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Mini Review

Current Progress in Pediatric Inflammatory Bowel Disease

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Abstract

Recent progress in pediatric IBD studies reveals that genetic factors play an important role in pediatric IBD; mutations associated with VEO-IBD have been identified from IL10 and IL10 receptors; the IL10 gene and genes in IL10 pathway are identified to be associated with pediatric IBD, and epistasis interaction of SNPs/genes in IL10 pathway is shown to contribute to pediatric IBD. IL10 is an anti-inflammatory cytokine and the IL10/STAT3 signaling pathway plays an important role in controlling inflammation and homeostasis. IL10 is a target candidate gene for IBD clinical therapy.

Keywords: Pediatric IBD; Anti-inflammatory cytokine; Inflammation

Introduction

Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), is a major gastrointestinal chronic inflammatory condition that affects approximately 1.4 million people in America. IBD is a very heterogeneous complex disease. Clinically it presents with a large range of symptoms. Severity differs in gender, race, diet, life style, and other factors [1, 2].

IBD can present at any age, but between 15% and 25% of cases will be diagnosed in childhood [3-5]. The general trend shows that the overall incidence for pediatric IBD is increasing over the past few decades; the incidence for pediatric IBD varies among different countries [6]. From a recent study showed an increase in the incidence of pediatric IBD in Ontario Canada from 9.54 (in 1994) to 11.43 (in 2005) per 100,000 populations [7].

Pediatric IBD

For use in clinical practice and basic scientific research in inflammatory bowel disease, IBD is classified into different groups based on IBD disease phenotype. Age of onset is one of the predominant phenotypic elements. According to age at diagnosis, the IBD was classified into two groups in Vienna classification (1998) [8]: A1, below and A2 above 40 years. The A1 group was further classified into two groups in Montreal classification (2006) [9]: A1 below 16 years and A2 between 17 and 40 years (Table 1). The Montreal A1 group is pediatric IBD [9]. Pediatric IBD presents with symptoms such as frequent diarrhea, stomach cramping, fevers, and weight loss. Some children may present with abdominal pain and depression. Pediatric IBD is more often found as Crohn's disease (CD) than ulcerative colitis (UC). Symptoms can begin slowly or come on suddenly and progress quickly. Symptoms can also range widely from very mild to sometimes severe. Most importantly, growth retardation is common in pediatric IBD.

In pediatric IBD, less than 1% of patients may also develop IBD in the neonatal or infantile period [10]. These are described as VEO (very early onset) IBD. Clinical characteristics of the VEO-IBD seem to be different from those of adult-onset or adolescent-onset IBD, such as severity and increased resistance to immunosuppressive treatment [11, 12].

As more VEO-IBD (diagnosis at 0-5 years) cases are reported and more genetic mutations/variations associated with VEO-IBD are identified, VEO/pediatric IBD becomes one of the front areas of IBD basic research and clinical investigation. The dynamic features of pediatric disease phenotype such as disease location, behavior, and growth failure were not sufficiently captured in the previous classification. Recently important modifications have been made in the Paris classification [13]. The Montreal A1 group (below 16 years) is further classified into the A1a (0-9 years) and A1b (10-16 years) subgroups [13] (Table 1). Patients who are diagnosed at very early age are often present with a different and more severe disease than older children and adults with IBD. Currently, the VEO-IBD has not been well characterized [14, 15]. Delays in treatment can make IBD worse and lead to severe anemia from gastrointestinal bleeding, poor food absorption, malnutrition and stunted growth. In advanced cases, although few cancers and deaths have been reported [16], IBD can cause serious damage to the colon and small intestine that requires surgery.

Genetics of Pediatric IBD

Three major factors involved in IBD pathogenesis are genetics, immunity, and environment. Increasing evidence indicated that genetic factors play an important role in IBD. Currently more than 163 genes have been identified to be associated with IBD [3,17-19], but as estimated these collectively represent only <20% of the overall disease risk [17, 20, 21], a complex interplay of multiple genes and environmental factors is still largely unknown [19]. The exact cause of IBD is currently still unclear.

