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The role of macrophages and dendritic cells in the initiation of inflammation in IBD

Erin C. Steinbach[*] and **Scott E. Plevy, M.D.**[*,†]

[*]Department of Microbiology and Immunology, University of North Carolina, School of Medicine, Chapel Hill, NC 27599, USA

[†]Center for Gastrointestinal Biology and Diseases, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA

Abstract

In the healthy gastrointestinal tract, homeostasis is an active process that requires a careful balance of host responses to the enteric luminal contents. Intestinal macrophages and dendritic cells comprise a unique group of tissue immune cells that are ideally situated at the interface of the host and the enteric luminal environment to appropriately respond to microbes and ingested stimuli. However, intrinsic defects in macrophage and dendritic cell function contribute to the pathogenesis of inflammatory bowel diseases (IBD), as highlighted by recent genome-wide association studies. Gastrointestinal macrophages and dendritic cells participate in IBD development through inappropriate responses to enteric microbial stimuli, inefficient clearance of microbes from host tissues, and impaired transition from appropriate pro-inflammatory responses to anti-inflammatory responses that promote resolution. By understanding how intestinal macrophages and dendritic cells initiate chronic inflammation, new pathogenesis-based therapeutic strategies to treat human IBD will be elucidated.

Keywords

Macrophages; dendritic cells; IBD; inflammation

Introduction

In the healthy gastrointestinal tract, homeostasis is an active process that requires a critical balance of host responses to the enteric luminal contents. Intestinal macrophages and dendritic cells comprise a unique group of tissue immune cells that are ideally situated at the interface of the host and the enteric luminal environment to appropriately respond to microbes and other potential stimuli. Both commensal and pathogenic bacteria are recognized through conserved molecular microbial patterns by pattern-recognition receptors (PRRs). Mechanisms by which the host distinguishes commensal from pathogenic bacteria are not well defined and represent a fundamental gap in the understanding of homeostatic immune function and IBD.

Corresponding Author: Scott E. Plevy, M.D., 103 Mason Farm Road, Campus Box 7032, 7341C MBRB, Chapel Hill, NC 27599-7032, Phone: (919) 966-4405, Fax: (919) 843-2585, scott_plevy@med.unc.edu.

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How do intestinal DCs and macrophages interact with the microbial environment?

Intestinal macrophages and dendritic cells (DCs) sense conserved molecular patterns on microbes (pathogen-associated molecular patterns, PAMPs) via germ-line encoded PRRs.[1, 2] PRRs are divided into four families based on shared functional domains: toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR) receptors (NLRs), C-type lectin receptors (CLRs), and retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs).[3] Signaling downstream of each family of PRRs culminates in activation of central immune response pathways: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the mitogen-activated protein kinases (MAPKs), and interferon regulatory factors (IRFs).[4] Upon engagement of PRRs, immune and non-immune cells produce inflammatory cytokines, type I interferons, chemokines, and antimicrobial peptides. As a result, neutrophils are recruited and macrophages are activated, leading to the direct killing and clearance of microbes. Additionally, these inflammatory products induce the maturation of DCs, promoting the induction of adaptive immune responses. A carefully orchestrated process, microbial sensing and subsequent immune responses are highly regulated. Dysregulation of these pathways can lead to both enhanced susceptibility to infections and development of chronic inflammatory diseases.[3]

PRR recognition of its cognate PAMPs culminates in the initiation of pathogen-specific programs designed to eradicate the prevailing insult. But how does the host recognize an intact microbe and decide which program to initiate? In reality, one microbe has many different PAMPs, and many PRRs may recognize one PAMP. Additionally, different cell types express unique sets of PRRs, and each PRR may play fundamentally different roles in the temporally distinct phases of an infection (i.e., initial infection versus memory response). The complex crosstalk between PRR families also confers specificity to and regulates each immune response. Thus, the assembly of a successful immune response to microbes depends on the context of the infection, the cell types responding to it, and the array of PRRs that are engaged during the infection.[3] Furthermore, the local microenvironment provides contextual cues to immune cells via cytokines and growth factors produced by host cells and metabolic products from microbes.[5] It is likely through this complex context of recognition that innate immune cells distinguish between commensal and pathogenic microbes and initiate an appropriate response program. However the precise mechanism of discernment of helpful from harmful microbes and regulation of subsequent immune responses and how this relates to intestinal homeostasis and IBDs remains incompletely understood.

PAMP recognition by PRRs on intestinal macrophages and DCs leads to the efficient removal of potential stimuli while remaining immunologically nonresponsive. This feature is unique to intestinal tissue resident macrophages and DCs.[6] The importance of remaining “inflammation anergic” is emphasized by the development of chronic intestinal inflammation in the absence or dysregulation of macrophage and DC responses to microbial stimuli.[7] Ultimately, inappropriate host responses to the luminal microbiota in genetically susceptible individuals disrupt homeostasis, leading to development of IBDs.

