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TOPIC HIGHLIGHT

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Inflammatory bowel disease: Pathogenesis

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Abstract

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is characterized by chronic relapsing intestinal inflammation. It has been a worldwide health-care problem with a continually increasing incidence. It is thought that IBD results from an aberrant and continuing immune response to the microbes in the gut, catalyzed by the genetic susceptibility of the individual. Although the etiology of IBD remains largely unknown, it involves a complex interaction between the genetic, environmental or microbial factors and the immune responses. Of the four components of IBD pathogenesis, most rapid progress has been made in the genetic study of gut inflammation. The latest internationally collaborative studies have ascertained 163 susceptibility gene loci for IBD. The genes implicated in childhood-onset and adult-onset IBD overlap, suggesting similar genetic predispositions. However, the fact that genetic factors account for only a portion of overall disease variance indicates that microbial and environmental factors may interact with genetic elements in the pathogenesis of IBD. Meanwhile, the adaptive immune response has been classically considered to play a major role in the pathogenesis of IBD, as new studies in immunology and genetics have clarified that the innate immune response maintains the same importance in inducing gut inflammation. Recent progress in understanding IBD pathogenesis sheds lights on relevant disease mechanisms, including the innate and adaptive immunity, and the interactions between genetic factors and microbial and environmental cues. In this review, we provide an update on the major advances that have occurred in above areas.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Pathogenesis; Genetics; Microbial factors; Immune responses

Core tip: Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis. Recent research indicated that the individual's genetic susceptibility, external environment, intestinal microbial flora and immune responses are all involved and functionally integrated in the pathogenesis of IBD. The main purpose of this review is to offer an update that have occurred in each of the above four areas, and to highlight the future work to find a clear understanding of IBD pathogenesis.

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INTRODUCTION

Inflammatory bowel disease (IBD) has been a global healthcare problem with a sustained increasing incidence[1]. It includes two major forms, Crohn's disease (CD)

and ulcerative colitis (UC), which are distinct chronic bowel-relapsing inflammatory disorders. CD can cause transmural inflammation and affect any part of the gastrointestinal tract (most commonly, the terminal ileum or the perianal region) in a non-continuous type. Unlike UC, CD is commonly associated with complications such as abscesses, fistulas and strictures. In contrast, UC is typified by mucosal inflammation and limited to the colon[2]. Although the etiology of IBD remains largely unknown, recent research indicated that the individual's genetic susceptibility, external environment, intestinal microbial flora and immune responses are all involved and functionally integrated in the pathogenesis of IBD[3-5]. The main purpose of this review is to offer an update that have occurred in each of the above four areas, and to highlight the future work to find a clear understanding of IBD pathogenesis.

GENETICS

Over the past decades, there have been huge advances in our understanding of genetic contributions to IBD[6]. This is due to the technological advances in DNA analysis and sequencing and the use of huge multinational databases[7]. Advances in genetic testing and analyzing technologies have allowed for the completion of many genome-wide association studies (GWAS) which identify single nucleotide polymorphisms (SNPs). Recent studies have brought the number of IBD-associated gene loci to 163, of which 110 are associated with both diseases, 30 CD specific and 23 UC specific[8]. Studies of gene loci shared by UC and CD may provide new way to find their common pathogenesis.

The era of modern IBD genetic research began in 2001 with the discovery of NOD2 (nucleotide-binding oligomerization domaincontaining 2), the first susceptibility gene for CD[9]. The NOD2 gene codes for a protein that was originally described as an intracellular receptor recognizing the muramyl dipeptide (MDP), a conserved motif present in peptidoglycan from both Gram-positive and -negative bacteria[10]. MDP stimulation induces autophagy which controls bacterial replication and antigen presentation[11,12], and modulates both innate and adaptive immune responses[13]. NOD2 participates in distinct MDP-independent pathways such as the regulation of the T-cell response[14]. The association between CD and NOD2 has already been replicated at the genome-wide significance level[15].

Genetic analyses have shown an indispensable role for autophagy in immune responses in IBD, and reported two autophagy-related genes named *ATG16L1* and *IRGM*[16-18]. Autophagy is involved in intracellular homeostasis, contributing to the degradation and recycling of cytosolic contents and organelles, as well as to the resistance against infection and removal of intracellular microbes[19]. *ATG16L1* is essential for all forms of autophagy, and the coding mutation T300A is associated with an increased risk of CD. *IRGM* belongs to the p47 immunity-related GTPase family. CD-associated polymorphisms in *IRGM* lead to reduced protein expression. Epithelial cells and dendritic cells containing *ATG16L1* and NOD2 variants show defects in antibacterial autophagy[12,20].

