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Review

Innate and adaptive immunity in inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). The exact cause of IBD remains unknown. Available evidence suggests that an abnormal immune response against the microorganisms of the intestinal flora is responsible for the disease in genetically susceptible individuals. The adaptive immune response has classically been considered to play a major role in the pathogenesis of IBD. However, recent advances in immunology and genetics have clarified that the innate immune response is equally as important in inducing gut inflammation in these patients. In particular, an altered epithelial barrier function contributes to intestinal inflammation in patients with UC, while aberrant innate immune responses, such as antimicrobial peptide production, innate microbial sensing and autophagy are particularly associated to CD pathogenesis. On the other hand, besides T helper cell type (Th)1 and Th2 immune responses, other subsets of T cells, namely Th17 and regulatory T (Treg) cells, are likely to play a role in IBD. However, given the complexity and probably the redundancy of pathways leading to IBD lesions, and the fact that Th17 cells may also have protective functions, neutralization of IL-17A failed to induce any improvement in CD. Studying the interactions between various constituents of the innate and adaptive immune systems will certainly open new horizons in the knowledge about the immunologic mechanisms implicated in gut inflammation.

Contents

1. Introduction

The gastrointestinal mucosa is continuously exposed to both food antigens and bacterial antigens from the extremely rich and diversified resident microbial flora [1]. The intestinal commensal flora benefits the host through the metabolism of non-absorbed food components and the production of vitamins. Yet, the gut lumen may also represent the route of entry for pathogenic microorganisms that can lead to tissue damage. The intestinal immune system therefore faces a very delicate

Abbreviations: CD, Crohn's disease; DC, dendritic cell; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; iNKT, invariant natural killer T; MyD88, myeloid differentiation primary response gene 88; NLR, NOD-like receptor; NOD, nucleotide-binding oligomerization domain; NF, nuclear factor; NK, natural killer; PAMP, pathogen associated molecular pattern; PRR, pattern recognition receptor; UC, ulcerative colitis; Th, T helper cell type; TLR, Toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell.

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task: to provide a rapid, effective immune response against pathogenic bacteria, while maintaining tolerance towards food and "good" bacterial antigens. This is achieved through the presence of a very efficient epithelial barrier and a complex and specialized immune system in the gut. Perturbation in this fine balance may result in aberrant inflammatory responses leading to chronic intestinal inflammation, such as IBD. IBD is a chronic inflammatory disorder of the gastrointestinal tract that encompasses CD and UC. The prevalence of IBD is around 1 in 1000 people in Europe, with higher prevalence and incidence rates observed in westernized and industrialized countries [2]. IBD is characterized by alternating phases of clinical relapse and remission and both long standing UC and CD have been associated with increased risk of intestinal cancers. Symptoms are mainly represented by diarrhea, abdominal pain and rectal bleeding. Nevertheless, extra-intestinal manifestations of the disease are also frequent, with possible involvement of joints, skin, eyes and kidneys [3]. Patients with IBD have also an increased risk of developing other chronic immune disorders, such as psoriasis, ankylosing spondylitis and primary sclerosing cholangitis [4]. Therapeutic strategies for patients with IBD include interventions on life-style habits and medical and surgical treatments. The medical management includes corticosteroids, immunosuppressant agents and biologic therapies (such as different anti-tumor necrosis factor (TNF)-α compounds) [5]. However no treatment strategy is curative or free of side effects.

The etiology of IBD remains unknown; it is however thought that IBD is caused in genetically susceptible individuals by an abnormal immune response against the microorganisms of the intestinal flora. Available evidence suggests that both dysregulated innate and adaptive immune pathways contribute to the aberrant intestinal inflammatory response in patients with IBD. Most studies conducted in the last thirty years have focused on the role of abnormal adaptive immune responses in the pathogenesis of IBD. In particular, while CD has long been considered to be driven by a Th1 response, UC has been rather associated with a non-conventional Th2 response [6]. Beside classical Th1 and Th2 responses, a role for Th17 cells, a subpopulation of inflammatory T cells which expand in response to the pro-inflammatory cytokine interleukin (IL)-23, has also emerged [7]. Advances arisen from genome-wide association studies (GWAS) and immunological studies have recently moved the focus of IBD pathogenesis on to mucosal innate immune responses, such as epithelial barrier integrity, innate microbial sensing, autophagy and unfolded protein response, as central pathogenic pathways in IBD. Here we aim to review the available evidence supporting a role for innate and adaptive immune responses and their crosstalk in IBD.

