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Peyer's patch dendritic cells as regulators of mucosal adaptive immunity

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Abstract. The mucosal immune system maintains a delicate balance between providing robust defense against infectious pathogens and, at the same time, regulating responses toward innocuous environmental and food antigens and commensal microbes. The Peyer's patch (PP) has been studied in detail as a major inductive site for mucosal immunity within the small intestine. While the mechanisms responsible for the induction of mucosal immunity versus tolerance are not yet fully understood, recent studies have highlighted mucosal dendritic cells (DCs) as regulators of the immune responses to orally administered antigens. Here we discuss recent studies that describe the role of PP DCs in immune induction and speculate on the mechanism by which the resident DCs regulate T cell and immunoglobulin A (IgA) responses in the gastrointestinal mucosa.

Key words. Mucosal immunity; Peyer's patch; IgA production; DC subsets; oral tolerance; chemokine.

Introduction

Although the gastrointestinal mucosa is indispensable to life for its absorptive functions, it also represents the port of entry for many pathogens. Not surprisingly, the mucosal immune system has developed a unique feature of inducing regulatory responses to certain types of antigens. This immunological unresponsiveness has been termed oral tolerance and is considered to be an important physiological mechanism that regulates hypersensitivity to food antigens.

Peyer's patches (PPs) are secondary lymphoid tissues that are located along the wall of the small intestine and that serve as the major sites for generation of immunity to intestinal antigens. Foreign antigens in the gut lumen are transported to the PP by specialized epithelial cells, called M cells, located in the follicle-associated epithelium (FAE) of the PP [1]. The incoming antigens are sampled by the dendritic cells (DCs) that reside just beneath the subepithelial dome (SED) region underlying the FAE [2–4]. This local sampling of antigens by DCs in the PP is believed to be critical to the induction of adaptive mucosal immunity [5].

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Here we present the current understanding of PP DCs with regard to their subset phenotype, localization, migratory capacity, and ability to induce appropriate adaptive immune responses to antigens acquired intestinally.

Localization of DC subsets in the Peyer's patch

Immunohistochemical and functional analysis of the mouse PP has revealed three distinct populations of classical DCs, which possess diverse functions (fig. 1) [6, 7]. DCs that specifically localize in the SED region of the PP express the CD11b molecule and secrete mainly interleukin (IL)-10 upon in vitro stimulation with CD40L or with killed *Staphylococcus aureus* [6, 7]. The second DC subset expresses the CD8$\alpha\alpha$ molecule and resides in the T cell-rich interfollicular region (IFR) of the PP. The third DC subset lacks the expression of CD11b and CD8α, thus named double negative (DN) DCs, and is found in the SED, the IFR and within the FAE. CD8α^+ and DN DCs share similar functional characteristics: namely, that they both secrete IL-12 p70 upon bacterial stimulation, and both induce predominantly T helper (Th) 1 responses in naïve T cell receptor (TCR) transgenic CD4$^+$ T cells in vitro. Furthermore, DN DCs were found to be present in higher percentages within the mucosal lymphoid organs,

