Review

Intestinal CD103$^+$ dendritic cells: master regulators of tolerance?

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CD103$^+$ dendritic cells (DCs) in the intestinal mucosa play a crucial role in tolerance to commensal bacteria and food antigens. These cells originate in the lamina propria (LP) and migrate to the mesenteric lymph nodes (MLNs), where they drive the differentiation of gut-homing FoxP3$^+$ regulatory T cells by producing retinoic acid from dietary vitamin A. Local 'conditioning' factors in the LP might also contribute to this tolerogenic profile of CD103$^+$ DCs. Considerably less is understood about the generation of active immunity or inflammation in the intestinal mucosa. This might require alterations in pre-existing CD103$^+$ DCs, arrival of new DCs, or the action of a distinct DC population. Here, we discuss our current knowledge of this as yet incompletely understood population.

Tolerance versus immunity in the intestine – a delicate balancing act

The intestinal immune system must discriminate between pathogens and harmless antigens such as commensal microorganisms and dietary constituents. In the case of pathogens and other harmful antigens, it is necessary to induce a strong and protective response, resulting in the elimination of the threat. However, the usual response to harmless antigens or nutrients is to induce tolerance [1,2], which prevents unnecessary inflammation and hypersensitivity. This state of hyporesponsiveness to fed antigen is known as oral tolerance. Traditionally, it has been defined by measuring reduced systemic immune responses after parenteral challenge with an antigen encountered previously by the oral route. All aspects of systemic immunity can be affected, although T cell-mediated effector functions such as delayed type hypersensitivity and interferon (IFN) γ production tend to be more susceptible to oral tolerance than serum antibody responses, apart from IgE antibody production which is readily tolerisable [3,4]. Importantly, there is also tolerance of effector T cells in the mucosa itself, and breakdown in oral tolerance appears to be the underlying reason for conditions such as coeliac disease, which is caused by an aberrant Th1-mediated hypersensitivity reaction directed at dietary gluten [3,5]. A similar defect might be responsible for the development of IgE-mediated food allergies [3,6]. An equivalent phenomenon of tolerance in the large intestine is thought to be responsible for preventing the hypersensitivity reactions against commensal bacteria that drive inflammatory bowel diseases such as Crohn's disease [7]. In this case however, the tolerance only seems to operate at the level of the intestinal mucosa and the rest of the immune system remains unaware of the bacteria, which cannot penetrate beyond the gut-associated lymphoid tissues [8,9]. In addition, tolerance of effector T cells against commensal bacteria is accompanied by maintained production of local IgA antibodies, which helps maintain the host–commensal mutualism and is not dangerous to the host, because of the non-inflammatory properties of IgA [8,10]. Several mechanisms have been implicated in oral tolerance, including T cell clonal deletion or anergy, and the induction of regulatory T (Treg) cells. The exact mechanism might depend on the nature and/or dose of fed antigen, and all might operate simultaneously [4,11]. However, recent work has focussed very much on the role of FoxP3$^+$ Treg cells, whose generation in the gut draining lymphoid tissues requires a specialised population of CD103$^+$ dendritic cells (DCs) that have migrated from the intestinal mucosa.

A range of physiological factors intrinsic to the local environment also play crucial roles in determining whether tolerance or active immunity is generated, including anatomical specialisations within the mucosal tissues and special properties of the various cells present. For example, differences in the cell populations in the Peyer's patches (PPs) compared to the lamina propria (LP) allows for variations in the modes of antigen uptake used in these locations, which might affect subsequent antigen presentation in the mesenteric lymph nodes (MLNs) [12–15]. In this review, we discuss the ways in which DCs contribute to these processes, focusing on the CD103$^+$ DCs found in the wall of the intestine.

DCs in the intestine

DCs can be found in all the lymphoid organs associated with the intestine such as PPs, isolated lymphoid follicles (ILFs) and MLNs, as well as scattered throughout the subepithelial LP of both the small intestine and colon [9,16,17]. Several DC populations have been described in the organised tissues of PPs and MLNs (see Table 1 and [18] for review), but recently it has become apparent that the DCs in the mucosa itself play a crucial role in directing immune responses to luminal antigens [16,19–21]. A better understanding of LP DCs was hampered for many years by difficulties associated with isolating these cells, and more recently, by increasing confusion over the specificity of the markers used to identify LP DCs. Although there are many different cells in the mucosa that express the typical DC markers CD11c and class II MHC, recent studies have

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Table 1. DC subsets in PPs and MLNs.

