TOPIC HIGHLIGHT

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Intestinal antigen-presenting cells in mucosal immune homeostasis: Crosstalk between dendritic cells, macrophages and B-cells

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Abstract

The intestinal immune system maintains a delicate balance between immunogenicity against invading pathogens and tolerance of the commensal microbiota. Inflammatory bowel disease (IBD) involves a breakdown in tolerance towards the microbiota. Dendritic cells (DC), macrophages (MΦ) and B-cells are known as professional antigen-presenting cells (APC) due to their specialization in presenting processed antigen to T-cells, and in turn shaping types of T-cell responses generated. Intestinal DC are migratory cells, unique in their ability to generate primary T-cell responses in mesenteric lymph nodes or Peyer's patches, whilst MΦ and B-cells contribute to polarization and differentiation of secondary T-cell responses in the gut lamina propria. The antigen-sampling function of gut DC and MΦ enables them to sample bacterial antigens from the gut lumen to determine types of T-cell responses generated. The primary function of intestinal B-cells involves their secretion of large amounts of immunoglobulin A, which in turn contributes to epithelial barrier function and limits immune responses towards to microbiota.

Here, we review the role of all three types of APC in intestinal immunity, both in the steady state and in inflammation, and how these cells interact with one another, as well as with the intestinal microenvironment, to shape mucosal immune responses. We describe mechanisms of maintaining intestinal immune tolerance in the steady state but also inappropriate responses of APC to components of the gut microbiota that contribute to pathology in IBD.

Core tip: The intestinal immune-system maintains a delicate balance between immunogenicity against invading pathogens and tolerance of the commensal microbiota. Inflammatory bowel disease involves a breakdown in tolerance towards the microbiota. Dendritic cells, macrophages and B-cells are known as professional antigen-presenting cells (APC) due to their specialization in presenting processed antigen to T-cells, and in turn shaping types of T-cell responses generated. Here, we present an updated knowledge toward the role of these APC in intestinal immunity, both in the steady state and in inflammation, and how they interact with one another and with the intestinal microenvironment to shape mucosal immune responses.

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INTRODUCTION

Dendritic cells (DC), macrophages (MΦ) and B-cells comprise heterogenous populations of cells, known as "professional antigen-presenting cells (APC)" due to their specialization in antigen presentation. APC are critical for initiating, maintaining and shaping T-cell mediated immune responses. DC are unique in their ability to drive primary T-cell responses (reviewed in[1,2]), but MΦ and B-cells can polarize effector T-cell responses[3-5]. All three types of APC also have other critical roles in both innate and adaptive immunity; at intestinal sites, a combination of these functions and crosstalk between APCs enable them to be critical for maintenance of immune homeostasis in the gut.

The gastrointestinal tract is in contact with a huge amount of antigens, including a diverse commensal microbiota, food antigens and also potentially pathogenic microbes. As effector cells of both innate and adaptive immune responses, DC, MΦ and B-cells are central to not only maintaining protective immunity against pathogens but also preventing inflammatory intestinal immune responses against the microbiota and food antigens (tolerance). The microbiota is recognized by pattern recognition receptors (PRRs) on all three types of APC, including Toll-like receptors (TLRs; reviewed in[6]). Similar effector functions to those involved in protective immunity against pathogens are engaged during inappropriate inflammatory responses against harmless antigens, such as those seen in inflammatory bowel disease (IBD). IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is thought to result from a dysregulated intestinal immune response to the gut microbiota[7] resulting in a breakdown in mucosal tolerance. Given the huge antigenic load in the normal healthy intestine, APC in the steady state maintain a tolerogenic or hyporesponsive state, giving these cells crucial roles in maintaining mucosal homeostasis. In this review, we discuss the different roles of the three "professional" APC: DC, MΦ and B-cells, in intestinal immune tolerance and inflammation, and how these APC interact with one other to shape their function and contribution to mucosal immune homeostasis.