With the widespread use of GWAS and SNPs, a significant association between IBD and the *IL23R* gene has recently been described[21]. The *IL23R* gene encodes a subunit of the receptor for the pro-inflammatory cytokine interleukin (IL)-23, a peptide involved in the generation of Th17 cells. The Th17 and IL-23 pathway is well established in the pathogenesis of IBD, with susceptibility gene loci *IL23R*, *IL12B*, *JAK2*, and *STAT3* having been identified in both UC and CD[22,23]. Variants in *IL12B*, which encodes the p40 subunit of IL-12 and IL-23, have been associated with IBD and other immune disorders. Defects in the function of IL-10 have also been associated with CD and UC[24]. Other susceptibility genes that regulate immune function include *CARD9*, *IL1R2*, *REL*, *SMAD3* and *PRDM1*.

Recent progress in the genetics of IBD holds several key messages in regard to the underlying mechanism of the disease. On one hand, the expanding number of susceptibility gene loci described in IBD indicates that genetic influences are critical components of the disease pathogenesis; while on the other hand, explainable susceptibility loci discovered so far account for only 20%-25% of the heritability found in the above-mentioned studies. This is not only true for IBD, but also true for many other polygenetic diseases, and the phenomenon has been called "the mystery of missing heritability of common traits" or "genetic vacuum"[25]. This issue is further proved by *GWAS* that has failed to add new susceptibility gene loci to fill the "genetic vacuum"[26,27]. The possibility was then proposed that, instead of missing genes, the interactions among genes and their products could explain much of the apparent vacuum and account for a considerable number of IBD[25]. These new insights into genetics and heritability of IBD implicate that future explorations of gene-gene interactions, gene-pathway interactions and gene-environment interactions are likely to give us more insights into IBD pathogenesis than finding new rare variants.

ENVIRONMENT

There is no doubt that environmental factors play an important role in the pathogenesis of IBD. A large number of environmental factors are considered risk factors for IBD, including smoking, diet, drugs, geography, social stress, and psychological element[28]. Among them, smoking remains the most widely studied and replicated environmental prompter for IBD. Since the first described inverse association between UC and smoking in 1982, subsequent studies have confirmed the protective effect of heavy smoking on the development of UC with a lower rate of relapse[29-31]. Contrary to its effect on UC, smoking increases the risk of CD and is associated with a

higher rate of postoperative disease[32].

Traditional conception for vitamin D's role is concentrated in calcium metabolism and bone health. Nowadays, there has been increasing recognition of the immunologic role of vitamin D[33]. Recent literature suggests that the role of vitamin D is multifarious and associated with diverse diseases including IBD. Leslie *et al*[34] found that vitamin D deficiency had been common in diagnosed IBD patients and pointed out that low vitamin D had contributed to the increased risk of IBD. In mouse models, vitamin D deficiency is associated with an increased susceptibility to dextran sodium sulfate-induced colitis and 1,25(OH)$_2$D3 supplementation ameliorates the severity of intestinal inflammation[35].

The effect of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in the gastrointestinal tract is well recognized. However, limited high quality evidence is available to support the notion that aspirin and NSAIDs have an effect in triggering onset or relapse of IBD. Ananthakrishnan *et al*[36] found no association between the dose, duration, or frequency of aspirin use and the risk for CD or UC; but the high dose, prolonged using duration, and frequent use of NSAIDs had been associated with an increased risk of CD and UC. A recent study has found that the use of antibiotics is an important environmental factor, influencing the risk of IBD through their effect on the microbiome. Antibiotic use within the first year of life is more common among pediatric IBD cases compared to controls[37].

Stress has long been proposed to play a role in the pathogenesis of CD and UC[38-40]. Bitton *et al*[41] suggested that individuals with lower levels of stress had a reduced risk of the disease onset. Mood components of perceived stress, including depression and anxiety, may play a strong role in mediating the deterioration of IBD[42]. A retrospective study by Goodhand *et al*[43] found a reduction in the number of symptomatic relapses in participants, and the antidepressants beneficially impact the course of IBD. However, a Cochrane review shows no benefit of psychological interventions in IBD[44].

Recent ecological and epidemiologic evidence suggests that air pollution may contribute to the risk of CD and UC. The rising incidence of CD and UC in developing countries parallels the development of industrialization[45]. Elevated air pollution is associated with an augment in circulating polymorphonuclear leukocytes and plasma cytokines[46,47]. Kaplan *et al*[48] using The Health Improvement Network Database in the United Kingdom, found that high levels of NO_2 and SO_2 correlate with the increased risk of CD and UC. In another study, total pollutant emission has been linked to increased rates of hospitalizations for both CD and UC, suggesting that ambient air pollution may also influence these established diseases[49].

