IBD REVIEWS REVIEW ARTICLE

Etiology of inflammatory bowel disease: new insights

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Abstract

This article reviews current knowledge about the main areas of research in regards the role of genetic, immunological, and environmental factors implicated in the onset and exacerbation of inflammatory bowel disease (IBD). Over the past decade, there has been enormous progress in the discovery of numerous genetic variants that increase or decrease the risk of IBD. (IBD Rev. 2018;4:3-11)

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Introduction

Inflammatory bowel diseases (IBD) are a group of chronic diseases including Crohn's disease (CD) and ulcerative colitis (UC) and are chronically relapsing and remitting inflammatory conditions that result from chronic dysregulation of the mucosal immune system in the intestinal tract[1].

The exact pathogenic mechanisms behind IBD are yet to be fully defined; the current hypothesis suggests that IBD develops at the interface of predisposing genetic variations, immunological alterations, shifts in the gut microbiome, and external environmental influences[1].

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Recently, multiple human genetic mutations are implicated in an increased susceptibility to IBD; however, not everyone who carries these mutations develops IBD, indicating that additional exposures are also involved[2].

Many of these additional factors can be linked to alterations in immune pathways and environmental factors such as microbial and lifestyle (Fig. 1).

In this review, we summarize the latest literature on genetical immunological and environmental influences in IBD.

Genetic factors contributing to IBD pathogenesis

The advent of advanced molecular biological techniques in the past two decades has allowed the study of genetic factors in IBD.

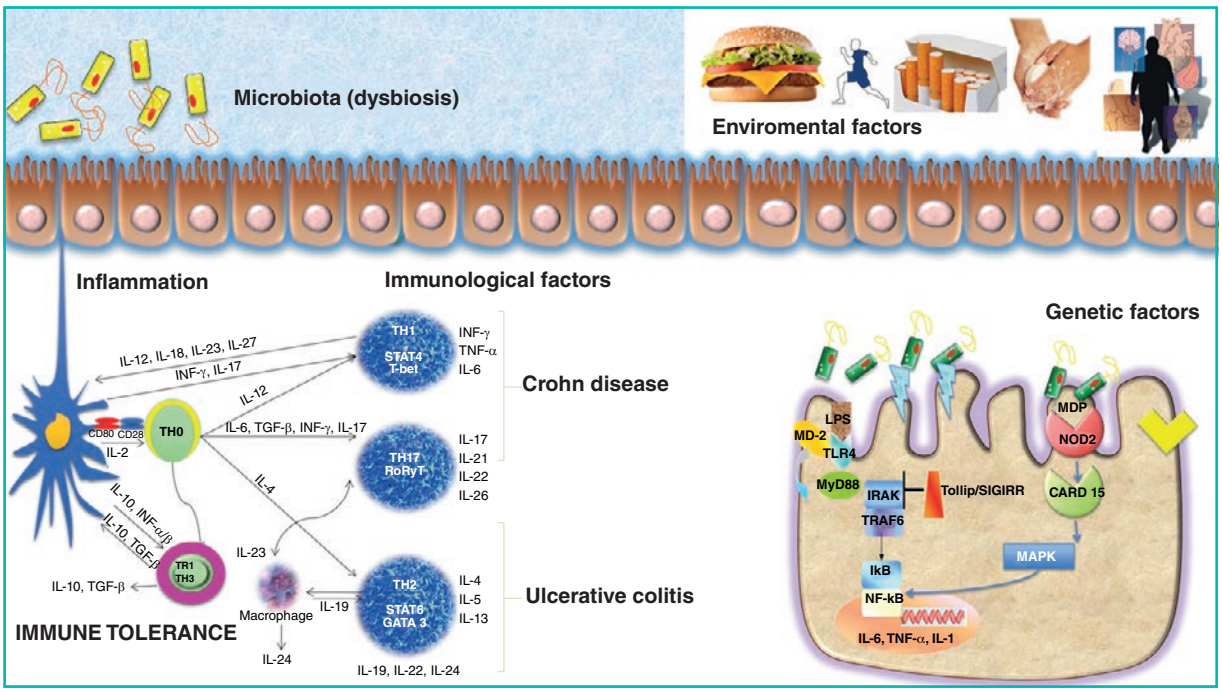

Figure 1.

