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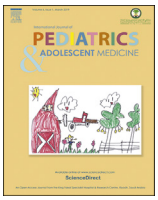

Invited review

Current concepts in pediatric inflammatory bowel disease; IL10/IL10R colitis as a model disease

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ABSTRACT

Inflammatory bowel disease (IBD) is a heterogeneous group of disorders composed mainly of ulcerative colitis (UC) and Crohn's disease (CD) and undetermined IBD. The peak incidence of occurrence is mainly beyond the pediatric age group. Recent knowledge about genetic factors had been strongly linked to pediatric IBD (PIBD). Recent advances in genomic technologies have prompted the identification of genetic defects underlying rare, very early-onset IBD (VEO-IBD) as a disease subgroup noted especially in populations with higher consanguinity rates. A better understanding of key players in the complex homeostasis of the immune system in the gut and illustrating the relationships between intestinal microbiome, systemic immune dysregulation and primary immunodeficiency have received growing recognition over the years. In this article, we provide a review of the key players of the immunity of the gut, compare between adult and pediatric IBD as an interesting module to investigate the relationship between monogenic and multifactorial/polygenic diseases, list genetic mutations confirmed to be linked to VEO IBD and summarize the scientific work that led to the discovery of one of the monogenic mutations related to infantile colitis, namely IL10 and IL10 receptor defects.

1. Introduction

Inflammatory bowel disease (IBD) is a heterogeneous group of disorders composed mainly of ulcerative colitis and Crohn's disease (CD) [1]. Inflammatory bowel disease has a multifactorial pathogenesis with complex interactions between polygenetic predispositions and environmental factors. However, IBD can also be caused by monogenic diseases, such as primary immunodeficiencies [2]. The peak incidence of occurrence is mainly beyond the pediatric age group (or late pediatric age in some countries), ranging between 15 and 30 years of age [3]. Pediatric IBD (PIBD) is defined as having an age of occurrence younger than 17 years. The latest modification of the IBD classification has further classified PIBD into early-onset (EO) IBD when it occurs between 10 and 17 years of age and very-early-onset (VEO) IBD in children younger than 10 years (some consider 6 years) [4], with that diagnosed before 1 year of age called *infantile IBD*. Very-early-onset inflammatory bowel disease is distinctly differentiated phenotypically and genetically from EO IBD and older-onset IBD.

A rapid increase in the incidence of VEO IBD has been reported in many studies from Canada, France, Ireland, and Scotland [5,6], and up to 20% of CD patients and 12% of ulcerative colitis patients fall in the pediatric age group according to one study (which included patients aged 20 years old or younger) [7]. Table 1 summarizes the causes of colitis in young children.

In Saudi Arabia, the biggest multicenter national study of patients presenting with EO IBD (defined as patient presentation at less than 6 years of age) was published by Al-Hussaini et al. [8] in 2016. It represents the single largest cohort of pediatric patients with confirmed EO IBD in the Middle East. Studies from North America, Europe, and Australia reported a prevalence of EO IBD ranging from 4% to 15% of PIBD, whereas Al-Hussaini et al. reported a higher prevalence of EO IBD of 21.6% and prevalence of infantile or toddler-onset IBD of 9%. The high prevalence was related to the high consanguinity rate (up to 60%) in the Saudi population, which might confer genetic susceptibility to the early development of IBD [8]. The incidence of PIBD in Saudi Arabia was found to be 0.59 per

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Table 1
Causes of colitis in young children.

Infections including *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Clostridium difficile*, *Giardia*, and cytomegalovirus infections, amoebiasis, tuberculosis, and HIV/AIDS
Allergic colitis
Eosinophilic colitis
Benign lymphoid hyperplasia
Hemolytic uremic syndrome
Beçhet's disease
Primary immunodeficiency, including SCIDs, Wiskott-Aldrich syndrome, CVID, CGD, IPEX syndrome, NEMO deficiency, GSD1b, *IL10R* defects, Hermansky-Pudlak syndrome
Autoimmune enteropathy
Hemophagocytic lymphohistiocytosis

GCD, chronic granulomatous disease; CVID, common variable immunodeficiency; GSD1b, glycogen storage disease type 1b; IPEX, immune dysregulation, polyendocrinopathy, and enteropathy X-linked; NEMO, nuclear factor κB essential modulator; SCID, severe combined immune deficiency.