ANTIGEN PRESENTING CELLS AND INTESTINAL HOMEOSTASIS

Dendritic cells

DC stimulate primary T-cell responses and determine whether these T-cell responses generated are immunogenic (*e.g.*, against invading pathogens) or tolerogenic (*e.g.*, against commensal bacterial antigens)[1,2]. The primary function of intestinal DC is to transport antigens into secondary lymphoid tissue [mesenteric lymph nodes (MLN) and Peyer's patches (PP)] and subsequently generate antigen-specific intestinal T-cell responses. Intestinal DC from the gut lamina propria (LP) transport intestinal bacterial antigens into MLN[8,9] and are essential for inducing oral tolerance to food antigens[10].

Intestinal DC in the steady state are generally hyporesponsive[11] and maintain immune tolerance in the gut by generation of tolerogenic T-cell responses[12,13] towards food antigens and commensal bacteria, preventing unnecessary inflammation and hypersensitivity. Although distinguishing DC from MΦ in the gut can be difficult, intestinal DC in mice can be identified as CD11c^{hi}MHC Class II$^+$CX3CR1$^-$F4/80$^-$ cells and further subdivided into DC subsets expressing combinations of CD11b, CD103 and CD8α[14]. Although previous studies suggested a subset of DC exist expressing CX3CR1, the receptor for the chemokine fractalkine, mononuclear phagocytes in the gut mucosa expressing CX3CR1 also express the pan-MΦ marker F4/80 and tissue macrophage marker CD68[15]. Subsequent studies confirmed that all CX3CR1^{hi} cells in the gut are indeed MΦ[16]. DC can also be distinguished from MΦ in both mice and humans on the basis of CD64 expression, with DC being CD64$^-$[17].

Several intestinal DC subsets contribute to regulatory T-cell (T-reg) generation in mice These include CD8α$^+$ DC that promote T-reg generation in the presence of transforming growth factor (TGF)-β[18,19], and CD103$^+$ DC. CD103 (α$_E$ integrin) is expressed by the majority of DC in the murine intestinal LP[20]; these DC are migratory and travel to the MLN *via* the afferent lymph[21-23]. In the steady state, this constitutive migration of CD103$^+$ DC from the LP to the MLN establishes T-cell responses specific for harmless luminal antigens, and is essential for the establishment of oral tolerance[10,13,21,24]. The ability of CD103$^+$ DC to synthesize retinoic acid (RA)[25,26], which enhances generation of gut-homing T-reg at the expense of Th17 cells[25-28], is one of the key mechanisms by which CD103$^+$ DC participate in immune tolerance in the gut. Human studies indicate DC from MLN maintain some of the unique tolerogenic properties of murine intestinal CD103$^+$ DC[21,29]. Furthermore, CD103$^+$ DC from the LP in both mice and humans express indoleamine 2,3-dioxygenase (IDO), an enzyme involved in the ability to drive T-reg development, is required for the establishment of immune tolerance in the gut[30]. Plasmacytoid DC (pDC) are also key participants in oral tolerance[31] likely to be due to their expression of IDO.

Intestinal CD103$^+$ DC can be subdivided into two major subsets; CD103$^+$CD11b$^+$ and CD103$^+$CD11b$^-$ DC[32]. CD103$^+$CD11b$^+$ DC stimulate Th17 and Th1 cell differentiation[33,34], whilst CD103$^+$CD11b$^-$ DC can drive Th1 polarisation and IFNγ-production from CD8$^+$ T-cells[34,35]. However, other studies have shown both CD103$^+$ subsets can generate T-reg responses[36]. Interpretation of the regulatory function of these intestinal subsets is further complicated by the fact that mice lacking either CD103$^+$CD11b$^{+[33,37]}$ or CD103$^+$CD11b$^-$ DC[38] have normal numbers of intestinal FoxP3$^+$ T-reg. CD103$^-$CD11b$^+$ intestinal DC are also potent inducers of both Th17 and Th1 responses, even in the absence of overt stimulation[35], and a subsequent study using comparative analysis of transcriptomes determined that CD103$^+$Sirpα$^-$ DC in the human gut are related to murine

CD103$^+$CD11b$^-$ DC (and human blood CD141$^+$ DC), whilst human intestinal CD103$^+$Sirpα$^+$ DC were related to murine CD103$^+$CD11b$^+$ DC (and human blood CD1c$^+$ DC). In this study, both these human intestinal DC subsets were able to induce Th17 cells, with only CD103$^+$Sirpα$^+$ supporting induction of T-reg[39].

