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MULTI-AUTHOR REVIEW

Inflammatory bowel disease: is it a primary immunodeficiency?

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Abstract Inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease are chronic and relapsing conditions, characterized by abdominal pain, diarrhea, bleeding and malabsorption. IBD has been considered a hyperinflammatory state due to disturbed interactions between the immune system and the commensal bacterial flora of the gut. However, there is evidence that Crohn's disease might be the consequence of a reduced release of pro-inflammatory cytokines and an impaired acute inflammatory response, thereby suggesting that IBD might be an immunodeficiency rather than an excessive inflammatory reaction. This theory has been supported by observations in patients with primary immunodeficiencies such as the Wiskott–Aldrich syndrome and IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). In contrary, defects in the anti-inflammatory down-regulation of the immune response as they are seen in patients with Mendelian defects in the IL10 signaling pathway support the hyper-inflammatory theory. In this review, we describe and discuss primary immunodeficiencies associated with IBD and show that the bowel is a highly sensitive indicator of dysregulations, making IBD a model disease to study and identify key regulators required to balance the human mucosal immune system.

Keywords Inflammatory bowel disease · Immunodeficiency · IL10 deficiency · IL10R deficiency · Crohn's disease · Wiskott–Aldrich syndrome · CGD · IPEX

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Introduction

Inflammatory bowel disease (IBD) is chronic in nature with a relapsing course and is accompanied by abdominal pain, diarrhea, bleeding, and malabsorption [1–3]. It comprises Crohn's disease (CD) and ulcerative colitis (UC) as well as indeterminate colitis with overlapping features of CD and UC [3]. IBD usually manifests in the second or third decade of life [4] but may also present in infancy, often with a severe and therapy resistant course of the disease [3]. IBD affects about 1.4 million people in the USA and 2.2 million in Europe [5, 6].

In general, IBD is suggested to result from disturbed interactions between the immune system and commensal bacteria of the gut [4, 6–8]. This theory is substantially backed by murine models showing that colitis does not develop in gnotobiotic mice, but emerges on reconstitution of the gut flora [4, 9, 10].

The intestinal integrity is maintained by several factors including the epithelial cell layer, mucus-secreting goblet cells, antimicrobial peptides-producing Paneth cells, IgA-releasing plasma cells, and gut-associated lymphoid tissue such as Peyer's patches [11, 12]. The chronic stimulation by

Table 1 Select number of genes associated with increased susceptibility to IBD (after van Limbergen et al. 18)

Function	Genes
Autophagy	*ATG16L1, IRGM, LRRK2*
Pattern-recognition receptors	*CARD9, NOD2, TLR4*
Th17 cell differentiation	*CCR6, ICOSLG, IL23R, JAK2, STAT3*
Maintenance of the epithelial barrier	*DLG5, DMBT1, ITLN1, OCTN1&2, ORMDL3, PTGER4, XPB1*
Shaping immune responses	*HLA region, IL12B, IL18RAP, IRF5, MST1, NKX2-3, PTPN22, TNFSF15*

ATG16L1: autophagy-related 16-like protein; *IRGM*: immunity-related GTPase family M; *LRRK2*: leucine-rich repeat kinase 2; *CARD9*: Caspase-recruitment domain containing protein 9; *NOD2*: nucleotide-binding oligomerization domain protein 2; *TLR4*: Toll-like receptor 4; *CCR6*: chemokine (C–C motif) receptor 6; *ICOSLG*: inducible T-cell co-stimulator ligand; *IL23R*: interleukin 23 receptor; *JAK2*: Janus kinase 2; *STAT3*: signal transducer and activator of transcription 3; *DLG5*: *Drosophila* discs large homologue; *DMBT1*: deleted in malignant brain tumors 1; *ITLN1*: intelectin 1, *OCTN1&2*: organic cation transporter 1&2; *ORMDL3*: ORM1-like 3; *PTGER4*: prostaglandin receptor EP4; *XPB1*: X-Box binding protein 1; *IL12B*: interleukin 12-β; *IL18RAP*: IL18 receptor accessory protein; *IRF5*: interferon regulatory factor 5; *MST1*: macrophage stimulating protein 1; *NKX2-3*: NK2 transcription factor related, locus 3; *PTPN22*: protein tyrosine phosphatase, nonreceptor type 22; *TNFSF15*: tumor necrosis factor superfamily member 15

the resident intestinal flora and food antigens requires tight control mechanisms and involves IL-10 producing regulatory T (Treg) cells, which are supposed to be key players in maintaining the immune balance [13]. Mice lacking Treg cells suffer from fatal multiorgan inflammation; and IL-10 deficient mice die of wasting disease and colitis [14–16].