2. Innate immunity in IBD

The innate immune response represents our first line of defense against pathogens. Different from the adaptive response, it is non-specific and does not confer long-lasting immunity (memory). Immune cells of the innate system, such as dendritic cells (DCs) and macrophages, but also intestinal epithelial cells and myofibroblasts, can sense the intestinal microbiota and respond to conserved structural motifs on microorganisms, known as pathogen associated molecular patterns (PAMPs), in a stereotypical manner (Fig. 1). This allows the initiation of rapid and effective inflammatory responses against microbial invasion. Furthermore, DCs are professional antigen presenting cells which are responsible for T cell activation and the induction of adaptive immune responses, representing key players in the crosstalk between innate and adaptive immunity.

2.1. Epithelial barrier function and antimicrobial peptides

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. Mucous is organized in an inner firm layer and an outer loose layer that are produced by polymerization of gel-forming mucins, which are secreted by goblet cells and expand in the lumen due to their capacity to bind water. The resulting mucin net is firm and dense in the inner layer, which is usually sterile, while the outer mucous layer appears to be more permeable and it is

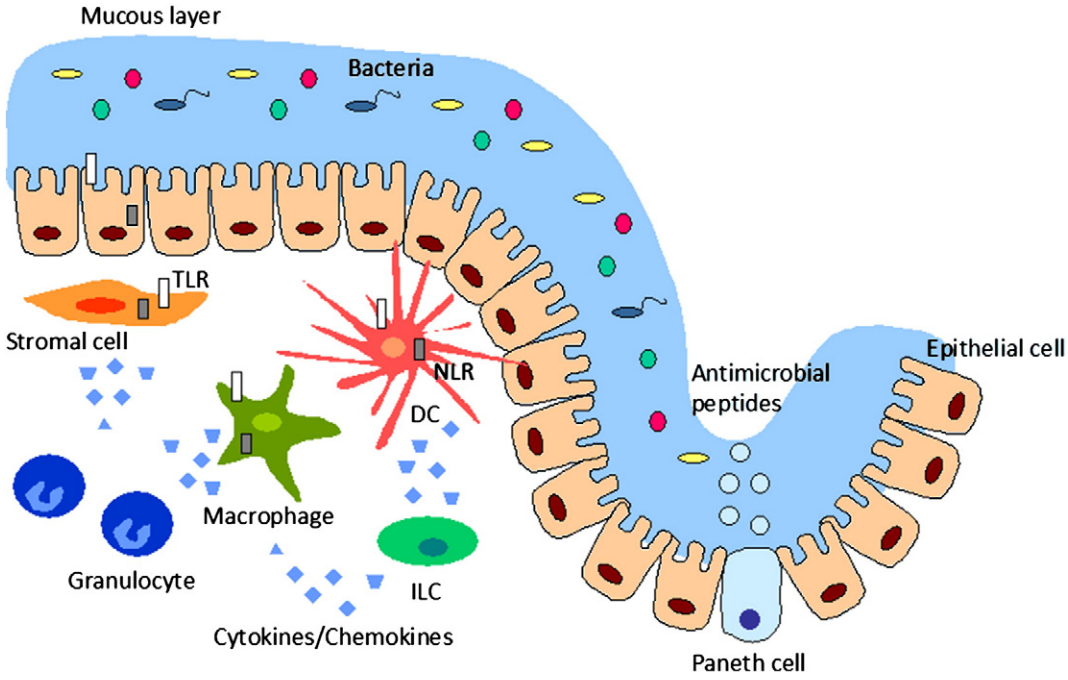

Fig. 1. Innate responses in the gut. Mucous layer and epithelial barrier represent the first line of defense against bacterial invasion. Paneth cells and other epithelial cells secrete antimicrobial peptides that contribute to limit bacterial growth and invasion. Epithelial cells, stromal cells and innate immune cells, such as macrophages and dendritic cells (DCs) can sense invading bacteria through extracellular and intracellular pattern recognition receptors (Toll-like receptors — TLRs and NOD-like receptors — NLRs) and initiate rapid inflammatory responses mediated by the secretion of cytokines and chemokines and recruitment of inflammatory cells. Innate lymphoid cells (ILCs) are also found in the human lamina propria where they may contribute to cytokine production and inflammatory cell recruitment.