IBD pathogenesis: A macrophage- and DC-centric view—The pathogenesis of IBDs, including Crohn's disease (CD) and ulcerative colitis (UC), is multifactorial, and

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encompasses incompletely defined and complex interactions between host immune responses, genetic susceptibility, environmental factors, and the enteric luminal contents.[8] Recent genome-wide association studies have highlighted the importance of host innate immune responses to microbes in the pathogenesis of IBDs.[9] Single nucleotide polymorphisms (SNPs) associated with increased risk of developing IBDs were identified in genes involving microbial sensing (*NOD2, IRF5, NFKB1, RELA, REL, RIPK2, CARD9*, and *PTPN22*) and clearance (*ATG16L1, IRGM, NCF4*), and integrating antimicrobial adaptive immune responses (*IL23R, IL10, IL12, IL18RAP/IL1R1, IFNGR/IFNAR1, JAK2, STAT3*, and *TYK2*).[10] Intestinal macrophages and DCs reside in the lamina propria (LP) and thus are ideally positioned to continuously sample intestinal luminal contents. LP mononuclear cells (LPMCs), including macrophages and DCs, are the sentinels and first-responders of the gut-associated lymphoid tissues (GALT). Additionally, resident LPMCs possess unique attributes that shape the gastrointestinal tract as a largely tolerant environment while maintaining effective clearance of microbes. Importantly, LPMCs direct subsequent adaptive immune responses, thereby regulating local inflammation.

This review will explore how macrophages and DCs help to initiate inflammation in the gastrointestinal tract by first describing how these cells maintain intestinal homeostasis under physiologic conditions. Next, the breakdown of homeostasis encouraged by macrophages and DCs as it pertains to the development of IBDs will be described. Intestinal macrophage and DC dysfunction is now widely recognized as a central component to the pathogenesis of IBDs, and understanding this phenomenon is vital to the development of effective therapies for these debilitating diseases.

Macrophages and DCs in GI Homeostasis

The gut-associated lymphoid tissue (GALT) represents the largest aggregate of lymphoid tissue in the body. GALT includes various organized collections of immune cells within the gastrointestinal tract, such as Peyer's patches in the small intestine, and cryp to patches in the large intestine; and the diffuse arrangement of intestinal mononuclear cells within the lamina propria. The close proximity of LPMCs to the enteric luminal compartment, separated by an epithelial cell monolayer, is important for several reasons: LPMCs (1) sample luminal antigens that gain access to the lamina propria under physiologic conditions to maintain local and systemic tolerance, and (2) efficiently clear microbes and stimuli that cross the IEC barrier. Resident LP macrophages demonstrate distinct attributes from peripheral monocyte populations. While LP macrophages maintain robust microbicidal effector functions, they do not produce inflammatory mediators upon encountering microbial stimuli.[6] Additionally, LP macrophages promote the transition from protective inflammatory responses to resolving anti-inflammatory responses upon encountering a danger signal. Thus, LPMCs are integral to directing appropriate immune responses and maintaining intestinal homeostasis in the gut.

There remains active debate about the classification and ontogeny of LP macrophages and LP dendritic cells (LPDCs). The surface integrins CD11b and CD11c are routinely used to distinguish between macrophages and DCs in peripheral lymphoid tissues ($CD11b^{+}CD11c^{-}$ and $CD11b^{+/-}CD11c^{high}$ are characterized as macrophages and DCs, respectively).

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However, the distinction between LP macrophages and LPDCs is less clear, as LP macrophages express both CD11b and CD11c.[6] It has been proposed that differential expression of CX_3CR1 (the receptor for the chemokine fractalkine, CX_3CL1) and CD103 ($\alpha_E\beta_7$ integrin) reliably distinguish between LP macrophages and LPDCs.[6, 11] $CD103^-CX_3CR1^{hi}$ LP macrophages express the classical macrophage marker F4/80, demonstrate ultrastructural characteristics of macrophages, and under physiologic conditions do not traffic to draining mesenteric lymph nodes (MLNs) where priming of adaptive immune responses is initiated. However, there is evidence that CX_3CR1^{hi} LP macrophages travel to MLNs during enteric microbial dysbiosis.[12] Conversely, $CD103^+CX_3CR1^{lo}$ LPDCs are $F4/80^-$ and perform functions typically associated with DC, including constitutive trafficking to MLN, antigen presentation to T lymphocytes, and inducing gut homing receptors on T cells. Both LP macrophages and LPDCs express high levels of MHC class II, demonstrating their ability to interact with and shape adaptive immune responses. While controversy remains over the exact nature and origin of these LP subsets, for our purposes, we will classify LP macrophages as $CD103^-CX_3CR1^{hi}$ and LPDCs as $CD103^+CX_3CR1^{lo}$ cells.

Lamina propria macrophages

Macrophages are a highly heterogeneous population of cells that demonstrate a continuum of activation states. The wide spectrum of macrophage phenotypes is often somewhat oversimplified into two functional groups: “inflammatory” M1 (high IL-12, low IL-10) and “wound healing” M2 (low IL-12, high IL-10) macrophages.[13] Additionally, a recently appreciated subset of macrophages that produces high levels of IL-10 is referred to as “regulatory macrophages.”