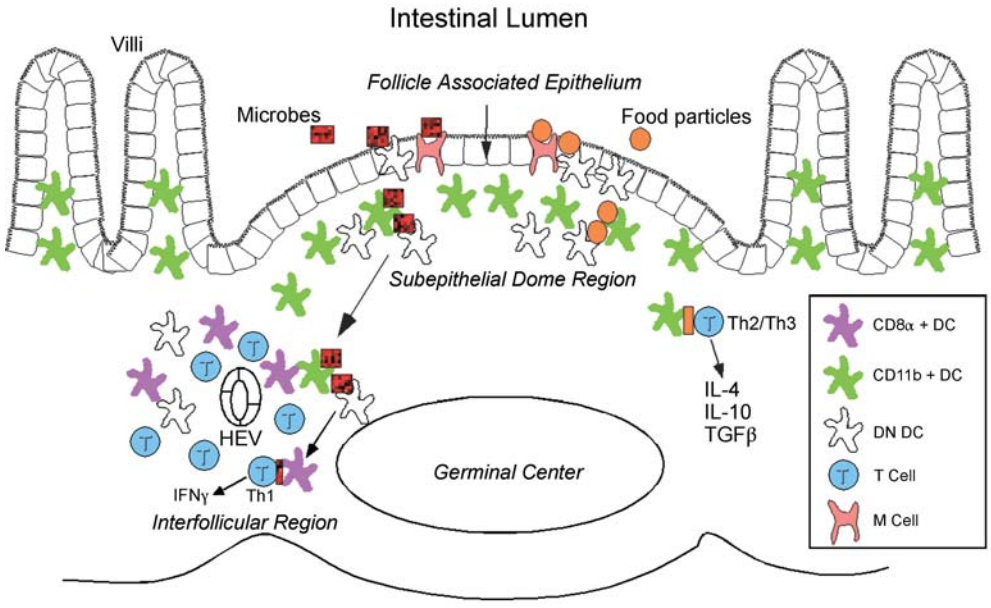

Figure 1. Distribution and function of dendritic cell (DC) subsets within Peyer's patch (PP). Antigens within the intestinal mucosa are transferred to the PP via M cells and are acquired by DCs. DCs residing in the subepithelial dome (SED) dominantly express the CD11b molecule, and DCs residing in the interfollicular region (IFR) express CD8α. A DC subset that lacks the expression of CD11b and CD8α, namely the double negative DCs (DN DCs), are localized in SED, IFR and within the follicle-associated epithelium (FAE). These three DC subsets possess distinct abilities to induce CD4$^+$ T cell differentiation, as described in the text. HEV, high endothelial venule; IFNγ, interferon γ; IL, interleukin; TGF-β, transforming growth factor β; Th, T helper.

such as the PPs (29%) and the mesenteric lymph nodes (MLNs) (30%), whereas they represent only a minor and indistinct population in the spleen (SP) and peripheral lymph nodes (13%) [7]. A recent report showed that DN DCs take up viral antigen from infected apoptotic enterocytes for presentation to CD4$^+$ T cells following reovirus infection [7a].

Distribution and chemokine receptor expression of DCs in the Peyer's patch

Analysis of the expression of chemokine receptors by the PP DC subsets revealed that all PP DC subsets express CCR7 [6]. CCL19 [macrophage inflammatory protein (MIP)-3β] and CCL21 (secondary lymphoid organ chemokine, SLC) are secreted by the IFR and are chemotactic to all PP DCs. It was shown that only CD11b$^+$ DCs express CCR6 in addition to CCR7 and migrate toward the CCR6 ligand, CCL20 (MIP-3α), secreted by the FAE overlying the dome region [6, 8]. Furthermore, CCR7 expression on CD11b$^+$ DCs was enhanced with maturation in vitro. Based on these observations, we speculated that blood-derived CCR6$^+$ DCs are constitutively recruited to the SED region in response to CCL20 secreted by the FAE, giving rise to the CD11b$^+$ subset, which remains there until it encounters antigens transported by M cells within the FAE. If the antigens are associated with microbial stimuli, the CD11b$^+$ DCs upregulate the surface expression of CCR7 and co-stimulatory molecules, leading to their migration toward the IFR and antigen presentation to T cells in the IFR.

In accordance with this hypothesis, two groups reported that CD11b$^+$ DCs were either absent or severely reduced in number in the SED of PPs in mice lacking CCR6 [9, 10]. More recently, in addition to the CCL20-CCR6 interaction, another chemokine-chemokine receptor pair that may contribute to the migration of CD11b$^+$ DCs toward the FAE was described [11]. A chemokine, CCL9 (MIP-1γ), is secreted by the FAE but not by the villus enterocytes, in a pattern similar to CCL20. CD11b$^+$ DCs express high levels of CCR1 and possess the ability to migrate to CCL9 (MIP-1γ). Antibody neutralization of CCL9 in vivo resulted in significant reduction of the CD11b$^+$ DC number in the SED of PPs in both wild-type and CCR6-deficient mice. Taken together, chemokines secreted by the FAE, such as CCL9 and CCL20, appear to play an important role in the localization of CD11b$^+$ DCs to the SED region of PPs.

