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Invited Review

Targeting the complex interactions between microbiota, host epithelial and immune cells in inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory intestinal disorder that includes two distinct disease categories: ulcerative colitis and Crohn's disease. Epidemiological, genetic, and experimental studies have revealed many important aspects of IBD. Genetic susceptibility, inappropriate immune responses, environmental changes, and intestinal microbiota are all associated with the development of IBD. However, the exact mechanisms of the disease and the interactions among these pathogenic factors are largely unknown. Here we introduce recent findings from experimental colitis models that investigated the interactions between host genetic susceptibility and gut microbiota. In addition, we discuss new strategies for the treatment of IBD, focusing on the complex interactions between microbiota and host epithelial and immune cells.

Contents

Abbreviations: AIEC, adherent-invasive *E. coli*; CD, Crohn's disease; DSS, dextran sodium sulphate; GI, gastrointestinal; GM-CSF, granulocyte-macrophage colony stimulating factor; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; KO, knockout; MAP, *Mycobacterium avium* subspecies *paratuberculosis*; OmpC, outer membrane porin C; Treg, regulatory T cells; TSLP, thymic stromal lymphopoietin; UC, ulcerative colitis; WT, wild type.

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1. Introduction

The gastrointestinal tract (GI tract) includes all the organs involved in food intake and acts as the primary tissue for digestion and absorption. Due to its openness to, and continuity with, the external environment, the GI tract essentially harbors numerous microbes. During food processing in the GI tract, digested nutrients are absorbed and undigested and unabsorbed materials are enriched at the distal end. The number and species of bacteria vary according to the GI tract locations and usually increase towards the distal end. The most distal end of the GI tract consists of the large intestine and anus, and an extremely large number of microbiota (-10^{11} cfu/g) reside here [1,2].

In the GI tract, epithelium separates the lumen from the host tissue. Food antigens and microbes, which are essentially non-self, can be immunogenic to the host, but immune systems and tolerance are established during growth and development, to control the host responses to these potential antigens. Therefore, in a healthy state, nutrients, microbes, and metabolites in the intestinal lumen and host counterparts, i.e., epithelial cells and immune cells, establish homeostasis to keep the immune systems in check. However, during ill health, which can be caused by many external and internal stimuli, disturbance of homeostasis leads to tissue inflammation and disease [1,3].

Inflammatory bowel disease (IBD) is a chronic disorder, mainly of the lower GI tract, which encompasses two major diseases: ulcerative colitis (UC), and Crohn's disease (CD). These diseases often affect young people and are usually chronic. The incidence of IBD varies according to geographic location, but it is generally increasing worldwide; therefore, control of IBD has become a major challenge for public health worldwide [4,5]. Genetic susceptibility, inappropriate immune responses that are sometimes caused by genetic factors, environmental factors, and gut microbiota are known to be involved in the pathogenesis of IBD [1,4,6,7]. Recent progress in our understanding of the disease has dramatically improved the treatment of IBD; however, the disease mechanisms remain largely unknown and some patients suffer refractory diseases, even with the new treatments.

Here, we provide an overview of the pathogenesis of IBD and introduce recent experimental progress, especially with respect to identification of interactions between microbes and host. Finally we propose potential pharmacological approaches to control intestinal homeostasis and IBD.

