World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i29.9653

*World J Gastroenterol* 2014 August 7; 20(29): 9653-9664
ISSN 1007-9327 (print) ISSN 2219-2840 (online)


TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

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

Elizabeth R Mann, Xuhang Li

Elizabeth R Mann, Xuhang Li, Division of Gastroenterology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States
Author contributions: All the authors contributed equally to this manuscript.
Correspondence to: Xuhang Li, PhD, Division of Gastroenterology, Department of Medicine, The Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross Research Bldg Rm 746, Baltimore, MD 21205, United States. xuhang@jhmi.edu
Telephone: +1-443-2874804 Fax: +1-410-9559677
Received: October 19, 2013 Revised: February 26, 2014
Accepted: April 27, 2014
Published online: August 7, 2014

## 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.



**Key words:** Antigen presenting cells; Dendritic cells; Macrophages; B cells; Inflammatory bowel disease

**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.

Mann ER, Li X. Intestinal antigen-presenting cells in mucosal immune homeostasis: Crosstalk between dendritic cells, macrophages and B-cells. *World J Gastroenterol* 2014; 20(29): 9653-9664 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i29/9653.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i29.9653

## 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 ($\alpha_E$ 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 $\alpha_v\beta_6$ (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 $\alpha_v\beta_6$ 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 $\alpha_4\beta_7$ 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<br>Humans: HLA-DR$^{+}$ Lineage cocktail (CD3/CD14/CD16/CD19/CD34)$^{-}$. Subsets based on CD103, CD11c, CD1c, CD141 and CD123 expression | Mice: CD11c$^{+}$ MHC Class II$^{+}$ F4/80$^{+}$ CD68$^{+}$ CD64$^{+}$ CX3CR1$^{hi}$<br>Subsets based on levels of expression of CX3CR1. Ly6C$^{+}$ in inflammation<br>Humans: HLA-DR$^{+}$ CD11c$^{+}$ CD64$^{+}$ CD68$^{+}$<br>Some CX3CR1 expression | CD19$^{+}$ CD20$^{+}$ CD79a$^{+}$<br>Immature B-cells: $^{+}$CD20<br>Plasma (antibody secreting) cells: CD38$^{+}$CD138$^{+}$ |
| Primary function | Antigen sampling<br>Migration to secondary lymphoid tissue and stimulation of naïve T-cells to generate primary T-cell responses | Antigen sampling<br>Phagocytosis of apoptotic cells, bactericidal activity, production of anti-inflammatory IL-10 | Antibody secretion as differentiated plasma cells (mainly IgA in the gut) |
| 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<br>Gut DC in general are hyporesponsive to TLR stimulation | CX3CR1$^{hi}$ MΦ produce IL-10 critical for T-reg generation<br>Hyporesponsive to TLR stimulation | IgA production limits immune responses against commensal bacteria<br>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<br>Infiltrates of CD103$^{-}$ DC in inflammation<br>CD103$^{+}$CD11b$^{+}$ can polarise inflammatory Th17 responses | TLR$^{hi}$ MΦ in colitis and IBD also likely to contribute to enhanced inappropriate responses to the microbiota<br>Ly6C$^{+}$CX3CR1$^{+}$ inflammatory macrophages arise from arrested differentiation in colitis | TLR$^{hi}$ B-cells enhanced in IBD<br>Eotaxin-1 producing B-cells enhanced in IBD<br>CD15$^{+}$ B-cells with functional surface IgM enhanced in IBD |
| Modulation by gut microbiota | Direct modulation by microbiota<br>Commensal bacteria can induce iNOS$^{+}$TNF$^{+}$ DC that promote IgA responses<br>Commensal bacteria induce regulatory cytokine production by DC, such as IL-10 and TGFβ, and also regulatory mediator RA | Direct modulation by microbiota<br>CX3CR1$^{+}$ MΦ directly sample luminal antigens; this process is dependent on the microbiota | Indirect modulation by microbiota<br>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 |

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-specifc 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-specifc 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.

