Innate and Adaptive Immunity in Inflammatory Bowel Diseases

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Key Words

Innate immune system · Adaptive immune system

Abstract

While barrier function and the effects of the intestinal microbiome have only recently moved into the focus of inflammatory bowel disease research, the role of the innate and the adaptive immune system in these gastrointestinal disorders has extensively been studied. Although still not completely understood, the increasing knowledge about the immune system's contribution to the pathophysiology of inflammatory bowel diseases has led to new diagnostic and therapeutic approaches. This review gives a compact overview on this important topic.

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two entities classically referred to as inflammatory bowel diseases (IBD) [1]. Both CD and UC are characterized by a chronic and relapsing idiopathic inflammation of the gastrointestinal tract. Moreover, IBD is accompanied by extraintestinal manifestations and an increased

risk of cancer development [2]. The main clinical symptoms include diarrhea, abdominal pain and fever, and patients are prone to increased morbidity and reduced quality of life. Although CD and UC partly differ in their clinical presentation and underlying pathophysiology, both entities are characterized by the dysfunction of three major mechanisms: (i) the intestinal barrier, (ii) the innate and the adaptive immune system and their interconnection, and (iii) effects of non-immune cells such as fibroblasts and the endothelium of mucosal vessels. While function and impairment of the intestinal barrier only recently moved in the focus of IBD research, the role of both the adaptive and innate immune system has been studied extensively and will be subject to this concise review.

Innate Immune System

Unlike any other organ, the gastrointestinal tract faces a unique challenge: while the intestinal mucosa has to provide protection from pathogens such as bacteria, fungi and viruses, it also has to tolerate beneficial commensal microbiota and physiological food-associated antigens. This 'hyporeactive' state has to be tightly regulated and seems to turn into immunologic 'hyperreactivity' in patients with IBD. The first barrier is constituted by a mucus

layer consisting of different antimicrobial agents [3], which are secreted by goblet cells and Paneth cells. Although not the focus of this review, these molecules and cell types seem to substantively contribute to the pathogenesis of IBD [4]. The innate immune system constitutes the first line of active immunologic defense. Various receptors such as Toll-like receptors (TLR), nucleotide oligomerization domain (NOD)-like receptors, C-type lectin receptors (CLR) or retinoic acid-inducible gene (RIG-1)-like receptors (RLR) sense different microbial molecules called pathogen-associated molecular patterns (PAMP). These receptors are located on macrophages, dendritic cells (DCs) and other cells of the lamina propria to initiate an inflammatory response [5]. Experimental models have shown some of these receptors to play an important role in IBD. For example, myeloid differentiation factor 88 (MyD88), a TLR signaling adaptor protein, is indispensable for development of enterocolitis in an IL-10-absent and IL-12/23-p40-dysregulated environment [6]. NF- κ B deficiency leads to apoptosis of colonic epithelial cells and consecutive translocation of bacteria into the mucosa. Deficiency of the gene encoding the adaptor protein MyD88 prevents the development of intestinal inflammation, demonstrating that TLR activation by intestinal bacteria is essential for disease pathogenesis an experimental model of colitis [7]. Additionally, polymorphisms in the genes for these receptors have been associated with IBD [8].

Macrophages are an integral part of the innate immune system of the gastrointestinal tract [9]. They clear luminal microbes that manage to overcome the intestinal barrier by phagocytosis. Intestinal macrophages are characterized by the markers F4/80, CD115 and CD14, but lack CD103 expression [10]. It has been shown that under healthy conditions, intestinal macrophages show profound anergy and contribute to tissue homeostasis through downregulation of proinflammatory cytokines [11, 12]. This attenuation mediates physiologic tolerance. In IBD, on the contrary, macrophages together with circulating monocytes orchestrate an exaggerated immunologic response. This is characterized by an increased expression of IL-12, IL-23 and TNF- α in vitro [13]. Animal models further showed an important role of IL-10, which controls immune regulation and macrophage function [14]. IL-10-deficient mice develop spontaneous colitis by shifting macrophage differentiation to a more proinflammatory subset. This can be rescued by macrophage depletion [15].

