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Phenotype and function of intestinal dendritic cells

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Abstract

It is now appreciated that dendritic cells (DCs) play a primary role in oral tolerance and defense against mucosal pathogens. Specific DC subpopulations are localized to discrete regions within primary inductive tissues, like the Peyer's patch and mesenteric lymph node, and effector sites, like the lamina propria, and may have unique roles in driving regulatory, effector and memory T cell responses. Certain DC subpopulations may also help maintain T cell responses at sites of abnormal intestinal inflammation. While early in our understanding, knowledge about the involvement of DC subpopulations in the regulation of mucosal immunity may well provide a basis for the development of novel vaccines and therapeutics.

Keywords: Intestine; Peyer's patches; Mesenteric lymph nodes; Lamina propria

1. Introduction

The central issue in mucosal immunology is how an individual is able to maintain immunologic tolerance to the myriad of innocuous environmental and food antigens and commensal bacteria, yet develop strong effector responses to invading pathogens. Over the past several years it has become clear that dendritic cells (DCs) are key players in this decision-making. First, DCs, which are known to be unique in their ability to bind and activate naïve T cells, are prominently localized to mucosal surfaces, both at sites of antigen uptake and within inductive lymphoid tissue. Second, mucosal DCs have been shown to process antigens given in both a tolerogenic and immunogenic form, and to directly sample endogenous flora and pathogenic microorganisms in vivo. And third, subpopulations of mucosal DCs have been identified to have unique functions when compared to DCs from non-mucosal sites, both with regards to the induction of regulatory T cells in the resting, or "steady" state, and in the processing and presentation of pathogens following mucosal infection. This review will briefly summarize what is known about DC subpopulations in the intestine and related lymphoid tissues, followed by a working model for how these subpopulations may be involved in mucosal tolerance and immunity. Because of the paucity of data for human intestinal DCs in general, and for intestinal subpopulations in particular, we will focus mainly on what is known in the mouse and subsequently comment on correlations with the human system.

2. DC populations

DCs can be divided into several subsets present to different degrees in tissues and organs (see Table 1). The subsets have primarily been defined by the expression of cell surface markers such as CD11c, CD8α, CD11b and CD4. The three main subsets are all $CD11c^{hi}$ and further divided into $CD8\alpha^{-}CD11b^{+}CD4^{+}$ (herein called $CD4^{+}CD11b^{+}$), $CD8\alpha^{-}CD11b^{+}CD4^{-}$ ("double negative", herein called $CD11b^{+}$) and $CD8\alpha^{+}CD11b^{-}CD4^{-}$ (herein called $CD8\alpha^{+}$). All $CD11b^{-}$ DCs have low expression of CD11b but are commonly designated as $CD11b^{-}$. All three DC subsets have a life span of 3–5 days and arise from independent precursors, i.e., one subset does not appear to mature into another under steady state conditions [1]. Intestinal mucosal lymph nodes (LNs), Peyer's patches (PPs) and mesenteric lymph nodes (MLNs), and the liver contain one additional population of DCs, the $CD8\alpha^{-}CD11b^{-}CD4^{-}$ DCs ("triple

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Table 1
Approximate percentage of DC subpopulations amongst $CD11c^+$ cells in different organs in mice [3,16,40,58]

DC subset	Spleen	MLN[a]	PP	PLN	LP[b]	Liver
$CD8\alpha^-CD11b^+CD4^+$	50	Few	Few	Few	5	5
$CD8\alpha^+CD11b^-CD4^-$	25	25	40	50	20	10
$CD8\alpha^-CD11b^+CD4^-$	20	40	30	40	55	35
$CD8\alpha^-CD11b^-CD4^-$	Few	30	30	10	20	50

[a] MLN, mesenteric lymph nodes; PP, Peyerĭs patches; PLN, peripheral lymph nodes; LP, lamina propria.
[b] Small intestine lamina propria from Flt3-L injected mice.

negative", herein called $CD8\alpha^-CD11b^-$) [2,3]. Another type of DCs, plasmacytoid DCs (pDCs), expresses intermediate levels of CD11c in addition to Ly6C and B220. pDCs are present in most organs, including the intestine [4,5]. A population of pDCs expressing CD8α may represent a more mature state, although this may not be the case in the mucosa (see [5]).

In addition to surface phenotype, functional specialization of these DC populations is suggested by a number of in vitro and in vivo studies. First, DC subsets localize to specific sites, indicating they interact with external antigens and with T and B cells to differing degrees. $CD8\alpha^+$ DCs are restricted to T cell zones while $CD8\alpha^-$ DCs (including $CD4^+CD11b^+$, $CD11b^+$ and $CD8\alpha^-CD11b^-$ DCs) are present at initial sites of antigen exposure, in B cell follicles, and at T–B junctions. Second, there may be differences in capacities of DC subsets to process and present certain antigens. For example, while $CD8\alpha^-$ DCs have an overall higher phagocytic capacity [6] $CD8\alpha^+$ DCs internalize apoptotic cells [7]. Consistent with this ability, $CD8\alpha^+$ DCs are also the major DC subset responsible for T cell tolerance following intra-venous (i.v.) injection of antigen-loaded apoptotic cells [7,8] and for the cross-presentation of self-antigens to $CD8^+$ T cells in vivo [9,10]. In addition, $CD8\alpha^+$ DCs can induce T cell tolerance following the targeting of soluble antigens to the C-type lectin antigen processing receptor DEC-205, which is expressed constitutively only on $CD8\alpha^+$ [11–13]. Third are studies demonstrating differences in the ability of DC populations to prime helper T cell responses. Early studies demonstrated that the adoptive transfer of antigen-pulsed $CD8\alpha^+$ DCs to naïve recipient mice preferentially induced Th1 responses, while $CD8\alpha^-$ DCs induce Th2 responses [14,15]. Consistent with this role in Th-cell induction, $CD8\alpha^+$ produce much higher amounts of IL-12p70 than $CD8\alpha^-$ DCs upon stimulation in vivo and in vitro with microbial products [14,16,17]. Furthermore, the ability of $CD8\alpha^+$ DCs to induce Th1 responses following adoptive transfer is dependent on their production of IL-12p40 (thus either IL-12p70 or IL-23), while $CD8\alpha^-$ DC induction of Th2 responses was dependent to some degree on autocrine production of IL-10 [18]. Finally, as discussed below, mucosal DCs in the steady state might prime T cells for IL-10 production, which may be a functional specialization of a particular DC subset.