Phenotype	Location	Function	Reference
CD11b$^+$ CD8α^-	PP	Th2 polarising ability IgA class switching IL-10 production	[41]
CD11b$^-$ CD8α^+	PP	Th1 polarising ability IL-12p70 production	[41]
CD11b$^-$ CD8α^-	PP	T_H1 polarising ability IL-12p70 production	[41]
CD103$^+$	MLN	Treg polarising Gut-homing T cell imprinting	[22,27,46]
CD103$^-$	MLN	Proinflammatory Th1/Th17 polarising ability	[22,102]

indicated that most of these are not genuine DCs, as defined by the ability to prime naïve T cells after migrating to the draining lymph nodes. The only cells that can do this in the resting mucosa express CD103 and not the fractalkine receptor CX3C chemokine (CX3CR)1 [15,19,22,23] (Box 1). These CD103$^+$ DCs have many unique properties and are the focus of this review. A minor population of plasmacytoid DCs (pDCs) is also present in the LP. These C–C chemokine receptor (CCR)9$^+$ cells have been suggested to play a role in driving the migration of DCs to the MLNs [24], but their role in antigen presentation and the regulation of mucosal immunity is unclear.

CD103$^+$ DCs in the LP

CD103 (α_E integrin), which binds the integrin β_7 to form the $\alpha_E\beta_7$ complex, was first detected as a marker of intraepithelial CD8$^+$ T cells in the gut [25,26], but its function remains unclear. Its best-known ligand, E-cadherin is expressed by intestinal epithelial cells (IECs) and is suggested to function in maintaining CD103$^+$ T cells and CD103$^+$ DCs in the intestine [26–28]. However, to the best of our knowledge, this has yet to be proven. An additional, uncharacterised ligand for CD103 has also been identified on vascular endothelium in the intestine [29], but the nature of this interaction remains to be elucidated.

Box 1. Definition of intestinal DCs

Based on work in non-intestinal lymphoid organs, murine DCs in the intestine were originally defined simply as CD11c$^+$ class II MHC$^+$ cells, and several functionally specialised subsets were described on this basis. Recently, it has become apparent that this is not sufficient to distinguish DCs from other myeloid cells such as macrophages, particularly in non-lymphoid tissues such as the gut [42,49]. There is an emerging consensus that many of the CD11c$^+$ class II MHC$^+$ cells in the intestinal mucosa do not fulfil the functional requirements of DCs, and two subsets of mononuclear phagocytes have now been defined in the murine gut on the basis of the expression of the mutually exclusive markers CD103 and the fractalkine receptor CX3CR1 [23]. Of these, only the CD103$^+$ CX3CR1$^-$ subset can migrate from the LP to the MLNs and present locally administered antigen to naïve CD4$^+$ T cells [15,22]. The CD103$^+$ subset is derived from the common DC precursor and its development depends on the DC-specific growth factor Flt3 ligand [49]. These CD11c$^+$ class II MHC$^+$ CD103$^+$ cells therefore appear to be *bona fide* DCs. Conversely, the CD103$^-$ CX3CR1$^+$ subset appears to be sessile in the mucosa and has little or no ability to prime naïve T cells. Furthermore, these cells express the macrophage marker F4/80; their development is controlled by macrophage CSFs; and they are derived from Ly6C^{hi} blood monocytes [49]. For these reasons, the latter cells are now considered to be macrophages [19].