Specific combinations of cytokines within the microenvironment polarize macrophages, and evidence suggests that macrophages maintain considerable plasticity between activation states. M1 macrophages are polarized by IFN-γ produced by NK and T helper (Th) 1 cells, TNF-α produced by granulocytes or other antigen presenting cells (APCs) and engagement of PRRs by PAMPs, which activates suppressor of cytokine signaling 3 (SOCS3) to induce the M1 phenotype.[14-16] M1 macrophages produce pro-inflammatory cytokines (TNFα, IL-12, IL-6), and reactive oxygen and nitrogen species. Production of these mediators promotes the differentiation and activation of Th1 and Th17 cells.[13, 17-19] The Th1 response in turn helps macrophages by enhancing their ability to clear intracellular pathogens. While M1 macrophages are essential for the eradication of intracellular infections, they also produce pro-inflammatory cytokines implicated in IBD pathogenesis. Furthermore, unregulated M1 macrophage activity can induce tissue damage, predispose the host to developing neoplastic lesions, and induce insulin resistance.[20, 21]

M2 macrophages are polarized by IL-4 produced by granulocytes or Th2 cells in response to tissue injury and activation by some fungi and parasites and initiation of SOCS2 signaling.[13] M2 macrophages produce matrix metalloproteases, growth factors, and demonstrate efficient phagocytosis of debris without producing pro-inflammatory cytokines. Th2 responses are aimed at inducing wound healing and clearing parasites, although the exact mechanisms underlying parasite eradication are unknown. Indeed, down regulation of microbicidal

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functions in M2 macrophages can render the host more susceptible to certain infections.[22-27] M2 macrophages are also efficient at recruiting Foxp3^{+} T regulatory (Treg) cells, which would further down regulate local immune responses.[16] Furthermore, unregulated M2 macrophage activity can promote the development of fibrotic lesions through elaboration of TGFβ and enhanced allergic responses.[28, 29]

Regulatory macrophages are polarized by a wide array of signals, including IgG immune complexes, IL-10, prostaglandins, and apoptotic cells, potentially by activation of the MAPK extracellular signal-regulated kinase (ERK).[13] However, typically two signals are necessary to induce regulatory macrophages, such as engagement of PRRs by PAMPs. Regulatory macrophages differ from M2 macrophages in that they do not produce extracellular matrix components but express high levels of costimulatory molecules (CD80, CD86) necessary for the activation of T cells. Like M2 macrophages, regulatory macrophages produce high amounts of the anti-inflammatory cytokine IL-10 and can render the host more susceptible to certain infections.[30-36] Furthermore, unregulated regulatory macrophage activity may also play a role in the induction of neoplastic lesions by dampening anti-tumor macrophage defenses and promoting angiogenesis.[37, 38]

LP macrophages are unique tissue resident macrophages characterized by the inability to produce inflammatory cytokines in response to microbial stimuli. However, these cells maintain robust phagocytic and microbicidal effector capabilities. The tolerant phenotype of LP macrophages is likely conditioned by locally produced IL-10 and TGF-β.[39, 40] However, the ontogeny of these cells is unknown. LP macrophage maintenance may depend on local proliferation rather than repopulation from migrating blood monocytes, but this is experimentally difficult to determine due to the extremely low turnover rate of these cells. Additionally, the context during which blood monocytes are recruited to the intestines may determine the final phenotype of the LP macrophages. During non-inflammatory homeostatic conditions, Ly6C^{hi} monocytes almost exclusively repopulate the lamina propria with CD11c^{+} (F4/80^{hi}CX$_3$CR1^{hi}CD11b^{+}CD103^{-}) LP macrophages.[41] In contrast, under inflammatory conditions, Ly6C^{hi} monocytes recruited to the lamina propria differentiate into CD103^{+}CX$_3$CR1^{int}CD11b^{+} DCs that produce high levels of the inflammatory cytokines IL-12, IL-23, iNOS, and TNF-α.[41]

CX$_3$CR1^{hi} LP macrophages extend dendrites between IECs to sample luminal antigens and promote local tolerance through constitutive production of the anti-inflammatory cytokine IL-10,[42] the absence of an inflammatory response to activating stimuli, very low expression of co-stimulatory molecules CD80, CD86 and of the macrophage activating receptor CD40.[40] Although these cells that sample the luminal environment were originally defined as DCs[43], recent work supports that they may represent a macrophage population.[44] IL-10 produced by LP macrophages promotes the persistence of Foxp3 expression in Treg cells in the intestine.[45] Additionally, CX$_3$CR1^{hi} LP macrophages participate in the induction of systemic oral tolerance.[42] It has been suggested that CX$_3$CR1^{hi} LP macrophages sample luminal antigens and deliver them to CD103^{+} LPDCs, which are then able to traffic to MLN to prime adaptive immune responses.[46] However, there is recent compelling evidence that CX$_3$CR1^{hi} LP macrophages do traffic to MLNs in a CCR7-dependent manner during dysbiosis of the enteric microbiota.[12]

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Unique intracellular signaling pathways contribute to the inflammation anergic characteristic of LP macrophages; however, it remains unclear exactly what makes LP macrophages distinct from circulating monocytes and other tissue resident macrophages. Additionally, inflammation anergic LP macrophages are distinct from the more widely studied endotoxin-resistant macrophages. For one, LP macrophages do express PRRs, contrary to conventional thought. Recent studies suggest that the enteric microbiota are not necessary to program LP macrophages to express high amounts of the anti-inflammatory cytokines IL-10 and TGF-β.[47, 48] One enticing candidate for inducing LP macrophage nonresponsiveness to PAMPs is IL-10. Importantly, IL-10-deficient mice[49] and mice with myeloid-specific ablation of the IL-10 signaling molecule STAT3[50] develop spontaneous colitis reminiscent of human IBD. Additionally, blocking IL-10 restores PAMP responsiveness in LP macrophages. Our lab described a mechanism for IL-10-mediated suppression of IL-12p40 via altering histone acetylation and RNA polymerase II accessibility to the *Il12b* promoter,[48] suggesting that IL-10 directly inhibits the production of pro-inflammatory cytokines in response to PAMP stimulation. IL-10 additionally exerts its anti-inflammatory effects on the innate immune system by regulating transcriptional elongation,[51] microRNA induction,[52] mRNA stability,[53] and transcriptional repressors and corepressors.[54]