3. Intestinal dendritic cells

Fundamental to understanding how mucosal immune responses are induced and regulated is the issue of where different types of antigens are processed and how they are presented by DCs to T and B cells. Primary sites for the induction of intestinal T and B cell responses are PPs, colonic lymphoid follicles and MLNs. In contrast, lamina propria (LP) and the intra-epithelial cell (IEC) compartments are primarily effector sites. Multiple DC populations are represented in the PPs, colonic lymphoid follicles, MLNs and the LP. While little is still known regarding the locations of antigen uptake for any particular antigen and which DC populations are involved, several general aspects of DC function are clear. Under steady state conditions (without infection, vaccination with mucosal adjuvants, or inflammation) DCs from the intestine migrate constitutively from the LP and/or PPs and to the MLNs. It is also clear that upon activation these DCs will migrate at a much more rapid rate to MLNs or within PPs to PP T cell zones. While the nature of the DCs migrating in the steady versus the stimulated state are not at all clear, it is logical to postulate that steady state DCs are responsible for tolerance induction to innocuous food antigens and commensal organisms via their ability to induce regulatory T cells or clonal deletion. This similar to what is thought for steady state DC migration in non-mucosal tissues. These DCs may also provide a stimulus for the production of IgA against commensal organisms from the colon or terminal ileum (where bacteria "spill-over" from the proximal colon). In contrast, DCs migrating upon exposure to pathogens or activating cytokines (like IL-1 or TNF-α) are active inducers of effector cells. What follows is that steady state DCs may be less-than-fully or alternatively "activated", while DCs induced to migrate are fully "activated" or "mature" to express the entire panoply of costimulatory molecules and cytokines to drive effector responses (Fig. 1). Given this theoretical model, what is presented in the following sections are details of what is known regarding subpopulations of DCs in the intestine and how they may be involved in decisions regarding the induction of tolerance and effector cells.

4. Peyer's patches

Luminal antigens gain access to the cells of PPs via specialized epithelial cells, M (micro-fold) cells, which are scattered among the columnar epithelial cells in the follicular associated epithelium (FAE) above the PPs [19,20]. After antigen transport into the PPs, DCs likely play a key role in uptake and antigen processing because there is a striking concentration of $CD11c^+$ DCs in the subepithelial dome (SED) and T cell zones (inter-follicular regions, IFR) [21,22]. DCs in the SED phagocytose orally administered *Salmonella typhimurium* [23,24] and are the first targets of *Listeria monocytogenes* infection [25]. In addition, PP DCs take up and process soluble protein antigens given orally to mice [21].

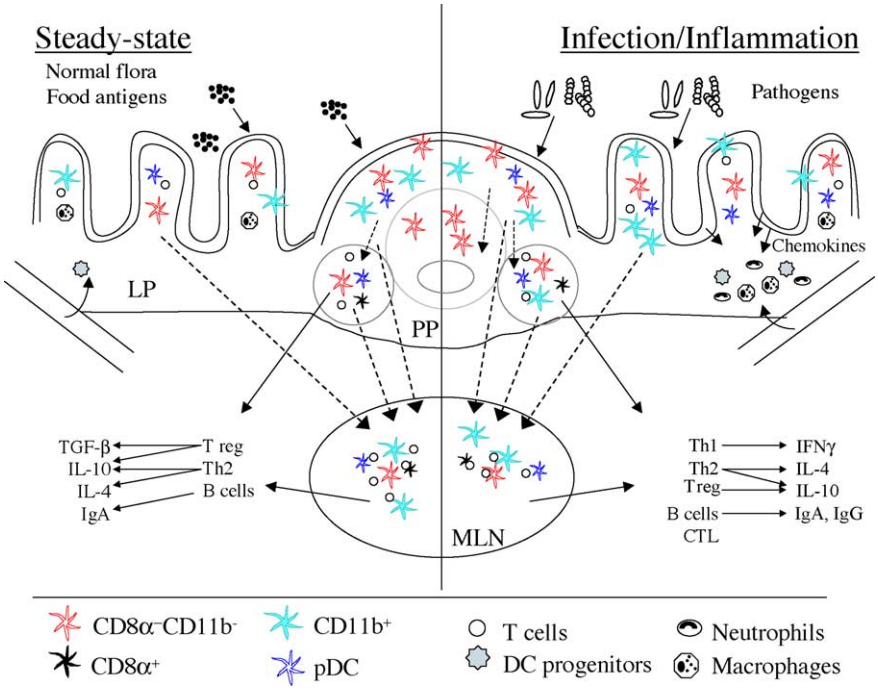

Fig. 1. Schematic model for mucosal DCs during steady state and inflammatory conditions. See text for details.

