Immune deficiency vs. immune excess in inflammatory bowel diseases—STAT3 as a rheo-STAT of intestinal homeostasis

Moritz Leppkes,* Markus F. Neurath,* Martin Herrmann,† and Christoph Becker*†

*Medical Clinic 1 and †Medical Clinic 3, University Clinic, Friedrich Alexander University, Erlangen, Germany

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ABSTRACT

Genome-wide association studies have provided many genetic alterations, conferring susceptibility to multifactorial polygenic diseases, such as inflammatory bowel diseases. Yet, how specific genetic alterations functionally affect intestinal inflammation often remains elusive. It is noteworthy that a large overlap of genes involved in immune deficiencies with those conferring inflammatory bowel disease risk has been noted. This has provided new arguments for the debate on whether inflammatory bowel disease arises from either an excess or a deficiency in the immune system. In this review, we highlight the functional effect of an inflammatory bowel disease-risk allele, which cannot be deduced from genome-wide association studies data alone. As exemplified by the transcription factor signal transducer and activator of transcription 3 (STAT3), we show that a single gene can have a plethora of effects in various cell types of the gut. These effects may individually contribute to the restoration of intestinal homeostasis on the one hand or pave the way for excessive immunopathology on the other, as an inflammatory “rheo-STAT”.


Introduction

The inflammatory bowel diseases IBDs, Crohn’s disease and ulcerative colitis, represent a major burden for afflicted patients, fueling a constant striving for therapeutic improvements. Understanding the etiopathogenesis of these diseases is crucial toward furthering that goal. In the current view, IBD arises from a dysregulated immune response in genetically susceptible individuals toward the commensal luminal flora, modified by environmental factors. In the past decade, there has been great progress in understanding the pathogenesis of IBDs [1]. That progress can primarily be attributed to major technological advances in the areas of GWAS and to analyses of experimental models employing genetically engineered mouse strains [2, 3]. The identification of IBD risk-conferring genetic loci and SNPs has provided a genetic backbone to guide further pathophysiological studies in established experimental models of disease [4]. This interdisciplinary interplay between genetics and pathophysiology has established novel concepts in intestinal inflammation during the past few years with potential translational relevance in the context of IBD [5, 6].

It is noteworthy that GWASs have highlighted a substantial overlap in genes conferring risk for IBD with those reportedly involved in PIDs or in immune-mediated diseases. This has renewed the long-standing discussion about whether IBD arises from an excess or a deficiency in the immune system [7]. PIDs are a group of rare, inherited disorders with defined defects in specific components of the immune system. Mostly, these immune defects result in increased susceptibilities to specific pathogens. Although defects of T cell-mediated lymphoid immunity, as in SCID, result in opportunistic infections (tuberculosis, cryptococcosis, toxoplasma, among others), defects in myeloid immunity, such as CGD, render individuals susceptible to pyogenic bacterial or fungal infections. The identification of the responsible genes has greatly advanced our understanding of the multiple arms of the immune system [8]. It is striking that many patients with PID not only suffer from infectious gastrointestinal diseases but also from noninfectious intestinal inflammation replicating features of IBD (Table 1) [9–42].

Experimental models of IBD provide crucial tools for understanding the pathophysiologic basis of risk-conferring genes [43] and may explain the overlap between IBD and PID. It is crucial that these studies supplement the genetic information provided by GWASs. The evidence derived from these models highlights the various modes from which intestinal inflammation may develop. In the following article, we will highlight the diverse effect of a single IBD–PID risk gene, STAT3, on various cell types and cellular functions. We show how alterations in certain components of the intestinal immune system might relate to a risk for IBD.

Abbreviations: AhR = aryl hydrocarbon receptor, APRT = aryl hydrocarbon receptor nuclear translocator, CD = cluster of differentiation, CGD = chronic granulomatous disease, CX3CR = CX3C chemokine receptor, GvHD = graft vs. host disease, GWAS = genome-wide association study, IBD = inflammatory bowel disease, IEC-KO = intestinal epithelial cell-specific deficiency, IEL = intraepithelial lymphocytes, ILC = innate lymphoid cells, PID = primary immunodeficiency, SCID = severe combined immunodeficiency, STAT = signal transducer and activator of transcription, TLR = toll-like receptor.

