Pediatric Inflammatory Bowel Disease: A Review of Immune Homeostasis and Genetics with an Emphasis on the IL-10 Pathway

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Abstract

Inflammatory bowel disease (IBD) is an auto-immune condition characterized by chronic gastrointestinal inflammation. The incidence of pediatric IBD, particularly the early onset disease subtypes, has been increasing internationally. In contrast to later-onset IBD, recent literature indicates that early-onset (between 3 - 5 years) and very early-onset (between 0 - 2 years) patients present with a more severe and aggressive disease. A comprehensive review of the literature indicates that the gut microbiome, which is heavily influenced in the early life, is reduced in IBD patients and hence plays a role in regulating gastrointestinal homeostasis. While many genes have been confirmed to be associated with IBD, only a portion of those genes have been shown to cause pediatric IBD.

The IL-10/STAT3 pathway is a well-studied gene pathway as is involved in maintaining immune homeostasis in both acute and chronic inflammation. Accumulating evidence indicates that IL-10/STAT3 pathway is a key player in pediatric IBD. New mutations identified within the IL-10 pathway have been shown to disrupt immune homeostasis and cause gastrointestinal inflammation. Furthermore, significant epistatic interactions have been demonstrated between different single-nucleotide polymorphisms of IL-10 genes suggesting that understanding gene interactions within the IL-10/STAT3 pathway may be key to understanding more about IBD pathogenesis. Heme oxygenase 1 (HO-1) is speculated to be regulated by the IL-10/STAT3 pathway and hence involved in pediatric IBD formation. This review aims to provide an overview of pediatric IBD and discuss the role of the gut microbiome, IL-10/STAT3 pathway, and HO-1 gene in modulating immune homeostasis in IBD pathogenesis.

Keywords: Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Pediatric; Early onset; Very early-onset; IL-10, STAT3; HO-1

Abbreviations: IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn’s Disease; NVDW: Neutrophil Volume Distribution width; PCDAI: Pediatric Crohn’s Disease Activity Index;

Introduction

Inflammatory bowel disease (IBD), mostly ulcerative colitis (UC) and Crohn’s disease (CD), is a chronic auto-immune condition affecting 0.4% to 0.6% of the North American population [1]. IBD is characterized by inflammatory destruction of the gastrointestinal mucosa [2]. IBD manifests as both gastrointestinal and extra-intestinal symptoms such as diarrhea, abdominal pain, hematocynosis, and joint pain [3,4]. The exact etiology of IBD is unknown; however, it has been postulated that IBD is a multifactorial disease caused by an immunological response to host gut microbiome and is modulated by a combination of genetics and environmental exposures [5,6]. Hence, disease severity and presentation often depends upon a variety of factors including diet, race, environment, sex, age, and life style [7]. According to the Montreal classification, IBD is classified based on age of disease onset as A1 (< 17 years), A2 (17 - 40 years), or A3 (> 40 years). A1 IBD can be further sub-classified as either A1a (0 - 9 years) or A1b (10 - 16 years). Some papers make a special distinction between early-onset (EO; disease onset between 3 - 5 years) or very early-onset (VEO; disease onset between 0 - 2 years).
onset (VEO; disease onset between 0 - 2 years) IBD [8-12] due to the unique phenotypes found in that age range discussed later in this review.