Additionally, the phosphoinositide 3-kinase (PI3K) pathway negatively regulates signaling through TLRs in macrophages. In particular, the p110δ isoform of PI3K is enriched in leukocytes and regulates IL-12p40 production in LP macrophages in response to microbial stimulation. PI3K p110δ is indispensable for intestinal homeostasis as mice harboring an inactivating point mutation in p110δ (p110δ kinase-dead, or p110δ^{KD} mice) develop spontaneous colonic inflammation. LP macrophages from p110δ^{KD} mice produce significantly more IL-12p40 and less IL-10 upon stimulation with heat-killed *Escherichia coli*.[55] Thus, a loss in the critical negative regulation of TLR signaling results in the disruption of intestinal homeostasis.

Lamina propria dendritic cells

Broadly speaking, DCs are professional APCs with the ability to initiate adaptive immune responses against pathogens. Like macrophages, DCs comprise a heterogeneous population of cells with functional diversity. DCs originate from blood monocytes or a common DC progenitor (CDP) in the bone marrow at steady state. DCs repopulating tissues from monocyte precursors rely on granulocyte-macrophage colony stimulating factor (GM-CSF) for local proliferation.[56] Conventional DCs (cDCs) arising from the CDP express high levels of CD11c, varying levels of CD8α and CD11b, and reside in secondary lymphoid tissues. Plasmacytoid DCs (pDCs) also originate from the CDP and are specialized in the production of type I interferons. In addition to functional subsets of DCs, the maturation state of DCs has important implications in immunity. Mature DCs that have previously encountered microbial products and inflammatory stimuli are highly specialized for antigen presentation. Thus, mature DCs express high levels of co-stimulatory molecules and tend to reside in secondary lymphoid organs where they are ideally positioned to prime antigen-specific T cells.[57] On the other hand, immature DCs demonstrate low surface expression of co-stimulatory molecules and constitutively migrate in low numbers to lymph nodes, perhaps to maintain tolerizing signals there.[57, 58]

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LPDCs also comprise a heterogeneous group of cells in the intestines. Only recently has it also been appreciated that LPDCs play an active and direct role in maintaining peripheral tolerance to self and intestinal luminal antigens. Like LP macrophages, LPDCs represent a spectrum of functionally distinct phenotypes. CD8α$^+$pDCs in the LP are capable of inducing regulatory T cells and supporting their function.[59] However, most LPDCs are CD11b$^+$CD8α$^-$, but CD11b$^-$CD8α$^+$ and CD11b$^-$CD8α$^-$ subsets are also present. These DCs weakly stimulate antigen-specific T cell proliferation and constitutively express IL-10 and type I interferons.[60] Furthermore, LPDCs are divided into CD103$^+$ and CD103$^-$ (E-cadherin receptor) populations, each demonstrating distinct functions. CD103$^+$ LPDCs are able to induce Foxp3-expressing Treg cells,[61-63] whereas CD103$^-$ LPDCs are efficient at inducing Th17 cells when stimulated with flagellin or microbial ATP.[64-66] While the Th17 response is important for antimicrobial immunity, dysregulation of Th17 lymphocytes and cytokines is implicated in a number of autoimmune disorders.[67]

CD103$^+$ LPDCs represent a population of tolerizing innate immune cells that express the enzyme retinaldehyde dehydrogenase (RALDH), which produces retinoic acid (RA) from retinaldehyde, and the important regulatory cytokine TGF-β. Both CD103$^+$ LPDC-produced RA and TGF-β are necessary for the induction of Treg lymphocytes in the intestine.[61-63] Additionally, CD103$^+$ LPDCs produce indoleamine 2,3-dioxygenase (IDO), which participates in the induction of Treg cells and suppression of Th cell proliferation.[68]

The induction of CD103 expression in LPDCs is dependent on the vitamin A metabolite RA and the local production of factors from IECs and stromal cells. IECs induce CD103 expression in LPDCs in an RA-, TGF-β-, and contact-dependent manner.[69] In addition to TGF-β, stromal cells in the LP constitutively produce prostaglandin E2, which inhibits the production of pro-inflammatory cytokines in DCs.[70] Importantly, thymic stromal lymphopoietin (TSLP) produced by IECs conditions LPDCs to induce Th2 cell differentiation, although its necessity in inducing and maintaining Treg cells is controversial.[69] Nonetheless, TSLP produced by IECs confers a homeostatic phenotype on LPDCs to protect mice from colitis.[69, 71-73] CD103$^+$LPDC differentiation is dependent on Notch2 signaling, as *Notch2*$^{-/-}$ mice demonstrate a selective loss of CD11b$^+$CD103$^+$ LPDCs.[74] Furthermore, the preferential expansion of CD103$^+$ LPDCs depends on the DC differentiating molecule Fms-related tyrosine kinase-3 ligand (Flt3L).[75] The function of CD103$^+$ LPDCs depends on several factors. Dietary vitamin A induces RALDH expression in CD103$^+$ LPDCs[76] and is necessary for these cells to imprint T cells with gut-homing receptors.[77, 78]

