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Review

Inflammatory bowel disease

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ABSTRACT

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing inflammatory condition of the gastrointestinal tract. CD and UC have distinct pathologic and clinical characteristics and despite the extensive amount of research conducted over the past decades, their pathogenesis remains still poorly understood. So far, the accepted dogma is that IBD results from dysregulated mucosal immune response to environmental factors in genetical susceptible hosts. Various components are implicated in the pathogenesis of IBD, including genetic susceptibility, environmental and microbial factors, intestinal epithelial cells and components of innate and adaptive immune system. Given the complexity of IBD, several different animal models of IBD have been developed during the last years. Animal models are very important tools to study the involvement of various factors in the pathogenesis of IBD and, importantly, to test new therapeutic options. This review examines some of the key components that have been found to be closely associated to IBD and describe the distinct features of some of the most important IBD models.

1. Inflammatory bowel disease

The idiopathic inflammatory bowel diseases (IBD) include two major forms of chronic intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). IBD is the second most common inflammatory disease, affects approximately 1.4 million Americans, and has a peak onset between 15 and 30 years of age [1]. CD mostly involves the ileum and colon, but it can affect, often discontinuously, any region of the gastrointestinal tract. Ulcerative colitis involves the rectum and may affect a part, or the entire colon in a continuous pattern. Transmural inflammation often characterizes CD, whereas in UC the inflammation is typically limited to the mucosa. CD can be associated with intestinal granulomas, strictures, and fistulas, but these are not typical findings in UC [2]. Although it is widely accepted that IBD results from a dysregulated mucosal immune response to environmental factors in genetically susceptible hosts, the precise cause of the disease has not yet been fully elucidated.

1.1. Genetic susceptibility

In the last few years, advances in genetic testing have allowed for the completion of many genome-wide association studies (GWAS), which have together identified 163 IBD-associated gene loci, of which 110 are associated with both diseases, 30 are specific for CD, and 23 for UC [3]. These studies indicate that the two major forms of IBD share many common genetic and, therefore, mechanistic features. The genetic variants that confer increased susceptibility to CD are primarily related to innate immunity, autophagy and phagocytosis [4]. For UC, the genetic variants are mostly related to barrier function. Detailed mapping of chromosome 16 identified polymorphisms within the *NOD2* gene (also designated *CARD15* and *IBD1*) as the most frequent genetic alterations associated with CD [5,6]. This gene encodes a cytoplasmic protein, nucleotide binding oligomerization domain containing 2 (NOD2) that is mainly expressed in monocyte-derived cells [7,8]. NOD2 has the essential role of initiating innate immune responses upon intracellular exposure to muramyl-dipeptide (MDP), a breakdown product of peptidoglycan that is present in the cell wall of both Gram-negative and Gram-positive bacteria, leading to the activation of NF-κB and MAPK signaling pathways [9]. Moreover, NOD2 activation has recently been shown to influence MHC cross-presentation, autophagy induction, and resistance to intracellular bacterial infection [10–12]. The associated risk is dose-dependent, with heterozygous carriers of the *NOD2* gene polymorphisms harboring a 2–4-fold increased risk of CD, and homozygous or

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compound heterozygous carriers having a 20–40-fold increased risk. Notably, the CD-associated *NOD2* gene polymorphisms cause a loss-of-function in the NOD2 pathway [13,14]. Genetic analyses have shown that polymorphisms in *ATG16L1* and *IRGM*, two genes that are critically involved in the autophagy pathways, are genetically linked to IBD [15,16]. Autophagy is an intracellular process that involves the lysosomal degradation of ingested bacteria, but also self-digestion of organelles. Interestingly, NOD2 signaling activation is capable of initiating the autophagy process. For effective intracellular digestion and bacterial clearance to be achieved, both intact NOD2 and ATG16L1 functions are required. In contrast, when CD-linked polymorphisms are present in either gene, autophagy in response to MDP is compromised, eventually resulting in reduced bacterial elimination [12]. Thus, these defects may affect adaptive immune responses and predispose to chronic intestinal inflammation.

A critical association between IBD and the *IL23R* gene has also been described [17]. The *IL23R* gene encodes a subunit of the receptor for interleukin (IL)-23, a pro-inflammatory cytokine also involved in the generation of Th17 cells [18,19]. In addition to *IL23R*, associations with CD have been observed in genomic regions encompassing multiple genes involved in the IL-23/Th17 signaling pathway, which is well established in IBD pathogenesis, with the presence of several susceptibility gene loci, such as *IL23R*, *IL12B*, *JAK2*, and *STAT3*, associated with the development of both UC and CD [5,20]. Variants in *IL12B*, which encodes the p40 subunit of both IL-12 and IL-23, have been associated with IBD as well as other autoimmune disorders, suggesting that a subset of IBD patients share common triggers with these conditions [17]. Significant associations observed in GWAS of UC are within the major histocompatibility complex class II region near HLA-DRA (α-chain). Distinct HLA-DRB1 (β-chain) alleles have been associated with both UC and CD [21,22].