100,000 compared with 5.2 per 100,000 in the UK [9,10], which might reflect underreporting of cases in respect to high consanguinity rate and inherited diseases [11–13].

In this review, we highlight the main causes of pediatric colitis, provide insight into the key players in the immunity of the gut, compare adult IBD and PIBD, provide an updated list of genetic mutations confirmed to be linked to VEO IBD, and summarize the scientific work that led to the discovery of some of the monogenic mutations related to infantile colitis; namely, interleukin 10 (IL10) gene (*IL10*) and IL10 receptor gene defects.

2. Pediatric versus adult IBD

Disease progression and pathogenesis of PIBD differ from those of adult IBD. Pediatrics inflammatory bowel disease has higher variability of clinical presentation, resistance to conventional immunosuppressant therapy, and unique complications [14,15]. Often PIBD presents with failure to thrive and delayed puberty in addition to classic IBD symptoms such as abdominal pain and diarrhea, whereas in adult IBD, the main clinical presentation is diarrhea [16]. Table 2 summarizes the differences between PIBD and adult IBD [17–19]. Because of the aggressive disease phenotype and strong family history of the disease, some types of VEO IBD are thought to be a monogenic disease, often involving genes associated with primary immunodeficiency owing to inherited variants that may contribute to dysregulated immunologic homeostasis in the intestine [20].

3. Intestinal hemostasis and immunity

Intestinal epithelial barrier function plays an essential role in maintaining intestinal health. Physical and biochemical barriers, including tight junctions, IgA, antimicrobial peptides, mucus, and the innate lymphoid cell type 3–interleukin 22 pathway, maintain intestinal epithelial barrier function. This is essential to maintain anatomic segregation between commensal bacteria and the mammalian immune system. Loss of this physical segregation can promote dysregulated innate and adaptive immune cell responses. Identified genetic variants that result in a loss-of-function or gain-of-function mutation and that are associated with VEO IBD include *ADAM17*, *IKBKG*, *COL7A1*, *FERMT1*, *TTC7A*, and *GUCY2* [21].

Table 2
Differences between pediatric inflammatory bowel disease (IBD) and adult IBD.

		Adult IBD	VEO IBD
Area of involvement	Colon	<20%	80%
	Ileum	80%	6–20%
Family history		14–20%	40–50%
Extensive disease		16%	40%
Need for surgery		55%	71%

VEO, very early onset.

The major components of the adaptive immune system interact starting with antigen-presenting cells that activate Th0 naïve cells. Subsequently released cytokines orchestrate the activation of other specialized T lymphocytes. Activation of Th1 cells induces cytotoxic killing of intracellular pathogens, while Th2 cells induce further differentiation of B cells into plasma cells that secrete antibodies flagging up the intruding pathogen, allowing an easier phagocytic effect for macrophages and neutrophils with opsonization. Furthermore, Th0 cells orchestrate the activation of Th17 cells and regulatory T cells [22].

At the beginning of an inflammatory process, the interaction between the antigen-presenting cells and the Th0 cells allows the latter to produce the cytokine transforming growth factor β in a low concentration, activating Th17 cells, which then recruit inflammatory cells to the intestinal mucosa, inducing inflammation. On the other hand, well into the maturation of the inflammatory process, the high concentrations of transforming growth factor β produced by Th0 cells activate regulatory T lymphocytes through forkhead box P3 gene (*FOXP3*) activation to produce the cytokine IL10. IL10 inhibits Th17 cells, and that function makes it a regulatory cytokine limiting severe inflammation and recruitment of inflammatory cells [22]. It is believed that the absence of IL10 causes an unopposed effect of Th17, resulting in severe enterocolitis [23].

