

# Dendritic cells in IBD pathogenesis: an area of therapeutic opportunity?

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## Abstract

Dysfunction of the mucosal immune system plays an important role in inflammatory bowel disease (IBD) pathogenesis. Dendritic cells are emerging as central players based on both our increasing understanding of how genetic susceptibility impacts the mucosal immune system and the key role of dendritic cells in regulating response to gut microflora. We discuss areas of therapeutic opportunity in this evolving landscape.

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## Introduction

The inflammatory bowel diseases (IBDs) are a heterogeneous group of disorders which have two major phenotypic forms, Crohn's disease and ulcerative colitis, characterized by chronic relapsing and remitting intestinal inflammation [1–4]. Ulcerative colitis is the most common of the IBDs [5] and is characterized by a continuous pattern of inflammation beginning in the rectum and extending progressively further into the colon with increasing disease severity. By contrast, Crohn's disease patients frequently develop a discontinuous pattern of inflammation which can occur anywhere in the gastrointestinal tract, although the distal small intestine and colon are the most common locations [6].

In ulcerative colitis, inflammatory infiltrates are confined to the mucosa and consist primarily of lymphocytes and plasma cells plus granulocytes in crypt abscesses and present in the mucosa during disease flares. Ulceration is common during active disease and colonic epithelial cell changes such as goblet cell depletion, distorted crypt architecture, and epithelial dysplasia are associated with chronic disease [7]. Transmural inflammation is a characteristic feature of Crohn's disease and this deeper tissue involvement in the inflammatory process appears to be responsible for many of the serious complications associated with Crohn's disease such as fibrostenotic disease, abscesses, and fistula formation [8,9]. Epithelioid granulomas are also associated with Crohn's disease and provide diagnostic differentiation from ulcerative colitis when identified histologically. Epithelioid cells, so named for a resemblance to epithelial cells, are

activated histiocytes with homogeneous eosinophilic cytoplasm, and a working definition of an epithelioid granuloma is a collection of at least five epithelioid cells with or without accompanying multinucleate giant cells [10]. However, these granulomas are found in only about 20–40% of biopsies and 60% of surgical resection specimens [11] and, when present, must be differentiated from those associated with infectious diseases such as tuberculosis.

When Crohn's disease inflammation is confined to the mucosa and no granulomatous lesions are present, it cannot be definitively differentiated from ulcerative colitis by histological evaluation. A subset of patients present with clinical and histological features of disease which do not clearly segregate into one of the established phenotypic forms. These patients are often diagnosed as having indeterminate colitis [12,13]. Some of these patients will eventually develop lesions more characteristic of one of the major forms of IBD.

Accurately determining the prevalence of inflammatory bowel disease is a challenging proposition given that IBD is not a reportable disease and that patients can have a multi-decade disease course. Prevalence estimates have been drawn based on either in-depth regional data [14] or administrative data from health plan databases [15,16]. Based on these data, there are between 1 and 1.5 million individuals with ulcerative colitis or Crohn's disease in the United States alone. Clinical manifestations of disease develop during childhood in up to 25% of patients [2], and disease prevalence in children under 20 years of age is 43 per 100 000 for Crohn's disease and 28 per 100 000 for ulcerative colitis [16]. As expected with a chronic disease, the prevalence increases with age to about 201 per 100 000

for Crohn's disease and 238 per 100 000 for ulcerative colitis. The incidence of Crohn's disease and ulcerative colitis in the United States increased after 1940; however, those rates appear to have stabilized over the past few decades [14]. Despite some uncertainty about the total number of IBD patients, it is clear that large numbers of patients exist and that many of these patients can anticipate the need for treatment over a span of decades. While the advent of biological therapies has improved the clinical situation, IBD remains a major unmet medical need.

Current models hypothesize that IBD arises from and is sustained by interactions between genetically susceptible hosts and the gut microflora as well as, potentially, other environmental triggers. While the pathogenesis of IBD remains incompletely understood, it is clear that dysfunction of the mucosal immune system plays an important role. Dendritic cells are a key player in the mucosal immune system, serving as a bridge between the innate and the adaptive immune response [17]. In this review, we will discuss the evidence for dendritic cells in IBD pathogenesis with emphasis on genetics and microbial interactions. The innate immune system is emerging as a potentially attractive therapeutic target in IBD and we will review some of the current information in this area.