The genetic background of IBD has been in focus for several years, and genome-wide genetic linkage and association studies have underscored the genetic complexity of IBD and identified a wealth of genes that may render individuals more susceptible to IBD [17, 18]. Polymorphisms or mutations in genes involved in autophagy such as *ATG16L1* (autophagy-related 16-like protein), *IRGM* (immunity-related GTPase family M); [19–22] intra- and extracellular pattern recognition receptors such as *NOD2* (nucleotide-binding oligomerization domain protein 2) or *TLR4* (Toll-like receptor 4); [23–26] Th17 cell differentiation such as *IL23R* (interleukin 23 receptor) and *STAT3* (signal transducer and activator of transcription 3); [19, 27–30] maintenance of the intestinal epithelium such as *DLG5* (*Drosophila* discs large homologue), *OCTN1&2* (organic cation transporter) and *XPB1* (X-Box-binding protein 1); [31, 32] and shaping immune responses such as *IL12B* (interleukin 12-β) and *IL18RAP* (IL18 receptor accessory protein) [19, 33] have been shown to be associated with or increase susceptibility to IBD (summarized in Table 1).

In contrast to the hypothesis, that IBD is a complex multigenic disorder, evidence arose that certain forms of IBD may (1) be congenital/inborn Mendelian traits as demonstrated in IL-10- and IL-10 receptor deficiency; and (2) reflect an immunodeficient state of the host as shown in primary immunodeficiencies (PID) such as Wiskott–Aldrich syndrome or chronic granulomatous disease (CGD) [34–38]. In this review, we will discuss the cases when a PID should be suspected in a patient with IBD.

Crohn's disease

CD is characterized by a segmental transmural inflammation of the gut with the formation of non-caseating granuloma, which consist of macrophages, epithelioid, and giant cells. CD may affect any site of the intestine, and involvement of the terminal ileum is most common [1, 2, 4].

The prevailing hypothesis on the pathogenesis suggests that CD, like other forms of IBD, may be the consequence of a hyperinflammatory state due to an inappropriate immune response to the intestinal flora [4, 40].

In the 1970s, the first evidence emerged that CD may be the consequence of an impaired acute inflammatory response with an incomplete removal of bacteria and foreign material in the gut [41]. This concept of CD as an immunodeficiency was backed and extended by a study of Marks et al., who showed that Crohn's patients had a weaker efflux of neutrophils into skin windows as compared to healthy controls or patients suffering from UC or rheumatoid arthritis [42]. Patients also revealed reduced amounts of pro-inflammatory cytokines such as IL-1β or IL-8 and a massively impaired migration of neutrophils in lesions of the rectum or ileum upon taking tissue samples [42]. In contrast to healthy individuals, CD's patients revealed an abnormal low change in blood flow on subcutaneous injection with heat-killed *Escherichia coli*, confirming a defective inflammatory response.

Recent work by Smith et al. [43] showed that the migration of ^{111}In labeled neutrophils and the clearance of subcutaneously injected ^{32}P labeled *E. coli* were substantially impaired in CD patients, the blood flow and the removal of bacteria was dose-dependent. Macrophages from CD patients had a substantially impaired release of pro-inflammatory cytokines such as TNF-α, IL-4, IL-5, IL-13, IL-15 and IFN-γ on stimulation with heat-killed *E. coli* or Toll-like receptor agonists when compared to healthy controls or patients suffering from UC. The authors' investigations revealed that intracellular levels of TNF-α in macrophages from CD patients were significantly lower than in healthy individuals, even though transcription and intracellular mRNA levels were normal. The addition of Brefeldin-A, an inhibitor of the transport of proteins

from the endoplasmic reticulum to the Golgi-apparatus, prevented the degradation of TNF-α, indicating that the decreased TNF-α release may be due to damaging events in the lysosomal compartments [43].