There is strong evidence that suggests a genetic basis for IBD, including familial clustering and racial and ethnic differences in risk for IBD[3]. 10-20% of affected individuals have a family history of IBD, with the highest risk among first-degree relatives. A positive family history is the principal risk factor for IBD, with relatives of affected individuals having at least a 10-fold increased risk for IBD. Genome-wide association studies have identified over 200 distinct single nucleotide polymorphisms predisposing to the development of CD or UC[4].

Increased rates of IBD between identical twins compared to fraternal twins, and siblings compared to spouses of affected individuals, suggests that genetic rather than environmental factors are primarily responsible for the observed familial aggregation for IBD[5].

The relationship between genetic and immunological factors for the development of IBD was demonstrated through studies with GWAS have revealed a great number of genetic variants predisposing to different complex diseases, but only three genetic polymorphisms related to NOD2, IL23/17, and autophagy have been well established for a direct role in IBD[5].

NOD2

In 2001, the first IBD susceptibility locus was found to involve NOD2. In some geographical regions, patients with CD had a high frequency of NOD2 variants. The major variants involving the leucine-rich repeat region include a frameshift mutation (L1007fsinsC) and two missense mutations (R720W and G908R) suggesting that a defect in peptidoglycan recognition may be associated with CD[6].

The NOD2 gene was the most important genetic factor, being an independent predictive factor for ileal location ($p = 2.02 \times 10$ (–06), odds ratio [OR] = 1.90), structuring ($p = 3.16 \times 10$ [–06], OR = 1.82) and penetrating behavior ($p = 1.26 \times 10$ (–02), OR = 1.25), the need for surgery ($p = 2.28 \times$ e–05, OR = 1.73), and complicated disease course ($p = 6.86 \times 10$ [–06], OR = 2.96). Immunomodulator (azathioprine/6-mercaptopurine and methotrexate) use within 3 years after diagnosis led to a reduction in bowel structuring disease ($p = 1.48 \times 10$ [–06], OR = 0.35) and surgical rate ($p = 1.71 \times 10$ [–07], OR = 0.34)[7].

HLA class II

Actually, there is significant evidence that specific HLA Class II associations contribute to overall disease pathogenesis, especially for UC. A meta-analysis combining results from 29 studies showed significant positive associations in UC to DR2, DR9, and DRB1*0103, whereas a negative association was found for DR4. For CD, a positive association was found with DR7, DRB3*0301, and DQ4, and a negative association with DR2 and DR3[8,9].

In Latinoamerica, previous studies confirmed the role of genetic factors in the development of IBD. Yamamoto-Furusho et al.[10] suggested that HLA-DRB1 alleles were associated with the clinical course of disease and steroid dependence in UC Mexican patients. The authors showed significant associations were found between some HLA-DRB1 alleles and the clinical course of disease: initial active and then inactive and the HLA-DRB1*14 allele (p = 0.03; OR = 4.63; 95% confidence interval [CI]: 1.08-21.23); and HLA-DRB1*08 allele (p = 0.04; OR = 4.34; 95% CI: 1.9-33.3). On the other hand, the HLA-DRB1*07 (p = 0.001; OR = 9.76, 95% CI: 1.55-65.56) was significantly associated with steroid dependence in UC Mexican patients.

IL-15

IL-15 has a pivotal role in life and death of natural killer (NK) and CD8 memory T cells. IL-15 is an inflammatory cytokine involved in immunological memory including that to self, thereby playing a role in autoimmune diseases. Dysregulated IL-15 expression was demonstrated in patients with rheumatoid arthritis, psoriasis, celiac disease, and IBD[11].

Previous studies reported the role of IL-15 gene polymorphisms as susceptibility markers in patients with UC. Seven polymorphisms of IL-15 (rs3806798, rs10833, rs4956403, rs2254514, rs2857261, rs10519613, and rs1057972) in a group of 199 Mexican patients with UC and 698 Mexican Mestizo healthy unrelated individuals[12]. The rs2254514 polymorphism was significantly associated with decreased risk of UC as compared to controls under both dominant and additive models (OR = 0.62, p_{dom} = 0.014 and OR = 0.65, p_{add}=0.02). The rs2254514 CC genotype was associated with young age at diagnosis 40 years (p = 0.03; OR = 3.67). Five polymorphisms (rs1051613, rs2254514, rs2857261, rs1057972, and rs10833) were in strong linkage disequilibrium and were included in six haplotypes: H1 (ACAAC), H2 (CCGTC), H3 (CTAAT), H4 (CCAAT), H5 (CTAAC), and H6 (CCAAC). UC patients showed an increased frequency of the H6 haplotype (p = 0.005; OR = 3.2) and a decreased frequency of the H5 haplotype (p = 0.031; OR = 0.40). These results suggest that the IL-15 rs2254514 polymorphism might have an important role in the development of UC in the Mexican population[12].