## Genetics of IBD

It is well established that host genetic susceptibility plays an important role in IBD pathogenesis. The first Crohn's disease susceptibility gene, nucleotide oligomerization domain receptor 2 (*NOD2*), which is encoded by the *CARD15* gene, was identified in 2001 [18,19]. In the intervening years, tremendous progress has been made using genome-wide linkage and association studies to reveal additional genetic polymorphisms associated with susceptibility to ulcerative colitis or Crohn's disease. Currently there are more than 160 IBD susceptibility genes or loci recognized [20]. A number of susceptibility genes are shared between ulcerative colitis and Crohn's disease [21,22], suggesting the presence of shared or interlinking pathways in inflammatory bowel disease pathogenesis. While the functional role of many loci or specific single nucleotide polymorphisms (SNPs) is incompletely understood, many of the genes are associated with aspects of mucosal immunity including innate immune response to microbial pathogens [20] (Figure 1).

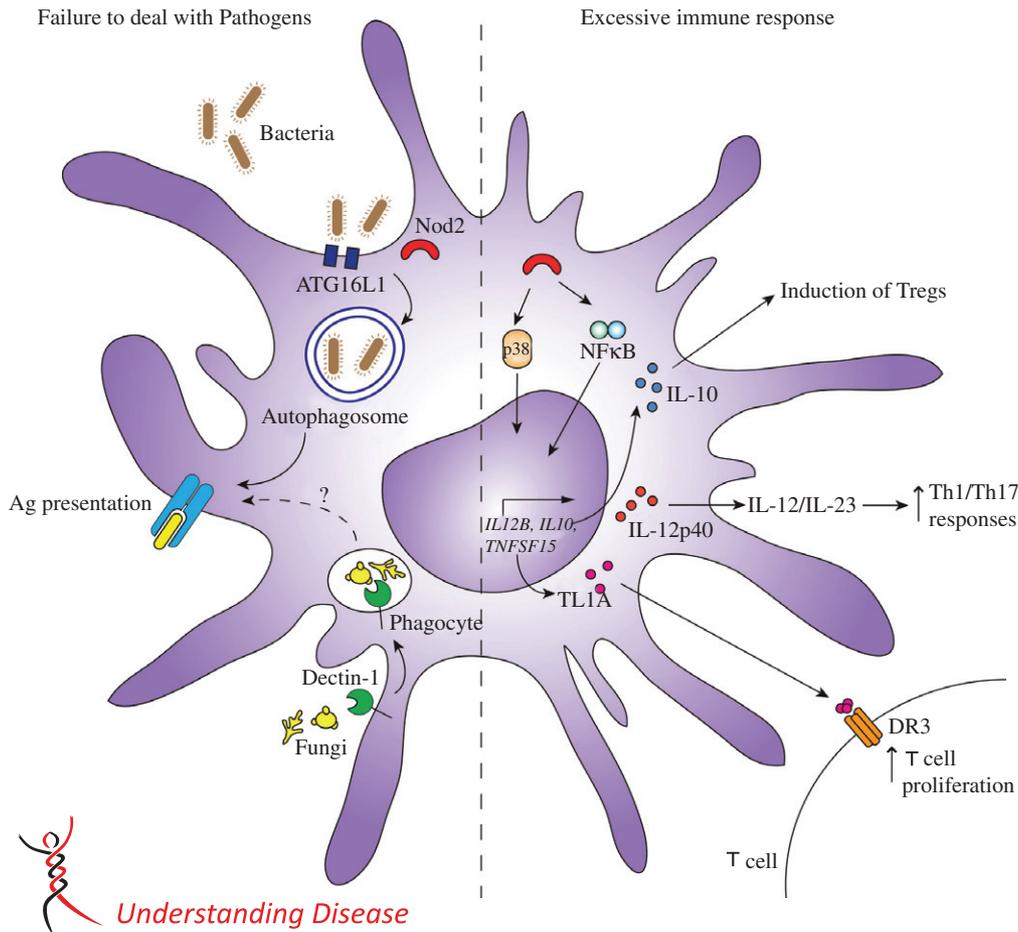
The importance of microbial recognition and the response of the innate immune system is underscored by the association between Crohn's disease and *NOD2*, which is a member of the NLR (NOD, leucine-rich repeat-containing protein) family of intracellular pathogen-associated molecular recognition receptors (PRRs) [23,24]. This association includes three *NOD2* polymorphisms which occur with greatest frequency in individuals of European descent but are not found in