4. The journey of finding genetic causes of inflammatory bowel disease

Genome-wide association scanning has identified loci in both ulcerative colitis and CD that are already known to be involved in adaptive immunity genes such as *IL23R*, *CARD15*, *IL12B*, and *STAT3*, and loci on chromosome band 3p21 (*MST1*) and chromosome band 10q24 (*NKX2-3*). Variants in innate immunity genes, particularly those mediating autophagy and bacterial sensing (*ATG16L1*, *IRGM*, and *NOD2*), have also been discovered through these methods in CD. A better understanding of the correlation between genotype and phenotype of different groups of IBD. To date, there are confirmed genetic mutations that are looked for especially in patients presenting with infantile colitis, many of which are linked to primary immunodeficiency (summarized in Table 3) [24].

In some cases, infantile IBD or VEO IBD can be caused by a number of rare, single genetic mutations; for example, IBD can be caused by mutations in *IL10*, *IL10*RA, *IL10*RB, *NCF2*, *NCF4*, *XIAP*, *LRBA*, *ADAM17*, or *TTC7*, among many other genes. Several other primary immunodeficiency disorders predispose to IBD, including leaky severe combined immune deficiency, bare lymphocyte syndrome, Wiskott-Aldrich syndrome, hyper-IgM syndrome, ataxia-telangiectasia, hyper-IgE syndrome, chronic granulomatous

Table 3
Summary of genetic mutations linked to inflammatory bowel disease (IBD) and associated primary immune deficiency and immune dysregulation disorders.

Genetic variants related to IBD	Resulting disorder presenting with inflammatory colitis
Intestinal epithelial barrier function	
IKBKG (encoding NEMO)	X-linked ectodermal dysplasia and immunodeficiency
COL7A1	Dystrophic epidermolysis bullosa
FERMT1	Kindler's syndrome
GUCY2 gain of function	Familial diarrhea
ADAM17	ADAM17 deficiency
TTC7A	Multiple intestinal atresia with combined immune deficiency
Microbial recognition and clearance	
CYBB, *CYBA*, *NCF1*, *NCF2*, *NCF4*	Chronic granulomatous disease
ITGB2	Leukocyte adhesion defect
GSD1b	Glycogen storage disease type 1b
XIAP	X-linked lymphoproliferative syndrome type 2
Adaptive immune system impairment	
RAG1, *RAG2*, *IL7R*	Leaky SCID/Omenn's syndrome
BTK	Agammaglobulinemia
LRBA/*CTLA4*	Polyautoimmunity and combined immune deficiency
WASP	Wiskott-Aldrich syndrome
STAT3	Hyper-IgE syndrome
CD40, *CD40L*	Hyper-IgM syndrome
MHCII	Bare lymphocyte syndrome
Regulatory-T-cell impairment	
FOXP3	IPEX syndrome
IL2-IL2R, *STAT5B*, *ITCH*, or gain-of-function mutations in *STAT1*	IPEX-like disease, Immune dysregulation disorders
IL10-IL10R pathway and related cytokine family members	
IL10 ligand and *IL10*RA and *IL10*RB	Folliculitis, arthritis, and fistulating colitis

IL10, interleukin 10; IL10R, interleukin 10 receptor; IPEX, immune dysregulation, polyendocrinopathy, and enteropathy X-linked; SCID, severe combined immune deficiency.

Table 4
Summary of reported cases with *IL10*, *IL10*RA, and *IL10*RB defects with hematopoietic stem cell transplantation (HSCT) and outcomes.

Study/ author	Patients	Age at transplant	Diagnosis	Type of defect	Treatment	Medications after treatment	Outcomes
Glocker et al. [27]	1	11 months	VEO IBD	*IL10*RB	HSCT with reduced-intensity conditioning	Not mentioned	Resolution of symptoms
Beier et al. [36]	4	1–13 years	VEO IBD/ EO IBD	*IL10*RA or *IL10*RB	HSCT with reduced-intensity conditioning	Not mentioned	1 patient had rejection, followed by successful retransplantation. 3 patients exhibited full chimerism and resolution of symptoms
Kotlarz et al. [28]	5	<5 years	VEO IBD	*IL10* (3 patients). *IL10*RA (5 patients). *IL10*RB (8 patients)	HSCT with reduced-intensity conditioning	Not mentioned	Resolution of symptoms. In vitro experiments showed reconstitution of IL10R-mediated signaling among all patients
Engelhardt et al. [29]	3	<1 month	VEO IBD	*IL10* (2 patients) *IL10*RA (1 patient)	HSCT with conditioning	Steroids, infliximab, adalimumab, azathioprine	Resolution of symptoms
Karaca et al. [33]	1	5 months	VEO IBD	*IL10*RB	HSCT with conditioning	Cyclosporine A and in the short term methotrexate	Resolution of symptoms
Peng et al. [37]	9	<1 month	VEO IBD	*IL10*RA	HSCT with conditioning	Not mentioned	Resolution of symptoms (6 patients), death (3 patients) due to sepsis and pneumonia