The lack of an initial acute inflammation with the reduced elimination of foreign material and bacteria may result in a chronic inflammation with T cell-mediated granuloma formation, which are supposed to confine hazardous material and protect the intestine from bacterial spreading [43, 44]. The development of a CD-like enterocolitis in CGD supports the theory that CD is an immunodeficiency due to impaired pro-inflammatory responses. The continuous secretion of pro-inflammatory cytokines by cells like macrophages that form the granuloma, sustains the chronic inflammation and finally results in extensive tissue damage. A general immunodeficiency of macrophages may also be an explanation for the occurrence of other CD manifestations such as arthritis or eye- and skin lesions [43–45].

IL-10- and IL-10 receptor deficiency

IL-10 is secreted by several cell types including monocytes, macrophages and dendritic cells, T cells, B cells, granulocytes, epithelial cells, keratinocytes, and mast cells [46]. It is critical in maintaining the balance of the immune system, restricts and terminates immune responses by limiting the secretion of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-12, and controls both the differentiation and proliferation of macrophages, T and B cells [46–49]. The relevance of IL-10 and its signaling for maintaining intestinal immune homeostasis became evident in murine models: Both IL-10- ($Il10^{-/-}$) and IL-10-receptor ($Il10rb^{-/-}$)-deficient mice develop severe enterocolitis when the gastrointestinal flora develops [7, 50, 51].

Due to its unique role in balancing the immune system, IL-10 has always been in the focus of IBD research. Genetic sequence variants in IL-10 were shown to contribute to susceptibility to ulcerative colitis [52], and mutations in the IL-10 leader sequence were found to modify the IL-10 release in patients with CD [53]. A study by Noguchi et al. [54] demonstrated that a mutant NOD2 protein that has been associated with CD inhibits the ribonucleoprotein hnRNP-A1 and thus actively suppress the transcription of IL-10. NOD2/CARD15 is an intracellular sensor that recognizes bacterial peptidoglycan and has been shown to be a risk factor for the development of IBD [23, 55, 56].

By analyzing two families with an autosomal-recessive inherited-type of enterocolitis, we recently demonstrated that IBD may be a monogenic disorder [34]. The patients presented within the first year of life with enterocolitis and perianal disease, and the formation of multiple abscesses and enterocutaneous fistula, which required several surgical interventions. Histopathology revealed ulcerations of the intestinal mucosa with inflammatory infiltrates of the epithelium and the formation of abscesses extending to the *muscularis propria*. Additionally, the patients suffered from chronic folliculitis and recurrent respiratory infections. The patients were treated with various anti-inflammatory drugs, including steroids, methotrexate, thalidomide, and anti-TNF-α monoclonal antibodies, but none of these therapies induced remission or long-term improvement [34].

Our genetic studies identified two patients with mutations in *IL10RA* (encoding the α-unit of the IL-10 receptor, IL10R1), which resulted in amino acid exchanges at position 84 (Thr84Ile) or 141 (Gly141Arg). The other patients, two siblings, harbored a mutation affecting the *IL10RB* gene, [encoding the β-unit (IL10R2)], which resulted in a premature stop codon (Try159Stop) [34]. Apart from the four patients published [34], further patients with mutations in the IL-10 receptor have been found: two additional patients were identified in the UK, four in Germany, one in the US, one in Canada and one in France (privileged communication; unpublished data).

The IL-10 receptor is a tetramer consisting of two α-chains (IL10R1) and two β-chains (IL10R2) molecules [46, 57]. Upon binding of IL-10 dimers to the α-chains, the accessory β-chain are recruited and a functional IL10 receptor tetramer assembled. This gives rise to the activation of Janus tyrosine kinases (JAK)1 and Tyk2, rapid phosphorylation of STAT3, and induction of STAT3-dependent genes such as the suppressor of cytokine signaling (SOCS)-3 gene [57–60].

The mutations found in these patients abolished IL-10-induced STAT3 phosphorylation and prevented IL-10-mediated inhibition of TNF-α release in LPS-stimulated macrophages and peripheral blood mononuclear cells (PBMCs) [34].

In contrast to IL10R1, which is unique to the IL-10 receptor, IL10R2 is also a component of the receptors for IL-22, IL-26, IL-28A, IL-28B, and IL-29 and expressed on a wide range of non-immune cells such as epithelial cells and keratinocytes [61–63]. In particular, IL-22 may add to the severe phenotype in IL10R2-deficient patients, since it was shown to protect against colitis and improved colitis in mice [64, 65]. IL-22 upregulates expression of the antimicrobial proteins RegIIIβ and -γ and enhances mucus production in murine colonic epithelial cells, thereby maintaining the epithelial barrier and protecting from infections with intestinal bacterial pathogens [64, 66].