PPs contain three predominant populations of $CD11c^+$ DCs; $CD11b^+$, $CD8\alpha^+$ and $CD8\alpha^-CD11b^-$ (Table 1, [2,16]). The latter population is highly over-represented in both the PPs and MLNs compared to the spleen and peripheral LNs. Following isolation these three DC subsets expressed similar levels of major histocompatibility complex (MHC) class II and costimulatory markers, with enhanced expression upon activation. All subsets maintained their CD8α and CD11b expression upon activation, suggesting one population is not simply a more differentiated or activated form of another population [2,16]. In addition, all three subsets were shown to arise from independent precursors as shown by BrdU incorporation (Johansson and Kelsall, unpublished observation). DCs expressing CD11b were found to be localized in the SED, whereas $CD8\alpha^+$ DCs were localized exclusively in the IFRs [2]. $CD8\alpha^-CD11b^-$ were present in both SED and IFR, and scattered throughout the B cell follicle, except the germinal centers. Furthermore, a population of $CD8\alpha^-CD11b^-$ DCs present within the FAE expressed high levels of intracellular (rather than surface) MHC class II, indicating an immature phenotype [16]. Some of these cells co-associated with UEA^+ M cells, suggesting at least some DCs reside in M cell pockets. MHC class II^{hi} cells were also identified within the FAE in the rat [26] and human [27].

Chemokines and chemokine receptors that govern the localization and migration of DC populations in the intestine are just beginning to be unraveled. In PPs in the steady state, $CD11b^+$ DCs appear to be recruited to SED by a number of chemokines expressed constitutively by epithelial cells in FAE, including CCL9 [28] and CCL20 [2,29]. The chemokines that attract $CD8\alpha^-CD11b^-$ DCs to this site have not been identified. PP DCs have been shown to express the integrin–ligand mucosal addressin–cell adhesion molecule-1 (MAdCAM-1), which preferentially binds the integrin molecule most associated with mucosal cell homing, α4β7 [30], suggesting that SED DCs express surface molecules that facilitate interactions with mucosal T and B cells. Furthermore, upon activation in vivo with a soluble tachyzoite antigen preparation from *T. gondii* trophozoites (STAg) the SED $CD11b^+$, and possibly some $CD8\alpha^-CD11b^-$ DCs migrated to the PP IFR [2]. This correlated with an upregulation of CCR7 upon overnight culture. CCR7 is the receptor for CCL7 and CCL8, which are constitutively expressed in the IFR [2]. These studies support the hypothesis that activation of DCs in the SED, as would occur following exposure to organisms entering via M cells, results in their migration to the IFR where T cell priming can occur. In contrast, $CD8\alpha^+$ DCs constitutively expressed CCR7 and not CCR6 and migrated towards CCL7, but not CCL20, suggesting that $CD8\alpha^+$ DCs are resident in the IFR throughout much of their life cycle.

In functional in vitro assays, PP $CD11b^+$ DCs produced very low levels of bioactive IL-12p70 upon stimulation with *Staphylococcus aureus* Cowan strain (SAC) and IFN-γ similar to spleen $CD11b^+$ DCs. However, when compared to either the $CD8\alpha^+$ or $CD8\alpha^-CD11b^-$ PP DCs, or to $CD11b^+$ DCs from the spleen or peripheral LNs, PP $CD11b^+$ DCs produced high levels of IL-10 in response to SAC and IFN-γ, as well as to CD40 stimulation with soluble trimerized CD40-ligand [16]. In addition, $CD11b^+$ PP DCs induced naïve T cells to differentiate in vitro into cells that produced much

higher levels of IL-10 than T cells primed with any other DC subset. In contrast, both $CD8\alpha^+$ and $CD8\alpha^-CD11b^-$ PP DCs produced IL-12 and little to no IL-10 after stimulation with CD40-L or SAC and IFN-γ and induced the differentiation of T cells producing only IFN-γ, similar to the $CD8\alpha^+$ splenic DCs [16]. The studies also showed that the $CD11b^+$ DCs from the PP are unique in their ability to induce IL-10-producing T cells and thus may have a role in the induction of regulatory T cells or the induction of IgA B cell responses. The latter was recently supported by studies demonstrating that when compared with splenic DCs, freshly isolated PP $CD11b^+$ DCs induced higher levels of IgA secretion from naive B cells in a DC–T cell–B cell coculture system [31]. Taken together, these studies support the hypothesis that IL-10, and possibly TGF-β, are produced by PP DCs upon interaction with naive T cells under steady state conditions, and that these cytokines either directly or indirectly drive T cells to differentiate into T cells producing IL-4, IL-10 and TGF-β. Similar findings have been reported for lung DCs (see [32]) suggesting that the production of IL-10, and the induction of IL-10-producing T cells appears to be a fundamental characteristic of DCs at mucosal sites under steady state conditions.