Epidemiology of Pediatric IBD

In recent years, the incidence and prevalence of IBD has been steadily increasing worldwide [13] and especially in the pediatric population (< 17 years) [14]. Approximately 25% of IBD patients contract the disease within their pediatric years [15] and it is estimated that the incidence of IBD has increased by over 50% over the past decade in children younger than 5 years [14,16]. A recent cohort study done in Ontario, Canada, found that IBD rates, while unchanging in the elderly, have been increasing significantly amongst the pediatric and adult populations from 1999 to 2008. The authors report that the incidence of IBD in patients younger than 10 years old and between 10 -19 years old increased by 9.7% and 3.8% per year, respectively [17]. Other North American studies show an EO-IBD incidence rate to be anywhere from 6% to 10% [8,18]. In France, a population based study of 1,412 pediatric patients showed a 116% increase in the incidence of EO-IBD [19]. VEO-IBD is a rare phenotype; in some studies, it occurs in only 21 of 2022 pediatric patients [20-22]. While pediatric IBD has mostly been studied within the United States of America, Canada, and European countries [23-25], it is clear that cases of pediatric IBD are increasing in other nations, such as China [26], Saudi Arabia [27], and Turkey [28], with similar clinical presentations. These studies cement the idea that pediatric IBD is a growing international problem, which needs to be understood.

Clinical Presentation and Diagnosis of Pediatric IBD

Recent literature supports the hypothesis that EO-IBD and VEO-IBD presents with a more aggressive and severe phenotype compared to later and adult-onset IBD [12,29-33]. In an age-group comparison of 160 IBD patients, those diagnosed between 5-10 years of age had greater IBD activity and extent than those diagnosed between 11-16 years of age [29]. The most common initial clinical findings are isolated colitis and rectal bleeding [29]. Furthermore, EO-IBD patients are more likely to be on immunomodulation therapy and require surgery compared to older patients [12,18,34-37]. In one study, Aloi et al analyzed a group of 506 pediatric IBD patients in Italy. The authors reported a higher prevalence of UC in the early-onset and a higher prevalence of CD in the later-onset populations. EO-UC was more likely to initially present with pancolitis. In addition, EO-CD was more likely to present with isolated colonic and upper gastrointestinal disease instead of ileocolic disease as commonly seen in older children [12].

A recent systematic review on pediatric IBD from 41 studies of 3505 CD patients, 2071 UC patients, and 461 indeterminate colitis patients indicated growth failure in CD patients more often than in UC patients, and the surgery rate in CD was much higher than in UC [38]. It is important for clinicians to be able to accurately recognize and diagnose IBD in a timely fashion so that treatment can be initiated as soon as possible. Although most patients have delayed growth charts, published studies indicate that pediatric patients catch up and reach appropriate adult height levels [39]. Delay in treatment can result in stunted growth development secondary to chronic inflammation and malnutrition among other factors [40]. However, diagnosis of EO-IBD can be difficult. Firstly, symptoms of EO-IBD are broad and non-specific. This results in a wide range of both gastrointestinal and extra-intestinal manifestations that can complicate diagnosis [3]. The non-specificity of findings can help explain why indeterminate IBD (instances of colitis in which classification as either CD or UC is unclear) and UC make up the majority of EO-IBD cases despite the fact that CD is the most common overall form of IBD [12,19].

Secondly, the gold standard for assessing IBD is an endoscopy study with biopsies. However, these tests are invasive and not often utilized, especially in pediatric patients [3,41]. Compounding this problem is that histological studies are often inconclusive or show non-specific findings [3]. These factors all lead to delayed diagnosis and contribute to extensive disease upon initial presentation [37,42]. Recently, several studies have investigated markers that can aid in diagnosis. Aydemir et al reported significantly higher neutrophil volume distribution width (NVDW) in UC and CD patients compared to normal controls and propose NVDW as an objective parameter for IBD diagnosis [41]. Eosinophilia-associated basal plasmacytosis has been postulated as a sensitive and early histological feature of inflammatory bowel disease [43]. Recently, certain single stranded RNA sequences, 18-24 nucleotides long, known as MicroRNA (MiRNA) [44], have been proposed to be associated with IBD [45] and could potentially be utilized as a diagnostic marker. Further research is still needed in this regard.