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1. Correspondence: Department of Medicine 1, Friedrich-Alexander-University Erlangen-Nuremberg Erlangen, Germany. E-mail: christoph.becker@uk-erlangen.de
STAT3 GENETICS—IBD MEETS IMMUNODEFICIENCY

The STAT3 gene encodes for at least 3 isoforms—α (p92), β (p83), and γ (p72)—with divergent functional properties [44]. STAT3 transduces the signals of diverse membrane-bound receptors to modify gene transcription. STAT3 has specific roles in the response to a plethora of mediators, including those of the IL-6 and IL-10 cytokine families (and IL-6, IL-10, IL-11, IL-19, IL-20, IL-21, IL-22, IL-24, IL-26, IL-27, IL-29, LIF, ciliary neurotrophic factor, CT-1, and oncostatin M, among others). When a cytokine of the IL-6 family binds its cellular surface receptor, the glycoprotein gp130 is recruited to the cytokine-binding receptor chain and acts as the core of a multiprotein receptor complex. Intracellular, autophosphorylation of receptor-associated tyrosine kinases, such as Jak1 or Jak2, finally lead to phosphorylation and activation of STAT3. The latter dimerizes and enters the nucleus, where it influences gene transcription. Another level of complexity is added by findings that further posttranslational modifications functionally alter STAT3, including acetylation [45], methylation [46], SUMOylation [47], and ubiquitination [48]. The observations that STAT3 can also localize to mitochondria (mitoSTAT3) and that nonphosphorylated STAT3 interacts with the NF-κB p65 subunit highlights the effects of this molecule, apart from its canonical signal transduction, and warrants further research [49, 50].

STAT3 is a prime example of a gene that has been implicated in the genetic basis of both PID and IBD. Dominant-negative mutations of the STAT3 gene lead to an autosomal-dominant primary immunodeficiency syndrome, in humans designated Job syndrome or hyper-IgE syndrome. These individuals suffer from skin eczema, recurrent (gram-positive) pneumonia, recurrent candidiasis, and alterations of facial morphology [51]. Somatic mutations in the SH2 domain that influence STAT3 dimerization are, furthermore, linked to T cell large granular lymphocytic leukemia, implicating STAT3 in T cell proliferative functions [24]. Activating germline mutations in the coding region of STAT3 have been found in multiple unrelated patients with an infantile-onset, multisystem autoimmune disease, including gastrointestinal inflammation and a delayed-onset, mycobacterial disease [25]. In a thorough characterization of the clinical manifestations of these patients, the gastrointestinal manifestations were described as either autoimmune enteropathy or lymphocytic colitis [52]. GWASs have first linked a polymorphism in the intronic region of the STAT3 gene (rs744166) to an increased risk of ulcerative colitis [53]. STAT3-risk haplotypes include a variety of SNPs (rs3809758, rs744166, rs1026916, rs12948909) associated with both major forms of IBD [54]. It has been shown that the IBD-related STAT3 polymorphism rs744166 correlates with an increased phosphorylation and activation of STAT3 in response to IL-6, an increased expression of STAT3 target genes, and a sustained neutrophil chemoattraction [55].

The analysis of GWASs of both IBD and PID has also renewed the debate about whether IBD and mycobacterial infection might be causally linked. Clinical studies aiming at mycobacteria in patients with IBD have largely failed to provide conclusive evidence [56]. However, these genetic studies have uncovered that a many loci that determine the risk of leprosy overlap with IBD-associated loci [2]. Furthermore, IBD-associated polymorphisms have been identified in most of the genes implicated in susceptibility to MSMD, including STAT3 [2, 52].

CELL-SPECIFIC FUNCTIONS OF STAT3 IN INTESTINAL INFLAMMATION

During IBD and in experimental models, STAT3 is activated in both the epithelial and hematopoietic compartments [57, 58]. As we will delineate below, it is crucial to dissect the role of STAT3 in a cell-specific manner because various phenotypically distinct diseases may arise depending on the cell type affected. This can be achieved with modern mouse genetics. The human intestine is the organ that harbors most of the body’s immune cells. The large surface area (approximately 30 m²) [59], adjacent to the world’s most densely inhabited ecosystem in the intestinal lumen [60], requires highly specialized and balanced responses to allow intestinal homeostasis [61]. Multiple studies have highlighted the complex, multidimensional interaction of the luminal microbiota and the host immune system [62–64]. Moreover, not only do immune cells of hematopoietic origin govern the intestinal immune response but also tissue-resident cells, such as in the intestinal epithelium, and lamina propria fibroblasts provide an essential contribution [63]. The following paragraphs will provide a glimpse into the pleiotropic functions of STAT3 in these cell types and its relation to intestinal inflammation (Fig. 1).