CD103$^+$ DCs make up 2–3% of total leukocytes in the small intestinal LP of normal mice, where they display a rapid turnover, migrate constitutively to the MLNs (800 000 DCs per day in rats [30]) and are replenished continually by blood-borne precursors [31]. Smaller numbers of CD103$^-$ expressing DCs have also been identified in PPs, MLNs and lymph [32], as well as in non-intestinal tissues including the skin, lungs, spleen and peripheral lymph nodes [22,33,34]. Recent work has suggested that regardless of their localisation, all CD103$^+$ DCs might share a common lineage. Like CD103$^-$ DCs, CD103$^+$ DCs are derived from a CX3CR1$^+$ c-kit$^+$ bone marrow precursor in an Fms-like tyrosine kinase 3 (Flt3) ligand-dependent manner. Despite this, CD103$^+$ and CD103$^-$ DCs are genetically distinct. CD103$^+$ DCs express higher levels of CCR6, CCR7, Toll-like receptor (TLR)5 and TLR9, but lower amounts of other TLRs, co-stimulatory molecules and proinflammatory mediators than CD103$^-$ DCs express [35]. It is not clear how non-intestinal CD103$^+$ DCs relate to those in the gut. Non intestinal CD103$^+$ DCs appear to be related to the CD8α^+ lineage of conventional DCs, which requires the transcription factors inhibitor of DNA-binding 2 (*Id2*), interferon regulatory factor 8 (*Irf8*) and basic leucine zipper transcription factor ATF-like 3 (*Batf3*) for their development, and are particularly effective at cross-presenting exogenous antigen to CD8$^+$ T cells [36]. Although CD103$^+$ LP DCs can also cross-present exogenous antigens to T cells [36] and express high levels of CCR7 [37], the expression and function of TLR by mucosal CD103$^+$ DCs remains an unresolved issue. Although migrating CD103$^+$ DCs in rat intestinal lymph appear to express all TLRs except TLR4 [38], early studies of TLR expression by LP DCs in mice used heterogeneous populations of mononuclear cells, and are now difficult to interpret [39,40]. A further important difference between CD103$^+$ DCs in the LP compared with other tissues is that the LP population is heterogeneous, and contains subsets of CD11b$^+$ CD8α^- and CD11b$^-$ CD8α^+ DCs that are found among CD103$^-$ DCs elsewhere [41,42]. Of these, only the CD11b$^-$ CD8α^+ subset of CD103$^+$ LP DCs requires *Id2, Irf8* and *Batf3* for its development [43]. Thus, more work is needed to determine if and how intestinal and non-intestinal populations of CD103$^+$ DCs are related.

Functions of LP DCs in resting intestine

CD103$^+$ LP DCs have several unique features that distinguish them from other DCs. The first documented of these is the ability to imprint the expression of the gut homing markers CCR9 and $\alpha_4\beta_7$ on interacting naïve T and B cells and to induce expression of FoxP3 by naïve CD4$^+$ T cells [22,44–46]. This occurs in the MLNs rather than in the mucosa itself, where naïve T lymphocytes are rare [47,48]. Although CD103$^+$ DCs appear to be the only cells that can present intestinal protein or bacterial antigens to T cells [15,49], it is unknown how they acquire antigen. They are probably not the cells that can extend processes through the epithelium into the lumen, as was originally thought, because this seems to be a property of mucosal CX3CR1$^+$ macrophages [15,49]. These macrophages might subsequently transfer antigen to CD103$^+$ DCs in the LP. After acquiring antigen, CD103$^+$ LP DCs migrate to the MLNs in

a CCR7-dependent manner [37]. Consistent with this idea, studies in mice and rats have confirmed that the majority of DCs migrating in intestinal lymph are $CD103^+$ [15,21,30,34]. Although this migration occurs constitutively, it can be further increased by TLR ligands or tumour necrosis factor (TNF)α [21,50]. The mechanism responsible for the migration of $CD103^+$ LP DCs are unclear, but it might involve TLR7- and TLR8-induced production of TNFα and/or type 1 IFN by $CCR9^+$ pDCs present in the LP [24,50]. $CD103^+$ MLN DCs share the functional specialisations of $CD103^+$ LP DCs, and a dramatic reduction in the proportion of $CD103^+$ migratory DCs is observed in the MLNs of CCR7-deficient mice [22]. Although $CD103^-$ and $CD103^+$ DCs exist in the MLNs, only the $CD103^+$ DCs can present orally administered antigen to naïve T cells [15,49].