MΦ

Intestinal MΦ have various innate functions that enable them to contribute to both immune tolerance *via* selective inertia and contribute to protective immune responses and inflammation in other circumstances[15]. Tissue MΦ do not usually migrate to lymphoid tissue, but can contribute to adaptive immune responses by presenting processed antigen to effector T-cells *in situ* in the LP[3,4]. Although intestinal MΦ share expression of MHC Class II, CD11c and CD11b with DC, F4/80, CD68 and CD64 can be used to identify MΦ in the gut. It has also now evident that all CX3CR1^{hi} mononuclear phagocytes are MΦ[16], although a subset of inflammatory, migratory CD103$^-$ DC expressing intermediate levels of CX3CR1 has recently been identified[23].

Resident intestinal MΦ express low levels of co-stimulatory molecules including CD80, CD86 and CD40[34-38], and like intestinal DC, are hyporesponsive to stimulation by TLR ligands[12,35,39,40] in the steady state. MΦ in the gut also contribute to maintaining intestinal immune tolerance by constitutively producing the anti-inflammatory cytokine interleukin (IL)-10[39,40]. Perhaps the most striking role for intestinal MΦ in maintaining mucosal homeostasis is their role in generation and maintaining survival of T-regs. F4/80 knockout (KO) mice do not develop tolerance or antigen-specific CD8$^+$ T-regs normally after being fed soluble antigen[41]. MΦ secretion of IL-10 plays a key role in maintaining FoxP3 expression on T-regs under inflammatory conditions, essential for maintaining regulatory activity and suppressing colitis[42]. Furthermore, tolerance induction following feeding with protein antigens in mice was associated with expansion and differentiation of FoxP3$^+$ T-reg by IL-10-producing CX3CR1$^+$ MΦ in the mucosal LP[4].

Intestinal CX3CR1$^+$ MΦ have recently been subcharacterised; CX3CR1^{hi} MΦ in the steady state represent regulatory MΦ that are resistant to TLR stimulation and produce IL-10 constitutively, whilst a smaller population of cells expressing intermediate levels of CX3CR1 represent cells partially differentiated from Ly6C$^+$CCR2$^+$ monocytes into regulatory CX3CR1^{hi} MΦ. These CX3CR1^{int} cells represent TLR-responsive, pro-inflammatory MΦ that accumulate during experimental colitis due to arrested differentiation[16]. This study demonstrated that both resident regulatory MΦ and inflammatory MΦ at intestinal sites are both derived from the same (Ly6C$^+$CCR2$^+$) precursor, but are at different phases of differentiation.

B-cells

The role of B-cells in intestinal inflammation and immune homeostasis have been underappreciated. B-cells perform several immunological functions; arguably their main function is antibody production, but B-cells also function as APC and secrete cytokines. At intestinal sites, B-cells follow a distinct differentiation pathway and are specialized in IgA production as differentiated plasma cells[43]. Most intestinal plasma cells secrete IgA[5]; in the gut lumen, secretory IgA (sIgA) acts as a barrier to protect the epithelium from pathogens. Within the gut lumen, sIgA interacts with intestinal antigens including the intestinal microbiota, food antigens and self antigens[44]. In such a manner, sIgA limits access of intestinal antigens into the bloodstream, and is able to control the intestinal microbiota[5]. The sIgA system in the gut is tightly integrated with both innate and adaptive immune mechanisms, contributing towards intestinal immune homeostasis. For example, sIgA can limit innate responses against commensal bacteria[45] whilst also functioning to influence adaptive T-cell responses[46]. Several regulatory compounds involved in intestinal tolerance also promote IgA secretion, including IL-10, TGFβ and RA[43].

The antigen-presenting function of B-cells enables them to interact with T-cells directly to polarize effector T-cell responses[47] (although they are not capable of inducing primary responses). Several disease models demonstrate that IL-10 produced by B-cells is important for the generation of mucosal T-regs[48-51]. However, IL-10 produced by DC and MΦ is also important in T-reg generation[42,52], and alone is not sufficient to induce T-regs directly; cognate T-cell/B-cell interactions are also required, mediated by co-stimulatory molecules CD80 and CD86[53,54].