2. IBD pathogenesis

2.1. Genetics

Epidemiological studies of IBD have revealed its polygenic and multifactorial nature [7–9]. Among the many potential causal factors, its genetics have been extensively investigated over the years, especially with recent advances in genotyping methods. First, chromosomal regions containing risk genes, such as *IBD1* on chromosome 16, were reported [10]. Next, single nucleotide polymorphisms in specific disease-associated genes, such as *NOD2* in CD, were discovered [11,12]. Later, owing improvements in genotyping techniques and platforms, genome-wide association studies (GWAS) were undertaken, and many disease-susceptible genes, such as *IL10*, *IL23R*, and *ATG16L1*, were identified [13,14]. A recent meta-analysis of GWAS reported 163 genetic loci associated with IBD [15]. Of these, 110 loci were shared by UC and CD, while 30 and 23 loci were specific to CD and UC, respectively. In addition, most of these disease-specific loci showed similar effects in non-associated IBD. Only two risk alleles of CD, *PTPN22* and *NOD2*, showed a protective effect against UC. These IBD loci involved those genes associated with immunodeficiency, T-cell functions and mycobacterial infection [8,15]; however, candidate genes that functionally contribute to disease susceptibility have not been identified for many of these loci. Nevertheless, genetic investigations have provided important information on the pathogenesis of IBD, by driving functional analysis of the candidate genes [6,9].

One of the strongest determinants of genetic susceptibility to CD is a *NOD2* variant. The NOD2 protein functions as an intracellular sensor of bacteria, thereby promoting exploration of the genes associated with immunodeficiency. GWAS studies have since revealed many such genes, including *RIPK2*, *TNFSF15*, *IFNGR1/2*, *TYK2*, *CARD9*, etc [15–17]. Conversely, some of these gene products functionally associate with the NOD2 protein in direct interactions, as well as in the same signal transduction pathways. These functional associations of the genes identified have highlighted the immunodeficient nature of CD [8,9,15,18].

Another novel pathogenesis suggested by GWAS was autophagy, stemming from the discovery that the T300A variant of *ATG16L1* is a strong risk factor for CD [14,19]. Autophagy has been recognized as a cellular function for the degradation of intracellular organelles, in response to starvation as well as infection. Functional studies indicated that ATG16L1 and the autophagy pathway control bacterial dissemination, cytokine production, Paneth cell function, and some measure of susceptibility to enteric bacterial infection, which might cause the intestinal inflammation associated with CD [19–22]. Furthermore, the discovery of *ATG16L1* helped to identify other autophagy-related susceptible genes, such as *IRGM1* [15,23], *SMURF1* [24], and *ATG16L2* [25].

These genetic and functional studies provide further valuable information on the responsible cell types of IBD. *NOD2* and *ATG16L1* variants were associated with morphological abnormalities of the Paneth cells in CD patients [26]. Mutations in *ATG16L1* and *XBP1* in a mouse model led to severe intestinal inflammation due to impairment of the Paneth cell functions [27]. In a GWAS meta-analysis, cell-type expression of susceptibility genes revealed dendritic cells to be the strongest gene expressers of the IBD loci [15]. Paneth cells are epithelial cells that reside in the small intestine and play a specific role in the control of intestinal bacteria, by secreting antimicrobial peptides [1,9]. Dendritic cells reside in the lamina propria of the intestine, and through their characteristic dendrites, survey luminal pathogens and act as initiators and organizers of immune responses against pathogens [1,7,28]. These findings revealed by recent genetic studies suggest that recognition and control of intestinal microbiota are important in the pathogenesis of IBD.

2.2. Environment

The increased prevalence of IBD, especially in westernized countries, has suggested a possible contribution of lifestyle factors, in addition to environmental factors, in the pathogenesis of IBD [5,7,29,30]. Environmental factors, as reflected in the so-called "hygiene hypothesis" in particular, have been implicated in many autoimmune diseases. Sanitary issues, such as poor access to hot water or toilets, contact with farm animals, etc., are associated with reduced risk for IBD [31,32]. Other lifestyle-related factors, such as increased consumption of saturated fats and refined sugar, the use of refrigerators, frequent use of antibiotics, and having fewer siblings at home, are also linked to IBD [29]. It has been speculated that improved sanitary conditions lead to less frequent parasite infection, which may in turn cause dysregulated, hyperactive immune responses against gut microbiota. It is also suggested that the use of antibiotics or changes in food composition patterns may disrupt the gut microbiota, eventually leading to IBD.