The recurrent and frequent folliculitis in the IL10R2-deficient patients may be at least in part attributed to a lack of IL-22 signaling, which is supposed to control immunity

of the skin by up-regulating the expression of the β-defensins 2 and 3 and the antimicrobial heterodimer S100A8/9 in keratinocytes [67–69]. The λ-interferons IL-28A, IL-28B, and IL-29 are known primarily to confer antiviral protection [70, 71], but since other vital antiviral defenses such as the IFN type I and II signaling pathways are still intact, this shortcoming may be of minor relevance.

Due to the dramatic clinical situation, a hematopoietic stem cell transplantation (HSCT) was performed in one of the patients with an IL10R2 mutation, which proved to be successful and cured the patient [34]. The sustained success of the HSCT suggests that IL-10 signaling in hematopoietic cells rather than signaling via IL-22/IL-26/IFN-λ in non-haematopoietic cells was critical to induce remission.

Most recently, we described two other patients with Crohn's-like disease and the formation of perianal and rectovaginal fistulae [35]. Endoscopy and histopathology revealed extensive ulceration of the ileum and focal active colitis with neutrophils infiltrating the surface epithelium. Both patients carried homozygous loss-of-function mutations in *IL-10* itself, leading to an amino acid exchange at codon 113 (Gly113Arg), which most likely impeded dimerization of IL-10 as shown by molecule modeling. The mutated IL-10 failed to induce STAT3 phosphorylation and to inhibit LPS-mediated TNF-α release in PBMCs [35].

The dramatic clinical findings in patients with either IL-10 or IL-10 receptor mutations emphasize the importance of this cytokine in controlling the intestinal immune system and show that the loss of IL-10 signaling cannot be compensated by any other pathway.

Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)

Due to the massive amount of resident colonizing bacteria in the gut, highly sophisticated mechanisms are required to maintain the integrity of the intestine, to balance the intestinal immune system and to sense and distinguish the physiological flora from invading pathogens. A plethora of different cells contribute to this challenge including epithelial cells, Paneth cells, goblet cells, and cells of the adaptive immune system [11].

A key player in maintaining the intestinal immune homeostasis are CD4+/CD25+/FoxP3+ Treg cells and FoxP3-Tr1-like cells, which both are important sources of IL-10 and suppress pro-inflammatory action [11, 72, 73]. Several murine models show the need for Treg cells: FoxP3+-deficient mice develop severe multiorgan inflammation, which improves upon transfer of FoxP3+ positive Treg cells [14], and Treg cells have been shown not only to control intestinal inflammation but also to cure manifest colitis [73, 74]. The majority of CD4+/CD25+/FoxP3+ Treg cells develop in the thymus, where their T cell receptors bind self-peptides with moderate affinity, which results in activation of NF-κB [11, 75, 76]. Co-stimulation via CD28 and IL-2 or IL-15 activate STAT5 and induce expression of FoxP3 [77]. Some Treg cells then may migrate from the thymus to the gastrointestinal tract and recognize intestinal antigens, thereby preventing excessive immune reactions [11, 78].

Patients with mutation in the *FOXP3* gene, located on the X-chromosome, suffer from IPEX syndrome that is characterized by a lack of Treg cells, leading to autoimmune lymphoproliferation and multiple autoimmune disorders [79–82]. If not fatal in early childhood, IPEX patients usually present with insulin-dependent diabetes mellitus, failure to thrive, skin disease such as eczema, hypo- or hyperthyroidism and recurrent infections including meningitis, pneumonia, and septicemia [82–85]. The predominant clinical feature is an autoimmune enteropathy that may mimic CD, UC, or celiac disease [83, 86]. The small intestine reveals complete or partial villous atrophy, the large intestine is frequently involved and shows inflammatory infiltrates with CD3+ cells and plasma cells [83, 86, 87]. The frequently atrophic thymus may show a substantial reduction of Hassall's corpuscles, which secrete thymic stromal lymphopoietin and activate dendritic cells, which then induce differentiation of Treg cells [86, 88, 89].