## REFERENCES


1 **Steinman RM**. Dendritic cells: understanding immunogenicity. *Eur J Immunol* 2007; **37** Suppl 1: S53-S60 [PMID: 17972346 DOI: 10.1002/eji.200737400]
2 **Steinman RM**. Decisions about dendritic cells: past, present, and future. *Annu Rev Immunol* 2012; **30**: 1-22 [PMID: 22136168 DOI: 10.1146/annurev-immunol-100311-102839]
3 **Platt AM**, Mowat AM. Mucosal macrophages and the regulation of immune responses in the intestine. *Immunol Lett* 2008; **119**: 22-31 [PMID: 18601952 DOI: 10.1016/j.imlet.2008.05.009]
4 **Hadis U**, Wahl B, Schulz O, Hardtke-Wolenski M, Schippers A, Wagner N, Müller W, Sparwasser T, Förster R, Pabst O. Intestinal tolerance requires gut homing and expansion of FoxP3+ regulatory T cells in the lamina propria. *Immunity* 2011; **34**: 237-246 [PMID: 21333554 DOI: 10.1016/j.immuni.2011.01.016]
5 **Pabst O**. New concepts in the generation and functions of IgA. *Nat Rev Immunol* 2012; **12**: 821-832 [PMID: 23103985 DOI: 10.1038/nri3322]
6 **Stagg AJ**, Hart AL, Knight SC, Kamm MA. The dendritic cell: its role in intestinal inflammation and relationship with gut bacteria. *Gut* 2003; **52**: 1522-1529 [PMID: 12970149 DOI: 10.1136/gut.52.10.1522]
7 **Strober W**, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. *J Clin Invest* 2007; **117**: 514-521 [PMID: 17332878 DOI: 10.1172/JCI30587]
8 **Voedisch S**, Koenecke C, David S, Herbrand H, Förster R, Rhen M, Pabst O. Mesenteric lymph nodes confine dendritic cell-mediated dissemination of Salmonella enterica serovar Typhimurium and limit systemic disease in mice. *Infect Immun* 2009; **77**: 3170-3180 [PMID: 19506012 DOI: 10.1128/IAI.00272-09]
9 **Macpherson AJ**, Uhr T. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science* 2004; **303**: 1662-1665 [PMID: 15016999 DOI: 10.1126/science.1091334]
10 **Worbs T**, Bode U, Yan S, Hoffmann MW, Hintzen G, Bernhardt G, Förster R, Pabst O. Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells. *J Exp Med* 2006; **203**: 519-527 [PMID: 16533884 DOI: 10.1084/jem.20052016]
11 **Coombes JL**, Powrie F. Dendritic cells in intestinal immune regulation. *Nat Rev Immunol* 2008; **8**: 435-446 [PMID: 18500229 DOI: 10.1038/nri2335]
12 **Chirdo FG**, Millington OR, Beacock-Sharp H, Mowat AM. Immunomodulatory dendritic cells in intestinal lamina propria. *Eur J Immunol* 2005; **35**: 1831-1840 [PMID: 16010704 DOI: 10.1002/eji.200425882]
13 **Coombes JL**, Maloy KJ. Control of intestinal homeostasis by regulatory T cells and dendritic cells. *Semin Immunol* 2007; **19**: 116-126 [PMID: 17320411 DOI: 10.1016/j.smim.2007.01.001]
14 **Pabst O**, Bernhardt G. The puzzle of intestinal lamina propria dendritic cells and macrophages. *Eur J Immunol* 2010; **40**: 2107-2111 [PMID: 20853495 DOI: 10.1002/eji.201040557]
15 **Mowat AM**, Bain CC. Mucosal macrophages in intestinal homeostasis and inflammation. *J Innate Immun* 2011; **3**: 550-564 [PMID: 22025201 DOI: 10.1159/000329099]
16 **Bain CC**, Scott CL, Uronen-Hansson H, Gudjonsson S, Jansson O, Grip O, Guilliams M, Malissen B, Agace WW, Mowat AM. Resident and pro-inflammatory macrophages in the colon represent alternative context-dependent fates of the same Ly6Chi monocyte precursors. *Mucosal Immunol* 2013; **6**: 498-510 [PMID: 22990622 DOI: 10.1038/mi.2012.89]
17 **Tamoutounour S**, Henri S, Lelouard H, de Bovis B, de Haar C, van der Woude CJ, Woltman AM, Reyal Y, Bonnet D, Sichien D, Bain CC, Mowat AM, Reis e Sousa C, Poulin LF, Malissen B, Guilliams M. CD64 distinguishes macrophages from dendritic cells in the gut and reveals the Th1-inducing role of mesenteric lymph node macrophages during colitis. *Eur J Immunol* 2012; **42**: 3150-3166 [PMID: 22936024 DOI: 10.1002/eji.201242847]
18 **Yamazaki S**, Dudziak D, Heidkamp GF, Fiorese C, Bonito AJ, Inaba K, Nussenzweig MC, Steinman RM. CD8+ CD205+ splenic dendritic cells are specialized to induce Foxp3+ regulatory T cells. *J Immunol* 2008; **181**: 6923-6933 [PMID: 18981112]
19 **Shortman K**, Heath WR. The CD8+ dendritic cell subset. *Immunol Rev* 2010; **234**: 18-31 [PMID: 20193009 DOI: 10.1111/j.0105-2896.2009.00870.x]
20 **Johansson-Lindbom B**, Svensson M, Pabst O, Palmqvist C, Marquez G, Förster R, Agace WW. Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing. *J Exp Med* 2005; **202**: 1063-1073 [PMID: 16216890 DOI: 10.1084/jem.20051100]
21 **Jaensson E**, Uronen-Hansson H, Pabst O, Eksteen B, Tian

J, Coombes JL, Berg PL, Davidsson T, Powrie F, Johansson-Lindbom B, Agace WW. Small intestinal CD103+ dendritic cells display unique functional properties that are conserved between mice and humans. *J Exp Med* 2008; **205**: 2139-2149 [PMID: 18710932 DOI: 10.1084/jem.20080414]

22 **Schulz O**, Jaensson E, Persson EK, Liu X, Worbs T, Agace WW, Pabst O. Intestinal CD103+, but not CX3CR1+, antigen sampling cells migrate in lymph and serve classical dendritic cell functions. *J Exp Med* 2009; **206**: 3101-3114 [PMID: 20008524 DOI: 10.1084/jem.20091925]

23 **Cerovic V**, Houston SA, Scott CL, Aumeunier A, Yrlid U, Mowat AM, Milling SW. Intestinal CD103(-) dendritic cells migrate in lymph and prime effector T cells. *Mucosal Immunol* 2013; **6**: 104-113 [PMID: 22718260 DOI: 10.1038/mi.2012.53]

24 **Scott CL**, Aumeunier AM, Mowat AM. Intestinal CD103+ dendritic cells: master regulators of tolerance? *Trends Immunol* 2011; **32**: 412-419 [PMID: 21816673 DOI: 10.1016/j.it.2011.06.003]

25 **Coombes JL**, Siddiqui KR, Arancibia-Cárcamo CV, Hall J, Sun CM, Belkaid Y, Powrie F. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med* 2007; **204**: 1757-1764 [PMID: 17620361 DOI: 10.1084/jem.20070590]

26 **Sun CM**, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, Belkaid Y. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J Exp Med* 2007; **204**: 1775-1785 [PMID: 17620362 DOI: 10.1084/jem.20070602]

27 **Benson MJ**, Pino-Lagos K, Rosemblatt M, Noelle RJ. All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. *J Exp Med* 2007; **204**: 1765-1774 [PMID: 17620363 DOI: 10.1084/jem.20070719]

28 **Mucida D**, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, Cheroutre H. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. *Science* 2007; **317**: 256-260 [PMID: 17569825 DOI: 10.1126/science.1145697]

29 **Iliev ID**, Mileti E, Matteoli G, Chieppa M, Rescigno M. Intestinal epithelial cells promote colitis-protective regulatory T-cell differentiation through dendritic cell conditioning. *Mucosal Immunol* 2009; **2**: 340-350 [PMID: 19387433 DOI: 10.1038/mi.2009.13]

30 **Matteoli G**, Mazzini E, Iliev ID, Mileti E, Fallarino F, Puccetti P, Chieppa M, Rescigno M. Gut CD103+ dendritic cells express indoleamine 2,3-dioxygenase which influences T regulatory/T effector cell balance and oral tolerance induction. *Gut* 2010; **59**: 595-604 [PMID: 20427394 DOI: 10.1136/gut.2009.185108]

31 **Goubier A**, Dubois B, Gheit H, Joubert G, Villard-Truc F, Asselin-Paturel C, Trinchieri G, Kaiserlian D. Plasmacytoid dendritic cells mediate oral tolerance. *Immunity* 2008; **29**: 464-475 [PMID: 18789731 DOI: 10.1016/j.immuni.2008.06.017]

