Review

GWA studies: rewriting the story of IBD

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Genome-wide association (GWA) studies are substantially improving our understanding of the molecular pathways leading to inflammatory bowel diseases (IBD). This is a result of the nature of these studies, which are comprehensive – leading to a dramatic increase in the number of validated genetic risk factors – and unbiased – leading to the identification of novel pathways not previously suspected in IBD. Such discoveries are not only driving the functional studies to understand the mechanisms by which genetic variants modify an individual's susceptibility to disease, but also hold the promise of guiding the development of more effective treatment strategies. In this review, we discuss how GWA studies are enabling us to rewrite the story of IBD pathogenesis, focusing on the interleukin-23 and autophagy pathways.

Understanding the basics of inflammatory bowel disease

The gut functions primarily to absorb nutrients from digested food and process waste for elimination. These activities are performed at the inner mucosal surface, which consists of a thin, permeable epithelium. In the small intestine, this surface is greatly expanded by the presence of fingerlike villi, making the mucosal lining of the gut the largest surface in the body with direct exposure to the external environment. The lumen is a nutrient-rich milieu with a complex microbial population that has coevolved with its host. These commensal microbes perform essential functions, such as digestion of complex carbohydrates and production of vitamins and other small molecules [1]. Microbial density in the colon is estimated to reach 10^{11}–10^{12} cells per ml [2], creating an enormous challenge to host defense. To prevent commensal and pathogenic microbes from crossing the gut epithelial barrier, the immune system must be in a state of constant readiness. The normal response to penetration of the epithelium is self-limiting inflammation. However, dysregulation of the immune response leads to chronic inflammation of the gastrointestinal tract, resulting in inflammatory bowel disease (IBD).

The two most important forms of idiopathic IBD are Crohn's disease (CD) and ulcerative colitis (UC) (for a comparison, see Table 1). CD is characterized by inflammation that can extend into all layers of the bowel wall (Box 1). Areas of deep ulceration can form localized regions of nodular inflammation (granulomas) or tube-like connections between loops of the intestines or nearby organs (fistulas). CD can present anywhere in the digestive tract, from the mouth to the anus. However, the most commonly affected segment is the terminal ileum. Another distinguishing feature of CD is its segmental distribution: regions of inflammation can be separated by tissue with normal appearance. By contrast, the inflammation seen in UC is restricted to the mucosa and, as the disease progresses, the submucosa. Intestinal fistulas, granulomas and deep fissures are not found in UC, and the inflammation usually involves the rectum and extends proximally to include part of or the entire colon. The region of inflammation is continuous without any skipped segments [3]. In ~5% cases of IBD, it is not possible to assign a definitive diagnosis of CD or UC because of the overlap in their pathologies [3].

IBD, like most common diseases, has a complex etiology involving multiple genetic and environmental factors. Identification of the specific genetic factors that contribute to IBD will help decode the pathways that are essential to the pathogenesis of these diseases, enabling a prioritization of targets for therapeutic intervention. Genome wide association (GWA) studies have recently been shown to be the most productive approach to discovering the genetic variation responsible for IBD susceptibility.

A family history – epidemiology of IBD

The incidence of IBD is highest in the populations of North America, the UK and northern Europe. It varies with ethnic background, with rates in North America highest for Ashkenazi Jews. The prevalence of IBD in North America and northern Europe increased rapidly during the early and mid-20th century and then stabilized at the higher levels [4]. An apparent increased incidence of IBD in association with affluence has given rise to the 'hygiene hypothesis', which proposes that lack of exposure to certain infectious agents in childhood results in an overactive immune response in later life [5].

As the rise in IBD over the past century indicates, there is a substantial environmental or lifestyle component to disease risk. Factors such as diet, breastfeeding, oral contraceptives and childhood infections have been proposed to contribute to the etiology of IBD. However, those with the strongest association are cigarette smoking and appendectomy [4]. Other proposed environmental factors cannot be ruled out but their effect is probably modest because the reported findings are conflicting or not statistically significant [4].

Several studies have shown that an individual with IBD is more likely to have a relative with the disease. Population-based studies find that 5–10% of patients have a first-degree family member with IBD [6], with the relative risk to siblings of affected individuals (λs) estimated to be 30–40-fold for CD and 10–20-fold for UC. Twin studies

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Table 1. A comparison of CD and UC[a]

	Crohn's disease (CD)	Ulcerative colitis (UC)
Incidence	3.1–14.6 per 100 000	6–14.3 per 100 000
Clinical presentation of disease	All gastrointestinal track from mouth to anus can be affected	Occurs first in the rectum and progresses proximally
	Most cases are in distal small bowel and proximal large bowel	Inflammation is restricted to the colon
	Half of patients have disease affecting both ileum and colon	
	A third of patients have disease confined to the small bowel (mostly the ileum)	
	20–25% have disease confined to the colon	
	Mucosal, submucosal and transmural inflammation	Mucosal, not transmural inflammation
	Discontinuous inflammation with skipped segments	Continuous inflammation
Sociogeographic distribution	Higher rates in northern latitudes and in industrialized, urban and richer populations	Higher rates in northern latitudes and in industrialized, urban and richer populations
Environmental risk factors	Smoking	Smoking and appendectomy seem to be protective

[a]For additional information, see Ref. [3].