IL-1 by binding to receptor IL-1 R1

IL-1 R1 and IL-1B polymorphisms were associated with the genetic susceptibility to develop UC. Yamamoto-Furusho et al.[13] found a significant increased frequencies of IL-1RN6/1 TC (rs315952) and RN6/2 CC (rs315951) and decreased the frequency of IL-1B-511 TC (rs16944) genotypes in UC Mexican patients as compared with healthy controls. Patients with UC showed increased frequencies of IL-1RN "CTC" and "TCG" haplotypes when compared with healthy controls (p = 0.019, OR = 1.43 and p < 10 [–7], OR = 2.63, respectively). Two haplotypes (TTG and CTG) showed decreased frequency in patients when compared with healthy controls (p = 9 × 10 [–7], OR = 0.11 and p = 8 × 10 [–6], OR = 0.11, respectively).

IL-19 (rs2243188 and rs2243193)

IL-19 belongs to the IL-10 family and is a potent immunomodulatory cytokine, with implications for pathogenesis in IBD. Yamamo-

to-Furusho et al.[14] studied the role of IL-19 gene polymorphisms as susceptibility markers for UC. Three polymorphisms of IL-19 gene (rs2243188, rs2243191, and rs2243193) were genotyped in a group of 200 Mexican Mestizo patients with UC and 698 healthy unrelated individuals with no family history of UC. Although genotypes AA (rs2243188) and AA (rs2243193) were significantly decreased in UC patients as compared with healthy controls ($p < 0.018$ and $p < 0.006$, respectively), a genetic additive effect for the alleles was not observed (Cochran–Armitage trend test, not significant). In the subgroup analysis, no differences were found between the IL-19 genotypes and the clinical characteristics of UC. The results suggest that IL-19 polymorphisms (rs2243188 and rs2243193) might have a protective role in the development of UC in Mexican individuals.

IL-20 (rs2981573 and rs2232360)

IL-20 belongs to the IL-10 family and is a potent immunomodulatory cytokine. The IL-20 gene is located within a 200kb region of q31-32 locus of chromosome 1. Yamamoto-Furusho et al.[15] evaluated the IL-20 gene polymorphisms as susceptibility markers for UC. Three polymorphisms of IL-20 gene (rs2981573, rs2232360, and rs1518108) were genotyped in a group of 198 Mexican Mestizo patients with UC and 698 ethnically matched healthy unrelated individuals with no family history of UC. We found significant decreased frequencies of two IL-20 genotypes: GG (rs2981573) (10.6% vs. 17.6%, p = 0.017, OR = 0.55, 95% CI = 0.33-0.93) and GG (rs2232360) (10.6% vs. 17.6%, p = 0.017, OR = 0.55, 95% CI = 0.33-0.93) in UC patients as compared to healthy controls. No significant differences in gene frequencies were found between UC patients and healthy controls in the rs1518108 polymorphism. In the subgroup analysis, no differences were found between the IL-20 genotypes and the clinical characteristics of UC. The results suggest that the GG genotypes of the IL-20 polymorphisms (rs2981573 and rs2232360) might have an important role in the development of UC in the Mexican population.

IL-27

Depending on the microenvironment, IL-27 has anti and pro-inflammatory properties. As an anti-inflammatory, IL-27 seems to induce a general negative feedback program that limits T and NK-T cell activity. At the onset of infection, IL-27 induces an IL-12 receptor on naïve CD4+ T cells, making them susceptible to subsequent IL-12 activity[16-18].