Gut Microbiome in Pediatric IBD

In addition to genetics, emerging research indicates a role of the gut microbiome in IBD pathophysiology [46]. Following birth, the neonatal immune system interacts with the gut microbiome and becomes resistant or susceptible to inflammation [47]. It has been recognized that Th1, Th2, Th17, and regulatory T cells play an important role in IBD development [48,49]. Paneth cells comprise an important part of the gut immunity and Paneth cell dysfunction has been associated with gut microbial dysbiosis and IBD [50,51]. In addition, children under the age of one taking antibiotics (and thus disrupting their gut microbiota) have been associated with pediatric IBD [52]. The composition of the gut microbiome is heavily influenced by early life exposures such as mode of delivery, diet, and environment [47,53]. The main bacteria that comprise the gut microbiome include species such as Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia [54], and Faecalibacterium [55].

These normal gut bacterial species are all reduced in patients with IBD [54,56]. One longitudinal study done by Shaw et al in a cohort of pediatric IBD patients discovered a correlation between gut microbial dysbiosis and clinical severity using Pediatric Crohn’s Disease Activity Index (PCDAI) score [57]. Of particular interest, Faecalibacterium prausnitzii is believed to play a pivotal role in gut homeostasis by secreting anti-inflammatory factors that interfere with NF-κB activation [58]. Indeed, patients with active IBD have significantly lower levels of F. prausnitzii [55,59] compared to healthy
controls. These findings all point to an intricate relationship among microbiome, host immunity, and anti-inflammation. Recent studies show that gut viruses, such as enteric viruses [60], and commensal fungi [61] may play a role in gastrointestinal inflammation. More research in this regard is needed to better understand the role that viruses and fungi may play in IBD pathogenesis.

Given the importance of the gut microbiome in potential disease formation, several therapies for IBD have been aimed towards restoring this equilibrium. Fecal microbiota transplantation, which is already being used to treat certain cases of *Clostridium difficile* infections [62], has shown promising results in the treatment of IBD [63,64]. Furthermore, nutritional therapies such as specific carbohydrate diet [65,66] and exclusive enteral nutrition [67] have shown improvement in pediatric IBD patients; however, data are still limited and further research in this area is needed.

**Genetics in Pediatric-IBD**

There is increasing evidence that IBD is influenced by genetics. The stable incidence, early age of onset, and characteristic clinical presentation of EO-IBD are strongly suggestive of a genetic etiology [19,35]. EO-IBD, frequently unclassifiable into CD and UC, is particularly treatment resistant, and can be related to an underlying primary immune defect [68]. A unique phenotype of EO-IBD has been described in the South Asian pediatric population in British Columbia [69], further supporting the notion of genetics as the cause of EO-IBD. Furthermore, studies have shown that IBD has a sanguineous pattern of inheritance [70] although spontaneous de novo whole gene deletions [71] and mutations in pediatric IBD susceptibility genes [72] have been implicated in disease formation.

**Table 1**: Genetic mutations in IL-10 and IL-10 receptors and resulting clinical presentation in pediatric IBD.

| Gene | Mutation | Function | Phenotype |
|------|----------|----------|-----------|
| IL-10 | Gly113Arg | Missense mutation | Defective IL-10 protein resulting in an inability to phosphorylate STAT3 [89] |
| IL-10 | c.458A>G, p.Glu153Asp | Missense mutation in exon 5 | EO-and pediatric IBD [113] |
| IL-10R1 | Gly141Arg, c.251T | Missense mutation | EO-IBD and folliculitis [30] |
| IL-10R1 | c.251T, p.Thr84Ile | Missense mutation | Pediatric IBD and folliculitis [30,114] |
| IL-10R1 | Arg262Cys | Missense mutation, signaling defect | VEO-IBD [33] |
| IL-10R1 | p.Arg101Trp, c.301T | Missense mutation, signaling defect | EO-IBD, failure to thrive, diarrhea, oral ulcers, eczema, and perianal fistulas/abscesses [113-115] |
| IL-10R1 | p.Tyr57Tyr/Cys, c.170A/G | Missense mutation | VEO-IBD, lower extremity arthritis and arthralgias, and Kawasaki disease [113] |
| IL-10R1 | Arg117Arg/Cys | Signaling defect | VEO-IBD [113] |
| IL-10R1 | p.R117H | Missense mutation, signaling defect | VEO-IBD [20] |
| IL-10R1 | c.506C>T, p.Ile169Thr | Missense mutation | Pediatric IBD, eczema, and folliculitis [113] |
| IL-10R1 | Pro206X | Premature stop codon | VEO-IBD [90] |
| IL-10R1 | c.583T>C | Missense mutation | VEO-IBD and functional IL-10RA deficiency [72] |
| IL-10R1 | c.1368G>T | Nonsense mutation | VEO-IBD and functional IL-10RA deficiency [72] |
| IL-10R1 | c.537G > A, p.T179T | Exon 4 mutation resulting in a splicing aberration, signaling defect | VEO-IBD, diarrhea, oral ulcers, eczema, and perianal fistulas/abscesses [108,115] |