Asian populations [25]. Approximately 30% of patients of European ancestry will have one or more of these mutations and these patients are at increased risk for ileal involvement and fibrostenotic disease [26]. Individuals heterozygous for a *NOD2* polymorphism have an increased Crohn's disease risk of 2.4-fold, while homozygous individuals have a 17.1-fold increase [25]. These are the highest relative risks associated with any IBD-risk gene.

*NOD2* is expressed by a variety of immune and non-immune cell types including dendritic cells and is upstream of the nuclear factor- $\kappa$ B (NF- $\kappa$ B) and mitogen-activated protein (MAP) kinase signalling pathways which drive pro-inflammatory cytokine production [27]. It encodes an intracellular sensor of peptidoglycan, a component of bacterial cell walls, and Crohn's disease-associated mutations are mainly located in the leucine-rich repeat region which interacts with the peptidoglycan muramyl dipeptide (MDP) motif, leading to altered bacterial recognition [28,29]. How *NOD2* polymorphisms predispose to Crohn's disease development remains incompletely understood, despite significant research effort in this field. Because the intestinal tract has continuous bacterial exposure, chronic activation of *NOD2* signalling should result in immune cell hyporesponsiveness to subsequent *NOD2* or Toll-like receptor (TLR) ligand stimulation [30,31]. While the *NOD2*-mediated mechanisms which down-regulate pro-inflammatory cytokines during exposure to commensal bacteria are not fully characterized, it is clear that the process is defective in patients with Crohn's disease-associated *NOD* polymorphisms [31]. One hypothesis is that *NOD2* normally acts to attenuate TLR signalling, resulting in reduced activation of NF- $\kappa$ B, and thereby prevents excessive activation of dendritic cells and subsequent pathogenic T-cell response [32].

There is increasing evidence that PRR signals intersect with other pathways that coordinate bacterial responses. For example, *NOD2* interaction with autophagy pathways has recently been recognized [33,34]. Autophagy is the process by which cytoplasmic components are sequestered into double membrane vacuoles which then fuse with lysosomes, and this process is important in microbial defence processes such as capture of intracellular bacteria during phagocytosis, antigen presentation, and inflammasome activation [35]. *ATG16L1* encodes an autophagy protein which is part of a complex responsible for proper subcellular localization of the autophagy machinery [36,37]. The *ATG16L1* polymorphism is associated with an increased risk of Crohn's disease [38] and similar to *NOD2*, shows an association with terminal ileal disease [38,39]. Interestingly, the affected domain of *ATG16L1* is non-conserved and is not required for all of its functions [40].

In human dendritic cells, autophagy is induced through *NOD2* stimulation, and dendritic cells isolated from Crohn's disease patients with *ATG16L1* and/or *NOD2* polymorphisms have defective autophagy



**Figure 1.** Impact of IBD genetic polymorphisms on dendritic cell function. Polymorphisms in IBD susceptibility genes in dendritic cells can be broadly categorized as either inhibiting the ability to effectively clear pathogens or contributing to excessive immune response. Dendritic cells play an important role in autophagy and presentation of bacterial antigens. SNPs associated with this pathway, including Nod2 and ATG16L1, can contribute to failure to deal with pathogens. Additionally, dectin-1 is important for the clearance of fungal pathogens by enabling dendritic cell recognition of  $\beta$ -1,3-glucans in fungal cell walls. A number of IBD susceptibility genes are linked to the excessive immune response which is characteristic of both Crohn's disease and ulcerative colitis. Nod2 in dendritic cells is upstream of MAPK and NF- $\kappa$ B, which are important regulators of pro-inflammatory cytokines. Impaired regulation of the inflammatory response caused by polymorphisms in Nod2, IL12B or TNFSF15 may result in excessive and prolonged pro-inflammatory T-cell responses. In addition, dendritic cells regulate the immune response through production of the anti-inflammatory cytokine IL-10. SNPs in IL-10 may result in loss of regulatory T cells, leading to excessive immune response.