Several characteristics have been shown for the $CD8\alpha^-CD11b^-$ DCs subset. A population of $CD11c^+$ $CD8\alpha^-CD11b^-$ cells in the SED has been shown to take up 0.2 μm fluorescent latex beads given orally [33]. These cells remained in the SED for up to 14 days and rapidly migrated to the IFR following the administration of cholera toxin, suggesting that they may represent a resident population of long-lived cells particularly capable of processing particulate antigens. In addition, recent studies from our laboratory demonstrate that $CD8\alpha^-CD11b^-$ DCs process and present antigens from type 1 *Reovirus*, at least some of which is in the form of apoptotic bodies from infected epithelial cells from the FAE [34]. Whether this "cross-presentation" pathway applies to other organisms shown to induce apoptosis of epithelial cells, such as *Salmonella* [35] is not clear.

Recently, $CD11c^{int}$ $B220^+$ pDCs were identified in the IFR of murine PPs [4]. In addition, pDCs were isolated from PPs and MLNs of mice treated with Flt-3-ligand, which dramatically and preferentially increases the numbers of DCs, including pDCs [36]. These cells expressed the typical markers of pDCs, including B220 and Ly6C, but also expressed CD8α. In unpublished data from our laboratory, we have identified both $CD8\alpha^+$ and $CD8\alpha^-CD11c^{int}$ $B220^+$, $Ly6C^+$ pDCs in the PPs of untreated mice and have confirmed the localization of pDCs in the IFR and SED (Contractor and Kelsall, unpublished observation). Functional studies of PP and MLN pDCs from Flt3-L injected mice showed that these cells produce IFN-α, and are poor stimulators of antigen-specific T cells, similar to pDCs from the blood and other tissues. However, these cells were capable of inducing differentiation and/or activation of IL-10 producing T cells from TCR-transgenic mice in vitro [36], similar to a $CD8\alpha^+$ pDC subset described from the spleen [37] suggesting that they might be important for the induction of regulatory T cells.

Finally, PP (and MLN, see below), but not splenic or peripheral LN DCs can induce the expression of the mucosal homing receptor α4β7 and the chemokine receptor CCR9 on T cells in vitro [38]. Upon adoptive transfer to naïve mice, PP DC-primed $CD8^+$ T cells preferentially migrate to mucosal lymphoid tissues. These studies demonstrated for the first time that DCs from different tissues have the capacity to imprint T cells with tissue-specific homing receptors. In addition, it has recently been shown that all PP DC subsets have the capability to induce α4β7 expression on $CD8^+$ T cells [39].

5. Mesenteric lymph node

The phenotype of DCs and the DC subsets in MLNs are very similar to those of the PPs (Table 1, [16]). $CD8\alpha^+$, $CD8\alpha^-CD11b^-$ and pDCs have been localized to the T cell zones, whereas $CD11b^+$ DCs are located primarily outside the T cell zones (Kelsall, unpublished observation and [4]). Whether the population we describe as $CD8\alpha^-CD11b^-$ corresponds to a $CD8\alpha^-CD11b^{lo}CD205^{int}$ DC population described in the MLNs by others (see [40]) has not yet been resolved. Interestingly, the $CD8\alpha^-CD11b^-$ DCs in the PP do not express CD205, or higher levels of MHC class II molecules than other subsets following isolation, although both surface antigens could be upregulated after overnight incubation in vitro with CD40-L trimer. Thus, the $CD8\alpha^-CD11b^{lo}CD205^{int}$ DCs in the MLNs may represent more "mature" (at least with regards to MHC class II expression) $CD8\alpha^-CD11b^-$DCs that have migrated from the PPs or LP under steady state conditions.

The site of antigen acquisition of MLN DCs is difficult to determine precisely. However, it is likely that antigen-loaded DCs migrate directly from the intestinal tract, since thoracic duct cells from normal rats contain very few DCs (<0.2%), when compared with rats that have had their MLNs removed (approximately 4%) [41]. Furthermore, i.v. injections of lipopolysaccharide (LPS) into rats have been shown to stimulate increased traffic of DCs from the intestine into the lymph [42]. These migrating DCs have rapid turnover in the intestine (estimated to be on the order of 3–4 days) similar to most other DC populations, which is significantly shortened following the induction of TNF-α production by systemically administered LPS [41,42]. Rat intestinal lymph contains at least two DC populations that have typical DC morphology, are MHC class II^{hi}, and express OX62, CD11c, and CD80. One population, $CD4^+$/OX41$(SIRP\alpha)^+$ DCs, are strong antigen presenting cells (APCs) in mixed lymphocyte reaction (MLR) assay, whereas the other population, $CD4^-$/$OX41^-$ DCs are weak APCs (see [43]). Both DC populations are also present in rat MLNs, where $CD4^-$ DCs are localized to T cell zones and $CD4^+$ DCs are found outside the T cell

zone in the parafollicular regions. A recent study showed that ∼70% of the DCs migrating from the intestine were $CD4^{hi}$. In addition, after LPS injection the ratio of $CD4^{hi}$ and $CD4^{lo}$ cells was the same [22] indicating that the subsets are migrating in a similar fashion. Many MLN $CD4^-$/$OX41^-$ DCs contain cytoplasmic apoptotic DNA, epithelial cell-restricted cytokeratins and non-specific esterase-positive inclusions, suggesting that these cells carry material from apoptotic epithelial cells to T cell zones of the MLNs [44]. In addition, $CD4^-$ DCs from the rat spleen produce IL-12 after stimulation in vitro, while the $CD4^+$ DCs do not. These studies suggest that rat $CD4^-$ DCs are similar to mouse $CD8\alpha^+$ DCs, whereas rat $CD4^+$ DCs resemble mouse $CD11b^+$ DCs (see [43]).