Aside from inducing Th17 differentiation, CD103$^-$ LPDCs are involved in the induction of immunoglobulin A (IgA) class switching of B lymphocytes, both in the Peyer's patches and intestinal LP. IgA is abundantly produced in the intestine and prevents the harmful effects of bacterial overgrowth and bacterial adhesion to IECs in the intestinal lumen.[79] In the isolated lymphoid follicles of the LP, CD70$^+$ LPDCs expressing TLR5 and any of various ATP receptors induce IgA class switching in RA-dependent and T lymphocyte-independent manners.[64] LPDCs that produce iNOS and TNF also support IgA class switching.[80] Cytokines produced by IECs, stromal cells, and LPDCs, including B cell activating factor

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(BAFF), a proliferation-inducing ligand (APRIL), IL-4, TGF-β, and IL-10, support the induction, maintenance, and expansion of IgA$^+$ plasma cells.[81]

LPDCs have a higher turnover rate than LP macrophages due to frequent trafficking to MLN to present antigen to naïve T lymphocytes.[57] Evidence suggests that CD103$^+$CD11b$^-$ LPDCs are replenished by DC-committed precursors (pre-cDC) in a Flt3L-dependent manner,[82] whereas CD103$^-$CD11b$^+$ LPDCs are derived from circulating Ly6C^{hi} monocytes in a GM-CSF-dependent manner.[83] Additionally, the preferential expansion of regulatory CD103$^+$ LPDCs is also Flt3L-dependent.[75] The conditions under which precursors are recruited to and the existing microenvironment of the LP likely determine the final phenotype of LPDCs. For instance, under steady-state conditions F4/80^{lo}CD103$^+$CD11c$^+$ LPDCs are repopulated from circulating Ly6C^{hi} monocytes, however during colitis Ly6C^{hi} monocytes repopulated inflammatory CD103$^-$CX3CR1^{int}CD11b$^+$ LPDCs and exacerbated inflammation.[41, 83]

Summary

Populations of macrophages and dendritic cells within the intestinal LP are diverse. LP macrophages and LPDCs interact with the intestinal environment and luminal contents to maintain homeostasis through the production of protective mediators, dampening of pro-inflammatory responses, and the active induction of adaptive immune tolerance. Distinct functional populations of LP macrophages and LPDCs actively promote tolerance while others have the propensity to enhance protective inflammatory responses to foreign antigens. However, an imbalance in any of these physiologic processes may tip the balance toward chronic intestinal inflammation and IBD, as we will explore in the next section.

Macrophages and DCs in IBD Pathogenesis

Murine Experimental IBD

There are a number of phenotypic and functional alterations described in LP macrophages and LPDCs during IBD development. Recent research highlights a central role for macrophages and DCs in the pathogenesis of colitis, as numerous IBD susceptibility SNPs affecting innate immune cell functions have been identified.[9] Additionally, the selective depletion of macrophage and DC subsets in mouse models of colitis has been particularly informative about the protective and pathogenic roles innate immune cells play during discrete stages of disease pathogenesis. Lymphocyte deficient mice (severe combined immunodeficiency, SCID) develop colitis upon treatment with the intestinal irritant dextran sodium sulfate (DSS), suggesting that macrophages and DCs are pathogenic in this model in the absence of mature lymphocytes.[84] Depletion of phagocytes in *Il10*$^{-/-}$ mice,[85] and blocking myeloid cell recruitment in both 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced[86] and T cell adoptive transfer[87] colitis ameliorate disease, as does selective depletion of LPDCs during DSS colitis.[88, 89] Contrary to these findings, depletion of LP macrophages and LPDCs *prior* to the induction of DSS colitis results in exacerbated disease.[90, 91] Furthermore, different subsets of macrophages and DCs have distinct effects on the severity of colitis in animal models. M2 polarized macrophages protect mice from DSS colitis, whereas M1 polarized macrophages contribute to disease pathogenesis.[92-94]

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Selective expansion of CD103$^+$ LPDCs by Flt3L protects TNF ARE mice from ileitis,[75] but E-cadherin-expressing DCs increase colonic pathology in DSS colitis.[95] Thus, the protective/pathogenic role of distinct macrophage and DC populations in the LP remains an active area of investigation.

In general, there are three ways in which defects in innate immune cell functions can initiate IBD development: (1) by responding inappropriately to normally benign stimuli such as commensal microbes, (2) by inefficiently clearing microbes, leading to chronic immune stimulation, and (3) by failing to switch from an appropriate pro-inflammatory response to an inflammation-resolving anti-inflammatory response. Here we will discuss each of these defects and how each leads to chronic inflammation and IBD.

The enteric microbiota is essential for the development of colonic inflammation in most murine models of colitis.[96, 97] Perturbations in the negative regulation of innate immune responses to stimuli enhance susceptibility to colitis development. The well-characterized *Il10*$^{-/-}$ murine model of spontaneously developing colitis demonstrates the necessity of the potent anti-inflammatory cytokine IL-10 in the maintenance of intestinal homeostasis.[49] Indeed, LP macrophages derived from germ free (GF) *Il10*$^{-/-}$ mice produce increased IL-12p40 compared to GF WT LP macrophages at baseline, suggesting that IL-10 is the critical driver of the LP macrophage phenotype.[48] Furthermore, IL-10 produced by CD11b$^+$ LP macrophages is necessary for the maintenance of Foxp3 expression in Treg cells and protection from colitis.[45] The IL-10- and microbiota-inducible nuclear transcription factor, interleukin-3 regulated (NFIL3) negatively regulates IL-12p40 production in LP macrophages and has been recently implicated in intestinal homeostasis.[98] Thus, studying the regulation of IL-10 production and its downstream signaling effects is crucial to understanding intestinal homeostasis.