IL-10-producing B-cells with suppressive capacity are known as regulatory B-cells (B-reg) and can suppress experimental colitis[55-57]. A subset of B-reg can also produce regulatory cytokine TGFβ in response to antigenic stimulation[58-60], demonstrating an important role for B-cells in avoiding inappropriate responses to the intestinal microbiota and food proteins. Indeed, functional impairment of this subset of TGFβ-producing B-cells is associated with food allergy pathogenesis[58-60]. It has recently been demonstrated that a subpopulation of B-cells carries the integrin α$_v$β$_6$ (not endogenously expressed) which is able to convert latent TGFβ into its active form. These cells also expressed CX3CR1, had high levels of TGFβ, generated T-regs, suppressed T-cell activation and inhibited food allergy symptoms[61]. This study suggests CX3CR1$^+$ B-cells carrying α$_v$β$_6$ may represent the TGF-β producing B-regs described in the studies above.

INAPPROPRIATE ANTIGEN-PRESENTING CELL RESPONSES TO MICROBIOTA AND INFLAMMATION

Despite playing essential roles in intestinal immune tolerance, APC are likely to be of fundamental importance in the pathogenesis of T-cell mediated inflammation in the

gut; all APC can influence T-cell responses directly and can secrete both pro- and anti-inflammatory cytokines. IBD is thought to result from a dysregulated immune response and breakdown of tolerance to the gut microbiota[7,62,63]. The intestinal microbiota is essential for development of colonic inflammation in most murine models of colitis[64], although in the steady state the gut microbiota functions to reduce bacterial trafficking to MLN by mononuclear phagocytes to downregulate inflammatory responses and autoimmunity[65]. Analysis of the intestinal microbiota of IBD patients demonstrates decreased biodiversity, with decreased proportions of Firmicutes but increased proportions of Gammaproteobacteria[66]. It is currently unclear whether intestinal dysbiosis in IBD patients contributes to or is a consequence of inflammation but the interplay between the host and the microbiota actively shapes intestinal homeostasis and contributes to IBD pathology. This provides a role for all APC in IBD pathogenesis due to their bacterial recognition properties *via* PRR expression. The ability of DC and MΦ to sample antigens from the gut lumen, and ability of B-cells to produce sIgA that modify immune responses to luminal antigens suggests APC play important roles in dysregulated immunity in IBD. Expression of TLRs on DC[67,68], MΦ[69-71] and B-cells[72] are upregulated in animal models of colitis and human IBD, potentially contributing to enhanced or inappropriate responses to luminal bacterial antigens.

Intestinal dendritic cells in gut inflammation

As the only cells capable of driving primary T-cell responses[73], intestinal DC would be expected to play an important role in T-cell dominated inflammatory diseases at intestinal sites, such as IBD. For example, animal models of colitis provide strong evidence that interactions between the intestinal microbiota and intestinal DC are essential for IBD pathogenesis[63,74]. Activated DC accumulate throughout the LP and MLN in colitis[75-77]; intestinal DC present during inflammation may be derived from newly recruited precursors[78], although it is likely that tissue-resident *in situ* DC can also generate inflammatory responses. Therefore, intestinal DC are likely to play both protective and pathogenic roles in intestinal immunity, fitting with their functional plasticity in their ability to generate either inflammatory or tolerogenic immune responses. In murine DSS-induced colitis, DC ablation during DSS administration ameliorated disease manifestation, but colitis was exacerbated if DC were ablated before DSS treatment[79]. In a T-cell transfer model of colitis induced by CD45RB^{hi}CD4^{+} T-cells, transplanted T-cells formed aggregates with subepithelial CD11c^{+} DC in the MLN[80]. Furthermore, colitis was associated with increased CD11c^{+} DC in MLN, and blocking OX40-OX40L interactions between DC and T-cells prevented the development of colitis[81]. In human IBD activated DC also accumulate at sites of intestinal inflammation[82-84]. Some human studies have shown an increase in number and maturation of DC within inflamed IBD tissue[85], but others suggest enhanced recruitment of immature DC into inflamed tissue associated with increased expression of chemokine CCL20 in the intestinal epithelium[86]. CCL20 may therefore regulate attraction of DC (and T-cells) in IBD.