32 **Persson EK**, Jaensson E, Agace WW. The diverse ontogeny and function of murine small intestinal dendritic cell/macrophage subsets. *Immunobiology* 2010; **215**: 692-697 [PMID: 20580119 DOI: 10.1016/j.imbio.2010.05.013]

33 **Persson EK**, Uronen-Hansson H, Semmrich M, Rivollier A, Hägerbrand K, Marsal J, Gudjonsson S, Håkansson U, Reizis B, Kotarsky K, Agace WW. IRF4 transcription-factor-dependent CD103(+)CD11b(+) dendritic cells drive mucosal T helper 17 cell differentiation. *Immunity* 2013; **38**: 958-969 [PMID: 23664832 DOI: 10.1016/j.immuni.2013.03.009]

34 **Rogler G**, Hausmann M, Vogl D, Aschenbrenner E, Andus T, Falk W, Andreesen R, Schölmerich J, Gross V. Isolation and phenotypic characterization of colonic macrophages. *Clin Exp Immunol* 1998; **112**: 205-215 [PMID: 9649182 DOI: 10.1046/j.1365-2249.1998.00557.x]

35 **Smith PD**, Smythies LE, Shen R, Greenwell-Wild T, Gliozzi M, Wahl SM. Intestinal macrophages and response to microbial encroachment. *Mucosal Immunol* 2011; **4**: 31-42 [PMID: 20962772 DOI: 10.1038/mi.2010.66]

36 **Uematsu S**, Jang MH, Chevrier N, Guo Z, Kumagai Y, Yamamoto M, Kato H, Sougawa N, Matsui H, Kuwata H, Hemmi H, Coban C, Kawai T, Ishii KJ, Takeuchi O, Miyasaka M, Takeda K, Akira S. Detection of pathogenic intestinal bacteria by Toll-like receptor 5 on intestinal CD11c+ lamina propria cells. *Nat Immunol* 2006; **7**: 868-874 [PMID: 16829963 DOI: 10.1038/ni1362]

37 **Carlsen HS**, Yamanaka T, Scott H, Rugtveit J, Brandtzaeg P. The proportion of CD40+ mucosal macrophages is increased in inflammatory bowel disease whereas CD40 ligand (CD154)+ T cells are relatively decreased, suggesting differential modulation of these costimulatory molecules in human gut lamina propria. *Inflamm Bowel Dis* 2006; **12**: 1013-1024 [PMID: 17075342 DOI: 10.1097/01.mib.0000234135.43336.72]

38 **Hirotani T**, Lee PY, Kuwata H, Yamamoto M, Matsumoto M, Kawase I, Akira S, Takeda K. The nuclear IkappaB protein IkappaBNS selectively inhibits lipopolysaccharide-induced IL-6 production in macrophages of the colonic lamina propria. *J Immunol* 2005; **174**: 3650-3657 [PMID: 15749903]

39 **Denning TL**, Wang YC, Patel SR, Williams IR, Pulendran B. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nat Immunol* 2007; **8**: 1086-1094 [PMID: 17873879 DOI: 10.1038/ni1511]

40 **Platt AM**, Bain CC, Bordon Y, Sester DP, Mowat AM. An independent subset of TLR expressing CCR2-dependent macrophages promotes colonic inflammation. *J Immunol* 2010; **184**: 6843-6854 [PMID: 20483766 DOI: 10.4049/jimmunol.0903987]

41 **Lin HH**, Faunce DE, Stacey M, Terajewicz A, Nakamura T, Zhang-Hoover J, Kerley M, Mucenski ML, Gordon S, Stein-Streilein J. The macrophage F4/80 receptor is required for the induction of antigen-specific efferent regulatory T cells in peripheral tolerance. *J Exp Med* 2005; **201**: 1615-1625 [PMID: 15883173 DOI: 10.1084/jem.20042307]

42 **Murai M**, Turovskaya O, Kim G, Madan R, Karp CL, Cheroutre H, Kronenberg M. Interleukin 10 acts on regulatory T cells to maintain expression of the transcription factor Foxp3 and suppressive function in mice with colitis. *Nat Immunol* 2009; **10**: 1178-1184 [PMID: 19783988 DOI: 10.1038/ni.1791]

43 **Cerutti A**. The regulation of IgA class switching. *Nat Rev Immunol* 2008; **8**: 421-434 [PMID: 18483500 DOI: 10.1038/nri2322]

44 **Mantis NJ**, Forbes SJ. Secretory IgA: arresting microbial pathogens at epithelial borders. *Immunol Invest* 2010; **39**: 383-406 [PMID: 20450284 DOI: 10.3109/08820131003622635]

45 **Peterson DA**, McNulty NP, Guruge JL, Gordon JI. IgA response to symbiotic bacteria as a mediator of gut homeostasis. *Cell Host Microbe* 2007; **2**: 328-339 [PMID: 18005754 DOI: 10.1016/j.chom.2007.09.013]

46 **Cong Y**, Feng T, Fujihashi K, Schoeb TR, Elson CO. A dominant, coordinated T regulatory cell-IgA response to the intestinal microbiota. *Proc Natl Acad Sci USA* 2009; **106**: 19256-19261 [PMID: 19889972 DOI: 10.1073/pnas.0812681106]

47 **Batista FD**, Harwood NE. The who, how and where of antigen presentation to B cells. *Nat Rev Immunol* 2009; **9**: 15-27 [PMID: 19079135 DOI: 10.1038/nri2454]

48 **Amu S**, Saunders SP, Kronenberg M, Mangan NE, Atzberger A, Fallon PG. Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model. *J Allergy Clin Immunol* 2010; **125**: 1114-1124.e8 [PMID: 20304473 DOI: 10.1016/j.jaci.2010.01.018]

49 **Tadmor T**, Zhang Y, Cho HM, Podack ER, Rosenblatt JD. The absence of B lymphocytes reduces the number and function of T-regulatory cells and enhances the anti-tumor response in a murine tumor model. *Cancer Immunol Immunother* 2011; **60**: 609-619 [PMID: 21253724 DOI: 10.1007/s00262-