In the MLNs, the immigrating $CD103^+$ LP DCs imprint gut homing molecules on T and B cells, and can induce the development of $FoxP3^+$ Treg cells [51]. These properties are dependent on retinoic acid (RA), a metabolite of dietary vitamin A, produced by $CD103^+$ DCs, which express the appropriate enzymes to catalyse vitamin A metabolism (Box 2) [15]. In addition to requiring RA, the differentiation of $FoxP3^+$ Treg cells is also dependent on transforming growth factor (TGF)-β [51]. There are several possible sources of TGF-β in the intestine, including $CD103^+$ LP DCs themselves, which express mRNA for *tgfb2*, as well as tissue plasminogen activator and latent TGF-β binding protein 3, both of which can activate latent TGF-β [52]. $CD103^+$ LP DCs also produce indoleamine 2,3-dioxygenase (IDO), which catalyses the metabolism of tryptophan, depleting it from the microenvironment and generating toxic metabolites (kynurenines). Together, these inhibit the generation of effector T cells and promote the induction of Treg cells [53,54]. Inhibition of IDO *in vivo* results in defective oral tolerance and exacerbated T cell-mediated and dextran-sulphate-sodium-induced colitis [55]. These data, together with the fact that oral tolerance is abolished in CCR7-deficient mice [37], indicate that $CD103^+$ LP DCs play a crucial role in the induction of tolerance in the intestine. This is further supported by studies demonstrating that the ability of Treg cells to prevent T cell-mediated colitis requires the presence of $CD103^+$ DCs [56]. $CD103^+$ DCs are also present in the human MLNs and mucosa, where they exhibit similar properties and functions [31]. Very recent studies have shown that $CD103^+$ DCs might not act alone in the induction of oral tolerance and Treg cells. Although the initial generation of adaptive $FoxP3^+$ Treg cells occurs in the gut-draining lymph nodes and requires presentation of fed antigen by migrating DCs, their full differentiation requires the Treg cells to leave the lymph nodes and home to the intestinal mucosa. There, they undergo secondary expansion under the influence of interleukin (IL)-10-producing $CX3CR1^+$ macrophages, indicating an intriguing cooperative interaction between different mucosal myeloid cells in local homeostasis [57].

The production of RA and TGF-β by $CD103^+$ DCs also allows them to drive the production of IgA by B cells [40], thus helping to explain how commensal bacteria induce concomitant generation of Treg cells and secretory IgA antibodies [8]. Furthermore, the unique role that $CD103^+$ DCs play in transporting luminal antigens directly to the draining lymph nodes might also account for the failure of non-invasive commensal microbes to be exposed to the systemic immune system.

Box 2. RA – the major player in establishing tolerance?

RA is a metabolite of dietary vitamin A, whose metabolism involves a two-step process that requires two enzyme families, ALDH and RALDH. Vitamin A is oxidised to retinaldehyde by ALDH, which is then further oxidised to RA by RALDH. Although recent studies have suggested that all DCs have the ability to produce these enzymes, at least *in vitro*, it is thought that RALDH expression is actively suppressed by negative regulators such as prostaglandin E2 (PGE2) in non-intestinal tissues [103]. The expression of these enzymes by $CD103^+$ LP DCs allows these cells to generate RA from vitamin A in the mucosa [104,105].

RA has a number of effects on immune responses that underpin the unique properties of $CD103^+$ DCs. The first identified of these is that RA induces the expression of the gut-homing molecules, CCR9 and $\alpha_4\beta_7$, on naïve cognate T and B cells that interact with antigen-bearing $CD103^+$ DCs in the MLNs. This ensures that the T and B cells can home back to the intestinal mucosa. In conjunction with TGF-β, RA promotes the differentiation of the $FoxP3^+$ Treg cells that are known to be responsible for inducing and maintaining tolerance to food proteins and commensal bacteria [51]. RA further contributes to the differentiation of Treg cells by inhibiting Th17 development [106–108]. RA from $CD103^+$ DCs also controls humoral immunity in the intestine by promoting IgA synthesis by gut-homing B cells [40], resulting in neutralisation of bacterial toxins and preventing commensal bacteria and pathogens from breaching the intestinal epithelial layer [10].

Despite these roles in the induction of tolerance, RA, in the absence of TGF-β, has recently been implicated in the induction of inflammatory responses by $CD4^+$ effector T cells, suggesting that this dietary metabolite plays previously unappreciated roles in the induction of active immune responses in the gut [98].

Conditioning of physiological properties on mucosal DCs

The studies discussed so far indicate that $CD103^+$ DCs are crucial for gut homeostasis, but how they acquire their unique tolerogenic and imprinting properties is not yet fully understood. Although it remains possible that there could be specific precursors that replenish the $CD103^+$ population, most evidence suggests that this is achieved by a local conditioning effect on DC precursors after they arrive in the mucosa. A number of such factors have been identified, including luminal bacteria, dietary constituents, intestinal epithelial cells (IEC), other leukocytes, stromal cells and neuroendocrine factors (Figure 1).