Role of DCs in T helper cell responses in the Peyer's patch

Appropriate activation of CD4$^+$ T cell responses is important for a variety of immune responses against in-

testinal pathogens and antigens. Depending on the context of the antigen encountered, diverse $CD4^+$ T cell responses are induced following oral antigen exposure. These include responses of the Th1 [interferon gamma (IFNγ)], Th2 (IL-4, IL-13), Th3 [transforming growth factor-β (TGF-β)], Tr-1 (IL-10) and Treg ($CD25^+Foxp3^+$) phenotypes. In the absence of pathogenic stimuli, protein antigens given orally normally result in the generation of suppressive immune responses [12, 13]. Th3, Tr-1 and Treg can suppress immune responses to ingested antigens and are likely responsible for mediating oral tolerance. Despite the capacity to generate Th2, Th3, Tr-1 or Treg responses in PPs, distinct Th1 responses are observed in PPs particularly after intestinal infection with pathogenic microorganisms. For instance, IFNγ secretion by PP T cells has been observed after gastrointestinal infection with *Salmonella typhimurium* [14, 15] and *Toxoplasma gondii* [16]. In addition, high-dose antigen feeding results in a transient Th1 response before T cell clonal deletion [17, 18]. The mechanism that explains the ability of the PP to generate regulatory $CD4^+$ T cell responses yet allow for the differentiation of Th1 responses after infection with pathogenic organisms is of great interest. One possible mechanism by which a diverse set of immune responses is generated within the PPs is that specialized DCs are present in the generation of distinct Th-type responses.

In support of this hypothesis, the total PP DCs prime naïve $CD4^+$ antigen-specific T cells to secrete IL-10, IL-4, and IFNγ, whereas SP DCs induce naïve $CD4^+$ T cells to secrete predominantly IFNγ [19]. In addition, only the PP DCs were shown to produce significant levels of IL-10 after stimulation in vitro with the CD40 ligand, and a higher level of messenger RNA (mRNA) expression for TGF-β was present in the freshly isolated PP DCs compared with the SP DCs. Further, IFNγ production by PP DC-primed T cells was enhanced by the addition of neutralizing antibody, against either TGF-β or IL-10, to the priming cultures. These data suggest that TGF-β and IL-10 secreted by PP DCs constitutively suppress differentiation of Th1 responses to oral antigens, and only following intestinal infection with pathogenic microorganisms do PP DCs trigger Th1 responses by secreting high levels of IL-12.

Thus, the PP contains specialized DCs that, by default, generate Th2/Th3 responses. How can one explain the diverse types of $CD4^+$ T cell responses observed following oral immunization or infection? An intriguing possibility is that the DC subsets described above are endowed with the ability to generate distinct $CD4^+$ T cell responses. In support of this theory, $CD11b^+$ DCs isolated from the PP were found to secrete IL-10 upon in vitro stimulation and induce naïve $CD4^+$ antigen-specific T cells to secrete high levels of IL-10 and IL-4. In contrast, $CD8\alpha^+$ DCs and the DN DCs isolated from the PP secreted IL-12 and induced Th1 responses.

Taken together, DCs present in the PP have the ability to influence the types of $CD4^+$ T cell responses to oral antigens. However, it is not clear where these responses are coordinated within the various gut-associated lymphoid tissues that exist in the small intestine. There are several conflicting reports showing the dependency on the PP in the induction of oral tolerance [20–22]. In contrast, other reports indicate the importance of MLNs in the induction of oral tolerance and immunoglobulin A (IgA) production (reviewed in [23]). After oral administration of protein antigens, MLN DCs induced $CD4^+$ T cells to secrete IL-10 and TGF-β [22, 24]. It is not clear whether these regulatory DCs in the MLNs originally migrated from another organ, such as the PP, the isolated lymphoid follicles (see review by Kiyono), or the lamina propria, or whether they represent MLN-indigenous DCs.