IL-10-independent regulation of innate immune responses also contributes to intestinal homeostasis. One negative regulator of intestinal macrophage activation is paired immunoglobulin-like receptor B (PIR-B). PIR-B is expressed on colonic LP macrophages, B cells, and neutrophils and contains several immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that activate intracellular phosphatases, negatively regulating TLR signaling.[99] PIR-B is highly upregulated on LP macrophages following DSS administration in mice. Furthermore, PIR-B-deficient (*Pirb*$^{-/-}$) macrophages produce significantly more TNFα and IL-6 in response to *Escherichia coli*, and WT mice reconstituted with *Pirb*$^{-/-}$ macrophages demonstrate increased susceptibility to DSS colitis. PIR-B expression is also important in human intestinal biology, as LP mononuclear cells from both healthy controls and patients with UC express immunoglobulin-like transcript-2/leukocyte Ig-like receptor-1 (ILT-2/LIR-1), a human homologue of PIR-B. Our lab recently described spontaneous colitis development in mice harboring a kinase-dead phosphoinositide 3-kinase (PI3K) catalytic subunit p110δ (p110δ^{KD}), a potent negative regulator of TLR responses in macrophages.[55] CD11b$^+$ LPMCs from p110δ^{KD} mice produced increased pro-inflammatory cytokines (IL-12p40, IL-23) and decreased anti-inflammatory IL-10 in response to enteric microbes compared to CD11b$^+$ LPMCs from WT mice. Conversely, triggering receptor expressed on myeloid cells-1 (TREM-1) *amplifies* TLR-induced inflammatory responses in macrophages, and blocking its activity attenuates murine colitis.[100, 101] Indeed, resident LP macrophages

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do not express TREM-1 but abundant TREM-1-expressing LP macrophages can be found in patients with IBD.[102, 103] Thus, unrestrained pro-inflammatory responses of LP macrophages and LPDCs participate in the induction of chronic inflammation by continued recruitment of inflammatory cells, inducing altered barrier function of the IEC layer, and promoting pathogenic adaptive immune responses.

The enteric microbiota interacts with host immune cells to induce protective anti-inflammatory responses and maintain intestinal homeostasis. Dysregulation of these protective pathways, either by enteric microbial dysbiosis or intrinsic defects in macrophage and DC responses to stimuli, may underlie IBD pathogenesis. Short chain fatty acids (SCFAs) are anti-inflammatory metabolites produced by specific phyla of enteric bacteria (Bacteroidetes, Firmicutes).[104] When DSS colitis is induced in immune cell-specific *Gpr43*$^{-/-}$ mice (a host receptor for SCFAs), colonic inflammation is exacerbated, pointing to the beneficial anti-inflammatory effect of SCFAs in the colon.[105] Interestingly, bacteria also actively suppress intestinal inflammatory responses, although a bacterium can exploit this to promote its pathogenicity. *Citrobacter rodentium* and *Helicobacter pylori* express bacterial proteins with domains similar to host ITIMs.[106] ITIMs negatively regulate immunoreceptor signaling pathways in immune cells, and bacterial ITIM-like-containing proteins dampen immune responses in murine colons. On the other hand, analysis of the enteric microbiota of patients with IBD demonstrates decreased biodiversity, decreased proportions of Firmicutes, and increased Gammaproteobacteria.[107] While it is unknown whether enteric dysbiosis in IBD patients contributes to or is a consequence of colonic inflammation, researchers demonstrate reproducible increases in bacteria with unique abilities to adhere and invade mucosal cells in patients with IBD (i.e., adherent-invasive *E. coli*),[108] as well as decreases in bacteria capable of producing protective SCFAs.[109] Furthermore, it was recently shown that *E. coli* is especially adept at using nitrates as electron acceptors, supporting its selective growth during intestinal inflammation, when nitrates are produced in abundance.[110] This suggests that the interplay between host and bacteria actively shapes intestinal homeostasis and participates in IBD pathogenesis.

Both macrophages and DCs actively promote the transition from inflammation to the return to homeostasis after immune system activation, and non-resolving inflammation is associated with many chronic diseases, including IBD.[111] A study found that the pro-resolution mediator prostaglandin D_2 (PGD_2) was upregulated only in UC patients who had achieved long-term remission, suggesting that intact pro-resolution pathways are necessary to halt damaging intestinal inflammation.[112] Additionally, a SNP associated with low expression of the immune cell ectonucleotidase CD39, which generates the pro-resolving mediator adenosine, is associated with CD.[113] Immune cells are major contributors of extracellular adenosine at inflammatory sites. Adenosine interacts with its receptor A_{2B} on macrophages and DCs to inhibit pro-inflammatory cytokine production, expression of co-stimulatory molecules, and induction of T lymphocyte proliferation while increasing IL-10 production.[114]

Other pro-resolving soluble mediators with diverse effects on macrophages and DCs are resolvins, lipoxins, protectins, and maresins.[115] These mediators are derived from polyunsaturated fatty acids (PUFAs), and both CD and UC patients have demonstrated