The disease onset of pediatric IBD, especially VEO-IBD, at very early age of life, suggests a strong genetic association. However, of the 163 IBD genes identified from adult IBD only a few genes have been linked to pediatric IBD. These include IL10 [22], NOD2 [23, 24, STAT4 [25], IL23R [26], 3p21 locus (BSN1 and MST1) [27]. The

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Table 1: Classification of pediatric IBD in Vienna, Montreal, and Paris classification.

Age at Diagnosis	Vienan, 1998	Montreal, 2006	Paris, 2011
0-9 years	A1	A1	A1a
10-16 years			A1b
17-40 years		A2	A2
Above 40 years	Above 40 years	Above 40 years	Above 40 years

limitation of GWAS for VEO-IBD associated gene identification, compared with adult IBD, is that VEO-IBD patients are a very select population, often carrying low-frequency mutations/variants. To this concern, alternative approaches such as next generation sequencing, exome sequencing, and targeted gene sequencing may be helpful for these rare disease-causing mutations/variants identification. This has been shown a success in identification of VEO-IBD associated mutations from IL10 and IL10 receptor genes as described below.

IL10 Pathway as Potential Therapeutic Target for Pediatric IBD

IL10 is one of the best studied anti-inflammatory cytokine in acute and chronic inflammation that is a crucial response to threats to homeostasis. Knock out mice lacking IL10 lead to unrelenting immune activation [28]. The IL10/STAT3 signaling pathway plays an important role in controlling inflammation and protecting the intestine tissue from damage [22, 29]. During the IL10 signaling transduction, IL10 binds to receptors IL10RA and IL10RB, and activates Jak1 and Tyk2, leading to phosphorylation of STAT3. Then the activated STAT3 trans locates into nucleus and regulates target gene transcription to promote an anti-inflammatory response [1, 30].

The IL10 gene was identified as IBD-associated gene in 2008 [31]. IL10 deficiency in Knock out mice develops IBD [28]. Our recent data (unpublished) indicate that IL10 is associated with pediatric IBD from a pediatric IBD population of central Pennsylvania USA.

IBD is a human immune-mediated complex disease. In the development and progression of IBD both the innate and adaptive immune systems play a critical role [20, 32, 33]. In the IL10/STAT3 pathway, IL10 [12, 34, 35], STAT3 [22], and Tyk2 [36] have been identified as IBD-associated genes in adults. Recently, mutations in the IL10 genes, IL10 receptors IL10R1 and IL10R2 have been identified to be linked to pediatric/VEO-IBD [15, 35, 37-42]. We hypothesize that IL10 and IL10/STAT3 pathway play an important role in anti-inflammation in IBD.

Our recent results (unpublished) indicate that IL10 gene and IL10 signaling pathway are not only associated with pediatric IBD and their epistasis interaction between SNP-SNP within IL10 gene and between gene-gene in the pathway also contributes to pediatric IBD. However, direct interaction between IL10/IL10 receptors and STAT3 has not been observed from epistasis analysis. We speculate that another gene Tyk2 may be involved interaction between IL10 and STAT3 in pediatric IBD pathogenesis, which has not been studied in our current IL10 pathway study. Tyk2 gene has been identified as an IBD-associated, but its function in IL10 pathway in pediatric IBD is currently unknown. The regulation of IL10 and IL10/STAT3 pathway in inflammation of IBD needs to be further studied. The future investigation of IL10/STAT3 signaling will help understanding the pathogenesis of pediatric IBD, and may provide target molecules for developing anti-inflammatory agents for clinical treatment of pediatric, as well as adult IBD [43].

Conclusion

Reclassification of pediatric IBD as 2 groups and characterization of VEO-IBD show the current interests and rapid progress in pediatric IBD research. Evidence indicates that genetics plays a role in pediatric IBD. As an excellent example, genetic variations/mutations are identified from the anti-inflammatory cytokine IL10 and IL10/STAT3 pathway to be associated with pediatric IBD, and the gene-gene interaction within genes in IL10/STAT3 pathway to be contributor to pediatric IBD. Further study on IL10 and IL10/STAT3 pathway will help understanding mechanism of pediatric IBD pathology and developing strategy for clinical therapy.

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