induction in addition to altered antigen presentation and bacterial handling [33] (Figure 1). Interestingly, promoter polymorphism in the autophagy gene *IRGM* has also been associated with increased risk of developing Crohn's disease [41], although characterization of the specific effects on dendritic cells is still preliminary. In aggregate, these data suggest that autophagy may be an attractive drug target area for modifying dendritic cell function in the treatment of Crohn's disease. Preliminary evidence in support of this concept has been generated using rapamycin, an antibiotic which triggers autophagy by forming a complex with FKBP12, which then inhibits mTOR and is commonly used to up-regulate autophagy in cell culture [42]. Rapamycin has been used successfully to treat a patient with severe refractory Crohn's disease and has also shown protection in a murine colitis model, suggesting that this therapeutic approach may be promising [43,44].

Genome-wide association studies (GWAS) have shown strong associations of polymorphisms in the *IL23R* and *IL12B* gene loci with Crohn's disease and ulcerative colitis [45,46]. *IL12B* encodes the IL-12p40 subunit, which is a component of both the IL-12 and the IL-23 cytokines, while *IL23R* encodes one of two subunits of the IL-23R [47]. IL-23 is induced in dendritic cells (DCs) by PRR stimulation and can promote a wide range of pathological responses in the intestine, mediated either through T cells or through excessive innate immune cell activation [48,49] (Figure 1). DC IL-23 production, which is augmented under conditions of endoplasmic reticulum stress and activation of the unfolded protein response (UPR), is an important component of anti-microbial defence linking innate and adaptive immune responses [50]. However, excessive or inappropriate DC IL-23 production favours pro-inflammatory T-cell responses including enhanced proliferation of effector T cells, reduced differentiation of

forkhead box P3 (FOXP3)-positive regulatory T cells, and emergence of the IL-17- and IFN- $\gamma$ -producing cells associated with chronic intestinal inflammation [49]. Conversely, IL-23R polymorphisms, which are associated with protection from IBD risk, have been functionally characterized and result in reduced T-cell activation [51–53]. Studies in mouse colitis models have shown that IL-23 plays an important role in chronic intestinal inflammation [54]. In addition, the anti-IL-12p40 monoclonal antibody ustekinumab has demonstrated some clinical efficacy in a subset of Crohn's disease patients who were resistant to TNF antagonists [55].

Some dendritic cell processes linked to IBD genetic susceptibility have been identified as potential therapeutic targets. For example, blocking interactions between dendritic cells and T cells has been proposed as a means of decreasing activity of the IL-23/IL-17 pro-inflammatory pathway important in IBD pathogenesis [56]. Activated dendritic cells express the TNF family cytokine TL1A (TNFSF15), which interacts with the DR3 receptor (TNFRSF25) on lymphocytes [57,58] (Figure 1). Polymorphisms in the *TNFSF15* gene have been shown to contribute to the risk of both ulcerative colitis and Crohn's disease [59,60]. Increased expression of TL1A has been shown in Crohn's disease tissue [61], and antibody to TL1A prevents colitis development in mouse models [62]. In addition, mice overexpressing TL1A develop spontaneous intestinal inflammation [63,64]. These results suggest that TL1A may be a viable dendritic cell target in IBD.

A role for IL-10 in IBD pathogenesis was first identified in mice deficient in either IL-10 or the IL-10 receptor 2 (IL-10R2) subunit, as these mice develop spontaneous colitis [65,66]. This has more recently been extended into humans, with the association of very early onset IBD with IL-10 or IL-10 receptor (IL-10R) deficiencies [67–69]. Patients with IL-10/IL-10R loss-of-function mutations present, often in the first 3 months of life, with severe and progressive colitis complicated by perianal disease [70]. While IL-10 and IL-10R deficiencies are fortunately rare, GWAS findings suggest that IL-10 may play a broader role in IBD pathogenesis. IL-10 SNPs have been associated with both ulcerative colitis and Crohn's disease in paediatric and adult populations [71–73].