The first study of IL-27 performed in UC patients from a Latin American country demonstrated the protective role of IL-27p28 (rs17855750) and IL-27EBI3 (rs428253, rs4740, and rs4905) polymorphisms in Mexican patients with UC compared to healthy controls. IL-27p28 rs17855750 polymorphism was associated with decreased risk of developing UC (OR = 0.27, 95% CI = 0.06-1.13, p = 0.031). Under recessive models adjusted by age and gender, the EBI3 rs428253 (OR = 0.54, 95% CI = 0.29-0.99, p = 0.035), rs4740 (OR = 0.60, 95% CI = 0.36-1.01, p = 0.046), and rs4905 (OR = 0.59, 95% CI = 0.35-1.01, p = 0.043) were associated with decreased risk of developing UC. Similar levels of IL-27 were observed among the genotypes of the studied polymorphisms. The authors proposed that IL-27 polymorphisms might play a protective role for the development of UC in the Mexican population[19].

Autophagy

At least 12 genes located at IBD risk loci play roles in autophagy. Lassen and Xavier discussed[20] the connection between autophagy and IBD. This association was first realized through the identification of a common coding polymorphism in the core autophagy gene ATG16L1 (ATG16L1 T300A) that confers an increased risk of CD[20-22]. Since this discovery, other genes associated with CD susceptibility, including IRGM, have also been associated

with anti-bacterial autophagy and the clearance of intracellular pathogens, underscoring the importance of this pathway in IBD[20]. Multiple studies have investigated the contribution of autophagy to IBD susceptibility and chronic disease[23]. Recent studies of CD patients who express the ATG16L1 T300A polymorphism have demonstrated increases in pro-inflammatory cytokines in response to specific stimuli[20].

In addition, defects in the size and number of Paneth cell granules are also found in patients harboring ATG16L1 T300A, suggesting that these cell types are highly susceptible to perturbations in autophagy and highlighting the role for autophagy in Paneth cell development and function[20,24]. In patients with quiescent disease, Paneth cells exhibit higher levels of ER stress when the ATG16L1 T300A polymorphism is present, further supporting a role for both ER stress and autophagy defects in disease pathogenesis[25,26].

Immunological factors

UC and CD are chronically relapsing and remitting inflammatory conditions that result from chronic dysregulation of the mucosal immune system in the intestinal tract[2].

In IBD, this loss of immune tolerance toward the enteric flora it is mediated by different molecules. Several types of innate immune cells have been shown to contribute to IBD pathogenesis.

Elevated levels of a large variety of inflammatory mediators, including chemokines and cytokines, have been measured in mucosal tissue samples from patients with IBD[27]. This dysregulation of the immune system with increased expression of pro-inflammatory cytokines are detected in active IBD and correlate with the severity of inflammation, indicating that these molecules may play an important role in the pathogenesis of IBD[28].

New therapeutic approaches to the treatment of IBD are based on the knowledge of the immunological mechanisms that characterize the pathogenesis of the diseases.

Studies in experimental models also indicate that IBD-related tissue damage results from dynamic intercommunications between immune and non-immune cells and that cytokine are crucial mediators of this cross-talk[29].

Pro-inflammatory cytokine secretion

IL-12 drives the development of T-helper-1 (Th1) immune responses by CD4+ Th lymphocytes, which secrete IL-1, IL-6, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). IL-4 drives the development of a T-helper-2 (Th2) immune response by CD4+ T cells, which secrete IL-4, IL-5, IL-10, and IL-13. Thus, IL-12 induces the aforementioned classical IFN-γ producing Th1 T cells, whereas IL-23 is involved in the possible maintenance and/or expansion of another polarized T-cell population, namely, Th17. This latter T-cell population is characterized by the secretion of IL-17, IL-6, and TNF-α These cytokines are intimately involved in innate host defense but also can play a primary role in the occurrence of tissue inflammation. Thus, IL-17 may act on cell populations to induce secretion of inflammatory chemokines that have a prompt role in rapid neutrophil recruitment. TNF-α can cause direct tissue injury, while IL-6 can enhance resistance to T cell-activated cell death (apoptosis) and survival of such inflammatory effector cells[30,31].

Chronic inflammation in IBD is characterized by an imbalance in the production of Th1, Th2, and Th17 and regulatory T subset cells. Defects in T regulatory (Treg) cells function or in their ability to contain effector cells are related to IBD pathogenesis[32].

Nonetheless, several immune-regulatory mediators such as some members of IL-10 family (IL-19, IL-20, and IL-24) and Indoleamine 2,3-dioxygenase are up-regulated in the intestinal mucosa of patients with IBD[33-36].