In further studies of DCs ability to stimulate naïve allogeneic T cells rat LP and PP DCs stimulated only modest proliferation in a MLR, compared to MLN and thoracic duct lymph DCs, which induced a potent response [45]. In addition, following overnight culture with GM-CSF, PP and LP DCs had significantly increased ability to induce a MLR, equivalent to that of lymph or MLN DCs, which did not have enhanced accessory activity following activation in vitro. This suggests that PP and LP DCs are less activated than DCs that have migrated to the MLNs, and support the general concept that DCs become more capable of inducing T cell differentiation after migration from sites of antigen acquisition. These studies raise questions as to the nature of DCs migrating in the steady state in that they indicate that such DCs are not functionally "immature" with regards to their ability to drive T cell proliferation. Additional studies of cytokine production and surface molecules, such as inducible-costimulator ligand (ICOS-L) [46], or PD-L1 (B7-H1) (see [47]) may be helpful in identifying the characteristics of these constitutively migrating DC that may results in tolerogenic responses.

Functional studies have also demonstrated similarities between MLN and PP DCs. Similar to PP DCs, MLN DCs from antigen-fed mice preferentially stimulate antigen-specific $CD4^+$ T cells to produce IL-4, IL-10 and TGF-β [48,49]. Similar results were obtained with both wild type and μMT mice, which lack B cells and well developed PPs, arguing that soluble antigen-loaded MLN DCs do not necessarily originate in the PPs [49]. Also in MLNs $CD8\alpha^+$ DCs are the major IL-12 producing subset after T cell or microbial stimuli [17,50]. Another feature shared by MLN and PP DCs, as mentioned above, is the capacity to induce the expression of α4β7 and CCR9 on T cells [51,52]. Additional studies indicated that MLN DC expressing CD103 are the only DCs with the ability to generate $\alpha4\beta7^+CCR9^+$ gut tropic CD8 T cells (W. Agace, personal communication). Retinoic acid produced by mucosal DCs maybe a key molecule produced by the DCs driving this mucosal-homing T cell phenotype [53]. Finally, as mentioned above, $CD8^+$ pDCs from the MLN can induce the differentiation and or activation of IL-10-producing T cells from TCR-transgenic mice [36].

6. Lamina propria

DCs are a major APC in the intestinal LP of the mouse [54] and rat [22,26,45]. Recently, DCs were found to be a dominant cell in the LP of the small bowel in mice but rare in the colon, except in colonic lymphoid follicles [55,56]. In addition, in mouse and rat, DCs have also been described within the epithelium of the intestine [26,56,57]. In the rat, they have been described to form an organized network that extended dendrites between epithelial cells [26], whereas in the mouse, dendrites from LP DCs extend into the intestinal lumen [56,57]. The ability of DC to extend dendrites to sample bacteria is likely related to the fact that DCs can express tight junction proteins following bacterial exposure. This well orchestrated process results in the formation of dendrites extending through the epithelium without a disruption in the intestinal barrier [57]. Recently, bacterial sampling by DC extensions was demonstrated to occur in the steady state in the terminal ileum, indicating that DCs can sample commensal organisms from the lumen [56]. In addition to direct sampling, LP DCs may capture pathogens that directly invade the epithelium. Alternatively LP DCs can take up soluble or particulate antigens that cross the epithelial barrier by receptor-mediated transport or paracellular transport following disruption of the epithelial barrier, as occurs during inflammation. Whether apoptotic epithelial cells are processed by DCs in the LP and transported to the MLNs [44], as has been shown for PP DCs [34] remains to be established.

The surface phenotype of LP DCs is not as well defined as that of PP DCs. Mowat et al. [58] recently detected the same three $CD11c^{hi}$ DC subsets and pDCs in the small intestinal LP that have been defined in the PPs (Table 1). However, the predominant DC subset present in LP is controversial. DCs in the terminal ileum have been shown be $CD11b^+$ [56] or $CD8\alpha^-CD11b^-$ [55]. Furthermore, $CD11b^+$ DCs have been identified in colonic LP [59] and studies by our laboratory show a predominance of $CD11b^+$ and possibly few $CD8\alpha^-CD11b^-$ and $CD8\alpha^+$ DCs in the colonic LP of mice (He and Kelsall, unpublished observations).

Immature DCs may be attracted to mucosal tissues as immature cells and upon activation migrate to the PP IFRs or to MLNs for priming of naïve or activation of central memory T cells. Studies of chemokines responsible for the migration of DCs to the LP in the steady state are lacking, although epithelial cell-expressed CCL25, the ligand for CCR9 or CCR10 is a possible candidate chemokine in the small intestine and CCL28 the ligand for CCR3 or CCR10 may be important in the colon [28,60,61]. During inflammation, however, a large number of inflammatory chemokines are produced by epithelial cells, which could attract DCs, including CCL20/CCR6, CCL2/CCR2, CCL5/CCR5 or CCR1 and CXCL-12/CXCR4 [60,62,63]. However, given the redundancy of the chemokine system, and the likely need for signals for both cell extravasation into and localization within tissues, multiple chemokines/receptors are certainly involved in DC migration in both inflamed and non-inflamed mucosa.