Epithelial immune deficiency

Although not regularly viewed as a key component of the immune system, the intestinal epithelium strongly participates in intestinal immune responses [65, 66]. It provides an important structural barrier, consisting of epithelial-derived mucus and cellular lining, which limits the amount of host immune–microbial interactions at the mucosal surface. It also actively shapes the luminal ecosystem via secretion of mucus and fluid and produces antimicrobial peptides [67]. The intestinal epithelium also orchestrates the host immune response and guides leukocytes to the sites of injury in a STAT3-dependent manner [68]. The intestinal epithelium consists of a diverse set of epithelial cell types, such as enterocytes, goblet cells, neuroendocrine cells, and Paneth cells, with versatile secretory and absorptive functions. Paneth cells, located at the bottom of small intestinal crypts, are specialized epithelial cells with immunologic functions. In recent years, these cells have gained increased attention in the context of IBD [69–73]. Indeed, products of several IBD-risk genes exert important functions within the intestinal epithelial immune response. This provides ample room
Table 1. Primary immunodeficiencies with described gastrointestinal affections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected gene</th>
<th>Affected cell types</th>
<th>Gastrointestinal manifestations</th>
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<tr>
<td>APECED</td>
<td>AIRE</td>
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<td>CD40 deficiency</td>
<td>CD40</td>
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<td>MHCI deficiency</td>
<td>CIT, RXF5, RXFAP, RXFANK</td>
<td>Antigen-presenting cells</td>
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<td>[29]</td>
</tr>
<tr>
<td>Autosomal recessive CGD (p22phox)</td>
<td>CYBA</td>
<td>Phagocytes</td>
<td>Granulomatous intestinal inflammation</td>
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<tr>
<td>X-linked CGD</td>
<td>CYBA</td>
<td>Phagocytes</td>
<td>Granulomatous intestinal inflammation</td>
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<td>Mucocutaneous candidiasis, IPEX-like enteropathy</td>
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<td>Multiple cell types</td>
<td>IPEX-like enteropathy, lymphocytic colitis, mycobacterial disease</td>
<td>[24, 25]</td>
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<td>Protracted diarrhea</td>
<td>[41]</td>
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<tr>
<td>XLP2</td>
<td>XIAP</td>
<td>Multiple cell types</td>
<td>Very early onset IBD</td>
<td>[42]</td>
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</table>

Primary immunodeficiency diseases as listed in the classification of the International Union of Immunological Societies, limited to those with a described gastrointestinal manifestation [13, 26–42]. APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; MHCI, major histocompatibility complex class II; XLp2, X-linked lymphoproliferative syndrome-2; XMEN, X-linked immunodeficiency with magnesium defect; Epstein-Barr virus infection, and neoplasia.

For the hypothesis of an epithelial immunodeficiency in the context of IBD [74], in recent studies, the STAT3 function in intestinal epithelial cells has been analyzed in vivo using mice carrying an intestinal epithelial cell-specific STAT3 deficiency (STAT3<sup>fl</sup>–/–). Interestingly, an epithelial STAT3 deficiency aggravated the course of experimental colitis [75] because STAT3 is vital in the transduction of IL-22-induced mucosal healing responses. STAT3 has been shown to exert essential effects in the context of epithelial wound healing, based on the support of epithelial survival, proliferation, and migration. STAT3 regulates the expression of prosurvival genes and cell cycle-related genes [76]. In another model, epithelial STAT3 signaling also proved host-protective in infectious colitis. In response to <i>C. rodentium</i>, mice defective in epithelial STAT3 signaling showed a markedly increased bacterial load, defective epithelial restitution, and a systemic spread of bacteria usually limited to the intestine by protective immune responses [77]. The IL-22–STAT3 axis dramatically regulates epithelial immunity in this model because antimicrobial peptides, such as Reg3β and Reg3γ, are strongly induced in intestinal epithelial cells in response to immune cell-derived IL-22 in a STAT3-dependent manner [78]. A recent study noted a regulatory effect from cytoplasmic STAT3 in autophagy; thereafter, cytoplasmic STAT3 modulates PKR activity and consequently represses autophagy [79]. Interestingly, this depicts the cross-talk of 2 cellular mechanisms, which have both been implied in the pathogenesis of IBD by GWAS. However, the importance of this axis in intestinal inflammation has not, to our knowledge, been studied. So far, many studies have relied on the Villin-Cre-guided STAT3 deletion, which affects all intestinal epithelial cell types. Therefore, there is little information on the specific function of STAT3 in the various epithelial cell types. It
has been proposed that STAT3 governs small intestinal stem cell renewal at the bottom of the crypts [80]. Especially regarding the central role of Paneth cells in ileal Crohn disease, it would be interesting to delineate the function of STAT3 in this cell type.