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deficiencies in these resolving mediators.[116, 117] Interestingly, there was found to be a very low incidence of IBD among a population in Northwest Greenland that consumes high amounts of PUFAs, suggesting that dietary precursors of pro-resolving factors helps to prevent chronic gastrointestinal inflammation.[118] PUFA-derived mediators enhance the capacity of macrophages and DCs to promote the resolution of inflammation by inducing efficient phagocytosis of apoptotic granulocytes and debris, preventing further recruitment of neutrophils, inducing anergy or deletion of effector T lymphocytes, and promoting repair of local damage.[115] Treatment with resolvin E1 ameliorates pathology in two experimental murine models of colitis, illustrating the powerful effects of PUFA-derived mediators on resolving inflammation.[119, 120]

Macrophages and DCs additionally respond to resolving mediators by switching to unique "resolution phase" phenotypes. DCs generated in the presence of resolvin E1 demonstrate decreased expression of co-stimulation molecules, TNF-α, and IL-12, while inducing antigen-specific $CD4^+$ T lymphocyte apoptosis via IDO production and activation.[121] A defining distinction of resolution phase DCs from tolerogenic DCs is the continued expression of CCR5, which enhances chemotaxis toward inflammatory sites, without upregulation of CCR7, which induces chemotaxis to lymph nodes, on resolution phase DCs.[121] Similarly, resolution phase macrophages demonstrate a distinct phenotype from both M1 and M2 macrophages. Like M2 macrophages, resolution phase macrophages express high levels of molecules associated with the recognition and clearance of apoptotic cells, TGF-β, IL-10, and arginase 1.[122, 123] However, resolution phase macrophages also possess features of M1 macrophages, such as expression of iNOS, COX2, and CCR5.[122, 123] It is likely that local factors condition both macrophages and DCs to switch phenotypes and promote the resolution of inflammation, and that generation of these local factors or innate immune cell responses to these factors are defective in IBD.

Human IBD

In human IBD, inflammatory lesions demonstrate an increase in accumulation of macrophages that display enhanced expression of co-stimulatory molecules (CD80, CD86) and macrophage activating receptors (CD40),[124] TLRs,[125] triggering receptor expressed on myeloid cells-1 (TREM-1),[101, 102] and CD14.[103, 126] Likewise, there are higher frequencies of LPDCs positive for markers of mature DCs (CD83, S-100, CD40)[127-130] and for PRRs (CD209, TLR2/4) found in patients with IBD.[128, 129]Interestingly, IECs from patients with CD secreted less TSLP, suggesting that the conditioning factors produced by IECs and stromal cells in the intestine that are necessary for inducing homeostatic LPDCs are deficient in IBDs.[72] Indeed, LPDCs from IBD patients also produce significantly more pro-inflammatory cytokines (IL-12, IL-6, IL-8, TNF-α) compared to those from healthy controls.[129, 130] Furthermore, there is an increase in frequency of LP pDC from IBD patients.[131] However, stimulated peripheral blood pDC from IBD patients secrete significantly less IFN-α compared to those from healthy controls, suggesting that a decrease in functional tolerogenic pDC in IBD patients contributes to disease pathogenesis.[131, 132]

There is accumulating evidence that inappropriate macrophage and DC responses to the enteric microbiota contribute to human IBD pathogenesis.[8] These include both inadequate

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protective and enhanced pathogenic responses to such stimuli. Macrophages isolated from both CD and UC patients demonstrate altered cytokine production in response to bacterial challenge: CD macrophages produce more pro-inflammatory IL-23 but less of the protective cytokine IL-10, whereas UC macrophages constitutively produce high levels of the pro-inflammatory cytokine IL-12.[133] This may be in part due to impaired regulation of TLR-induced inflammatory responses in macrophages. For instance, patients with IBD demonstrate significantly decreased expression of intestinal NFIL3, an IL-10- and microbiota-induced transcriptional repressor of IL-12p40 expression, compared to tissue from healthy, non-inflamed control patients.[98] Additionally, increased numbers of TREM-1-expressing LP macrophages are found in intestinal tissue from patients with IBD compared to tissue from control patients.[102] TREM-1 critically amplifies TLR-induced inflammatory responses of macrophages and is implicated in IBD pathogenesis. Conversely, LP macrophages from IBD patients produce less of the cytokine G-CSF, which is protective in experimental models of colitis, in response to the probiotic *Lactobacillus rhamnosus* GR-1 compared to those from healthy controls.[134]

There has long been evidence that patients with IBD demonstrate impaired ability to eradicate bacteria,[135] and antibiotic therapy in certain clinical situations is efficacious for the induction and maintenance of remission in IBD.[136, 137] The human IBD susceptibility polymorphisms associated with *NOD2* and *ATG16L1* encode proteins involved in the autophagy pathway and lead to defective bacterial clearance.[138] Macrophages isolated from patients with CD demonstrate decreased reactive oxygen species (ROS) production and impaired eradication of bacteria.[139, 140] Additionally, peripheral blood monocytes isolated from patients with both CD and UC demonstrate decreased phagocytosis and killing of bacteria.[141] Perhaps the most compelling evidence of the link between bacterial persistence and IBD is the long list of primary immunodeficiencies, such as chronic granulomatous disease (CGD), associated with IBD-like clinical manifestations.[142-146] Approximately 50% of patients with CGD, in which phagocyte ROS production and bacterial clearance are greatly impaired, develop IBD-like manifestations that share clinical and pathological features of CD.[142] Bacterial persistence and chronic stimulation of macrophages and DCs may contribute to IBD development by producing increased pro-inflammatory cytokines that shape pathogenic adaptive immune responses.

