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Issue: *The Year in Human and Medical Genetics: Inborn Errors of Immunity***IL-10 and IL-10 receptor defects in humans****Erik-Oliver Glocker,¹ Daniel Kotlarz,² Christoph Klein,² Neil Shah,³ and Bodo Grimbacher^{4,5}**¹Institute of Medical Microbiology and Hygiene, University Hospital Freiburg, Germany. ²Department of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, Germany. ³Department of Paediatric Gastroenterology, Great Ormond Street Hospital, University College London, London, United Kingdom. ⁴Department of Immunology, University College London Medical School (Royal Free Campus), London, United Kingdom. ⁵Centre for Chronic Immune Deficiency, University Hospital Freiburg, Germany

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Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is chronic in nature and is characterized by abdominal pain, diarrhea, bleeding, and malabsorption. It is considered a complex multigenic and multifactorial disorder that results from disturbed interactions between the immune system and commensal bacteria of the gut. Recent work has demonstrated that IBD with an early-onset within the first months of life can be monogenic: mutations in IL-10 or its receptor lead to a loss of IL-10 function and cause severe intractable enterocolitis in infants and small children. Both IL-10 and IL-10 receptor deficiency can be successfully treated by hematopoietic stem cell transplantation.

Keywords: IL-10; IL-10 receptor; mutation; STAT3; inflammatory bowel disease

Introduction

Interleukin (IL)-10 may be considered the most important anti-inflammatory cytokine in humans. Secreted by a variety of cells including monocytes, macrophages, dendritic cells, T cells, B cells, granulocytes, epithelial cells, keratinocytes, and mast cells,¹ IL-10 limits secretion of pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, and IL-12; it deactivates macrophages,² inhibits secretion of Th1 cytokines such as IL-2 and IFN- γ , and controls differentiation and proliferation of macrophages, T cells, and B cells.^{1,3,4} By keeping pro-inflammatory events under control, it protects against excessive immune responses and tissue damage. Since IL-10 is a critical player in maintaining immune system balance, mutations in IL-10 or components of its signaling pathway that reduce or abolish their anti-inflammatory properties were thought to be involved in the pathogenesis of hyperinflammatory disorders such as rheumatoid arthritis or inflammatory bowel disease (IBD). IBD is relatively frequent, affecting about 1.4 million people in the United

States and 2.2 million in Europe.^{5,6} Most often it manifests in the second or third decade of life, but IBD may also present in childhood with a severe and therapy-resistant course.^{7,8}

Genome-wide linkage and association studies have emphasized the genetic complexity of IBD and identified a number of genes that may render individuals more susceptible to it;^{9,10} for example, variations in genes involved in autophagy, in genes encoding proteins for intra- and extracellular pattern recognition receptors, in genes required for T helper 17 cell differentiation, in genes required for maintenance of the intestinal epithelium, and in genes required for shaping immune responses have been associated with susceptibility to IBD.

In contrast to the prevailing hypothesis that IBD is a multigenic disorder, recent work showed that certain variants of IBD or IL-10 and IL-10 receptor (IL-10R)-deficiency are monogenic autosomal recessive diseases. In this short review, we discuss the clinical phenotype and aspects of the pathogenesis of these novel entities and outline diagnostic procedures to confirm or rule-out these rare diseases.

IL-10: a “shield” against hyperinflammation

To keep continuously ongoing pro-inflammatory events in the gut in check, a powerful countervailing activity capable of downregulating the immune system is required. The critical role of IL-10 as one such downregulator has been demonstrated in animal models; for example, mice deficient in IL-10 (*Il10^{-/-}*) or the IL-10R β -chain (*Il10rb^{-/-}*) develop severe enterocolitis.^{11–13} Such murine phenotypes hint at a possible involvement of IL-10 signaling in the pathogenesis of human IBD. In support of that possibility, genetic variants of *IL10* in humans are associated with increased susceptibility to ulcerative colitis (UC),¹⁴ and in patients suffering from Crohn’s disease (CD), mutations in the leader sequence of IL-10 protein were shown to reduce its release from cells.¹⁵ A frameshift insertion (3020insC) in the intracellular sensor molecule nucleotide-binding oligomerization domain containing 2 (NOD2), previously associated with CD, inhibits the ribonucleoprotein hnRNP-A1 and thereby actively blocks transcription of IL-10.¹⁶

Even though 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, it is incontestable that IL-10 is the most relevant factor to protect against immunological imbalances.^{17,18}