In agreement with STAT3-related intestinal epithelial immune function and its deficiency in rodent models, there is clinical data pointing to the role of epithelial immune deficiency in humans with Job syndrome, that is, patients with dominant-negative STAT3 display reduced levels of antimicrobial peptides in the saliva, which might contribute to Job syndrome-associated chronic mucocutaneous candidiasis [12]. However, no STAT3-specific evidence is yet available linking epithelial immune deficiency to human IBD.

**Myeloid immune deficiency or immune excess?**

Inflammatory responses are executed in a complex, multicellular environment. In this context, STAT3-mediated effects in one cell type can influence STAT3 activity in other cells, which was demonstrated in experiments employing epithelial STAT3 deficiency. Epithelial STAT3 deficiency was associated with increased STAT3 activation in infiltrating immune cells [81], presumably due to inflammatory cytokine signaling.

Myeloid cellular dysfunction may contribute to the pathogenesis of IBD. Specific defects in phagocyte function are associated with fistulizing enterocolitis in humans (Table 1) [82]. Foremost, the natural course of primary phagocyte deficiencies is linked to chronic fistulizing granulomatous enteritis, which is histologically indistinguishable from Crohn disease. Noninfectious granulomatous intestinal inflammation has been described in Chédiak-Higashi syndrome, Hermansky-Pudlak syndrome, Griscelli syndrome, and in up to 30% of patients with CGD caused by defective genes in the NADPH oxidase complex. This complex generates ROS and thus initiates the oxidative burst in phagocytes [28]. GWASs have linked genes of the NADPH oxidase complex (e.g., Ncf4) to susceptibility to IBD [83]. Segal and Loewi [84] proposed that neutrophil dysfunction occurs in patients with IBD, apart from the known primary phagocyte deficiencies and functional differences in neutrophil response in vitro that have been observed by various groups [85, 86]. The concept of how myeloid immune deficiency may lead to IBD is explained as an incomplete restitution of acute inflammatory attacks followed by the consecutive development of chronicity [7].

The transcription factor STAT3 has diverse effects in myeloid cells. As in epithelial cells, STAT3 exerts functions in proliferation and survival of myeloid cells [87]. Moreover, G-CSF/GM-CSF-induced differentiation of myeloid precursors depends strongly on functional STAT3 [88]. IL-10 induces tolerogenic effects in a STAT3-dependent manner. Defects in tolerogenic cytokine pathways, such as the IL-10 signaling pathway, contribute to the pathogenesis of IBD in experimental models: 20 yr ago, IL-10-deficient mice were found to develop severe experimental colitis spontaneously [89]. A more recent study found loss-of-function mutations in IL-10 receptor chains in 2 families with severe Crohn disease (Table 1) [90]. The myeloid-restricted deletion of STAT3 in neutrophils and macrophages also resulted in the development of spontaneous colitis [91], so the anti-inflammatory IL-10–STAT3 axis in myeloid cells is an established contributor to intestinal homeostasis. Disturbances in this pathway are classical examples of immune excess in IBD. STAT3-deficient myeloid cells produce more proinflammatory cytokines and chemokines than do their wild-type littermates [92]. However, a deficiency in the myeloid effector mechanisms because of STAT3 dysfunction cannot be ruled out. Recently, a thorough workup underlined the importance of IL-10 signaling in CX3CR1+ macrophages because a restricted deficiency in IL-10RA in CX3CR1+ macrophages was sufficient to cause spontaneous enterocolitis in mice [93]. This work, furthermore, nicely connected IL-10 signaling in macrophages to regulatory T cell-mediated immune limitations. Zigmund et al. [93] implied that differentially expressed lipid mediators were a consequence of myeloid STAT3 deficiency, yet functional evidence is missing.