Epithelial-cell-derived and other cytokines

One of the best-described components in this interplay is IECs, which can produce several immunoregulatory factors. The best characterised is thymic stromal lymphopoietin (TSLP), which was initially shown to account for the ability of human IEC supernatants to condition monocyte-derived DCs to drive Th2-like anti-inflammatory T cell differentiation [58]. This is consistent with the known role of TSLP in inducing Th2-dependent inflammation in skin and lung [59]. In other studies, TSLP drives DC-dependent differentiation of natural Treg cells in the thymus [60]. Further experiments have indicated that TSLP induces expression of CD103 by human monocyte-derived DCs, which are subsequently capable of inducing $FoxP3^+$ Treg

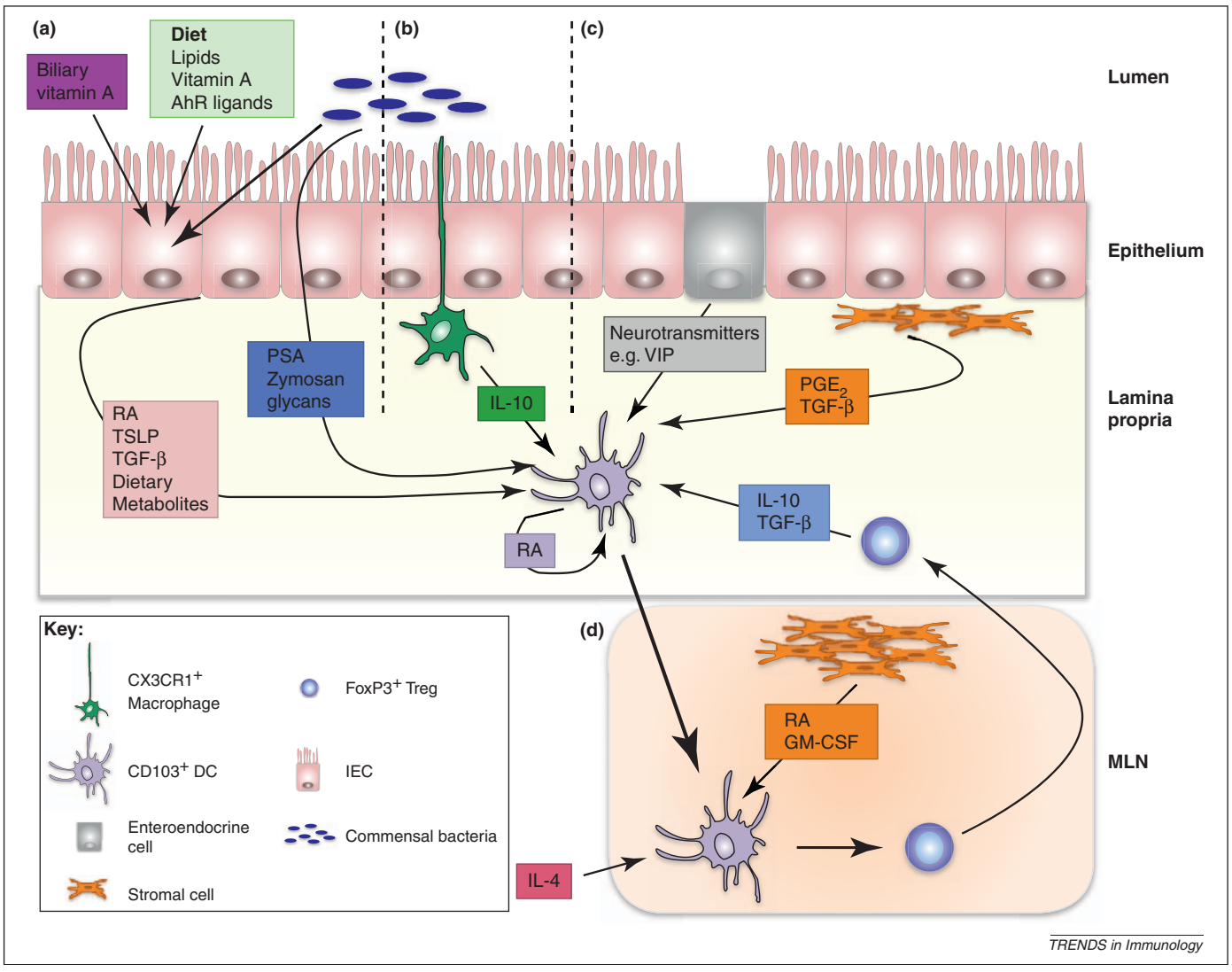

Figure 1. Conditioning of resting CD103$^+$ DCs by the intestinal microenvironment. A number of different factors might act in concert to condition mucosal CD103$^+$ LP DCs with their unique physiological properties. These include **(a)** dietary components such as vitamin A or lipid ligands of PPARγ or AhR, as well as components of local commensal bacteria and yeast. The bile is a further source of vitamin A, which has been stored in the liver. Epithelial cells can produce factors such as TGF-β, TSLP or RA, either constitutively or under the influence of exogenous signals from the diet or the microbiota. The exact role of these individual mediators might be species dependent, with TSLP appearing to be more important in humans than in mice. **(b)** Intestinal bacteria might gain access to mucosal DCs after being taken up by resident CX3CR1$^+$ macrophages. These macrophages also produce IL-10 that is required for the survival of FoxP3$^+$ Treg cells [57], which in turn might be additional sources of IL-10 and TGF-β. **(c)** Neurotransmitters such as VIP are produced by enteroendocrine cells in the epithelium, whereas mucosal stromal cells can produce IL-10, TGF-β, RA or PGE2. **(d)** Initial conditioning of CD103$^+$ DCs in the mucosa might be further enforced after their migration to the MLNs by GM-CSF and RA produced by stromal cells, as well as IL-4 from unknown sources.

cell differentiation [61]. However, the role of TSLP in mice is less clear. Although DCs from *Tslpr* (TSLP receptor) knockout mice are biased to skewing Th1 cells, MLN DCs and IEC-conditioned bone marrow-derived DCs (BMDCs) from *Tslpr*$^{-/-}$ mice are as efficient as their wild-type counterparts in inducing FoxP3$^+$ Treg cells [62]. Thus, TSLP might play a dispensable role in the DC conditioning effects of mouse IECs.