011-0972-z]
50 **Sun JB**, Flach CF, Czerkinsky C, Holmgren J. B lymphocytes promote expansion of regulatory T cells in oral tolerance: powerful induction by antigen coupled to cholera toxin B subunit. *J Immunol* 2008; **181**: 8278-8287 [PMID: 19050244]
51 **Mangan NE**, Fallon RE, Smith P, van Rooijen N, McKenzie AN, Fallon PG. Helminth infection protects mice from anaphylaxis via IL-10-producing B cells. *J Immunol* 2004; **173**: 6346-6356 [PMID: 15528374]
52 **Darrasse-Jèze G**, Deroubaix S, Mouquet H, Victora GD, Eisenreich T, Yao KH, Masilamani RF, Dustin ML, Rudensky A, Liu K, Nussenzweig MC. Feedback control of regulatory T cell homeostasis by dendritic cells in vivo. *J Exp Med* 2009; **206**: 1853-1862 [PMID: 19667061 DOI: 10.1084/jem.20090746]
53 **Carter NA**, Vasconcellos R, Rosser EC, Tulone C, Muñoz-Suano A, Kamanaka M, Ehrenstein MR, Flavell RA, Mauri C. Mice lacking endogenous IL-10-producing regulatory B cells develop exacerbated disease and present with an increased frequency of Th1/Th17 but a decrease in regulatory T cells. *J Immunol* 2011; **186**: 5569-5579 [PMID: 21464089 DOI: 10.4049/jimmunol.1100284]
54 **Mann MK**, Maresz K, Shriver LP, Tan Y, Dittel BN. B cell regulation of CD4+CD25+ T regulatory cells and IL-10 via B7 is essential for recovery from experimental autoimmune encephalomyelitis. *J Immunol* 2007; **178**: 3447-3456 [PMID: 17339439]
55 **Mizoguchi A**, Mizoguchi E, Takedatsu H, Blumberg RS, Bhan AK. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. *Immunity* 2002; **16**: 219-230 [PMID: 11869683 DOI: 10.1016/S1074-7613(02)00274-1]
56 **Fillatreau S**, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. *Nat Immunol* 2002; **3**: 944-950 [PMID: 12244307 DOI: 10.1038/ni833]
57 **Mauri C**, Gray D, Mushtaq N, Londei M. Prevention of arthritis by interleukin 10-producing B cells. *J Exp Med* 2003; **197**: 489-501 [PMID: 12591906 DOI: 10.1084/jem.20021293]
58 **Noh G**, Lee JH. Regulatory B cells and allergic diseases. *Allergy Asthma Immunol Res* 2011; **3**: 168-177 [PMID: 21738882 DOI: 10.4168/aair.2011.3.3.168]
59 **Jamin C**, Morva A, Lemoine S, Daridon C, de Mendoza AR, Youinou P. Regulatory B lymphocytes in humans: a potential role in autoimmunity. *Arthritis Rheum* 2008; **58**: 1900-1906 [PMID: 18576353 DOI: 10.1002/art.23487]
60 **Lee JH**, Noh J, Noh G, Choi WS, Cho S, Lee SS. Allergen-specific transforming growth factor-β-producing CD19+CD5+ regulatory B-cell (Br3) responses in human late eczematous allergic reactions to cow's milk. *J Interferon Cytokine Res* 2011; **31**: 441-449 [PMID: 21291325 DOI: 10.1089/jir.2010.0020]
61 **Liu ZQ**, Wu Y, Song JP, Liu X, Liu Z, Zheng PY, Yang PC. Tolerogenic CX3CR1+ B cells suppress food allergy-induced intestinal inflammation in mice. *Allergy* 2013; **68**: 1241-1248 [PMID: 24033604 DOI: 10.1111/all.12218]
62 **Duchmann R**, Kaiser I, Hermann E, Mayet W, Ewe K, Meyer zum Büschenfelde KH. Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD) *Clin Exp Immunol* 1995; **102**: 448-455 [PMID: 8536356 DOI: 10.1111/j.1365-2249.1995.tb03836.x]
63 **Karlis J**, Penttila I, Tran TB, Jones B, Nobbs S, Zola H, Flesch IE. Characterization of colonic and mesenteric lymph node dendritic cell subpopulations in a murine adoptive transfer model of inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 834-847 [PMID: 15626902 DOI: 10.1097/00054725-200411000-00018]
64 **Sartor RB**. Microbial influences in inflammatory bowel diseases. *Gastroenterology* 2008; **134**: 577-594 [PMID: 18242222 DOI: 10.1053/j.gastro.2007.11.059]
65 **Diehl GE**, Longman RS, Zhang JX, Breart B, Galan C, Cuesta A, Schwab SR, Littman DR. Microbiota restricts trafficking of bacteria to mesenteric lymph nodes by CX(3)CR1(hi) cells. *Nature* 2013; **494**: 116-120 [PMID: 23334413 DOI: 10.1038/nature11809]
66 **Sokol H**, Seksik P. The intestinal microbiota in inflammatory bowel diseases: time to connect with the host. *Curr Opin Gastroenterol* 2010; **26**: 327-331 [PMID: 20445446 DOI: 10.1097/MOG.0b013e328339536b]
67 **Takenaka S**, Safroneeva E, Xing Z, Gauldie J. Dendritic cells derived from murine colonic mucosa have unique functional and phenotypic characteristics. *J Immunol* 2007; **178**: 7984-7993 [PMID: 17548635]
68 **Hart AL**, Al-Hassi HO, Rigby RJ, Bell SJ, Emmanuel AV, Knight SC, Kamm MA, Stagg AJ. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* 2005; **129**: 50-65 [PMID: 16012934 DOI: 10.1053/j.gastro.2005.05.013]
69 **Hausmann M**, Kiessling S, Mestermann S, Webb G, Spöttl T, Andus T, Schölmerich J, Herfarth H, Ray K, Falk W, Rogler G. Toll-like receptors 2 and 4 are up-regulated during intestinal inflammation. *Gastroenterology* 2002; **122**: 1987-2000 [PMID: 12055604 DOI: 10.1053/gast.2002.33662]
70 **Zigmond E**, Varol C, Farache J, Elmaliah E, Satpathy AT, Friedlander G, Mack M, Shpigel N, Boneca IG, Murphy KM, Shakhar G, Halpern Z, Jung S. Ly6C hi monocytes in the inflamed colon give rise to proinflammatory effector cells and migratory antigen-presenting cells. *Immunity* 2012; **37**: 1076-1090 [PMID: 23219392 DOI: 10.1016/j.immuni.2012.08.026]
71 **Candia E**, Díaz-Jiménez D, Langjahr P, Núñez LE, de la Fuente M, Farfán N, López-Kostner F, Abedrapo M, Alvarez-Lobos M, Pinedo G, Beltrán CJ, González C, González MJ, Quera R, Hermoso MA. Increased production of soluble TLR2 by lamina propria mononuclear cells from ulcerative colitis patients. *Immunobiology* 2012; **217**: 634-642 [PMID: 22101184 DOI: 10.1016/j.imbio.2011.10.023]
72 **Berkowitz D**, Peri R, Lavy A, Kessel A. Increased Toll-like receptor 9 expression by B cells from inflammatory bowel disease patients. *Hum Immunol* 2013; **74**: 1519-1523 [PMID: 24007656 DOI: 10.1016/j.humimm.2013.08.285]
73 **Banchereau J**, Steinman RM. Dendritic cells and the control of immunity. *Nature* 1998; **392**: 245-252 [PMID: 9521319 DOI: 10.1038/32588]
74 **Niess JH**. Role of mucosal dendritic cells in inflammatory bowel disease. *World J Gastroenterol* 2008; **14**: 5138-5148 [PMID: 18777590 DOI: 10.3748/wjg.14.5138]
75 **Leach MW**, Bean AG, Mauze S, Coffman RL, Powrie F. Inflammatory bowel disease in C.B-17 scid mice reconstituted with the CD45RBhigh subset of CD4+ T cells. *Am J Pathol* 1996; **148**: 1503-1515 [PMID: 8623920]
76 **Strober W**, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. *Annu Rev Immunol* 2002; **20**: 495-549 [PMID: 11861611 DOI: 10.1146/annurev.immunol.20.100301.064816]
77 **Krajina T**, Leithäuser F, Möller P, Trobonjaca Z, Reimann J. Colonic lamina propria dendritic cells in mice with CD4+ T cell-induced colitis. *Eur J Immunol* 2003; **33**: 1073-1083 [PMID: 12672074 DOI: 10.1002/eji.200323518]
78 **Rivollier A**, He J, Kole A, Valatas V, Kelsall BL. Inflammation switches the differentiation program of Ly6Chi monocytes from antiinflammatory macrophages to inflammatory dendritic cells in the colon. *J Exp Med* 2012; **209**: 139-155 [PMID: 22231304 DOI: 10.1084/jem.20101387]
79 **Abe K**, Nguyen KP, Fine SD, Mo JH, Shen C, Shenouda S, Corr M, Jung S, Lee J, Eckmann L, Raz E. Conventional dendritic cells regulate the outcome of colonic inflammation independently of T cells. *Proc Natl Acad Sci USA* 2007; **104**: 17022-17027 [PMID: 17942668 DOI: 10.1073/pnas.0708469104]
80 **Leithäuser F**, Trobonjaca Z, Möller P, Reimann J. Clustering of colonic lamina propria CD4(+) T cells to subepithelial