In agreement with a fundamental role for lipid mediators, sphingosine-1-phosphate has been implicated in controlling STAT3-dependent inflammation [94]. Because of the pleiotropic role of STAT3 in myeloid cells, the debate will continue about which of the multitude of STAT3-dependent target genes and affected cellular mechanisms are responsible for the striking intestinal phenotype.

In conclusion, although dominant-negative STAT3 mutations do not lead to IBD, early onset IBD has been described in both the setting of IL-10 and IL-10 receptor deficiency (Table 1). Disease development might be explained by defective myeloid regulation and consecutive immune excess in these patients.

**Figure 1. Multiple cell-specific functions of STAT3 keep intestinal homeostasis in check.** T effector/ILC STAT3 activation directs a lymphocyte–epithelial antimicrobial axis via IL-22 leading to the epithelial STAT3-dependent up-regulation of antimicrobial peptides, such as Reg3β/γ. STAT3-dependent IL-17 production in T effector (Teff)–ILC populations guides neutrophil chemotraction. Epithelial STAT3 activation is crucial for mucosal healing responses in the control of proliferation, survival, and migration. An ARNT–STAT3 axis directs differentiation of IEL. STAT3 directs fibroblast collagen production in intestinal strictures [23]. STAT3 directs myeloid differentiation via G-CSF and GM-CSF/Rip3L in granulocytes and macrophages/dendritic cells, respectively. STAT3 limits myeloid activation via Treg-derived IL-10, and STAT3 in Tregs suppresses pathogenic Th17 differentiation.
Currently, this would rather qualify as a primary immune excess situation, whereas CGD-associated fusulating enteritis would preferentially be considered a primary myeloid immune deficiency.

**Lymphoid regulatory deficiency or effector excess?**

Patients with IBD often have dysbalances of effector Th cell subsets [95]. Regardless of which effector T cell lineage is involved in either Crohn disease or ulcerative colitis, compelling evidence highlights the presence of a protective effector–regulatory T cell balance in the human bowel [96]. A rare human condition, known as IPEX syndrome is caused by mutations of the regulatory T cell marker protein FOXP3 [97]. Patients die of multiorgan autoimmunity early in life, which also affects the intestine. This highlights the immensely important roles of suppressive T cell properties. The importance of the effector–regulatory T cell homeostasis in the bowel is underscored by an adoptive transfer model of colitis [98]; in the absence of these regulatory cell populations, CD4+CD45RBhigh CD25 cells were potently able to elicit colitis in T cell-deficient Rag1−/− mice, whereas adoptive transferring of unselected CD4+ T cells did not do so. Multiple transcription factors, including RORγt and STAT3, guide the differentiation of the IL-17A- and IL-17F-producing Th17 lineage, which has been implicated as a major driver of disease in this model [99]. The effector–regulatory T cell balance not only protects the healthy bowel from uncontrolled activation of the intestinal immune system but also corrects a dysbalanced T cell repertoire by transferring induced Treg to suppress colitis activity: TGFb-inducible Foxp3+ Treg were able to control inflammation in this T cell-dependent experimental colitis model [100]. It is noteworthy that the STAT3 rheostat is reportedly preeminent in modulating the effector–regulatory T cell balance to uphold intestinal homeostasis [101]. A recent study demonstrated that IL-1β tips this balance in an inflammatory micromilieu toward a STAT3-driven effector Th17 differentiation [102]. In these experiments, regulation of the rheostat STAT3 by repression of inhibitory Socs3 strongly overrode retinoic acid-induced iTreg development. The effects of Treg are mediated in part by the secretion of the tolerogenic cytokine IL-10 [103]. Deficiency in IL-10, IL-10RA, and IL-10RB lead to primary immune deficiency syndromes with clinical features of IBD (Table 1). As described above, T cell-derived IL-10 limits myeloid inflammation in part via macrophage STAT3 [104, 105]. Myeloid STAT3, on the other hand, can induce regulatory T cell populations fostering a synergistic anti-inflammatory cycle [106]. Treg with a Foxp3-restricted deficiency of STAT3 (Foxp3-Cre) were capable of suppressing T cell proliferation, yet failed to control Th17 differentiation. As a consequence, these mice suffered from fatal intestinal inflammation [107].