Immunoregulatory pathways

Many immunoregulatory abnormalities are noted in IBD, including the ratio of proinflam-

matory to immunosuppressive cytokines, selective activation of T(H) lymphocyte subsets, and abnormalities in epithelial antigen presentation. When activated during the initial inflammatory process, macrophages and T lymphocytes secrete a host of cytokines, which recruit other inflammatory cell types, thereby continuing the process. Tissue injury is the net result of the soluble products of the activated inflammatory cells[37].

Treg exerts a potent anti-inflammatory action in experimental colitis, and they are depleted in peripheral blood of patients with active IBD compared to inactive IBD patients and control subjects[38,39].

Interestingly, in the intestinal mucosa of IBD, patients Treg are increased, and their function is to suppress the proliferation of effector T cells[33-36]. The main findings regarding colitis protection by Treg cells emerged from cell transfer colitis models to mice with the impaired immune system[40].

Regulatory T cells (Tregs) and B cells present in gut-associated lymphoid tissues are both implicated in the resolution of colitis. The onset of dextran sulfate sodium (DSS) colitis in severe combined immunodeficient (SCID) mice does not require the presence of T or B cells, making it an excellent model in which to study specific immune regulation[40,41]. In this regard, the expansion of Tregs with a super agonist CD28 antibody led to a reduction in the severity of DSS colitis[40,42].

A regulatory role for B cells in colitis was first shown in TCRα–/– mice that spontaneously develop chronic colitis, exhibiting more severe disease in the absence of B cells[40,43].

Similarly, the severity of spontaneous colitis in SCID mice induced by the adoptive transfer of CD4+CD45RBhi cells was attenuated by the cotransfer of B cells[40,44].

Regulatory cytokine secretion

The immunoregulatory cytokines play a critical role in the immune response of IBD. Regulatory cytokines such as IL-10, IL-35, and IL-37 are essential for maintaining the integrity and homeostasis of intestinal tissue epithelial layers. These cytokines can promote innate immune responses from tissue epithelia to limit the damage caused by viral and bacterial infections. These cytokines can also facilitate the tissue-healing process in injuries caused by inflammation[45].

IL-35

IL-35 is a member of IL-12 family, and it has anti-inflammatory/immunosuppressive properties. Li et al. showed that the IL-35 is not constitutively expressed in non-stimulated human tissues; IL-35 is produced by regulatory T cells (Foxp3+ Tregs) and by activated dendritic cells (DCs)[46] and this novel cytokine can down-regulate Th17 cell development and inhibits autoimmune inflammation[47].

The increased immunity found in mice lacking the IL-35 production by B cells was associated with higher activation of macrophages and inflammatory T cells, as well as an increased function of B cells as antigen-presenting cells[48]. Moreover, Wirtz et al. have demonstrated that IL-35 protects against the development of T-cell–dependent colitis in mice[39].

IL-37

IL-37 is an anti-inflammatory cytokine in the IL-1 ligand family[49]. The IL-37 plays an important role in the development and progression of inflammatory and autoimmune diseases[50]; it may be associated with the development of pediatric IBD[51]. IL-37, which is normally expressed at low levels in peripheral blood mononuclear cells (PBMCs), mainly monocytes, and DCs is rapidly up-regulated in the inflammatory context[52], and therefore IL-37 conversely inhibits the production of inflammatory cytokines in PBMCs and DCs of patients with systemic lupus erythematosus. In addition, IL-37 effectively suppresses the activation of macrophage and DCs. DCs expressing IL-37 are

tolerogenic, thereby impairing activation of effector T-cell responses and inducing Treg cells. The IL-37 thus emerges as an inhibitor of adaptive immunity[53].

Environmental factors in the pathogenesis Of IBD

Recently, Ananthakrishnan and Bernstein et al.[1] have discussed the current conceptualization, evidence, progress, and direction surrounding the association of environmental factors with IBD. The authors suggest an important role of environmental factors such as diet, exercise, smoking, infections, microbiota, pollution, geography, psychological state, education level, and mode of birth contributing to IBD pathogenesis.

In this context, this review discusses some of these relevant factors involved in the pathogenic of IBD, such as diet and microbiota.