1.2. Environment and microbial factors

Although genetics variants clearly play a central role in conferring risk for IBD, studies conducted in identical twins clearly demonstrate that the actual development of disease depends on additional factors. A wide range of environmental factors are also thought to confer risk for IBD, including smoking, diet drugs, social stress, and microbial factors [23]. Smoking appears to have a divergent effect on the two forms of IBD, being protective in UC, while increasing disease risk in CD [24]. The implications of diet as a cause of IBD remains equivocal, although data suggest that a "Western" style diet is associated with an increased risk for developing CD, and possibly also UC [25]. Food antigens are thought to be a factor in the pathogenesis of IBD. Non-steroidal anti-inflammatory agents (NSAIDs) have been associated with an increased risk for both CD and UC, and are thought to influence the progress of IBD by directly damaging the intestinal mucosa through the reduction of prostaglandin production [26]. Social stress has been proposed to also have a role in both diseases. In fact, mood components of perceived stress, such as depression, may play a strong role in mediating the deterioration of IBD [27].

Accumulating evidence suggests that the dynamic balance between commensal flora and host defensive responses within the intestinal mucosa play a pivotal role in both the initiation and perpetuation of IBD [28]. Several studies conducted in patients and animal models have shown the central role of bacteria in the pathogenesis of IBD. For example, the use of antibiotics are effective in subsets of patients with IBD, and most of the mouse models require the presence of intestinal bacteria for inflammation to occur [29]. In addition, several findings suggest that the use of "beneficial bacteria" or probiotics can ameliorate IBD [30,31]. Studies analyzing the composition of the gut microflora have shown that CD patients exhibit a relative lack of *Firmicutes* and *Bacteroidetes* and an overrepresentation of *Enterobacteria*; a reduction in *Clostridium* spp. and an increase in *Escherichia coli* (*E. Coli*) have been reported for UC [32,33]. In addition, there is a marked increase in mucosa-associated *E. coli* in both the ileum and colon, particularly in CD patients, suggesting a possible pathogenic role [34].

Our understanding of the relevant microbial factors affecting the pathogenesis of IBD is still quite incomplete. The use of metagenomic and computational analysis of the microbiome in both patients and animal models of IBD will provide more insight into our understanding of the functional diversity of the flora and, importantly, the regional distribution of disease.

1.3. The intestinal epithelium

The intestinal epithelium represents a physical barrier bacterial entry from the intestinal lumen into the circulation. In order to discriminate between commensal and invasive pathogenic bacteria, intestinal epithelial cells (IECs) exhibit expression of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), as well as differential regulation of transcription networks in response to their ligands. It is well recognized that under steady state conditions, sensing of microbiota and basal PRRs signaling in IECs is important for intestinal immune homeostasis and constant renewal of the epithelial barrier [35,36]. In this context, epithelial-cell-specific NF-κB activation or suppression seems to be crucial in the suppression and recruitment of immune responses in IBD.

As early as 1972, Shorter et al. [37] proposed the hypothesis that the primary defect in CD may be due to an abnormal gut epithelial barrier, and further stipulated that compromised barrier function allows for increased passage of antigens across the intestinal mucosa, resulting in an overactive immune response and chronic inflammation. Further support for this concept comes from studies demonstrating that patients with IBD display increased intestinal epithelial permeability compared to control subjects and disrupted barrier function that is not isolated to sites of active inflammation. In addition, CD patients have increased gut permeability prior to disease relapse [38]. It remains unclear, however, how barrier dysfunction can lead to chronic intestinal inflammation. In fact, increased permeability alone in healthy individuals is not sufficient to cause IBD. Therefore, there must be some other component in the epithelial-associated dysfunction influencing the development of chronic intestinal inflammation. One hypothesis is that in the presence of epithelial barrier dysfunction, the intestinal epithelial-dendritic cell (DCs) interactions lead to aberrant activation of lamina propria DCs that ultimately results in chronic gut inflammation [39].

Although the intestinal epithelium is not sufficient by itself to sustain the inflammatory process, it plays a primary role in the onset and maintenance of disease. Further investigation in this field of investigation will, therefore, provide more targeted therapies aimed at boosting intestinal epithelial barrier function in order to prevent or treat patients with IBD.

1.4. Immune responses in IBD

The combined effects of genetic, environmental, and/or epithelial barrier dysfunction culminate in persistent activation of intestinal mucosal immune responses. Several studies conducted in both patients with IBD and animal models provide substantial characterization of immune-cell populations and inflammatory mediators that lead to the onset and perpetuation of intestinal inflammation. The focus on the adaptive immune response has led to the reasonable consensus that the mucosa of patients with established CD is dominated by $CD4^+$ lymphocytes with a type 1 helper-T-cell (Th1) phenotype. In contrast, the mucosa in patients