Neutralisation of TGF-β also reduces the ability of murine IECs to condition DCs to drive FoxP3$^+$ Treg cell differentiation [61,62]. However, several other cell types might also contribute to TGF-β production *in vivo*, including Treg cells themselves [63,64], macrophages [65] and stromal cells. TGF-β alone is not sufficient to drive tolerogenic DCs, possibly because high levels of RA are also required [62], and recent studies have shown that RA can act as a conditioning factor for mucosal DCs, by inducing retinaldehyde dehydrogenase (RALDH) [66,67]. Blockade of the RA receptor on IEC-conditioned BMDCs inhibits their induction of Treg cells and favours the differentiation of Th17 cells [62]. Moreover, although long-term vitamin-A-deprived animals do not have a major defect in the number of CD103$^+$ DCs in MLNs or small intestine LP, these cells display reversibly impaired RA-metabolizing activity [67]. However restoring vitamin A to the diet can reverse this. Additional sources of RA include CD103$^+$ DCs themselves, as well as MLN stromal cells [68,69]. RA is also present in high concentrations in the bile and has been shown to influence CD103$^+$ DC function by this route [67].

Other local factors that have been reported to enhance the conditioning effects of TGF-β and RA include IL-4, granulocyte–macrophage colony stimulating factor (GM-CSF), and TLR signalling [49,70]. However it should be noted that MLN DCs from germ-free, *Myd88*$^{-/-}$ and *Trif*$^{-/-}$

mice exhibit normal levels of maturation markers and RALDH activity [71,72]. Conflicting results have also been reported on whether intestinal DC functions develop normally in IL-4 receptor-deficient mice [70,73]. Thus, multiple factors from several sources might contribute to the generation of RA production and T cell polarising activity by mucosal DCs.

Intestinal microbes regulate mucosal DC function

Although TLR signalling pathways might not be essential for conditioning of CD103$^+$ DC function, there is ample evidence that local microbes contribute to conditioning. Several individual species of commensal bacteria that can shape immune responses via effects on DCs have been identified recently. For example, several commensal *Bacteroides* and *Bifidobacteria* strains can directly induce monocyte-derived DCs to acquire a tolerogenic phenotype [74]. Polysaccharide A from *Bacteroides fragilis*, a Gram-negative anaerobic commensal bacteria, can also associate with CD11c$^+$ cells in MLNs and drive a mixture of Th1 systemic responses and IL-10-producing Treg cells in the colonic LP [75]. Recently, much attention has focussed on segmented filamentous bacteria (SFBs) as major players in the microbial control of mucosal immune responses. Indeed, the presence of SFBs induces Th17 and FoxP3$^+$ Treg cell differentiation in the mucosa. These effects are associated with the modulation of CD11c$^+$ cell function in the LP, although these cells remain to be conclusively identified as DCs [76–78].