Over 163 genes have been confirmed to be associated with IBD [73-75]. However, only a portion of these genes have been associated with pediatric IBD. Variants in the NOD2, EOBID [76], IL-23R, ATG16L1, IBDS, TNF-α [77], IL-10, IL-10R [30], XIAP [71], MSH5, CD19 [78], DMBT1 [79], CYBB, CYBA, NCF1, NCF2, NCF4, FOXP3, WAS, MEFV, and ITGB2 have been linked to pediatric IBD. Interestingly, a number of immunity genes such as IL-10 and IL-10R have been associated with pediatric IBD. The small and large intestines are the largest source of lymphoid tissue in newborns; therefore, immune dysregulation in response to gastrointestinal microorganisms within the first few weeks of life can lead to inflammation and injury [68,80]. Chandrakasan et al in their study categorize EO-IBD as either, a disorder of T-cell immune tolerance, IL-10 signaling, neutrophil function, epithelial barrier function, hyperinflammation, or B-/T-cells [68]. Recently an exome sequencing analysis revealed variants in IL-10RA, MSH5, and CD19 that could lead to primary immunodeficiency in patients with VEO-IBD [78].

Accumulating evidence indicates that IL-10/STAT3 pathway is a key player in both pediatric- and adult-onset IBD. IL-10 and STAT3 have been identified as IBD-associated genes in children and adults [16,81-87]. Mutations in IL-10 and IL-10 receptors (IL-10RA and IL-10RB) have been linked to VEO-IBD (Table 1) [20,30,81,88-90]. In the following sections, we will discuss in greater detail the GI immune homeostasis and the role of chronic inflammation in IBD. In addition, we will analyze the genetics of the IL-10/STAT3 pathway, including the heme oxygenase 1 (HO-1) gene, in pediatric IBD.

There is increasing evidence that IBD is influenced by genetics.
Immune Homeostasis in Pediatric IBD

Inflammation, regulated by pro- and anti-inflammatory cytokines, is the immune response to threats to homeostasis and results in the elimination of foreign pathogens and repair of damaged tissues [91]. Interleukin-1 (IL-1), IL-12, IL-18, tumor necrosis factor, interferon gamma (IFN-γ), and granulocyte macrophage colony stimulating factor are all cytokines which stimulate inflammation. On the other hand, IL-4, IL-10, IL-13, IFN-α, and transforming growth factor beta are all cytokines which inhibit inflammation [92]. Because IBD is mediated by chronic inflammation, understanding the role of these anti-inflammatory cytokines is vital for IBD clinical therapy. IL-10 is a well-studied anti-inflammatory cytokine in acute and chronic inflammation [93] and plays a key role in regulating gastrointestinal immune homeostasis and inflammation [94,95].