Chronic granulomatous disease (CGD)

Several congenital disorders affecting the function phagocytes including glycogen storage disease-1b, Chediak-Higashi- and Hermannsky–Pudlak-syndrome, cyclical neutropenia, and leukocyte adhesion deficiency 1 have been shown to be associated with forms of enterocolitis [39, 90]. A prototype of neutrophil disorder that resembles CD is chronic granulomatous disease (CGD). CGD is a rare disorder in which the respiratory burst of neutrophils is dramatically impaired due to mutations in the components $gp91^{Phox}$, $p47^{Phox}$, $p67^{Phox}$ and $p22^{Phox}$ of the NADPH oxidase complex [91]. Together with p22rac, these proteins form a complex in the wall of the phagocytic vacuole [39, 92], which enables the electron transport from NADPH on O_2 to generate microbicidal O_2^- and H_2O_2 in the vacuole, which are required for intracellular killing of microbes or digestion of other material [39, 93]. The most frequent form of CGD is X-linked with mutations in $gp91^{Phox}$, accounting for about 65% of cases [39]. The impaired killing of microorganisms including possible pathogens render patients with CGD highly susceptible to severe recurrent bacterial and fungal infections, in particular *Staphylococcus aureus, Salmonella* spp., and *Aspergillus* spp [94, 95].

A hallmark of CGD is the formation of abnormal inflammatory granuloma that may result in colitis and may obstruct organ systems such as the urinary tract [38, 95–97]. The formation of granuloma in the absence of infectious agents may be the result of an incapability of neutrophils to digest foreign material. This is followed by a second chronic stage of inflammation with the formation of granuloma, which results in inflammatory bowel disease that resembles CD [38, 39].

Wiskott–Aldrich syndrome

The Wiskott–Aldrich syndrome (WAS) is a rare immunodeficiency caused by mutations in the Wiskott–Aldrich syndrome protein (WASP) gene that is located on the X chromosome. WASP is exclusively expressed in hematopoietic cells and transduces signals from the cell surface to the actin cytoskeleton. The actin cytoskeleton is required to control cell–cell interaction, cell movement, cell signaling and cell division [98]. WASP is inactive in the cytoplasm due to an auto-inhibitory mechanism mediated by interaction between the verprolin–cofilin homology domains acidic region (VCA) and the GTPase-binding domain (GBD) [99]. Upon activation by the Rho GTPase cell division cycle 42 (Cdc42) or non-catalytic region of tyrosine kinase 1 (Nck1), this inhibition is abolished, enabling the VCA domain to bind the actin-related protein (ARP) 2/3 complex and stimulates actin polymerization [99–101]. Numerous mutations have been described to date, and there is a clear-cut correlation between the type of mutation and the clinical phenotype: if WASP is not expressed, patients present with the classic WAS, expression of mutated WASP results in X-linked thrombocytopenia, and mutation in the binding site of the small rho GTPase Cdc42 gives rise to X-linked neutropenia [102–105]. Recurrent infections due to immunodeficiency, eczema, microthrombocytopenia, and increased frequencies of autoimmune diseases are the clinical hallmarks of the Wiskott–Aldrich syndrome [102, 106, 107]. Autoimmune conditions are found in up to 40% of the patients and include hemolytic anemia, vasculitis, Henoch–Schönlein-like purpura and inflammatory bowel disease [102, 108], which may resemble UC and has been documented for up to 10% of WAS patients [109, 110]. WASP-deficient Treg cells showed impaired suppressive activity in vitro and failed to control autoimmunity in several murine models [99]. Why the other 90% of WAS patients do not suffer from IBD is unclear.

Conclusions

IBD comprises a group of diseases that may be caused by a variety of different irregularities of the immune system. The occurrence of an IBD phenotype in WAS, IPEX, Artemis deficiency [111] and in particular CGD indicates that IBD may be the final stage of several complex immunodeficiencies. Recent work confirmed that a classical form of IBD, namely CD, may be an immunodeficiency due to a malfunction of macrophages with faulty release of cytokines and subsequent impaired acute inflammatory response to bacteria and foreign material in the intestine. This contradicts the previous prevailing hypothesis that CD is a hyper-inflammatory disorder due to an inadequate reaction of the innate and adaptive immune system to the flora of the gut and may suggest new therapeutic strategies.

The detection of mutations in the IL-10 signaling pathway demonstrates the importance of immunoregulatory factors that keep the intestinal immune system in balance; it also shows that in a subgroup of patients IBD may be monogenic and distinct from more complex forms like UC and CD. Even though the progress in IBD research has broadened our knowledge of the intestinal mucosal immunity and the components that keep it in balance, there are still many other factors that need to be identified to make us understand the complex eco-system of the gut.

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