A main source of IL-10 in the gut are regulatory T (T_{reg}) cells, which tightly control chronic stimulation by resident intestinal flora and food antigens.¹⁹ Scurvy mice lacking the T_{reg} cell lineage defining transcription factor forkhead box P3 (Foxp3) suffer from fatal multiorgan inflammation, and mice devoid of IL-10, a key cytokine of T_{reg} cells, die of wasting disease and colitis.^{20–22} A similar phenotype occurs in humans; patients with mutations in *FOXP3*, located on the X chromosome, suffer from immunodysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is characterized by a lack of $CD4^+ CD25^+ FOXP3^+$ T_{reg} cells. Affected individuals develop autoimmune lymphoproliferation and multiple autoimmune disorders.^{23–25} If not fatal in early childhood, patients with IPEX develop severe eczema, insulin-

dependent diabetes mellitus, hypo- or hyperthyroidism, and recurrent, sometimes severe, infections.^{26–29} The predominant clinical feature, however, is an autoimmune enteropathy that starts as watery diarrhea and may turn slimy and bloody and mimic CD, UC, or celiac disease—all of which emphasize the indispensable role of IL-10 for intestinal homeostasis.^{27,30}

The finding that loss-of-function mutations in either the IL-10 or IL-10R gene cause severe early-onset IBD in humans demonstrates the importance of IL-10 and shows that loss of IL-10 signaling significantly impairs life.^{31,32} IL-10 appears to be of particular relevance for the integrity and homeostasis of the gut, which highlights the fact that the gut/bowel is highly vulnerable to disturbances of immunological balance.

IL-10 signaling pathway

To exert its actions, IL-10 dimerizes and binds to a cell-bound cytokine receptor made up of two molecules of the IL-10R α -chain (IL-10R1) and two molecules of the accessory IL-10R β -chain (IL-10R2).^{1,4,33} Upon binding of IL-10 to the tetrameric receptor IL-10R complex, two members of the Janus kinase family—Janus kinase (JAK)1 and tyrosine kinase (Tyk)2—are activated and catalyze phosphorylation of themselves and then of IL-10R1 at specific intracellular tyrosine residues (tyrosine 446 and 496), thereby forming docking sites for STAT3.³³ STAT3 is then phosphorylated by JAK1 and Tyk2, which causes STAT3 dimerization and translocation to the nucleus where it induces expression of its target genes (summarized in Fig. 1).³³ In contrast to IL-10R1, which is unique to the IL-10R, IL-10R2 is shared by several other cytokines, including IL-22, IL-26, and the λ -interferons IL-28A/B and IL-29.^{34,35} Both IL-10R1 and IL-10R2 are required for IL-10 signaling, as loss-of-function mutations in either one result in a complete signaling failure that cannot be compensated by any other pathway.

Clinical phenotypes of IL-10- and IL-10R-deficient patients

From investigations of two families with autosomal-recessive inherited enterocolitis, recent work has identified four patients with mutations in IL-10R: two patients carried homozygous missense mutations in *IL10RA* (encoding IL-10R1), resulting in

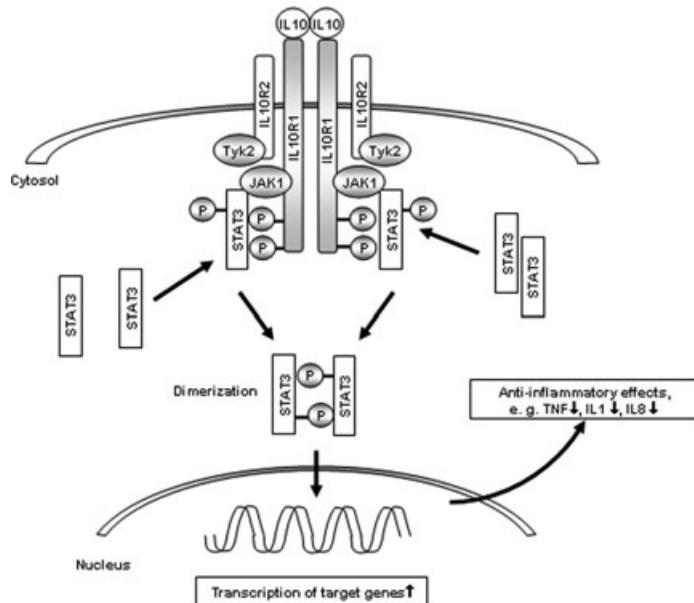


Figure 1. IL-10 signaling pathway.