IL-10 knockout mice have been shown to develop IBD [96]. In addition to IL-10, other cytokines are involved in the inflammatory process in IBD. Rafa et al. after analyzing blood plasma from IBD patients showed that the IL-23/IL-17A axis and NO synthase pathway are involved in inflammation regulation in IBD [97]. As illustrated in Figure 1a, signal transduction within the IL-10/STAT3 pathway is initiated by the association of IL-10 to its receptors, IL-10RA and IL-10RB. The binding of IL-10 to its receptors creates a receptor complex which then activates JAK1 and Tyk2. JAK1 and Tyk2 are both tyrosine kinases which phosphorylate IL-10RA and create a signal transduction path which leads to the activation of STAT3. STAT3 then promotes the transcription of anti-inflammatory genes. Functional studies showing STAT3 phosphorylation to IL-10 stimulation in vitro suggest a role for macrophage-intrinsic IL-10R in regulating inflammatory response. Rafa et al. after analyzing blood plasma from IBD patients showed that the IL-23/IL-17A axis and NO synthase pathway are involved in inflammation regulation in IBD [97]. As illustrated in Figure 1a, signal transduction within the IL-10/STAT3 pathway is initiated by the association of IL-10 to its receptors, IL-10RA and IL-10RB. The binding of IL-10 to its receptors creates a receptor complex which then activates JAK1 and Tyk2. JAK1 and Tyk2 are both tyrosine kinases which phosphorylate IL-10RA and create a signal transduction path which leads to the activation of STAT3. STAT3 then promotes the transcription of anti-inflammatory genes. Functional studies showing STAT3 phosphorylation to IL-10 stimulation in vitro suggest a role for macrophage-intrinsic IL-10R in regulating inflammatory response.
an important role in regulating intestinal homeostasis through anti-apoptosis and angiogenesis in cancer [102].

**IL-10/STAT3 Pathway Mutations in Pediatric IBD**

Given its role in regulating inflammation, it is no surprise that IL-10/STAT3 is involved with IBD. We observed an association between IL-10 SNP rs1800872 and rs304498 with adult IBD in a population of 122 adult IBD with 172 controls, as shown in Figure 1b [103]. There was also an association between IL-10 rs304496 (p = 0.022) and rs1800872 (dominant model: p = 0.0277) in pediatric IBD using a case-control [103] and case-trio study [104] respectively. STAT3 was not found to be associated with pediatric IBD in either case-control or case-trio studies [103,104]. New mutations within the IL-10 receptors have recently been identified. IL-10 receptor mutations will block signals from IL-10 and cause inflammation resulting in gastrointestinal tissue damage [95,105]. One IL-10RB (cG477A, p.Trp159*) and 2 novel IL-10RA (cT192G, p.Tyr64* and cT133G, p.Trp45Gly) mutations were discovered in a cohort of 17 pediatric patients < 4 years of age [106].

From Chinese populations, 10 novel and 6 previously described mutations were found in IL-10RA and IL-10RB. Of these mutations, IL-10RA (c.C301T, p.R101RW; c.G537A, p.T179T) was the most common [107]. A novel exonic mutation of IL-10RA (c.G537A, p.T179T) was identified in a child later diagnosed with VEO-IBD [108]. 16 mutations, among which IL-10RA p.Y64C was a novel mutation, were discovered in the IL-10, IL-10RA, and IL-10RB genes in a cohort of 13 Chinese VEO-IBD patients. The results from the mutation screening indicated that IL-10RA and IL-10RB mutations were associated with the development of VEO-IBD (Table 1) [109]. Our research, using a newly developed method, demonstrated significant epistatic interactions between IL-10 rs1800872 and rs304496 (additive-additive p=0.00015), and between IL-10 rs1800872, rs3024496, and IL-10 RA (additive-additive-additive, p=0.003) (Figure 1b) [103]. Hence, understanding more about the gene interactions in the IL-10/STAT3 pathway may be the key to unlocking more knowledge regarding IBD disease formation.