dendritic cell aggregates precedes the development of colitis in a murine adoptive transfer model. *Lab Invest* 2001; **81**: 1339-1349 [PMID: 11598147 DOI: 10.1038/labinvest.3780348]
81 **Malmström V**, Shipton D, Singh B, Al-Shamkhani A, Puklavec MJ, Barclay AN, Powrie F. CD134L expression on dendritic cells in the mesenteric lymph nodes drives colitis in T cell-restored SCID mice. *J Immunol* 2001; **166**: 6972-6981 [PMID: 11359859]
82 **Bell SJ**, Rigby R, English N, Mann SD, Knight SC, Kamm MA, Stagg AJ. Migration and maturation of human colonic dendritic cells. *J Immunol* 2001; **166**: 4958-4967 [PMID: 11290774]
83 **Silva MA**. Intestinal dendritic cells and epithelial barrier dysfunction in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 436-453 [PMID: 18821596 DOI: 10.1002/ibd.20660]
84 **Verstege MI**, ten Kate FJ, Reinartz SM, van Drunen CM, Slors FJ, Bemelman WA, Vyth-Dreese FA, te Velde AA. Dendritic cell populations in colon and mesenteric lymph nodes of patients with Crohn's disease. *J Histochem Cytochem* 2008; **56**: 233-241 [PMID: 18040077 DOI: 10.1369/jhc.7A7308.2007]
85 **te Velde AA**, van Kooyk Y, Braat H, Hommes DW, Dellemijn TA, Slors JF, van Deventer SJ, Vyth-Dreese FA. Increased expression of DC-SIGN+IL-12+IL-18+ and CD83+IL-12-IL-18- dendritic cell populations in the colonic mucosa of patients with Crohn's disease. *Eur J Immunol* 2003; **33**: 143-151 [PMID: 12594843 DOI: 10.1002/immu.200390017]
86 **Kaser A**, Ludwiczek O, Holzmann S, Moschen AR, Weiss G, Enrich B, Graziadei I, Dunzendorfer S, Wiedermann CJ, Mürzl E, Grasl E, Jasarevic Z, Romani N, Offner FA, Tilg H. Increased expression of CCL20 in human inflammatory bowel disease. *J Clin Immunol* 2004; **24**: 74-85 [PMID: 14997037 DOI: 10.1023/B:JOCI.0000018066.46279.6b]
87 **Mann ER**, Bernardo D, Al-Hassi HO, English NR, Clark SK, McCarthy NE, Milestone AN, Cochrane SA, Hart AL, Stagg AJ, Knight SC. Human gut-specific homeostatic dendritic cells are generated from blood precursors by the gut microenvironment. *Inflamm Bowel Dis* 2012; **18**: 1275-1286 [PMID: 21987473 DOI: 10.1002/ibd.21893]
88 **Mann ER**, You J, Horneffer-van der Sluis V, Bernardo D, Omar Al-Hassi H, Landy J, Peake ST, Thomas LV, Tee CT, Lee GH, Hart AL, Yaqoob P, Knight SC. Dysregulated circulating dendritic cell function in ulcerative colitis is partially restored by probiotic strain Lactobacillus casei Shirota. *Mediators Inflamm* 2013; **2013**: 573576 [PMID: 23970814]
89 **Stagg AJ**, Kamm MA, Knight SC. Intestinal dendritic cells increase T cell expression of alpha4beta7 integrin. *Eur J Immunol* 2002; **32**: 1445-1454 [PMID: 11981833]
90 **Mora JR**, Bono MR, Manjunath N, Weninger W, Cavanagh LL, Rosemblatt M, Von Andrian UH. Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. *Nature* 2003; **424**: 88-93 [PMID: 12840763 DOI: 10.1038/nature01726]
91 **Johansson-Lindbom B**, Svensson M, Wurbel MA, Malissen B, Márquez G, Agace W. Selective generation of gut tropic T cells in gut-associated lymphoid tissue (GALT): requirement for GALT dendritic cells and adjuvant. *J Exp Med* 2003; **198**: 963-969 [PMID: 12963696 DOI: 10.1084/jem.20031244]
92 **Campbell DJ**, Butcher EC. Rapid acquisition of tissue-specific homing phenotypes by CD4(+) T cells activated in cutaneous or mucosal lymphoid tissues. *J Exp Med* 2002; **195**: 135-141 [PMID: 11781372 DOI: 10.1084/jem.20011502]
93 **Annacker O**, Coombes JL, Malmstrom V, Uhlig HH, Bourne T, Johansson-Lindbom B, Agace WW, Parker CM, Powrie F. Essential role for CD103 in the T cell-mediated regulation of experimental colitis. *J Exp Med* 2005; **202**: 1051-1061 [PMID: 16216886 DOI: 10.1084/jem.20040662]
94 **Mora JR**, Iwata M, Eksteen B, Song SY, Junt T, Senman B, Otipoby KL, Yokota A, Takeuchi H, Ricciardi-Castagnoli P, Rajewsky K, Adams DH, von Andrian UH. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. *Science* 2006; **314**: 1157-1160 [PMID: 17110582 DOI: 10.1126/science.1132742]