amino acid exchanges at position 84 (Thr→Ile) or 141 (Gly→Arg); the other patients, two siblings, harbored a mutation affecting *IL10RB* (encoding IL-10R2), resulting in a premature stop codon (Try→Stop).³¹ The patients presented within the first year of life with severe enterocolitis and perianal disease; subsequent formation of multiple abscesses and enterocutaneous fistula required several surgical interventions, eventually including complete colectomy. Histopathology revealed circumscribed, deep-set, thick, rolled-edged ulcers of the intestinal mucosa with inflammatory infiltrates of the epithelium, and the formation of abscesses extending to the *muscularis propria*. In addition, the patients suffered from chronic folliculitis and had a history of several recurring infections of their respiratory tract. The patients were treated with a wide spectrum of anti-inflammatory drugs, including steroids, methotrexate, thalidomide, and anti-TNF- α monoclonal antibodies, but none of these therapies induced sustained remission or long-term improvement.³¹

The discovery of the underlying genetic mutation opened novel therapeutic strategies. Since IL-10R1 and IL-10R2 double-deficiency described above has a very similar phenotype to severe colitis, it was hypothesized that severe colitis—the main clinical problem/phenotype in the above patients—was

due to defective IL-10 signaling in hematopoietic cells rather than defective IL-22, IL-26, and IFN- λ signaling in nonhematopoietic cells. In view of the life-threatening clinical course of the IL-10R mutations, allogeneic hematopoietic stem cell transplantation (HSCT) was proposed. The index patient with a loss-of-function mutation in IL-10R2 was successfully transplanted and showed sustained remission,³¹ thus supporting the notion that IL-10 signaling in hematopoietic cells was critical to control hyperinflammation in the gut.

More recently, two other unrelated patients have been described with severe Crohn's-like colitis and the formation of perianal and rectovaginal fistulae, a phenotype resembling IL-10R deficiency.³² Endoscopy and histopathology revealed extensive ulceration of the ileum and focal active colitis, with neutrophils infiltrating the surface epithelium. Both patients were found to have homozygous point mutations in *IL10* itself, leading to an amino acid change at codon 113 (Gly→Arg) that most likely changes the tertiary structure of the cytokine and results in impaired dimerization of IL-10. In contrast to wild-type IL-10, the mutated IL-10 failed to induce STAT3 phosphorylation or to inhibit lipopolysaccharide (LPS)-mediated TNF- α release in peripheral blood mononuclear cells (PBMCs).³²

Recently, Begue *et al.* investigated a cohort of 75 pediatric IBD patients for failures in IL-10 signaling.³⁶ They found one patient with a mutant IL-10R1 (Arg262Cys) and another patient with a mutant IL-10R2 (Glu141Stop). Both children presented with onset of symptoms at the first three months of life, including granuloma-positive colitis.³⁶ As anticipated, the patient harboring the IL-10R2 mutation showed impaired IL-22 signaling, whereas the patient with the IL-10R1 mutation (as well all other patients evaluated) did not. Also, typical for IL-10 and IL-10R deficiency, routine immunological work-up of the patients appeared to be normal.

Possible impact of defective IL-22, IL-26, and IFN- λ signaling

Since IL-10R2 is shared by the receptors for IL-22, IL-26 and λ -interferons and is expressed on various nonimmune cells, such as epithelial cells and keratinocytes,^{35,37,38} one might presume that mutations in IL-10R2 result in more severe phenotypes than mutations in either IL-10R1 or IL-10. In particular, lack of IL-22 signaling may be additive to the phenotype of IL-10R2 deficiency because IL-22 protects against colitis and significantly improved colitis in a murine model of UC.^{39,40} Among other activities, IL-22 upregulates expression of the antimicrobial proteins RegIII- β and RegIII- γ and enhances mucus production in murine colonic epithelial cells, which thereby maintains the epithelial barrier and prevents infection by intestinal bacterial pathogens.^{39,41}

The folliculitis observed in IL-10R2-deficient patients may be at least in part attributed to impeded IL-22 signaling, which has been shown to control immunity of the skin by upregulating the expression of the β -defensins 2 and 3 and the antimicrobial heterodimer S100A8/9 in keratinocytes.⁴²⁻⁴⁴ Furthermore, Nagalakshmi *et al.* demonstrated *in vitro* that IL-22 induces production of IL-10,⁴⁵ a similar activity was also found for IL-26.⁴⁶ In addition, IL-26 activates both STAT1 and STAT3, induces the release of IL-8 in colon epithelial cells, and keratinocytes, and increases the expression of intercellular cell adhesion molecule 1.⁴⁶ In murine lung epithelial cells, IL-22 regulates the innate immune defense by mediating expression of lipocalin-2, a protein capable of sequestering iron from Gram-negative bacteria and improving the killing of *Klebsiella pneumoniae*.⁴⁷ Recently, Celia *et al.* identified

a subset of natural killer cells that releases IL-22 and thereby controls inflammation and contributes to mucosal immunity.⁴⁸

IL-28A, IL-28B, and IL-29 are primarily known to protect against viral infections,^{49,50} but since other vital antiviral defense mechanisms—such as the IFN type I and II signaling pathways—are present, the antiviral activity of IL-28A, IL-28B, and IL-29 in general may be of minor importance. Further studies are required to properly assess their role and relevance in humans.