EO, early onset; IBD, inflammatory bowel disease; IL10R, interleukin 10 receptor; VEO, very early onset.

disease, common variable immunodeficiency, and immune dysregulation disorders such as immune dysregulation, polyendocrinopathy, and enteropathy X-linked (IPEX) syndrome (Table 3) [20–25].

5. The novel finding of IL10 and related colitis

The continuous search for the molecular basis of inflammatory diseases affecting the gut and other systems was ignited by the novel finding of Sakaguchi et al. [26] in 1985, following the discovery of the occurrence of autoimmune diseases in T-cell-deficient mice. Scientists then started developing mice with defective genes that encoded different pathways involving innate and acquired immunity, specifically studying the effects of cytokines and regulatory T lymphocyte interactions and their role in normal and inflamed mucosa. In 1993, Kuhn et al. [21] studied the effect of IL10 specifically by generating a knockout gene disrupting IL10 production in laboratory mice. This resulted in the development of severe enterocolitis. Following this finding, many studies have been published from different research centers focusing on

genetic inheritance of T-cell defects as the possible cause of infantile colitis [27,28]. The current understanding of immune dysregulation and autoimmunity in certain genetic mutations has alerted clinicians to the use of advanced genetic testing modalities and immune system evaluation tools to better understand IBD and determine a better tailored therapeutic modality. Considerable progress has been made in the last decade in studies of the genetics of the IBDs.

In 2010, Glocker et al. [27] reported two infants with VEO IBD that was resistant to treatment with immunosuppressants and that was aggressive in nature, leading to hemicolectomy in one case. They examined thoroughly the genetic codons encoding IL10 receptors and found no abnormalities. The sequencing of *IL10* in both cases confirmed a homozygous genetic defect in codon 113 replacing glycine with arginine and interrupting the production of normal IL10. This discovery confirmed previous literature knowledge. It also established an understanding that a unified phenotype of severe, resistant PIBD could be caused by a defect in *IL10R*, or in the normal production of IL10 as well. Furthermore, new discoveries have shown several genetic defects that are linked to a shared VEO IBD phenotype (Table 3) [21]. Screening was expanded for a genetic cause in VEO IBD patients to identify IL10 pathway defects. Kotlarz et al. [28] reported mutation in 16 of 66 infants. Shim and Seo [30] in Korea found 7 affected infants among 40 infants tested, as did Engelhardt et al. [29]. Begue et al. [31] in France found 2 infants with mutations among 13 infants. A Malaysian group who screened 48 Asian infants with infantile colitis for *IL10* and *IL10R* mutation found no mutation to be present [32] To date, there have been 78 cases of VEO IBD caused by IL10 signaling defects, calculated by our best effort from reading the published cases in the literature; most are summarized by Zhu et al. [23].

6. The current treatment options for VEO IBD caused by IL10 signaling defect

The current treatment options are disease-controlling/modifying modalities. Trials of providing IL10 intravenously and through bacterial vectors to the gastrointestinal tract showed limited results [36,37], although it is unclear if the results' limitation is true for patients with a IL10 pathway defect. The only curative disease modality is with hematopoietic stem cells. Table 4 summarizes the studies published (Table 4). Multiple cases have been reported, and treatment with hematopoietic stem cells with a variable donor source and conditioning protocols seems promising and shows notable disease remission [29, 31, 35, 37–39].

Conflicts of interest

Authors ensure no conflict of interest exists.

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