**HO-1 as a Potential Player in Pediatric IBD**

Given that HO-1 is regulated by the IL-10/STAT3 pathway, it is reasonable to speculate that HO-1 plays a potent role in controlling inflammation in pediatric IBD. However, using genetic variations of HO-1, a (GT)n dinucleotide repeat within the promoter region and SNP rs2071746 upstream of the HO-1 gene [110], was shown to be neither associated with adult IBD [111,112] nor pediatric CD [111]. In our own research, HO-1 rs2071746 was not associated with pediatric IBD using a case-control study [103]; however, rs2071746 was found to be significantly associated with pediatric IBD using a case-trio study (additive model: p = 1.87 x 10^-4) [104]. In addition, we demonstrated a significant epistatic interaction between HO-1 and different IL-10 and IL-10 receptor SNPs including IL-10 rs1800872 and IL-10 rs2834167 [104] (Figure 1b). These results indicate that HO-1 may be regulated by the IL-10/STAT3 pathway via gene interaction of HO-1 with IL-10 and its receptors.

In order to better understand the anti-inflammatory properties of HO-1 and its interaction with IL-10/STAT3 pathway to regulate immune homeostasis, we analyzed HO-1 gene expression in B lymphocyte cell lines isolated from pediatric IBD cases. Lipopolysaccharides (LPS) and TNF-α are well-known pro-inflammatory agents. When exposed to lipopolysaccharides and TNF-α, cell lines containing a mutation within the IL-10/STAT3 pathway showed reduced HO-1 gene expression. Therefore, we speculate that the HO-1 gene is a target of regulation by the IL-10/STAT3 pathway and both HO-1 and the IL-10/STAT3 pathway is involved in IBD disease [104].

**Figure 1:**

(A) IL-10 binds with its associated receptors and activates JAK1 and Tyk2. In combination with the IL-10 receptor complex, JAK1 and Tyk2 activate STAT3, a transcription factor. STAT3 regulates the transcription of HO-1 and other genes responsible for controlling inflammation and immune homeostasis. (B) Mutations within the IL-10/STAT3 pathway leads to the chronic GI inflammation seen in pediatric IBD. Our research shows the epistatic interactions of SNPs of IL-10, IL-10 receptors, and HO-1. Dotted red arrows show epistatic interactions between (1) different SNPs of IL-10, (2) IL-10 and IL-10RA, (3) IL-10 and IL-10RB, and (4) IL-10RB and HO-1.
Conclusion

The available evidence supports the growing belief that EO-IBD is determined largely by genetics. Most of these genes are implicated in the immune regulation. The IL-10/STAT3 pathway is a well-studied gene pathway that is involved in maintaining immune homeostasis in both acute and chronic inflammation. IL-10 binds to its associated receptors and forms a complex activating Jak1 and Tyk2. These two proteins then phosphorylate and activate STAT3 that in turn leads to anti-inflammatory gene transcription. SNP’s within IL-10, IL-10RA, IL-10RB, and STAT3 have been implicated in both pediatric and adult IBD. In particular, mutations within the IL-10 receptors have been shown to associate with VEO-IBD. The IL-10/STAT3 pathway regulates the HO-1 gene and the HO-1 gene may be key in understanding EO-IBD pathogenesis. While studies did not find an association between HO-1 and IBD, our case-trio study found a correlation between pediatric IBD and HO-1.

In summary, pediatric IBD, especially EO- and VEO-IBD, has been steadily increasing in incidence in both developed and developing nations. Recent studies show a complicated interplay among the gut microbiome, immune homeostasis, and microbial dysbiosis to be associated with worsening IBD. The IL-10/STAT3 pathway in addition with the HO-1 gene, plays an important role in IBD pathogenesis. Furthermore, significant epistatic interactions between IL-10 and HO-1 have been identified. Specific investigation into the IL-10 signaling pathway in pediatric IBD pathogenesis will help to better understand pediatric IBD and provide target molecules to potentially develop anti-inflammatory agents for clinical treatment of pediatric IBD.

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