The specific microenvironment of the gut, including microbes, various types of intestinal cells such as epithelial cells, and active cellular mediators can dynamically shape the properties and functions of DC. For example, human blood DC express both skin and gut homing markers; however, they lost homing marker expression when cultured *in vitro*. Conditioning of human enriched blood DC with colonic biopsy extract induced a gut-homing phenotype and a homeostatic profile, mediated by retinoid acid and TGFβ, respectively[87]. In UC patients, circulating DC displayed a reduced stimulatory capacity for T cells and enhanced expression of skin-homing markers CLA and CCR4 on stimulated T cells that were negative for gut-homing marker β7; and this dysregulation of DC could be partially restored by probiotic bacterial strain *Lactobacillus casei* Shirota[88].

Bacterial recognition by dendritic cells and gut-homing

An important function of DC is their ability to imprint homing properties on T-cells and B-cells, in order to localize immune responses to a particular tissue[89-92]. Murine intestinal DC specifically imprint gut-homing molecules $\alpha_4\beta_7$ and CCR9 on T-cells and B-cells from different sources, thus targeting lymphocytes to intestinal tissue[89-91]; this gut-specific imprinting property of DC is confined to the CD103^{+} "tolerogenic" intestinal DC subset. T-cells imprinted with gut-homing capacities in such a manner are T-regs, linking gut-homing with intestinal immune tolerance. Furthermore, CD103^{+} DC induce B-cell class switching to IgA-producing cells with known tolerogenic properties, alongside imprinting gut-homing properties[20,93,94]. These functional properties of CD103^{+} DC are dependent on RA and TGFβ[39,95,96]. A loss of CD103^{+} DC from inflamed murine intestine has been reported[97,98], suggesting the increased DC infiltrates in colitis/IBD represent alternative inflammatory DC subsets. Further evidence to link gut-homing and intestinal immune tolerance was provided by studies showing that expression of gut-homing markers $\alpha_4\beta_7$ and CCR9 on T-cells is essential for induction of oral immune tolerance in mice[99]. Both CCR9 and $\alpha_4\beta_7$ expression on DC also confer tolerogenic properties[98,100,101], and a loss of $\alpha_4\beta_7^+$ DC impairs induction of IL-10-producing T-regs and accelerates T-cell mediated colitis[98].

MyD88 is an essential intracellular signaling adapter for most TLR signals[102], which are induced in APC following bacterial recognition. MyD88-dependent TLR signaling in DC specifically enables them to imprint gut-specific homing properties *via* an increased RA synthesizing capacity[103]. In this study, TLR stimulation was sufficient to educate extraintestinal DC with gut-homing imprinting capacity providing a crucial role for the microbiota in shaping gut DC function in intestinal homeostasis. Although it is unclear whether the intestinal dysbiosis in

IBD patients is a cause or a result of intestinal inflammation[66], it is likely that such alterations in bacterial populations will have knock on effects on gut DC function in tolerance and immunity, perhaps disrupting the delicate balance that is maintained in the healthy gut and further contributing to pathology.

Intestinal macrophages and B-cells in inflammation

Intestinal MΦ and B-cells can contribute to adaptive immune responses by presenting processed antigen to effector T-cells *in situ* in the LP[3,4,47], and polarizing effector T-cell responses, thereby providing a role for MΦ and B-cells in IBD pathogenesis. Properties of intestinal MΦ are strikingly different in inflammation compared with the steady state. Under inflammatory conditions, MΦ infiltration into intestinal sites of inflammation occurs; these MΦ express high levels of TLRs, co-stimulatory and inflammatory receptors[35,37,69,104], and produce large quantities of pro-inflammatory cytokines and mediators[104-108]. Inflammatory MΦ in the murine intestine are derived from Ly6C$^+$ monocytes; CCR2 is essential for recruitment of these Ly6C$^+$ monocytes to sites of inflammation and in an inflammatory context, these monocytes upregulate expression of TLR2 and NOD2, suggesting an enhanced responses to the microbiota and bacterial products[70]. Although this study actually suggests these inflammatory monocyte precursors develop into CX3CR1$^+$ regulatory DC, concurrent studies have shown Ly6C$^+$CCR2$^+$ monocytes differentiate into regulatory CX3CR1^{hi} MΦ but that in colitis, there is accumulation of inflammatory Ly6C$^+$CX3CR1$^+$, TLR-responsive, pro-inflammatory semi-mature MΦ arising from arrested differentiation[16]. The upregulated expression of TLRs on both inflammatory monocytes and macrophages during intestinal inflammation strongly suggests interactions of these cells with the microbiota and bacterial products play a key role in IBD.