Conclusions

Innate immune cells are central to the pathogenesis of IBD, as susceptibility loci have been identified in genes encoding for innate immune cell functions.[9] We are beginning to understand how macrophages and DCs maintain homeostasis in the gastrointestinal tract, a uniquely tolerant environment. Homeostasis requires an active process, and disruption of this balance contributes to chronic inflammation and IBD development. Defects in how macrophages and DCs respond to enteric antigens, eradicate bacteria, and induce resolution of inflammation underlie IBD pathogenesis (See Figure 1 for summary of pathways and phenotypes). By understanding these pathways, we will be able to exploit them for the development of novel and more effective therapies.

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Abbreviations

APC	antigen presenting cell
CARD	caspase recruitment domain
CD	Crohn's disease
cDC	conventional dendritic cell
CLR	C-type lectin receptor
DC	dendritic cell
DSS	dextran sulfate sodium
Flt3	Fms-like tyrosine kinase 3
Flt3L	Flt3 ligand
GALT	gut-associated lymphoid tissue
GM-CSF	granulocyte-macrophage colony stimulating factor
IBD	inflammatory bowel disease
IDO	indoleamine 2,3-dioxygenase
IEC	intestinal epithelial cell
Ig	immunoglobulin
IRF	interferon regulatory factor
ITIM	immunoreceptor tyrosine-based inhibition motif
LP	lamina propria
LPDC	lamina propria dendritic cell
LPMC	lamina propria mononuclear cell
LRR	leucine-rich repeat
MAPK	mitogen-activated protein kinase
MLN	mesenteric lymph node
MyD88	myeloid differentiation primary response gene 88
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NFIL3	nuclear factor, interleukin 3 regulated

NLR	nucleotide-binding oligomerization domain, leucine-rich repeat receptor
PAMP	pathogen-associated molecular pattern
pDC	plasmacytoid dendritic cell
PI3K	phosphoinositide 3-kinase
PIR-B	paired immunoglobulin-like receptor B
PRR	pattern recognition receptor
RA	retinoic acid
RALDH	retinaldehyde dehydrogenase
RLR	RIG-I-like receptor
ROS	reactive oxygen species
SNP	single nucleotide polymorphism
TAK1	TGF-β-activated kinase 1
Th	T helper cell
TIR	toll/interleukin 1 receptor
TLR	toll-like receptor
Treg	regulatory T cell
TREM-1	triggering receptor expressed on myeloid cells-1
TRIF	TIR-domain-containing adapter-inducing interferon-β
TSLP	thymic stromal lymphopoietin
UC	ulcerative colitis

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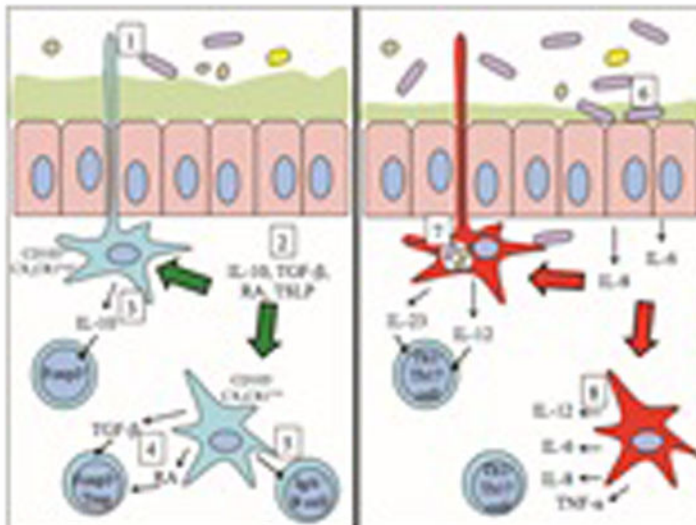

Figure 1.
LPMCs affect intestinal homeostasis in health and disease. LPMCs participate in maintaining intestinal homeostasis and in initiating disease when homeostasis is perturbed. (1) CD103–CX3CR1high LPMCs extend dendrites across the IEC barrier to sample luminal bacteria and antigens. (2) IECs and stromal cells produce local factors that condition LPMCs to be tolerant. (3) LP macrophages constitutively produce high levels of IL-10, which is necessary for the maintenance of Foxp3 expression in LP Tregs. (4) CD103+CX3CR1low LPDCs produce TGF-β and RA to induce Treg cells and imprint gut-homing receptors in adaptive immune cells. (5) CD103+CX3CR1low LPDCs induce IgA class switching in B cells. IgA is important in controlling the growth and composition of the enteric microbiota. (6) During perturbation of intestinal homeostasis, the enteric microbiota demonstrates dysbiosis. Additionally, the mucous layer just superficial to the IEC layer can break down, exposing IECs to the microbiota and inducing IECs to produce inflammatory cytokines. (7) Defects in intracellular bacterial clearance leads to persistent stimulation of LPMCs and induction of proinflammatory cytokines. IL-12 and IL-23 support the maintenance and differentiation of Th1 and Th17 cells, respectively. (8) CD103+CX3CR1low cells become inflammatory, producing increased amounts of IL-12, IL-6, IL-8, and TNF-α, supporting the differentiation of pathogenic T cells and the recruitment of inflammatory cells to the intestines.

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