MICROBIAL FACTORS

The whole human gut microbiome consists of approximately 1150 bacterial species, with each individual host having roughly 160 species[50]. Gut microbiome is established within the first 2 wk of life and then usually remains remarkably stable thereafter. Although it is only possible to culture 20%-30% of the gut microbiome, the association between the changes in the microbiome and IBD has been established[51]. Many studies have examined the gut flora in CD and UC in both inflamed and non-inflamed segments, and found that there is a significantly reduced biodiversity in faecal microbiome in IBD patients compared to that in healthy controls[52]. Other research has also found that the microbiota in IBD patients is unstable than that in healthy individual[53]. In healthy intestine, the Firmicutes and Bacteroidetes phyla predominate, and contribute to the production of epithelial metabolic substrates. In contrast, the microbiota is characterized by a relative lack of Firmicutes and Bacteroidetes, and an over-representation of enterobacteria in CD; meanwhile, a reduction in Clostridium spp. and an increase in *Escherichia coli* (*E. coli*) have been reported in UC[54].

In healthy colon, there is a continuous mucus coating consisting of two layers of sub-structures: the outer is a loosely adherent layer, good for bacterial growth; while the inner is a tightly adherent layer, normally sterile. In IBD, particularly CD, there is a marked increase in bacteria associated with the colonic adherent mucus layer[55,56]. In CD, a consistent increase in mucosa-associated *E. coli* and reduction in Firmicutes are reported[57,58]. There is strong evidence for an increase in mucosa-associated *E. coli* in both the ileum and colon, and their presence within the granulomas in CD implicates a primary pathogenic role[59]. An adherent and invasive *E. coli* (AIEC) phenotype has been found in CD, which is typified by bacterial invasion into epithelial cells and replication within macrophages[60]. AIEC has also been shown to induce granuloma *in vitro* and granulomatous colitis in Boxer dogs[61].

IMMUNOLOGICAL FACTORS

The investigation of IBD pathogenesis has been dominated for a long time by the studies of mucosal immunity, especially the T cell response. Available evidence suggests that the dysfunctions of innate and adaptive immune pathways contribute to the aberrant intestinal inflammatory response in patients with IBD. Most studies in the last two decades have focused on the role of abnormal adaptive immune responses in the pathogenesis of IBD. The focus on the adaptive immune response has ultimately led to the notion that the two main types of IBD represent clearly distinct forms of gut inflammation: CD has long been considered to be driven by a Th1 response and UC has been associated with a non-conventional Th2 response[62,63]. The newly described Th17 cells are also involved in the gut inflammatory response in IBD[64]. Immunological studies have recently focused on the mucosal innate immune responses, such as epithelial barrier integrity, innate microbial sensing, autophagy and unfolded protein response.

Innate immunity

The innate immune response represents our first line of defense against pathogens. It is non-specific, allowing the body to quickly respond to stimuli often within minutes or hours. The innate immune response is mediated by a large variety of different cell types including epithelial cells, neutrophils, dendritic cells, monocytes, macrophages and natural killer cells[65]. This form of immunity is initiated by the recognition of microbial antigens, which is mediated by pattern recognition receptors including toll-like receptors (TLRs) on the cell surface and NOD-like receptors in the cytoplasm[66]. Recent studies have found that the behavior of the cells mediating innate immunity and the expression and function of both TLRs and NOD proteins are altered significantly in individuals with IBD.

A British study shows that mucosal neutrophil accumulation and production of IL-1β and IL-8 in response to trauma are selectively reduced in CD patients but not in UC patients[67]. GWAS reveal that the NOD2 mutations most commonly associated with CD induce a defective ability of the gut to respond to LPS, and this defect may contribute to disease susceptibility[68]. Although the functional role of NOD2 mutations is still controversial, available evidence suggests that they represent loss-of-function mutations that lead to reduced activation of NF-κB[69]. This inadequate response might result in reduced antibacterial agent production and pathogenic microbial invasion[70]. Other studies suggest that the loss of function of NOD2 may result in the lack of inhibition of TLR2 stimulation, leading to activation of inflammatory pathways and excessive Th-1 responses[71]. Furthermore, NOD2 also contributes to immune tolerance. These effects are impaired in cells from patients with NOD2 mutation 3020insC[72].

IL-23 is a key cytokine both in innate and adaptive immunity and possesses a central role in driving early responses against microbes. IL23R polymorphisms have been associated with both CD and UC, suggesting that IL-23 may represent a shared inflammatory molecule in chronic intestinal inflammation. Recent studies have shown that, besides its activity on Th17 cells, IL-23 can also act on cells of the innate immune system. IL-23 has been shown to induce Th17 cytokine production by innate lymphoid cells (ILCs) that share the phenotype of lymphoid tissue-induced cells[73].

