating PTP22 in CD and PTP11 in UC, respectively. These data further underline the importance of Th1 response in CD but again emphasize an overlap of Th1-cells which also contributes to UC and weaken the hypothesis of the specific role of Th1 in CD.

Thirdly, in contrast to lymphocytes, the JAK/STAT pathway has a more regulatory impact on myeloid cells in IBD. Only STAT1, mainly increased in UC-derived myeloid cells, seems to be associated with rather inflammatory features which points to a more inflammatory role of the JAK/STAT pathway in UC than CD and might partially explain the clinical response to tofacitinib in UC compared to patients with CD.

CONCLUSION

To conclude, the summarized data strongly indicate that development of sophisticated JAK/STAT inhibitors might further improve the efficacy and safety profiles of this drug class and improve their positioning in the therapeutic algorithm. This might be achieved by specific targeting of JAK/STAT components or cell subset specific JAK/STAT inhibition in T-cells to minimize the effects of JAK/STAT blockade on myeloid cells. Finally, assessment of specific genotypes as part of a personalized treatment approach might not only increase safety and efficacy of JAK/STAT inhibition including optimized dosing, but could also serve as a predictive marker for disease course in CD.

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