B-cells can also present antigen to effector T-cells in the LP, but their unique antibody-secreting function enables B-cells to directly control the intestinal microbiota *via* sIgA[5]. Due to the regulatory function of IgA in contributing to maintenance of epithelial barrier function[109,110], aberrations in the mucosal IgA system are likely to be part of IBD pathogenesis. However, IgA has been reported to play a pathogenic role in the pathogenesis of other gut-based inflammatory disorders, including Coeliac disease[111]. Although production of sIgA directly links B-cells to immune regulation and homeostasis, their role in IBD is unclear due to their other cytokine- and chemokine-producing functions. Intestinal B-cells in IBD are increased[112] and highly activated, producing chemokines including Eotaxin-1, leading to acute eosinophilia[113]. Furthermore, a loss of anti-inflammatory IL-10 production by B-cells in IBD has been reported[114] alongside unusual B-cell morphology[115], changes in DNA methylation[116] and other B-cell gene alterations[117]. However, the role of B-cell in IBD pathogenesis is unclear and warrants further investigation.

ANTIGEN-PRESENTING CELL CROSSTALK

As established, DC, MΦ and B-cells have critical roles both in maintaining mucosal immune tolerance to the gut microbiota and food antigens, but also in driving inflammatory responses that can be protective in healthy individuals, but detrimental in IBD. Although each type of APC exhibits unique functions allowing them to participate in gut immunity, with knock on effects on adaptive T-cell responses, APC can also interact with one another to directly shape immune responses generated. DC in particular are at the centre of virtually all multi-cellular signalling networks underlying intestinal immune homeostasis[118].

Activation of intestinal B-cells by dendritic cells and macrophages

The interplay between innate immunity and B-cells at the intestinal mucosal interface play a key role in maintaining mucosal immune homeostasis[119]. Although DC are usually described for their ability to prime T-cell responses, DC can also directly activate B-cells[120,121], present unprocessed antigens to B-cells[122,123] and influence the differentiation and survival of antibody-secreting cells[124]. Intestinal DC release powerful B-cell stimulating factors including BAFF and APRIL[125,126]; pDC in particular induce IgA production by B-cells in the gut, independently of T-cells, in this manner. In the steady state, this process is dependent on stromal cell-derived type I IFN signalling[127]. Macrophages also release BAFF at levels sufficient to potently induce B-cell proliferation[128]. BAFF and APRIL promote survival of B-cells and plasma cells but also activate IgA production[129-134]. Intestinal DC and MΦ also produce IgA-inducing cytokines including IL-10 and TGFβ[39,118,135]. Some intestinal DC can also produce IL-6, which is a cytokine implicated in the differentiation of IgA class-switched B-cells into IgA class-switched plasma cells[124,136]. Alongside directly shaping B-cell responses, gut DC induce expression of gut-homing receptors CCR9 and α$_4$β$_7$ by B-cells[94].

RA is essential for induction of gut-homing receptors on B-cells[94], as is the case for T-cells[137]. The IgA promoting effects of gut DC is at least partially dependent on RA and TGFβ[94,138,139] and intestinal MΦ also secrete RA/TGFβ[39]. A key question that remains unanswered is whether intestinal MΦ can also imprint tissue homing properties on B-cells and directly promote IgA class switching, properties that are both dependent on the presence of RA. Secretion of RA by intestinal DC and MΦ is dependent upon their expression of retinal dehydrogenases, which are critical for RA synthesis[25,137-139]. The expression of these enzymes by intestinal DC is restricted to CD103$^+$ DC[25,140], and CD103$^+$ intestinal DC do indeed promote IgA synthesis by gut-homing B-cells[138]. Studies have since demonstrated that follicular DC also promote IgA generation in the gut in response to bacterial stimuli, and express key factors for B-cell mi-