CD has also been associated with *ATG16L1* and *IRGM* genes, which are involved in autophagy. ATG16L1 is essential for all forms of autophagy, and the coding mutation T300A is associated with an increased risk of CD. Autophagy is one of the mechanisms for maintaining cellular homeostasis and considered very important for host defense against intracellular microorganisms. Normally, autophagy is induced by bactericidal effects and presentation of endogenous antigens, and these processes are impaired in patients with mutations in NOD2 or Atg16L1. Closely relating to autophagy and innate immunity, dysregulation of the unfolded protein response may also contribute to IBD pathogenesis. This response is induced by endoplasmic reticulum stress and finally induces apoptotic cell death and causes IBD[74].

In addition, defective epithelial barrier and increased intestinal permeability have long been observed in IBD patients[75]. The first physical barrier that intestinal bacteria and food antigens encounter on the mucosal surface is represented by the mucous layer that covers the intestinal epithelium. The importance of mucus in the prevention of bacterial break-through and intestinal inflammation has been proved by many studies[76]. The second line of defense against bacterial invasion is formed by the intestinal epithelium which consists of enterocytes and specialized epithelial cells, such as goblet cells and Paneth cells. Besides forming a physical barrier against bacteria, epithelial cells can secrete a number of antimicrobial peptides. Defective expression of antimicrobial peptides has been observed in patients with CD[77].

Adaptive immunity

As opposed to the innate immune response, the adaptive immunity is highly specific, often takes several days to respond and depends on the type and number of T cells. Th1 cells, induced by IL-12, produce a high amount of IFN-γ, whereas Th2 cells release IL-4, IL-5 and IL-13[78]. An abnormal Th1 immune response is thought to cause intestinal inflammation in CD, and it has been observed that mucosal T cells from CD patients produce higher amounts of IL-2 and IFN-γ than T cells from UC patients or controls do[79]. It has also been shown that in UC, atypical NK T cells release higher amounts of the Th2 cytokine IL-13 than T cells from controls or CD patients do[80,81]. Therefore, CD has been thought to be characterized by a Th1 immune response, while UC has been considered as a Th2-mediated disease[82]. However, there have also been different observations about mucosal Th1 and Th2 cytokines in IBD. Both UC and CD biopsies cultured *in vitro* release high and comparable amounts of IFN-γ[83]. Lower levels of IL-13 are found in the colonic mucosa of UC patients compared to those in CD patients and subjects of the control group. Recent studies on experimental colitis have suggested an anti-inflammatory effect of IL-13 in the gut[84,85]. It has been also observed that IL-13 levels in the supernatants of intestinal biopsies cultured *in vitro* are lower than IFN-γ concentration and the concentrations are comparable among CD, UC and control groups[86]. Similar observations have been reported by Bernardo *et al*[87] who have described the presence of a mixed cytokine profile with predominance of IL-6 and the absence of IL-13 in supernatants of UC biopsies cultured *in vitro*. Collectively, these data should lead us to reconsider the Th1/Th2 paradigm in CD and UC[82], but the conception that UC is a Th2-mediated disease remains controversial.

Th17 cells are a T cell subset characterized by the production of large amounts of IL-17A, IL-17F, IL-21 and IL-22. They are induced by a combination of IL-6 and transforming growth factor (TGF)-β, and their ex-

pansion is promoted by IL-23[88]. The involvement of Th17 cells and, in particular, their signature cytokine IL-17A in intestinal inflammation has been extensively studied. High transcript levels of IL-17A have been detected both in CD and UC mucosa in comparison to normal gut[89,90]. Moreover, the inflamed IBD mucosa cultured *in vitro* produces higher levels of IL-17A than the control[79]. Furthermore, Th17 cells are an important source of IL-21, an IL-2-related cytokine which is up-regulated in inflamed IBD mucosa[91,92]. The true role of Th17 cells in IBD pathogenesis is currently undergoing intense scrutiny, and it is particularly fascinating that Th17 cells express the IL-23R on their surface[93].

CONCLUSION

There is no doubt that an unprecedented progress in our understanding of IBD pathogenesis has been achieved during the past few years. The key factors responsible for IBD include genetic components, environmental elements, microbial flora and immune responses. It is hard to dispute the popular belief that IBD arises from an extremely complex interaction among genetic and environmental elements, dysregulated immune responses and alterations of the microbiome, and that none of these factors alone is likely to cause the disease. More detailed information on their composition, function, and interaction is becoming increasingly accessible through high genomic approaches, investigation of environmental changes, molecular analysis of gut bacteria flora, and a more integrated understanding of the interaction between innate and adaptive immune responses. The growing number and diversity of genetic loci associated with IBD provide major challenges to the investigation of how they impact immunity and inflammation in susceptible individuals. Future research needs to further clarify and integrate the effects of the microbiome and environment on the immune response, and it shall be essential to gain further insights into the mechanisms and pathways of how bacteria, viruses or even fungi can modulate innate and adaptive immune responses.

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