Freshly isolated LP DC are similar to PP DC in the expression of costimulatory molecules, antigen uptake and stimulation of antigen-specific T cells in vitro [58]. Functional studies of LP DCs from all species have confirmed that these cells are potent inducers of a MLR [45,54]. DCs in the terminal ileum of mice (but not of the more proximal small intestine) were shown to express IL-12p40 in the steady state, as well as mRNA for p19 (much greater than IL-12p35) suggesting they constitutively express IL-23 [55]. How this constitutively expressed IL-23 relates to immune regulation, in particular to commensal organisms, is not yet clear. In addition, these cells were associated with bacteria in vivo suggesting that DCs in the terminal ileum may normally process endogenous bacterial microflora, likely following direct uptake of bacteria in the intestinal lumen (as discussed above). Finally, it has been suggested that DCs from the small intestine LP may be particularly capable of inducing oral tolerance [58]. In these studies, soluble protein given orally was preferentially taken up by small bowel LP DCs compared to PP DCs. LP DCs isolated and adoptively transferred to a naïve mouse could transfer tolerance to the fed protein. However, whether specific subsets of DCs preferentially process soluble mucosal antigens and are responsible for oral tolerance induction in this or any other model is not yet clear.

During experimental inflammatory bowel disease (IBD) DCs have been shown to accumulate throughout the colon LP and in MLNs [59]. Approximately 50% of the colonic DCs were $CD11b^+$ and 50% were pDC ($CD11b^-B220^+$). In addition, a role has been suggested for local DCs in a model of IBD induced by the adoptive transfer of naïve $CD4^+CD45RB^{hi}$ T cells (i.e., in the absence of $CD4^+CD45RB^{lo}CD25^+$ regulatory T cells) into *rag1*$^{-/-}$ mice which results in uncontrolled colonic inflammation. In this model, subsequent transfer of $CD25^+$ regulatory T cells during active colitis results in amelioration of the inflammation, and DCs were found in close approximation to actively dividing populations of both effector and regulatory T cell populations [64]. Taken together, these studies suggest that $CD11b^+$ DCs are important for driving T cell responses during colonic inflammation. It is likely that the presence of inflammatory cytokines in the tissue microenvironment causes activation of $CD11b^+$ DCs, which results in the local induction of pathogenic and possibly regulatory T cells. Whether this represents a different $CD11b^+$ DC population to that in the MLNs or PPs which are poor producers of IL-12 and induce IL-10 producing T cells in the steady state is not yet clear. One interesting possibility is that $CD11b^+$ DCs in the inflamed colon produce IL-23, not IL-12, and expand pathogenic T cells in situ (see [65]).

7. Intestinal dendritic cells in the human

Whether all murine DC subpopulations have phenotypic and functional equivalents in humans is also not yet elucidated (see [40]). This is because most studies of human DCs, out of experimental necessity, are using DCs generated in vitro from blood monocytes, or $CD34^+$ precursors from either cord blood or bone marrow treated with cytokines. In addition, surface markers of human DC subsets are not analogous to those of the mouse. In particular, CD11c, which is a key marker to identify DCs in the mouse is broadly expressed by many human hematopoetic cells, and is present only on certain subpopulations of human DCs. Despite these limitations, however, studies of human and mouse DCs generated in vitro and the few studies of DCs in situ, or directly isolated from human tissue, suggest that functional equivalents will be identified.

The importance of DCs in the induction of mucosal immune responses in humans was initially suggested by studies that identified MHC class II^+ cells with the morphology of DCs in PPs [27,66] and the LP of the intestine [67] and demonstrated their ability to act as APCs, primarily via their ability to stimulate a MLR. However, overall there is a tremendous paucity of data on intestinal DCs in humans.

In human PPs, MHC class II^+, S-100 $protein^+$ cells, most likely DCs, were identified in the IFR and SED, and the cells in the SED had cytoplasmic processes that extended into the dome epithelium [27,66]. In more recent studies, PP DCs were more clearly identified in humans and macaques. Furthermore, DCs in the IFR and some in the SED expressed DC-SIGN [68], suggesting that these cells may be targets of HIV and other mucosal pathogens that attach to this lectin receptor (see [69]). In addition, cells expressing the M-DC8 antigen, a marker of DCs, were found in the SED region of tonsils and PPs from inflamed tissues [70]. The latter produced high levels of TNF-α, and may have a role in driving T cell responses during inflammation.

DCs in the human MLNs are $HLA\text{-}DR^{hi}$, large dendriform cells in the T cell areas that co-express CD40, CD54, CD80, CD83, CD86 and the S-100 protein but lack CD1a. These DCs are attached to numerous $CD4^+$ T cells and IgD^+ naive B cells in vivo and preferentially form clusters with IgD^+ IgM^+, but not IgA^+ or IgG^+ B cells in vitro. These findings suggest that human MLN DCs may induce T cell help for primary B cell responses [71].