Given its crucial role in Treg, what is the function of STAT3 in effector T cell populations? STAT3 is an integrator of multiple signaling events of effector T cells. STAT3 supports the proliferation of T cells and guides IL-6/IL-21-induced Th17 cell differentiation [101, 108]. Chronic intestinal inflammation may also arise after bone marrow transplantation as a consequence of GVHD [109]. In this setting, CD4+ T cells displaying phosphorylated STAT3 are associated with acute GVHD, and the amounts of tissue-borne, STAT3-dependent Th17 cells also correlate with disease severity [110]. Inhibition of STAT3 signaling by over-expression of PIAS8-attenuated acute GVHD in a murine model [111] implements yet another regulator of the STAT3 rheostat. Apart from T cell-mediated immunopathology, STAT3 expressed in CD4+ T cells is also beneficial for the clearance of attaching/effacing pathogens in the intestine. Mice with a CD4+ T cell-restricted STAT3 deficiency suffered from a significantly prolonged disease course after infection with C. rodentium. In these experiments, T cell-borne STAT3 was crucial to evoking the IL-22-dependent epithelial antimicrobial defense [112]. In experimental infections with an enterotoxigenic variant of the commensal Bacteroides fragilis STAT3 was activated in both the epithelial and the immune compartments when clearance of infection failed. Chronic intestinal inflammation was associated with a STAT3-dependent Th17-type inflammation, and a loss of fecal enterotoxigenic B. fragilis shedding was associated with a decrease in STAT3 activation [113]. In Job syndrome, STAT3 deficiency is associated with a lack of Th17 cells, which might contribute to impaired antifungal immunity in these patients [114]. On the other hand, no increase of Th17 cells was observed in the patients with activating STAT3 mutations, whereas CD4+ CD25-Foxp3+ regulatory T cells were lacking [52].

Taken together, T cell immunity is tightly regulated, in part by the rheostat STAT3 and has an important role, especially in intestinal immunity. A dysregulation of the STAT3 pathway in T cells has detrimental consequences in the regulation of protective pathogen-directed immune responses and may pave the way for excessive immunopathology.

The B cell lineage is relatively neglected in the research on the pathogenesis of IBD [115]. Yet, polymeric IgA, produced by B cell-derived intestinal plasma cells, has an important role in the intestinal immune response. After its secretion, it is shuttled by polymeric immunoglobulin (poly-Ig) receptor to the basolateral surface of the intestinal epithelium for recycling and excretion through the epithelial junction [116]. Selective IgA-deficiency may predispose a patient to mucosal infections and can be found in patients suffering from autoimmune diseases [117], whereas a large fraction of patients remain asymptomatic. Pathogen-related IgA opsonizes its specific target organisms, whereas the amount of high-affinity IgA toward commensals is scarce and species-specific [118]. Phenotypic and functional alterations have been observed in B cells from patients suffering from IBD [119]. They have been found to constitutively produce IL-8, and relative changes in immunoglobulin isotypes were reported. STAT3 relays the response of B cells to cytokines, including IL-21. The IL-21–STAT3 axis contributes to the generation of human memory B cells and antigen-specific B cells. Additionally, STAT3 promotes proliferation and survival of naïve B cells [120]. Although the importance of STAT3 in B cells is well established, little is known about the influence of STAT3 polymorphisms on intestinal B cell function. B cells might indeed have a role in intestinal homeostasis: regulatory CD1dhi B cell populations have been described, which are characterized by the expression of IL-10 [121]. It is noteworthy that B cell deficiency in CD19−/− mice led to an aggravated disease course in chemically-induced colitis. This aggravation was reversed by the transfer of IL-10-producing B2 cells [122]. The regulatory role of B cells in intestinal immunity is also underscored by clinical case
reports, which observed the respective onset or exacerbation of ulcerative colitis after rituximab-mediated B cell depletion [123, 124]. On the other hand, a randomized controlled trial showed tolerance to this agent in patients with ulcerative colitis [9].

Studies in recent years have highlighted the function of ILC populations, which govern intestinal inflammatory responses before adaptive immune responses develop [63]. ILC populations closely parallel the described adaptive Th cell populations, including Th1/ILC1, Th2/ILC2 or Rorc-dependent Th17/ILC3. STAT3 in the innate lymphoid compartment protects against attaching/effacing pathogens in the early phase of defense [22]. Mice with a Rorc-Cre-restricted deficiency in STAT3 succumb to C. rodentium infection, which can be rescued by transfer of STAT3-proficient CD90hiCD45lo ILC3s. Guo et al. [22] show that this again is explained by the STAT3 dependency of protective IL-22 expression.