Diagnosis of IL-10 and IL-10R deficiency

Defects in the IL-10R may be easily tested by functional assays. PBMCs from healthy individuals show strong phosphorylation of STAT3 upon stimulation with IL-10, whereas PBMCs from IL-10R-deficient patients do not. In contrast to patients with IL-10R mutations, where administration of exogenous IL-10 has no effect at all, stimulation by IL-10 completely abrogates LPS-mediated TNF- α release in PBMCs from healthy controls.^{2,11,31}

Of course, any functional abnormalities, such as the above, should always be confirmed by sequencing the IL10R genes *IL10RA* and *IL10RB*. Even though rarer and more challenging to rule out, lack of functional IL-10 should always be considered in cases of early-onset colitis with normal responses to exogenous IL-10. If sequencing of *IL10* reveals putative mutations, *in vitro* synthesis of the protein and subsequent functional testing, using STAT3 and/or TNF- α assays, should be carried out to prove that the observed mutation leads to a defective protein. Diagnostic procedures to confirm/rule out IL-10 and IL-10R mutations are summarized in Figure 2.

Conclusions

The functional consequences of IL-10 and IL-10R deficiency demonstrate the importance of IL-10 as a critical immunomodulatory factor that controls chronic stimulation by microbes in the intestine and keeps the immune system in balance; it also shows that in a subgroup of patients, IBD may be inherited as monogenic autosomal-recessive disease that is distinct from classical and more complex variants such as UC and CD. Allogeneic HSCT that restores IL-10 signaling in hematopoietic cells proved to be a promising therapeutical approach that may cure patients with IL-10 or IL-10R deficiency and sustain long-term remission. The progress in IBD research

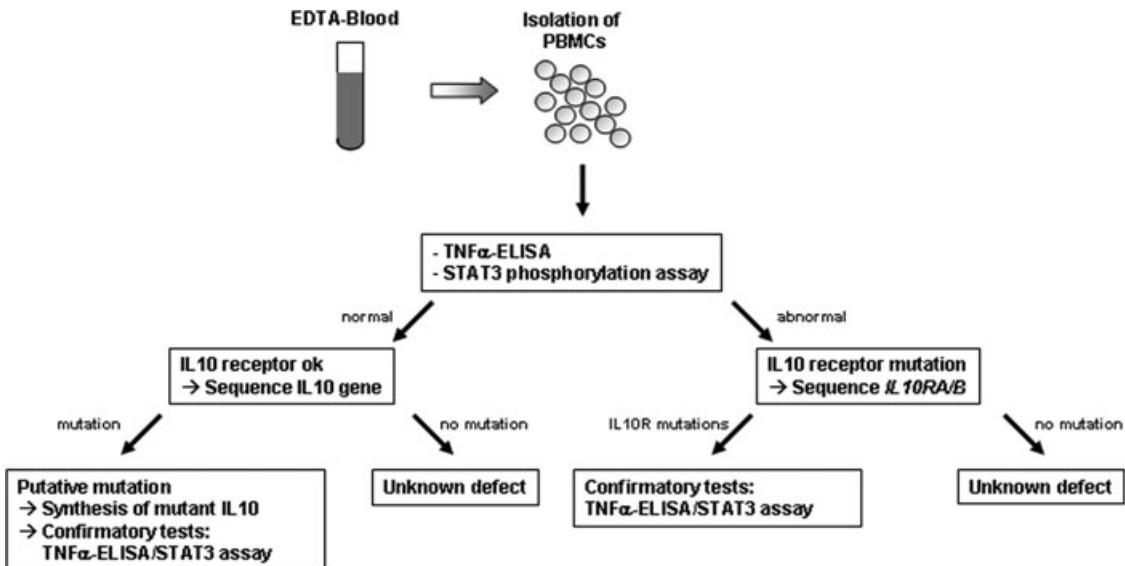


Figure 2. Diagnostic procedures to detect IL-10 and IL-10R mutations.

has broadened our knowledge of the mucosal immunity, the components that keep it in balance and genes that control susceptibility to IBD. However, there are still many unknown players that need to be identified to make us understand the complex immunity and ecosystem of the intestine.

Conflicts of interest

The authors declare no conflicts of interest.

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