95 **Strober W**. Vitamin A rewrites the ABCs of oral tolerance. *Mucosal Immunol* 2008; **1**: 92-95 [PMID: 19079166 DOI: 10.1038/mi.2007.22]
96 **Mora JR**, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* 2008; **8**: 685-698 [PMID: 19172691 DOI: 10.1038/nri2378]
97 **Laffont S**, Siddiqui KR, Powrie F. Intestinal inflammation abrogates the tolerogenic properties of MLN CD103+ dendritic cells. *Eur J Immunol* 2010; **40**: 1877-1883 [PMID: 20432234 DOI: 10.1002/eji.200939957]
98 **Villablanca EJ**, De Calisto J, Torregrosa Paredes P, Cassani B, Nguyen DD, Gabrielsson S, Mora JR. β7 integrins are required to give rise to intestinal mononuclear phagocytes with tolerogenic potential. *Gut* 2013; Epub ahead of print [PMID: 24030488 DOI: 10.1136/gutjnl-2013-305386]
99 **Cassani B**, Villablanca EJ, Quintana FJ, Love PE, Lacy-Hulbert A, Blaner WS, Sparwasser T, Snapper SB, Weiner HL, Mora JR. Gut-tropic T cells that express integrin α4β7 and CCR9 are required for induction of oral immune tolerance in mice. *Gastroenterology* 2011; **141**: 2109-2118 [PMID: 21925467 DOI: 10.1053/j.gastro.2011.09.015]
100 **Mizuno S**, Kanai T, Mikami Y, Sujino T, Ono Y, Hayashi A, Handa T, Matsumoto A, Nakamoto N, Matsuoka K, Hisamatsu T, Takaishi H, Hibi T. CCR9+ plasmacytoid dendritic cells in the small intestine suppress development of intestinal inflammation in mice. *Immunol Lett* 2012; **146**: 64-69 [PMID: 22626536 DOI: 10.1016/j.imlet.2012.05.001]
101 **Drakes ML**, Stiff PJ, Blanchard TG. Inverse relationship between dendritic cell CCR9 expression and maturation state. *Immunology* 2009; **127**: 466-476 [PMID: 19604301 DOI: 10.1111/j.1365-2567.2009.03043.x]
102 **Kawai T**, Akira S. Toll-like receptor and RIG-I-like receptor signaling. *Ann N Y Acad Sci* 2008; **1143**: 1-20 [PMID: 19076341 DOI: 10.1196/annals.1443.020]
103 **Wang S**, Villablanca EJ, De Calisto J, Gomes DC, Nguyen DD, Mizoguchi E, Kagan JC, Reinecker HC, Hacohen N, Nagler C, Xavier RJ, Rossi-Bergmann B, Chen YB, Blomhoff R, Snapper SB, Mora JR. MyD88-dependent TLR1/2 signals educate dendritic cells with gut-specific imprinting properties. *J Immunol* 2011; **187**: 141-150 [PMID: 21646294 DOI: 10.4049/jimmunol.1003740]
104 **Rugtveit J**, Bakka A, Brandtzaeg P. Differential distribution of B7.1 (CD80) and B7.2 (CD86) costimulatory molecules on mucosal macrophage subsets in human inflammatory bowel disease (IBD). *Clin Exp Immunol* 1997; **110**: 104-113 [PMID: 9353156 DOI: 10.1111/j.1365-2249.1997.507-ce1404.x]
105 **Mahida YR**, Wu K, Jewell DP. Enhanced production of interleukin 1-beta by mononuclear cells isolated from mucosa with active ulcerative colitis of Crohn's disease. *Gut* 1989; **30**: 835-838 [PMID: 2787769 DOI: 10.1136/gut.30.6.835]
106 **Rogler G**, Brand K, Vogl D, Page S, Hofmeister R, Andus T, Knuechel R, Baeuerle PA, Schölmerich J, Gross V. Nuclear factor kappaB is activated in macrophages and epithelial cells of inflamed intestinal mucosa. *Gastroenterology* 1998; **115**: 357-369 [PMID: 9679041 DOI: 10.1016/S0016-5085(98)70202-1]
107 **Hausmann M**, Spöttl T, Andus T, Rothe G, Falk W, Schölmerich J, Herfarth H, Rogler G. Subtractive screening reveals up-regulation of NADPH oxidase expression in Crohn's disease intestinal macrophages. *Clin Exp Immunol* 2001; **125**: 48-55 [PMID: 11472425 DOI: 10.1046/j.1365-2249.2001.01567.x]
108 **Hausmann M**, Obermeier F, Schreiter K, Spottl T, Falk W, Schölmerich J, Herfarth H, Saftig P, Rogler G. Cathepsin D is up-regulated in inflammatory bowel disease macrophages. *Clin Exp Immunol* 2004; **136**: 157-167 [PMID: 15030527 DOI: 10.1111/j.1365-2249.2004.02420.x]
109 **Cerutti A**, Rescigno M. The biology of intestinal immuno-