A further microbe-derived product that can influence mucosal DC function is zymosan. This component of yeast cell walls induces IL-10 production and *Aldh1a2* expression [encoding an aldehyde dehydrogenase (ALDH)] in DCs, and the induction of FoxP3$^+$ Treg cells in a TLR2 and dectin-1-dependent manner [79,80]. Dectin-1 is a C-type lectin receptor (CLR) that recognises microbial glycans. Another member of the CLR family that might participate in DC imprinting is the DC-SIGN homologue SIGNR1. Recent studies in mice have shown that orally administered mannosylated protein directly targets CD103$^+$ LP DCs via SIGNR1 and induces them to produce IL-10, which leads to induction of oral tolerance in a model of food allergy [69]. Collectively, these results suggest an important role of microbial-derived products in conditioning LP DCs to become tolerogenic. However, some of these materials can also have the opposite effect, because TLR9 stimulation appears to impair the ability of LP DCs to induce FoxP3$^+$ Treg cell differentiation [81].

Role of dietary constituents

Mucosal DCs are continuously exposed to dietary constituents and some specific nutrients have striking effects on the regulation of mucosal immune responses. The most extensively studied of these is vitamin A, whose only source in mammals is the diet, and as we have discussed, RA is responsible for several functions of CD103$^+$ DCs. Depletion of vitamin A from the diet impairs the ability of CD103$^+$ DCs in MLNs to induce Treg cell differentiation and imprint gut homing receptors on lymphocytes [70,82]. Tryptophan is also only derived from the diet in mammals and is needed for the IDO-dependent tolerogenic effects of mucosal DCs [54] (see above). Other dietary metabolites might have immunomodulatory effects on DCs, including lipid mediators that activate anti-inflammatory peroxisome proliferator-activated receptor (PPAR)γ [83] and ligands of the aryl hydrocarbon receptor (AhR) that regulate the balance between Th17 and Treg cell differentiation [84–86]. An interesting example of a specific dietary component that can influence DCs is curcumin; a spice that has a long history of medical use in India and Southeast Asia. Curcumin-treated DCs acquire a tolerogenic phenotype, expressing *Aldh1a2*, producing IL-10, and inducing the differentiation of FoxP3$^+$ Treg cells [87]. Strikingly, administration of curcumin inhibits several forms of inflammation *in vivo*, including *Toxoplasma gondii* induced ileitis [88].

Neuroendocrine pathways and mucosal DC function

The intestine has a dense nervous system that rivals the central nervous system in size and complexity, and mucosal neural anatomy is disrupted in inflammatory bowel diseases [89]. Haematopoietic cells express many receptors for various neurotransmitters, and several products of the enteric nervous system exert immunoregulatory functions (see [89] and [90] for reviews). One of the best-described examples is vasoactive intestinal peptide (VIP). This product of intestinal enteroendocrine cells is a vasodilator and regulator of epithelial permeability. It is also produced by several immune cells, including lymphocytes, and is found in resting lymphoid organs [91]. VIP modulates DC maturation, inhibits their migration by suppressing lipopolysaccharide-induced CCR7 expression [92], and confers the ability to induce differentiation of IL-10- and TGF-β-secreting Treg cells [93]. In parallel, VIP-matured or VIP-expressing DCs have been found to prevent trinitrobenzene sulphonic acid-induced colitis [94], as well as other forms of inflammatory and autoimmune diseases in association with enhanced IL-10 production [95]. The role of VIP and other neurotransmitters in the conditioning of resident mucosal DCs remains to be determined.

Taken together, these studies highlight the several and complex interactions between mucosal DCs, non-immune cells, the microbiota and ingested nutrients (Figure 1). Although all these factors help maintain the tolerogenic properties of intestinal DCs under physiological conditions, no individual factor appears to play an exclusive role. On the contrary, it appears that numerous redundant mechanisms have evolved to ensure that homeostasis is established.