In the small bowel LP, DCs have been identified in poorly defined lymphoid aggregates that do not have the structure of PPs [72]. In the large bowel, $CD11c^+HLA\text{-}DR^+lin^-$ ($CD3^-CD14^-CD16^-CD19^-CD34^-$) DCs in colonic and rectal biopsies have been reported to be of an immature phenotype, but to mature into fully immunostimulatory DCs following overnight culture [73]. Similarly, $CD83^+$ and DC-$SIGN^+$ cells have been identified in the LP and may produce IL-12 and IL-18 during intestinal inflammation from Crohn's disease [68,74]. In addition, M-$DC8^+$ cells were shown to infiltrate ileum during Crohn's disease [70]. Furthermore, CCL20 is overexpressed in the intestinal epithelium associated with human IBD lesions and this was reported to correlate with an increase in the number of immature $Langerin^+$ DC in situ [75]. Because TNF-α increased the expression of CCL-20 in colonic explant cultures from nor-

mal patients, immature DCs (as well as T cells) expressing CCR6 may be attracted to enhanced expression of CCL20 by epithelial cells in the inflamed intestine [75]. In tissues from patients with ulcerative colitis (UC) there is an increase in the number of $CD83^+$ and $CD86^+$ LP cells, most likely DCs, which produce macrophage inhibitory factor (MIF). MIF in turn can induce IL-1 and IL-8 production by monocytes and DCs [76], which may contribute to neutrophil recruitment and activation. Also in UC, colonic LP has been shown to contain numerous basal aggregates composed of lymphocytes and $CD80^+$ dendritiform cells that most likely represent activated DCs [77]. Finally DC-SIGN-expressing cells are found diffusely throughout the human and rhesus macaque rectal LP, and some of these cells co-express CCR5 and CD4, suggesting they could be targets of HIV infection [68].

Taken together these data suggest that, similar to mouse models, DCs are important for the regulation of intestinal immunity in humans. Intestinal DCs appear to be localized in similar sites in the mouse and human, and are likely involved in the induction of oral tolerance, defense against intestinal pathogens and pathogenesis of abnormal mucosal inflammation. However, studies of human mucosal DCs are hampered by the lack of adequate tissue samples for evaluation, especially of purified cells, so there is little consistent data regarding the phenotype or function of specific DC subpopulations within the human intestine. This is a difficult but important area of future research.

8. Intestinal DC populations in tolerance and immunity

Based on the information presented above (as summarized in Table 2), it is possible to present a model of how DC subsets may play a role in the induction of oral tolerance and immunity to mucosal pathogens (Fig. 1). Under steady state conditions, immature or precursor DCs continuously enter the mucosal LP and PPs and become localized to different regions by the local constitutive expression of specific chemokines, such as CCL9, CCL19, CCL20 and CCL21. After transport of antigens across M cells, or epithelial cells, or possibly via uptake of antigen associated with apoptotic bodies from epithelial cells, DCs migrate from the LP to the MLNs or from the PP SED to the PP IFR. This is accompanied by an upregulation of chemokine receptors for T cell zone chemokines, such as CCR7, but low levels of co-stimulatory molecules and cytokines. What triggers this migration during steady state conditions is not clear. Migration from the PPs to the MLNs is less likely since the PPs contains T cell zone chemokines, such as CCL19 and CCL21, that will attract activated or "quiescent" DCs. These "quiescent" DCs migrate to T cell zones in the PPs or MLNs and induce clonal deletion of T cells and stimulate T cells to differentiate into regulatory T cells that can mediate bystander tolerance following subsequent antigen encounter. These DCs could also interact with B cells and induce IgA responses to commensal bacteria [78].

The induction of regulatory cells may involve one or more DC populations. $CD11b^+$ DCs are ideally located for antigen capture in the PP SED and LP, produce IL-10, and induce IL-4, IL-10 and likely TGF-β-producing T cells. PP DCs could either induce regulatory T cells to differentiate in the SED or migrate to the IFR to induce regulatory CD4 (or CD8) T cell responses. LP DCs could activate regulatory T cells in the LP, or migrate to the MLNs to induce or expand regulatory CD4 or CD8 T cells. In the PPs or LP, it is possible that innocuous antigens are also processed by the $CD8\alpha^-CD11b^-$ DCs, but in the absence of a strong activating signal, such as an adjuvant, these cells produce little IL-12, and may potentially induce T cell deletion (similar to high dose antigen feeding as discussed below) or contribute to regulatory T cell differentiation under the influence of bystander IL-10 or TGF-β.

In addition to $CD11b^+$ DCs, another candidate for regulatory T cell induction is the pDCs, which, as mentioned above is also located with in the PP SED and IFR, and LP. In particular, $CD8\alpha^+B220^+$ pDCs from the PPs and MLNs were shown to induce the differentiation of IL-10-producing regulatory T cells in vitro that could mediate suppression [36]. The phenotype of PP and MLN DCs that induce regulatory T cells may be influenced by local stromal factors, such as TGF-β and PGE_2 [79–81]. Thus, intestinal stromal cells may promote a suppressive environment that conditions DCs to induce regulatory T cells.

In contrast to tolerogenic responses to innocuous antigens, during infection or inflammation, DCs become activated, migrate more rapidly and induce both innate and adaptive immune responses (Fig. 1). The nature of ensuing immune responses depends on the signals to which DCs are exposed during their activation and interaction with T cells. Such signals include cytokines, chemokines (CCL20, CCL5, IL-8, CCL2), prostaglandins, PAMPs, costimulatory molecules (CD40-L), complement fragments, Ig and products from damaged cells, such as uric acid [82,83]. A change of the microenvironment during active infection or inflammation promotes the recruitment of DC precursors, in addition to neutrophils and inflammatory macrophages. The local production of mediators such as, IL-1, IL-6, IL-12, IL-18, IL-23 and TNF-α enhances pathogen clearance, and in the case of IBD, contributes to abnormal intestinal inflammation.