globulin A responses. *Immunity* 2008; **28**: 740-750 [PMID: 18549797 DOI: 10.1016/j.immuni.2008.05.001]
110 **Macpherson AJ**, McCoy KD, Johansen FE, Brandtzaeg P. The immune geography of IgA induction and function. *Mucosal Immunol* 2008; **1**: 11-22 [PMID: 19079156 DOI: 10.1038/mi.2007.6]
111 **Brandtzaeg P**. The changing immunological paradigm in coeliac disease. *Immunol Lett* 2006; **105**: 127-139 [PMID: 16647763 DOI: 10.1016/j.imlet.2006.03.004]
112 **Polese L**, Boetto R, De Franchis G, Angriman I, Porzionato A, Norberto L, Sturniolo GC, Macchi V, De Caro R, Merigliano S. B1a lymphocytes in the rectal mucosa of ulcerative colitis patients. *World J Gastroenterol* 2012; **18**: 144-149 [PMID: 22253520 DOI: 10.3748/wjg.v18.i2.144]
113 **Rehman MQ**, Beal D, Liang Y, Noronha A, Winter H, Farraye FA, Ganley-Leal L. B cells secrete eotaxin-1 in human inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 922-933 [PMID: 23511032 DOI: 10.1097/MIB.0b013e3182802950]
114 **Bloch DB**, Nobre R, Steinbicker AU, Al-Herz W, Notarangelo LD, Recher M. Decreased IL-10 production by EBV-transformed B cells from patients with VODI: implications for the pathogenesis of Crohn disease. *J Allergy Clin Immunol* 2012; **129**: 1678-1680 [PMID: 22341038 DOI: 10.1016/j.jaci.2012.01.046]
115 **Defendenti C**, Grosso S, Atzeni F, Croce A, Senesi O, Saibeni S, Bollani S, Almasio PL, Bruno S, Sarzi-Puttini P. Unusual B cell morphology in inflammatory bowel disease. *Pathol Res Pract* 2012; **208**: 387-391 [PMID: 22658383 DOI: 10.1016/j.prp.2012.05.003]
116 **Lin Z**, Hegarty JP, Yu W, Cappel JA, Chen X, Faber PW, Wang Y, Poritz LS, Fan JB, Koltun WA. Identification of disease-associated DNA methylation in B cells from Crohn' s disease and ulcerative colitis patients. *Dig Dis Sci* 2012; **57**: 3145-3153 [PMID: 22821069 DOI: 10.1007/s10620-012-2288-z]
117 **Yu W**, Lin Z, Hegarty JP, Chen X, Kelly AA, Wang Y, Poritz LS, Koltun WA. Genes differentially regulated by NKX2-3 in B cells between ulcerative colitis and Crohn's disease patients and possible involvement of EGR1. *Inflammation* 2012; **35**: 889-899 [PMID: 21968973 DOI: 10.1007/s10753-011-9390-9]
118 **Iwasaki A**. Mucosal dendritic cells. *Annu Rev Immunol* 2007; **25**: 381-418 [PMID: 17378762 DOI: 10.1146/annurev.immunol.25.022106.141634]
119 **Cerutti A**, Puga I, Cols M. Innate control of B cell responses. *Trends Immunol* 2011; **32**: 202-211 [PMID: 21419699 DOI: 10.1016/j.it.2011.02.004]
120 **Fayette J**, Dubois B, Vandenabeele S, Bridon JM, Vanbervliet B, Durand I, Banchereau J, Caux C, Brière F. Human dendritic cells skew isotype switching of CD40-activated naive B cells towards IgA1 and IgA2. *J Exp Med* 1997; **185**: 1909-1918 [PMID: 9166420 DOI: 10.1084/jem.185.11.1909]
121 **Wykes M**, Pombo A, Jenkins C, MacPherson GG. Dendritic cells interact directly with naive B lymphocytes to transfer antigen and initiate class switching in a primary T-dependent response. *J Immunol* 1998; **161**: 1313-1319 [PMID: 9686593]
122 **Bergtold A**, Desai DD, Gavhane A, Clynes R. Cell surface recycling of internalized antigen permits dendritic cell priming of B cells. *Immunity* 2005; **23**: 503-514 [PMID: 16286018 DOI: 10.1016/j.immuni.2005.09.013]
123 **Qi H**, Egen JG, Huang AY, Germain RN. Extrafollicular activation of lymph node B cells by antigen-bearing dendritic cells. *Science* 2006; **312**: 1672-1676 [PMID: 16778060 DOI: 10.1126/science.1125703]
124 **Jego G**, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. *Immunity* 2003; **19**: 225-234 [PMID: 12932356 DOI: 10.1016/S1074-7613(03)00208-5]
125 **He B**, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, Shan M, Chadburn A, Villanacci V, Plebani A, Knowles DM, Rescigno M, Cerutti A. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. *Immunity* 2007; **26**: 812-826 [PMID: 17570691 DOI: 10.1016/j.immuni.2007.04.014]
126 **Shang L**, Fukata M, Thirunarayanan N, Martin AP, Arnaboldi P, Maussang D, Berin C, Unkeless JC, Mayer L, Abreu MT, Lira SA. Toll-like receptor signaling in small intestinal epithelium promotes B-cell recruitment and IgA production in lamina propria. *Gastroenterology* 2008; **135**: 529-538 [PMID: 18522803 DOI: 10.1053/j.gastro.2008.04.020]
127 **Tezuka H**, Abe Y, Asano J, Sato T, Liu J, Iwata M, Ohteki T. Prominent role for plasmacytoid dendritic cells in mucosal T cell-independent IgA induction. *Immunity* 2011; **34**: 247-257 [PMID: 21333555 DOI: 10.1016/j.immuni.2011.02.002]
128 **Craxton A**, Magaletti D, Ryan EJ, Clark EA. Macrophage- and dendritic cell--dependent regulation of human B-cell proliferation requires the TNF family ligand BAFF. *Blood* 2003; **101**: 4464-4471 [PMID: 12531790 DOI: 10.1182/blood-2002-10-3123]
129 **Castigli E**, Scott S, Dedeoglu F, Bryce P, Jabara H, Bhan AK, Mizoguchi E, Geha RS. Impaired IgA class switching in APRIL-deficient mice. *Proc Natl Acad Sci USA* 2004; **101**: 3903-3908 [PMID: 14988498 DOI: 10.1073/pnas.0307348101]
130 **Castigli E**, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP, Bram RJ, Jabara H, Geha RS. TACI and BAFF-R mediate isotype switching in B cells. *J Exp Med* 2005; **201**: 35-39 [PMID: 15630136 DOI: 10.1084/jem.20032000]
131 **Dillon SR**, Gross JA, Ansell SM, Novak AJ. An APRIL to remember: novel TNF ligands as therapeutic targets. *Nat Rev Drug Discov* 2006; **5**: 235-246 [PMID: 16474316 DOI: 10.1038/nrd1982]
132 **Litinskiy MB**, Nardelli B, Hilbert DM, He B, Schaffer A, Casali P, Cerutti A. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. *Nat Immunol* 2002; **3**: 822-829 [PMID: 12154359 DOI: 10.1038/ni829]
133 **Schneider P**, MacKay F, Steiner V, Hofmann K, Bodmer JL, Holler N, Ambrose C, Lawton P, Bixler S, Acha-Orbea H, Valmori D, Romero P, Werner-Favre C, Zubler RH, Browning JL, Tschopp J. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. *J Exp Med* 1999; **189**: 1747-1756 [PMID: 10359578 DOI: 10.1084/jem.189.11.1747]
134 **Schneider P**. The role of APRIL and BAFF in lymphocyte activation. *Curr Opin Immunol* 2005; **17**: 282-289 [PMID: 15886118 DOI: 10.1016/j.coi.2005.04.005]
135 **Smythies LE**, Sellers M, Clements RH, Mosteller-Barnum M, Meng G, Benjamin WH, Orenstein JM, Smith PD. Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity. *J Clin Invest* 2005; **115**: 66-75 [PMID: 15630445 DOI: 10.1172/JCI200519229]
136 **Sato A**, Hashiguchi M, Toda E, Iwasaki A, Hachimura S, Kaminogawa S. CD11b+ Peyer's patch dendritic cells secrete IL-6 and induce IgA secretion from naive B cells. *J Immunol* 2003; **171**: 3684-3690 [PMID: 14500666]
137 **Iwata M**, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on T cells. *Immunity* 2004; **21**: 527-538 [PMID: 15485630 DOI: 10.1016/j.immuni.2004.08.011]
138 **Uematsu S**, Fujimoto K, Jang MH, Yang BG, Jung YJ, Nishiyama M, Sato S, Tsujimura T, Yamamoto M, Yokota Y, Kiyono H, Miyasaka M, Ishii KJ, Akira S. Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5. *Nat Immunol* 2008; **9**: 769-776 [PMID: 18516037 DOI: 10.1038/ni.1622]
139 **Massacand JC**, Kaiser P, Ernst B, Tardivel A, Bürki K, Schneider P, Harris NL. Intestinal bacteria condition dendritic cells to promote IgA production. *PLoS One* 2008; **3**: e2588 [PMID: 18596964]
140 **Svensson M**, Johansson-Lindbom B, Zapata F, Jaensson E, Austenaa LM, Blomhoff R, Agace WW. Retinoic acid recep-