Table 1 Summary of information available regarding classification of gut antigen-presenting cells, primary functions of gut antigen-presenting cells and their effects on T-cells, tolerogenic and inflammatory properties of antigen-presenting cells at intestinal sites, and effects of immunomodulation of gut antigen-presenting cells by the microbiota

Classification	Dendritic cells	Macrophages	B-cells
	Mice: CD11c^{hi} MHC Class Ⅱ^{+} CX3CR1[-/med] F4/80^{-} CD64^{-}. Subsets based on CD11b, CD103 and CD8á expression	Mice: CD11c^{+} MHC Class Ⅱ^{+} F4/80^{+} CD68^{+} CD64^{+} CX3CR1^{hi}	CD19^{+} CD20^{+} CD79a^{+}
	Humans: HLA-DR^{+} Lineage cocktail (CD3/CD14/CD16/CD19/CD34)[-]. Subsets based on CD103, CD11c, CD1c, CD141 and CD123 expression	Subsets based on levels of expression of CX3CR1. Ly6C^{+} in inflammation	Immature B-cells: [+]CD20
		Humans: HLA-DR^{+} CD11c^{+} CD64^{+} CD68^{+} Some CX3CR1 expression	Plasma (antibody secreting) cells: CD38^{+}CD138^{+}
Primary function	Antigen sampling	Antigen sampling	Antibody secretion as differentiated plasma cells (mainly IgA in the gut)
	Migration to secondary lymphoid tissue and stimulation of naïve T-cells to generate primary T-cell responses	Phagocytosis of apoptotic cells, bactericidal activity, production of anti-inflammatory IL-10	
Effects on T-cells	Determine whether primary T-cell responses are immunogenic or tolerogenic, imprint gut-homing receptors on T-cells during stimulation	Contribute to effector T-cell responses *in situ* in the lamina propria, including expansion and differentiation of T-regs *via* IL-10 production	Contribute to effector T-cell responses *in situ* in lamina propria and also induce differentiation of T-regs *via* both IL-10 production and direct interaction
Tolerogenic properties/ subsets	CD103^{+} CD11b^{-} DC generate RA for T-regs/IgA secretion by B-cells, and imprinting gut-homing properties on lymphocytes. CD8á^{+} DC and pDC generate T-reg	CX3CR1[hi] MΦ produce IL-10 critical for T-reg generation	IgA production limits immune responses against commensal bacteria
	Gut DC in general are hyporesponsive to TLR stimulation	Hyporesponsive to TLR stimulation	Regulatory B-cells produce IL-10, induce differentiation of T-regs and also produce TGFβ
Inflammatory properties/ subsets	TLR[hi] gut DC in IBD likely to contribute to enhanced inappropriate responses to the microbiota	TLR[hi] MΦ in colitis and IBD also likely to contribute to enhanced inappropriate responses to the microbiota	TLR^{hi} B-cells enhanced in IBD
	Infiltrates of CD103^{-} DC in inflammation		Eotaxin-1 producing B-cells enhanced in IBD
	CD103^{+}CD11b^{+} can polarise inflammatory Th17 responses	Ly6C^{+}CX3CR1^{+} inflammatory macrophages arise from arrested differentiation in colitis	CD15^{+} B-cells with functional surface IgM enhanced in IBD
Modulation by gut microbiota	Direct modulation by microbiota	Direct modulation by microbiota	Indirect modulation by microbiota
	Commensal bacteria can induce iNOS[+]TNF[+] DC that promote IgA responses	CX3CR1[+] MΦ directly sample luminal antigens; this process is dependent on the microbiota	DC and MΦ sampling commensal bacteria induce IgA production by B-cells *via* BAFF and APRIL release, and production of IgA-inducing cytokines IL-10 and TGFβ
	Commensal bacteria induce regulatory cytokine production by DC, such as IL-10 and TGFβ, and also regulatory mediator RA		

TGFβ: Transforming growth factor beta; TNF: Tumor necrosis factor; DC: Dendritic cells; MΦ: Macrophages; IL-10: Interleukin 10; T-reg: Regulatory T cells; TLR: Toll-like receptors; pDC: Plasmacytoid DC; RA: Retinoic acid; HLA: Human leukocyte antigen; IBD: Inflammatory bowel disease.

gration and survival. However, this process is dependent on the presence of exogenous RA[141].