In the mouse, $CD11b^+$, or $CD8\alpha^-CD11b^-$ DCs in the SED of PP or LP are, due to their localization, most likely involved in the initial interaction and uptake of invading pathogens. $CD8\alpha^+$ DCs may be involved in the direct presentation of disseminated pathogens or in the cross presentation of antigens carried to the IFRs by DCs, or antigens from exosomes from epithelial cells. Direct activation of pDCs in the PP or LP by viruses will result in type 1 IFN production, which can activate innate defense mechanisms, as well as contribute to the activation of non-pDCs. pDCs may also be driven to mature into immunostimulatory DCs by viral pathogens. Thus, the induction or expansion of specific T cell

Table 2
Summary of phenotype, location and suggested functional properties of intestinal DC subpopulations in PP, MLN and LP in mouse[a]

Subset	Phenotype	Localization	Function	References
$CD8\alpha^+$	$CD11c^+$ $CD8\alpha^+$ $CD11b^-$ $CD4^-$	PP: IFR MLN: ? LP: ?	PP: Produce high IL-12, low IL-10 Present reovirus antigens to CD4 T cells MLN: Produce IL-12 LP: ?	[2,16,17,34,40,50,58]
$CD11b^+$	$CD11c^+$ $CD8\alpha^-$ $CD11b^+$ $CD4^-$	PP: SED MLN: ? LP: Scattered, intra-epithelial dendrites in terminal ileum	PP: Produce high IL-10, low IL-12 Induce differentiation of IL-10-producing reg T cells Induce differentiation of T cells that drive IgA production from B cells MLN: ? LP: Accumulate at sites of colonic inflammation Take up bacteria in the terminal ileum	[2,16,31,40,56,58,59,64]
$CD8\alpha^-CD11b^-$	$CD11c^+$ $CD8\alpha^-$ $CD11b^-$ $CD4^-$	PP: FAE, SED, IFR, B cell follicle MLN: ? LP: Scattered	PP: Produce high IL-12, low IL-10 Take up reovirus-infected apoptotic epithelial cells in the SED Present reovirus antigens to CD4 T cells MLN: ? LP: Express IL-23 in steady state Take up bacteria in terminal ileum	[16,34,40,55,58]
pDC	$CD11c^{int}$ $B220^+$ $Ly6C^+$ $CD8\alpha^{-/+}$ $CD11b^-$	PP: SED, IFR MLN: T cell zones LP: ?	PP/MLN: Produce IFN-α Poor stimulators of antigen-specific T cells Induce differentation of IL-10-producing reg T cells LP: Accumulate at sites of colonic inflammation.	[4,36,59]

[a] PP, Peyer's patches; MLN, mesenteric lymph nodes; PLN, peripheral lymph nodes; LP, lamina propria; IFR, inter-follicular region; SED, subepithelial dome; FAE, follicular associated epithelium; reg, regulatory.

responses by mucosal DCs following infection will depend on the subset of DC involved, the particular compilation of surface receptors engaged by the pathogen, microenvironmental factors and the combined effects of antigen dose and duration and/or frequency of T cell–DC contacts.

9. Concluding comments

The major role of mucosal DCs in regulating immune responses is yet to be elucidated. Mucosal DCs have potential roles in initiating immune responses to pathogens as well as control of regulatory T cell activity regulation and oral tolerance. In addition, mucosal DCs might also have an important function in induction, maintenance or down regulation of abnormal mucosal inflammation, as occurs in allergy and IBD. All mucosal DCs are working in a steady state suppressive milieu containing factors like thymic stromal lymphopoeitin (TLSP), PGE_2, IL-10 and TGF-β. They have a particular capacity to induce regulatory T cell differentiation in the steady (non-infected, non-immunized) state, but however, allow for the induction of effector T cell responses, depending on both the particular subpopulation involved, and the surface receptors engaged during DC activation and T cell priming. In addition, mucosal DCs may contribute to innate defense by the production of cytokines, such as type-1 IFN, IL-12 and TNF-α, following direct exposure to pathogens, as well as contribute to the maintenance of secondary T cell responses within inflamed mucosa.

Many questions remain regarding the function of mucosal DC populations in the intestine. Much of the data generated thus far are descriptive and based on staining of tissue sections or in vitro studies of isolated cells. While this information is important for developing appropriate working models of the involvement of DC populations in mucosal immunity, many fundamental questions concerning antigen uptake, trafficking and function remain unanswered or even unaddressed. One particular question is whether the functional diversity of DCs is a result from functionally independent DC subpopulations or not? In other words, are different subpopulations of DCs involved in the induction of Th1, Th2 or regulatory T cell responses in vivo? This is still unanswered, and will likely require the generation of DC subset specific knockout mice to address adequately. A broader issue in this regard is

whether current definitions of DC subpopulations based on a few surface markers are appropriate for understanding all DC functions. Future studies will need to be open-minded with regard to the definition of DC subtypes. Another fundamental question is whether mucosal DCs are truly unique in their capacity to induce T cells that mediate IgA B cell switching or oral tolerance, or whether the microenvironment in which activation occurs is more important? While in vitro studies suggest that mucosal DCs, and in particular certain populations of mucosal DCs, are directing these unique responses, the translation of these findings to in vivo models is still inadequate. Finally, the role of DC populations in the expansion of central memory T cells in draining LNs, or the activation of effector and regulatory T cells at local sites during abnormal intestinal inflammation needs to be addressed. The hope is that a better understanding of the biology of mucosal DC will eventually translate into novel methods for inducing or suppressing mucosal and systemic immunity.

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