Apart from macrophages, DCs are the other key cell type of the innate immune system in the gastrointestinal

tract. DCs are located in the lamina propria, especially in the Peyer's patches and also in the mesenteric lymph nodes. Under healthy conditions, luminal antigens are presented to DCs by epithelial cells and microfold cells (M cells). It has been demonstrated that DCs even have dendrites reaching between epithelial cells directly into the lumen [16]. Upon activation, DCs migrate to the mesenteric lymph nodes to interact with B and T cells and thus provide a link between the innate and the adaptive immune system. Moreover, DCs coordinate T-cell generation and differentiation. Under healthy conditions, they can induce regulatory T cells, which suppress the function of effector T cells [14, 17]. In a proinflammatory setting with high levels of IL-1 and TNF- α , as can be found in patients with IBD, DC trafficking is enhanced and they orchestrate the T-cell response (either Th1, Th2 or Th17) [18]. For example, in CD, increased IL-12 production of DCs leads to Th1-mediated inflammation [16].

Adaptive Immune System

Apart from the innate immune system, the adaptive immune response and their interconnection play an important role under healthy and pathologic conditions. Cells of the adaptive immune system include T and B cells and their various subtypes, and can be found in the mucosa-associated lymphoid tissues (MALT). The general hallmark of these cells are surface receptors whose structures derive from gene rearrangement. This leads to high specificity and enables an immunologic 'memory' function. Although the epithelial layer and the innate immune system constitute a robust barrier, constant representation of antigens of the commensal flora to the peripheral T-cell pool occurs [19]. Landmark studies by Powrie et al. [20] and others showed that the T-cell repertoire includes specificities that can facilitate inflammatory responses to the microbiota. Transferring this cell type into immunodeficient mice depleted of endogenous regulatory cells resulted in the development of features of IBD.

There are currently three described subsets of effector CD4⁺ T cells: Th1, Th2, and Th17 cells, all of which are also found in CD or UC, respectively. Differentiation into one of these cell subtypes is driven by cytokines mostly released from cells of the innate immune response. Additionally, interconversion between various subsets has been proposed [21]. Th1 response was originally associated with CD and starts with activation of STAT1 and STAT4 by IL-12 and interferons [22]. The specific transcription factor for the Th1 cells is T-bet, surface markers

Fig. 1. Cell types, chemokines and pathways involved in the pathogenesis of inflammatory bowel disease.

include CCR1 and -5 and CXCR3 [23, 24]. A Th17-cell response is activated for example upon detection of extracellular bacteria and fungi. The differentiation is induced by proinflammatory IL-6, IL-23 and TGF- β via STAT3 and ROR γ T [25]. IL-23, which shares the p40 subunit with IL-12, has been proposed as a key factor in experimental models of CD [26]. IL-17A and IL-17F are Th17 cytokines and involved in neutrophil recruitment and activation [27]. Th17 cells have also been associated with CD. UC, on the other hand, is connected to a modified Th2 response associated with IL-5 and IL-13 responses that results in the specific activation of transcription factor GATA3 [28]. Th2 cells express CCR3 and -4 as surface markers. Effector T cells are the target of several clinically effective therapies. For instance, it was shown in patients with IBD that therapeutic anti-TNF antibodies induce T-cell apoptosis, when co-cultured with CD14 $^{+}$ macrophages [29]. Recently, an additional T-cell pool moved into the focus of IBD pathogenesis. IL-33, a cytokine of the IL-1 family, IL-23 and IL-25 are able to expand so-called innate lymphoid cells (ILCs). While these cells show normal lymphocyte morphology, they lack antigen receptors derived from rearrangement. Different subsets of ILCs have been proposed including NK cells, ROR γ T-

dependent ILC and ROR α -dependent ILC2 and others. ILCs secrete IL-5, IL-9 and IL-13 and seem to play a role in IBD as well as tissue fibrosis, infection and allergic reaction [30–32].

The role of B cells in IBD is only poorly examined and understood. This cell type primarily resides in the lymphoid follicles of the gastrointestinal tract and as plasma cells in the stroma of the lamina propria. IgA and IgM are constantly secreted by intestinal B cells and an important component of the epithelial barrier [33]. In IBD, a reduced expression of secretory IgA by dysfunctional B cells can be found [34]. Furthermore, anti-epithelial cell autoantibodies have been proposed in UC, highlighting the potential role of B cells in these patients [35]. It was also shown that peripheral blood B cells constitutively secrete proinflammatory IL-8 in patients with CD. This IL-8 production by peripheral B cells correlated directly with disease severity (fig. 1) [36].

In summary, cells of the innate and the adaptive immune system have been identified as the key regulators of IBD. The innate immune system initiates an exaggerated inflammatory response and cells of the adaptive immune system contribute to the preservation of this pathologic condition. Using new tools, such as next-generation se-

quencing [37] techniques or new imaging technologies [38], could help to gain an even better understanding of the underlying pathophysiology of CD and UC and contribute to the identification of new therapeutic targets.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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