Mucosal surface epithelia are characterized by resident intraepithelial lymphocytes in the gastrointestinal, genitourinary, and respiratory tract. This population responds to dietary components via the AhR. Deficiency of the AhR and lack of dietary AhR ligands led to an increased susceptibility to chemically induced colitis [10]. STAT3 has been implicated in the regulation of this axis because an AhR nuclear translocator (ARNT)–STAT3 axis directs the differentiation of intestinal intraepithelial TCRαβ+ CD8αα cells [21]. Furthermore, dietary AhR ligands protect from colitis by supporting protective IL-22 responses and limiting IL-17A [14, 15]. Taken together, this highlights the central role of STAT3 at the interface of both microbial-induced and diet-modulated immune interactions. To date, no human immunology data on ILC or IEL populations in either Job syndrome or hyperactive STAT3 mutations is available.

CONCLUSIONS

We argue that, in the context of both IBD and PID, deficiency and excess of the immune system represent 2 sides of the same coin. There is an overlap in PID- and IBD-associated genes [2, 13, 16]. Primary immune deficiencies may present clinical features of immune excess indistinguishable from IBD, showing that features of IBD can result from a wide variety of causative immune alterations. Failure to clear pathogens in patients with PID often leads to debilitating features of immune excess. Therefore, clinical signs of immune excess do not allow simple conclusions regarding their generation. In the absence of a confirmed mendelian genetic basis, it is not possible to distinguish between primary immune excess or primary immune deficiency because both elements contribute to immune-mediated diseases. Failed clearance of pathogens or associated danger signals (danger- and pathogen-associated molecular pattern molecules) may pave the way for immunopathology. The intestinal immune system is part of the body’s vanguard and may show clinical manifestations even in the absence of bona fide pathogens because of its constant battle with commensal microorganisms of the intestinal flora. Once surface barriers are breached, commensals alone may cause life-threatening infections [17]. Researchers should not be too puzzled by the dilemma of inflammatory excess vs. deficiency; classic immune excess disorders, such as the autoinflammatory diseases, are also part of the international classification of primary immune deficiencies [13]. The diverse roles of STAT3 in intestinal inflammation and autoimmunity set an example of how these disease states can be closely related and clinically intertwined.

GWASs have provided many genes with unknown functions in inflammation, which remain to be explored. IBD-associated SNPs still miss strong heritability, limiting the diagnostic potential of sequencing studies in these patients [18]. The value and use of sequencing studies in primary immune deficiencies is still under debate [19]. Apart from the dichotomy of immune excess vs. deficiency, this survey highlights the complexity of assigning specific functions to a single risk-associated gene and its polymorphisms, as exemplified by STAT3. Although more genes and their specific functions are being analyzed in the context of experimental colitis models, the translation of experimental findings to clinical practice is evolving slowly. Current therapeutic approaches with successful use in patients with IBD are mainly limited to canonical immunosuppressive drugs, including steroids, azathioprine, or cyclosporine A. Successful amendments to classic immune suppression arrived in the form of anti-TNF strategies (infliximab, adalimumab, or certolizumab) and vedolizumab, limiting αβ-integrin-mediated intestinal leukocyte homing [20]. All of these approaches limit inflammation of the intestine independent of its primary cause. The identification of a primary immune deficiency in a patient presenting with features of IBD could potentially alter the therapeutic approach to the individual patient and should be a diagnostic goal in patient care. Although an identified immune deficiency may constitute the underlying problem in some cases of IBD, it is often difficult to establish this diagnosis in a setting of a multifactorial, polygenic, chronic inflammatory disease state [11]. IBD-like symptoms displayed at very early onset during infancy suggest a monogenic origin and should entail further diagnostic workup [11]. The mainstay of therapy for IBD, meanwhile, still consists of immunosuppressive therapy that limits immune excess. Further progress in this area is desperately awaited.

AUTHORSHIP

M.L. drafted the manuscript based on the talk of C.B. at the Italian Society of Immunology, Clinical Immunology, and Allergology (SIICA) meeting in Milan, Italy; M.F.N., M.H., and C.B. edited the manuscript.

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DISCLOSURES

The authors declare no competing financial interests.
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Immune deficiency vs. immune excess in inflammatory bowel diseases—STAT3 as a rheo-STAT of intestinal homeostasis

Moritz Leppkes, Markus F. Neurath, Martin Herrmann, et al.

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