Diet

The increasing incidence of IBD in developing countries suggests that environmental factors, such as diet, are also critical components of disease susceptibility. A recent report from the European Prospective Investigation in Cancer study, did not identify a correlation between body mass index (a measure of obesity) and IBD morbidity, therefore proposing that a hypercaloric diet *per se* is not enough to trigger the development of IBD. The result not support the hypothesis that dietary fiber is involved in the etiology of UC[54]. Evidence suggests that consumption of a Western diet, enriched with saturated fat, refined carbohydrates, and food additives, is associated with increased IBD risk[55].

Westernized diet, defined as high dietary intake of saturated fats and sucrose and low intake of fiber, represent a growing health risk contributing to the increased occurrence of metabolic diseases, e.g., IBD, diabetes, and obesity in countries adapting a westernized lifestyle[56].

Recently Dixon et al.[55] in a recent review discussed how genetic and dietary risk factors synergize to promote IBD, and they remark the relevance between IBD-associated polymorphisms with alterations in mucosal barrier function, innate bacterial killing, immune regulation, and microbiota function. Dietary risk factors also influence many of these functions and may combine with genetic factors to either exaggerate a primary defect or impair multiple intestinal homeostasis mechanisms. The authors discuss the example where individuals with genetic polymorphisms in ECM1 have increased epithelial permeability that could be increased further by consumption of a high-fat diet, leading to the increased presence of microbial antigens or microbes that overwhelm normal regulatory mechanisms[55].

Microbiota

In this context, the authors discussed the relationship between genetic factors and microbiota. They suggest alternately mechanism diet can influence the functional properties microbes leading to increased epithelial adherence and invasion, that when combined with genetic defects in innate bacterial killing (ATG16L1 or NOD2 polymorphisms), results in persistent infections that drive chronic inflammation[55].

Other study suggests that the changes associated with NOD2 genotype might only be seen at the mucosal level, or that environmental factors and prior inflammation are the predominant determinants of the observed dysbiosis in gut microbiota[57].

In recent study Atsushi Hirano, Junji Umeno, and Yasuharu Okamoto et al.[58] investigated paired mucosa-associated microbiota obtained from both inflamed and non-inflamed sites of UC patients and corresponding sites of non-IBD controls. The authors observed that microbial alpha diversity in both inflamed and non-inflamed sites was significantly lower in UC patients compared with non-IBD controls. There were more microbes of the genus

Cloacibacterium and the Tissierellaceae family, and there were less microbes of the genus Neisseria at the inflamed site when compared with the non-inflamed site in UC patients. Decreased abundance of the genera Prevotella, Eubacterium, Neisseria, Leptotrichia, Bilophila, Desulfovibrio, and Butyricimonas was evident at the inflamed site of UC patients compared with the corresponding site of non-IBD controls. Among these taxa, the genera Prevotella and Butyricimonas were also less abundant at the non-inflamed site of UC patients compared with the corresponding site in non-IBD controls. Finally, they conclude mucosal microbial dysbiosis occurs at both inflamed and non-inflamed sites in UC patients. The taxa showing altered abundance in UC patients might mediate colonic inflammation[58].

In other recent study, in-depth analysis of microbial composition and functional properties at baseline and during the administration of vedolizumab treatment in patients with IBD in conjunction with clinical data using sophisticated mathematical modelling revealed, that the functional microbial profile (including an increase in butyrate-producing microbes in responding CD patients) could be associated with therapeutic response[59].

Eom et al.[60] discussed the current understanding of microbiota- and dietary-therapies for treating IBD.They suggested the treatments of IBD usually includes medications such as corticosteroids, 5-aminosalicylates, antibiotics, immunomodulators, and anti-TNF agents, restoration of gut dysbiosis seems to be a safer and more sustainable approach. Bacteriotherapy and dietary interventions are an effective way to modulate gut microbiota. In this review, we summarize factors involved in IBD and studies attempted to treat IBD with probiotics. The authors also discuss the potential use of microbiota therapies as one promising approach in treating IBD. As therapies based on the modulation of gut microbiota becomes more common, future studies should include individual gut microbiota differences to develop a personalized therapy for IBD[60].

Conclusion

Recent studies have demonstrated the importance of different factors such as genetic factors, autophagy, immunoregulatory pathways mediated by several immunological cells subtypes and cytokines, and environmental factors including diet, exercise, smoking, infections, microbiota, pollution, geography, psychological state, education level, and mode of birth are all involved in the etiology of IBD. The study of this field might have a potential role in the future treatment of this kind of patients.

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