IL-10 is secreted by a variety of immune cell types including dendritic cells [74] and plays an important anti-inflammatory role through interactions with regulatory T cells, leading to inhibition of effector T-cell response [75] (Figure 1). This effect of IL-10 on T cells is mediated primarily by antigen-presenting cells such as dendritic cells and macrophages [76]. This suggests that dendritic cells may be important in the pathogenesis of IL-10 SNP-related IBD. IL-10 has been explored as a potential therapeutic in inflammatory bowel disease with limited success [77] and is currently of most interest in association with probiotic therapeutic strategies [78].

Recently, an association has been identified between polymorphism in the dectin-1 gene (*CLEC7A*) and severe ulcerative colitis [79]. The risk haplotype was strongly associated with the development of medically refractory ulcerative colitis and overrepresented in patients requiring colectomy. Dectin-1 is a C-type lectin receptor expressed by dendritic cells and macrophages which recognizes  $\beta$ -1,3-glucans found in fungal cell walls [80]. Dectin-1 deficiency had previously been associated with increased susceptibility to fungal disease in humans and mice [81,82]. The mechanisms by which dectin-1 influences fungal control and IBD pathogenesis are still being delineated, but evidence is emerging that it may be necessary to enable dendritic cell antigen presentation to T cells [83]. Therapeutic strategies for enhancing the control of microflora in IBD, except for antibiotics and probiotics, are largely unexplored.

### Microbiota in IBD

Intestinal microbes represent the largest microbial community in the body, where up to 100 trillion ( $10^{14}$ ) microbes may exist in a commensal relationship with the human host [84–86]. This relationship is facilitated by the intestinal mucus layer which creates a physical boundary between the host and microbe, by specific characteristics of the microbial community which reduce their immune cell-activating properties, and by direct influence on the immune cells. The intestinal microflora develops in early life and then the composition remains largely stable under healthy conditions [87–90]. Despite the large number of individual organisms, the number of bacterial species is estimated to be about 1000 per individual and represents only a small fraction of the existing phyla, which supports the idea that the commensal relationship is the product of a tight co-evolutionary history between the host and microbiota [86].

Shifts in the bacterial makeup on human intestinal microflora have been documented in IBD using 16S rRNA sequencing. These studies show that a subset of Crohn's disease and ulcerative colitis patients have depletion of commensal bacteria, especially members of the phyla *Firmicutes* and *Bacteroidetes* [91]. Overall bacterial burden is typically lower in patients with Crohn's disease than in those with ulcerative colitis but both are lower than healthy control individuals [92]. Even within the same patient, bacterial diversity is reduced in inflamed regions when compared with non-inflamed regions. These data suggest that not only is the host inflammatory response likely contributing to the loss of diversity characteristic of IBD patients but it is also providing a selective advantage to the subset of microbiota which have an increased presence in the disease state [93].

A role for microflora in IBD pathogenesis is supported by studies showing that exposure to the faecal

stream is required for endoscopic and histological disease manifestations [94–96] and that faecal transplants from healthy individuals can also have therapeutic benefit [97,98]. In addition, antibiotic therapy has shown some efficacy in clinical trials, with predominantly symptomatic improvement but also some endoscopic improvement and induction of remission, depending on the antibiotic and on the trial design [99–101]. Experimental colitis models also support the contention that microflora is a key component, as most mouse models of IBD require the presence of intestinal microbiota for colitis to develop [102,103].

Enteric flora plays an important role in intestinal immune cell development including dendritic cells. Dendritic cells discriminate between pathogenic and commensal bacteria by utilizing PRRs which recognize specific pathogen-associated molecular patterns. These include the toll-like receptors (TLRs) and C-type lectins such as mannose receptor and dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) [104]. The microbial environment encountered by an immature dendritic cell can determine the ability of the mature dendritic cell to drive T-cell differentiation towards T helper 1 (TH1), T helper 2 (TH2) or regulatory polarization [105–110]. This makes the dendritic cell a key player in determining whether a tolerant or protective immune response is mounted at the mucosal surface in response to specific microflora [111].