tor signaling levels and antigen dose regulate gut homing receptor expression on CD8+ T cells. *Mucosal Immunol* 2008; **1**: 38-48 [PMID: 19079159 DOI: 10.1038/mi.2007.4]
141 **Suzuki K**, Maruya M, Kawamoto S, Sitnik K, Kitamura H, Agace WW, Fagarasan S. The sensing of environmental stimuli by follicular dendritic cells promotes immunoglobulin A generation in the gut. *Immunity* 2010; **33**: 71-83 [PMID: 20643338 DOI: 10.1016/j.immuni.2010.07.003]
142 **Di Caro V**, Phillips B, Engman C, Harnaha J, Trucco M, Giannoukakis N. Retinoic acid-producing, ex-vivo-generated human tolerogenic dendritic cells induce the proliferation of immunosuppressive B lymphocytes. *Clin Exp Immunol* 2013; **174**: 302-317 [PMID: 23865694]
143 **Zietara N**, Łyszkiewicz M, Puchałka J, Pei G, Gutierrez MG, Lienenklaus S, Hobeika E, Reth M, Martins dos Santos VA, Krueger A, Weiss S. Immunoglobulins drive terminal maturation of splenic dendritic cells. *Proc Natl Acad Sci USA* 2013; **110**: 2282-2287 [PMID: 23345431 DOI: 10.1073/pnas.1210654110]
144 **Diana J**, Simoni Y, Furio L, Beaudoin L, Agerberth B, Barrat F, Lehuen A. Crosstalk between neutrophils, B-1a cells and plasmacytoid dendritic cells initiates autoimmune diabetes. *Nat Med* 2013; **19**: 65-73 [PMID: 23242473 DOI: 10.1038/nm.3042]
145 **Rescigno M**, Di Sabatino A. Dendritic cells in intestinal homeostasis and disease. *J Clin Invest* 2009; **119**: 2441-2450 [PMID: 19729841 DOI: 10.1172/JCI39134]
146 **Laffont S**, Powrie F. Immunology: Dendritic-cell genealogy. *Nature* 2009; **462**: 732-733 [PMID: 20010677 DOI: 10.1038/462732a]
147 **Reis e Sousa C**. Dendritic cells in a mature age. *Nat Rev Immunol* 2006; **6**: 476-483 [PMID: 16691244 DOI: 10.1038/nri1845]
148 **Tezuka H**, Abe Y, Iwata M, Takeuchi H, Ishikawa H, Matsushita M, Shiohara T, Akira S, Ohteki T. Regulation of IgA production by naturally occurring TNF/iNOS-producing dendritic cells. *Nature* 2007; **448**: 929-933 [PMID: 17713535 DOI: 10.1038/nature06033]
149 **Niess JH**, Brand S, Gu X, Landsman L, Jung S, McCormick BA, Vyas JM, Boes M, Ploegh HL, Fox JG, Littman DR, Reinecker HC. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science* 2005; **307**: 254-258 [PMID: 15653504 DOI: 10.1126/science.1102901]
150 **Wykes M**, MacPherson G. Dendritic cell-B-cell interaction: dendritic cells provide B cells with CD40-independent proliferation signals and CD40-dependent survival signals. *Immunology* 2000; **100**: 1-3 [PMID: 10809952 DOI: 10.1046/j.1365-2567.2000.00044.x]
151 **Chieppa M**, Rescigno M, Huang AY, Germain RN. Dynamic imaging of dendritic cell extension into the small bowel lumen in response to epithelial cell TLR engagement. *J Exp Med* 2006; **203**: 2841-2852 [PMID: 17145958 DOI: 10.1084/jem.20061884]
152 **Belz GT**, Nutt SL. Transcriptional programming of the dendritic cell network. *Nat Rev Immunol* 2012; **12**: 101-113 [PMID: 22273772 DOI: 10.1038/nri3149]
153 **Rönnblom L**, Eloranta ML. The interferon signature in autoimmune diseases. *Curr Opin Rheumatol* 2013; **25**: 248-253 [PMID: 23249830 DOI: 10.1097/BOR.0b013e32835c7e32]

**P- Reviewer**: Berardinis P, Guglielmi FW, Kato T
**S- Editor**: Gou SX **L- Editor**: A **E- Editor**: Wang CH