Box 1. Anatomy and defense mechanisms of the gut

The epithelium of the gut has an active role in protecting against invasion by microbes present in the lumen. The intestinal wall is composed of multiple sheets of tissue (Figure Ia): the innermost layer (i) is the mucosa and consists of luminal epithelial cells. The submucosa (ii) supports and joins the mucosa to the underlying muscular layers (iii–iv). The serosa (v) lines the outer muscular layer. The epithelial layer (Figure Ib) is composed of several different cell types. Specialized goblet cells secrete mucins that form a protective layer on the luminal surface (Figure Ic). Paneth cells and neutrophils produce several classes of anti-microbial peptides, such as α defensins, β defensins, cathelicidins and lysozyme [8,56] (Figure Id). A crucial role of Paneth cells in CD has been shown by studies of the *NOD2* and *ATG16L1* genes in mice and humans [40,41,43]. Normally, microbes from the gut flora do not penetrate this physical and biochemical barrier. If microbes do penetrate, the cells of the innate immune system, such as macrophages and neutrophils, attempt to control the infection via non-specific killing mechanisms. If the infection persists, the adaptive immune system begins to have a role. Lymphocytes constituting the intestinal adaptive immune system are organized in discrete lymphoid tissues such as Peyer's patches (PP) and isolated lymphoid follicles. The lymphocytes consist primarily of effector T cells and terminally differentiated B lymphocytes [57]. Often located adjacent to PP are the M cells and dendritic cells (DCs) that sample the microflora particles and present them to lymphocytes, thus acting as antigen presenting cells (APCs) [58]. Naïve T cells are stimulated by cytokines TGF-β and IL-10 to differentiate into regulatory T cells. Interestingly, *IL10* has recently been associated to UC [26]. During infection or chronic inflammation, naïve T cells receive a different set of signals from APCs that activate inflammatory pathways producing T_H1, T_H2 or T_H17 helper cells, which release signals for different effector responses. T_H1 cells stimulate the activation of macrophages and effector T cells. T_H2 cells promote B-cell differentiation and immunoglobulin class switching. T_H17 cells activate a neutrophil response to acute infection. IL-23 is a cytokine involved in the differentiation of naïve T cells into T_H17. With the discovery of the involvement of IL-23R in IBD and characterization of T_H17 cells, it is becoming clear that these T cells also have a key role in inflammation [59].

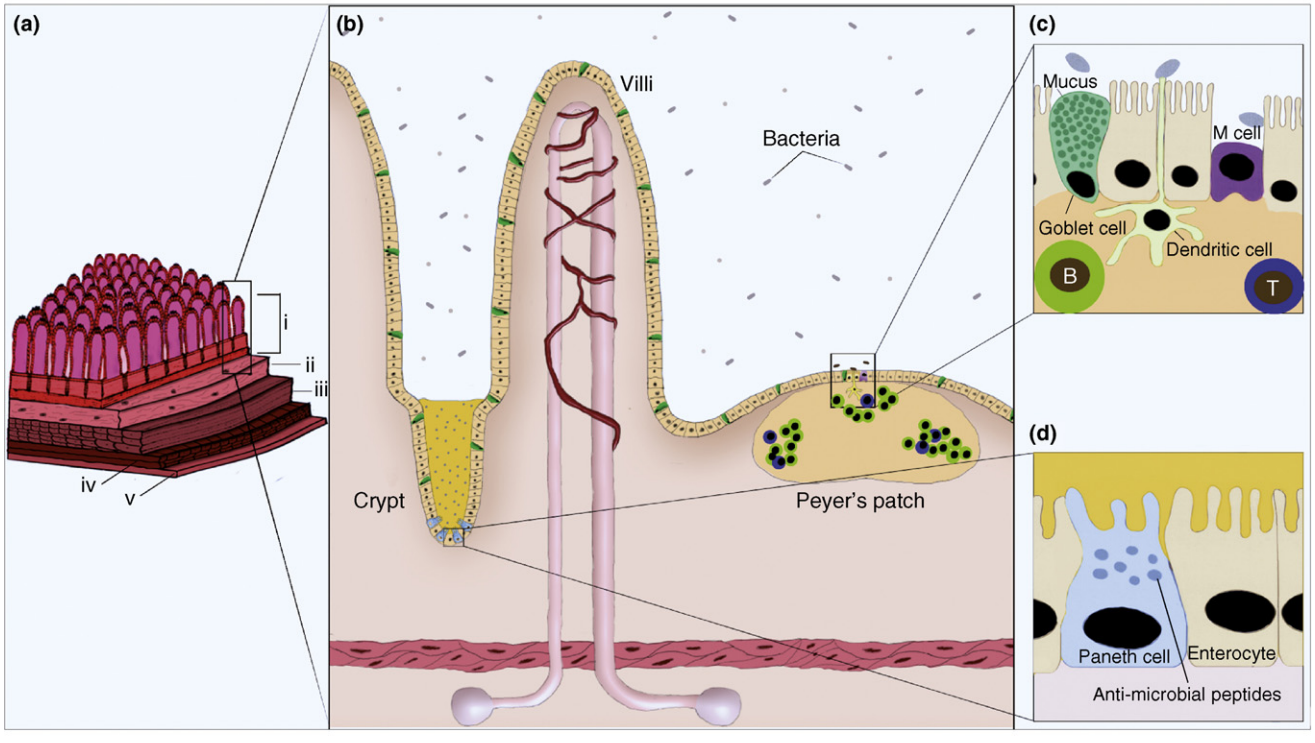

Figure I. Structure and protective function of the intestine.