Tolerogenic properties of dendritic cells are potentially attractive in a therapeutic setting. This is one of the mechanistic tenants underlying the interest in probiotic therapy. For example, probiotics might help to restore normal microbial populations in the intestine [112]; however, to date, these efforts have not generated consistently promising results in IBD, particularly in Crohn's disease [113–115]. Therefore, many investigators have turned to investigating the immunomodulatory effects of specific bacteria or bacterial components in murine models to identify promising candidates. There is emerging evidence that alterations of cell surface components of lactobacilli can alter the immunoregulatory responses of dendritic cells, and this might provide a better defined therapeutic pathway in inflammatory diseases of the gastrointestinal tract [116]. The feasibility of utilizing genetically modified bacteria as a therapeutic agent has been established [117].

### Mucosal dendritic cells and IBD

The innate immune system exists to provide a rapid initial response to pathogens but it must also identify and minimize immune response to commensal microflora. Initiation of the gut mucosal immune response takes place following antigen uptake by dendritic cells and presentation to adaptive immune effector cells. However, in the absence of pathogen recognition, mucosal

dendritic cells primarily function to regulate immune responsiveness [118]. While there is general consensus that dendritic cells from a healthy intestinal tract are hyporesponsive to commensal bacterial components, the mechanisms by which this is achieved are not fully understood. In fact, the scientific literature surrounding this phenomenon is becoming increasingly more complex. One example of this is the evolving understanding of the role of CD103<sup>+</sup> dendritic cells in mucosal homeostasis.

Dendritic cell subsets are typically defined based on expression of surface markers, especially CD11b (integrin  $\alpha_M$ ) and CD103 ( $\alpha_E$  integrin). The majority of this work has been done in mice and dendritic cell subsets are not identical between mice and humans. CD103<sup>+</sup> dendritic cells comprise a substantial subset of murine mucosal dendritic cells and develop from classical precursors [119,120]. These have been considered 'tolerogenic' DCs in mice [121], which are believed to be important in initiating T-cell responses including induction of FOXP3<sup>+</sup> regulatory T cells (Tregs), and in the establishment of oral tolerance [122].

While CD103<sup>+</sup> dendritic cells have been credited with a major role in the maintenance of mucosal hyporesponsiveness, in part due to their ability to produce retinoic acid necessary for the development of FoxP3<sup>+</sup> Tregs [123], there remains some controversy on this point. Recently, *Batf3* KO mice that lack a CD103<sup>+</sup> DC subset have been reported to have normal Treg populations in the lamina propria [124], suggesting that other dendritic subsets have the potential to support Treg development. Also, recent work has shown that CD103<sup>+</sup> dendritic cells are capable of directly sampling, transporting, and presenting luminal antigens, and therefore are not restricted to a purely immunoregulatory role in the mucosa [125,126]. Moreover, CD103<sup>+</sup> mucosal dendritic cell populations are heterogeneous and can be further subdivided into two major populations of CD11b<sup>+</sup> and CD11b<sup>-</sup> subsets, which vary in terms of transcription factors required for their development as well as in geographical distribution within the intestinal mucosa [127,128].

Substantially less is known about the origin and function of human intestinal dendritic cells. CD103<sup>+</sup> dendritic cells have been identified in the human colon [129] but, unlike in mice, these cells do not constitute the dominant mucosal subset. This suggests that other distinct dendritic cell subsets may contribute to the tolerogenic intestinal mucosal environment. Therefore, although the data suggest that a subset of CD103<sup>+</sup> dendritic cells may be very important for maintaining mucosal immune hyporesponsiveness in normal individuals, the scientific understanding of these aspects of dendritic cell biology is still evolving.

As noted previously, dendritic cells are implicated in IBD pathogenesis by both genetics and their central role in the control of microbial interactions. Activated dendritic cells accumulate at sites of intestinal inflammation in human IBD and in murine models

of intestinal inflammation [130–132]. These cells express increased levels of a variety of activation markers, enhanced TLR responsiveness, and are phenotypically distinct from the hyporesponsive dendritic cells which help to mediate mucosal homeostasis [119,120,133–135]. These activated dendritic cells likely contribute to intestinal pathology and may prove to be valuable therapeutic targets in IBD. As our understanding of dendritic cell biology continues to grow and with increasing definition of mechanistic pathways, we expect to see the emergence of new dendritic cell-related drug targets.

### Author contribution statement

Both authors contributed to the conceptualization and writing of this review paper.

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