Regulatory effects of DC/B-cell interactions are not restricted to induction of IgA production by B-cells; B-cell conversion into immunosuppressive B-cells (regulatory B-cells) is partially dependent on DC production of RA[142]. However the *in vivo* effects of intestinal DC and MΦ on conversion of gut-specific regulatory B-cells is unknown. Crosstalk between intestinal DC and B-cells can also lead to active immunity as well as regulatory immune responses; murine CD11b^{+} CD11c^{+} DC from the small intestine lamina propria express TLR5 and respond to flagellin from flagellated bacteria by inducing IgA^{+} plasma cells and antigen-specific Th17 and Th1 subsets to generate protective immunity[138]. Crosstalk between gut DC/MΦ is bidirectional; immunoglobulins secreted by B-cells can have a direct effects on DC differentiation and activation[143,144], though this process at intestinal sites has not been described in detail.

Role of the gut microbiota in antigen-presenting cell crosstalk

In response to pathogenic bacteria or the commensal microbiota, APC contribute to both innate and adaptive immune responses that can be either immunogenic or tolerogenic through TLR stimulation[11,145]. TLR-dependent activation of DC in particular can determine protection or immune tolerance that maintains immune homeostasis at intestinal sites[146,147]. Commensal bacteria can induce intestinal iNOS[+]/TNF[+] DC that, in the intestinal lamina propria, promote IgA responses by releasing BAFF and APRIL in response to nitric oxide[148]. These DC may also enhance IgA responses in Peyer's patches by upregulating expression of TGFβ receptor type Ⅱ on follicular B-cells[148]. IgA-inducing cytokines including IL-10 and TGFβ are secreted by DC and MΦ in response to microbial TLR ligands[118,136]. Gut DC also produce RA and IL-6 in response to microbial TLR ligands[94,136] which have direct effects on both B-cell secretion of IgA and imprinting gut-homing markers on B-cells[94], as mentioned above.

Non-migratory APC expressing CX3CR1, likely to be MΦ[15], continuously sample antigens by extending transepithelial projections without disrupting tight junctions[149]; CX3CR1[+] APC may be able to directly present commensal antigens to subepithelial B-cells[43,47]; Murine

intestinal APC initiate production of commensal reactive IgA by presenting commensal bacterial antigens to B-cells[9,150]. It is likely that CX3CR1^{+} APC transfer antigen to CD103^{+} migratory DC prior to DC migration to secondary lymphoid tissue to prime tolerogenic T-cell responses towards the microbiota[15]. Commensal bacteria play a critical role in antigen sampling by CX3CR1[+] APC as antibiotic treatment reduces the number of transepithelial projections[145,151]. However, it has recently been shown that CX3CR1^{hi} cells can migrate to MLN and traffic *Salmonella* antigen to induce T-cell responses and IgA production in the absence of MyD88 or following antibiotic treatment[65]. In this study, MyD88-dependent recognition of commensal bacteria in the gut reduced bacterial trafficking to MLN by CX3CR1[hi] APC to down regulate excess inflammation and autoimmunity.

A subset of intestinal pDC expressing TLR7 and TLR9 are capable of producing high levels of type I IFN[152] which in turn promotes not only maturation and differentiation of myeloid DC, but also class-switching of antibodies produced by B-cells[153] (Table 1).

CONCLUSION

DC, MΦ and B-cells are professional APC that are fundamental components of both the innate and adaptive immune system in the gut; their plasticity allows these cells to function in an environment where they are constantly exposed to the commensal microflora and food antigens, but can also be exposed to harmful pathogens. Intestinal APC are individually specialized to perform specific functions but their role in shaping both primary and secondary T-cell responses, including generation and differentiation of T-regs, highlights their importance in intestinal immune homeostasis and IBD pathogenesis. APC function in the gut is in turn directly shaped by the microbiota. Furthermore, crosstalk between APC is essential for intestinal immunity and tolerance. Clarification and a better understanding of the functions of intestinal APC subsets, especially in humans, may provide novel therapeutic targets for manipulating mucosal immunity and tolerance, leading to new and more effective treatment for IBD.

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