Mucosal DCs and active immune responses

Thus far, we have focussed on CD103$^+$ DCs as the lynchpin of tolerance under steady state conditions, and a paradigm has evolved that they might be inherently tolerogenic in nature [1]. By contrast, the antigen-presenting cells (APCs) involved in the induction of protective immunity or inflammatory reactions in the gut have not yet been identified precisely. Several groups have proposed that such responses might involve a distinct population of CD103$^-$ DCs that are hard-wired to drive effector T cell responses via production of proinflammatory mediators such as IL-6, TNFα, IL-12 or IL-23 [96]. However, as we

have discussed, $CD103^-$ $CD11c^+$ class II MHC^+ cells in the mucosa do not fulfil the requirement to be effective APCs, and although *bona fide* DCs might exist within this population during inflammation, this has never been examined directly. An alternative possibility is that $CD103^+$ LP DCs themselves adapt to the altered environment of the infected/inflamed mucosa and acquire the co-stimulatory molecules and proinflammatory mediators that allow active T cell responses to be generated [97]. This is consistent with the fact that $CD103^+$ DCs appear to be the only cells able to generate gut homing T and B cells in the steady state and indeed, the original work describing their capacity to imprint CCR9 on T cells used an adjuvant to prime lymphocytes [46]. Recent work has shown that $CD103^+$ DCs in MLNs can acquire proinflammatory properties during experimental colitis in mice, although a mucosal origin of these cells has not been confirmed [97]. Therefore, it is important to assess the APC activity of $CD103^+$ DCs under different conditions and to determine if they retain their special properties of migrating to MLNs, producing RA and imprinting gut homing receptors on T cells. Consistent with this idea, a role for RA in the development of $CD4^+$ effector T cell responses in the systemic immune system has recently been identified, suggesting that RA–RA receptor (RAR)α signalling can induce regulatory or inflammatory responses, depending on the additional signals in the local environment such as TGF-β [98]. It is well known that the presence of IL-6, IL-12 and IL-23 can determine whether naïve $CD4^+$ T cells differentiate into Treg or proinflammatory Th1 or Th17 cells [99]; these would be important factors to measure in mucosal $CD103^+$ DCs under different conditions.

A final intriguing idea is that the $CD11b^+$ and $CD8\alpha^+$ subsets among $CD103^+$ LP DCs could exert distinct functions, as they were originally suggested to in non-intestinal lymphoid tissues [100]. However, more recent work has indicated that these subsets are more plastic than originally believed, with only cross-presentation of exogenous antigens by $CD8\alpha^+$ DCs being a definitive association [18]. A further complication is that it is not clear if both $CD11b^+$ and $CD8\alpha^+$ subsets of mucosal $CD103^+$ DCs are present in the correct locations to show functional flexibility. In particular, it has been suggested that the $CD8\alpha^+$ DCs found in preparations of LP cells are contaminants from the microscopic ILFs, which are related to PPs in function, rather than villous mucosa [23]. Thus, the functions of these subsets in the gut might be determined by their anatomical location, rather than an intrinsic developmental property.

Concluding remarks

The special properties of $CD103^+$ DCs and the likelihood that local factors determine their functions make these attractive targets for manipulating the intestinal immune response. In particular, if these DCs are inherently tolerogenic, it is tempting to propose that this could be exploited to reverse inflammatory diseases and food allergies, perhaps by delivery of specific antigen to $CD103^+$ DCs. Alternatively, if specific intrinsic or environmental mediators underlying the tolerogenic properties of $CD103^+$ DCs can be identified, these might be useful as general immunomodulators.

How $CD103^+$ LP DCs could be exploited in the development of vaccines to promote protective immunity in the gut provides an overlapping, but somewhat distinct, set of problems. Given the fact that RA-producing $CD103^+$ DCs are thought to have a unique and essential role in priming gut homing effector T and B cells, targeted antigen–anti-CD103 constructs would seem an appropriate approach to try. However, this will run into problems if $CD103^+$ DCs are indeed intrinsically tolerogenic, and it will be necessary to add an adjuvant, as shown in studies using non-mucosal DC-targeting strategies [101]. Furthermore, as it is not yet known whether $CD103^+$ LP DCs change or are replaced during active immune responses, the exploitation of these DCs in the development of such vaccines is problematic. A better understanding of both the origin and biology of this fascinating DC population is needed before further therapeutic advances can be made.

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