Peyer's patch and MLN DCs regulate T cell migration

It was shown that the homing of antigen-activated effector/memory T cells is mediated by DCs of the PP [25] and MLN [26]. Oral antigens induce effector/memory T cells that express essential receptors for intestinal homing, namely the integrin $\alpha4\beta7$ and the chemokine receptor CCR9, the receptors for the mucosal addressin cell-adhesion molecule 1 (MAdCAM-1) and thymus-expressed chemokine (TECK)/CCL25, respectively [27–29]. PP DCs [25] and MLN DCs [26] enhance expression of $\alpha4\beta7$ and CCR9 on $CD8^+$ T cells. Only the DCs in the gut-associated lymphoid tissues, but not those isolated from the SP or peripheral lymph nodes, induced high levels of $\alpha4\beta7$, responsiveness to TECK and the ability to home to the small intestine in $CD8^+$ T cells. Efficient induction of $CCR9^+\alpha4\beta7^+CD62L^{low}CD8^+$ T cells in the MLNs in vivo requires an adjuvant, including those that are Toll-like receptor (TLR)-dependent and independent [26]. These findings assigned yet another important role for the intestinal mucosal DCs-in directing T cell homing to the gut mucosa.

Role of Peyer's patch DCs in IgA responses

Secretory IgA provides protection at the mucosal surfaces on the luminal side against many pathogens. The PP has been considered to be the major inductive site of IgA. The following studies demonstrated the importance of PP DCs in the induction of IgA production. Induction of significant polyclonal IgA secretion by both PP and SP B cells was shown in the co-culture of B cells with DC-T cell mixtures derived from murine PP, but not from SP

[30]. Non-transformed pre-B cells were induced to differentiate in vitro to secrete IgA only with PP DCs and antigen-stimulated T lymphocytes [31]. This study showed that PP DCs induced high levels of IgA in combination with T cells derived from either the SP or the PP, and that both the isotype of antibody secreted and the extent of pre-B cell differentiation were determined by the lymphoid tissue source of the DCs, and not that of the T cells. The importance and sufficiency of PP DCs in IgA induction from B cells were demonstrated in a study in which PP DCs, but not T helper cells, were able to promote IgA secretion from B cells in a microculture [32]. Although these data suggest the importance of PP DCs in the generation of IgA responses in the intestine, the mechanisms of induction of IgA production by PP DCs have not be elucidated. One possibility is that PP DCs secrete optimal cytokines that enable B cells to undergo IgA switching. Cytokines such as TGF-β [33–35], IL-5 [36–41] and IL-6 [40, 42, 43] are known to be important for the development of IgA-producing B cells.

Table 1. Induction of IgA production by dendritic cells (DCs) freshly isolated from Peyer's patches (PPs) and spleen (SP). Naïve $CD4^+/CD62L^{high}$ T cells from SP of ovalbumin (OVA)-specific T cell receptor transgenic mice and naïve $sIgD^+$ B cells from SP of BALB/c mice were co-incubated with DCs sorted from PP or SP for 7 days in the presence or absence of OVA, interleukin 6 (IL-6) or antibodies. IgA titers were determined by ELISA.

	PP DC µg/ml	SP DC µg/ml	no DC µg/ml
Medium	0.06 ± 0.04	0.04 ± 0.02	0.04 ± 0.02
OVA + isotype control	1.15 ± 0.55	0.13 ± 0.08	0.13 ± 0.08
OVA + anti-IL-6 antibody	0.55 ± 0.19	0.17 ± 0.14	0.09 ± 0.02
OVA + mouse recombinant IL-6	1.46 ± 0.89	0.38 ± 0.32	0.33 ± 0.40

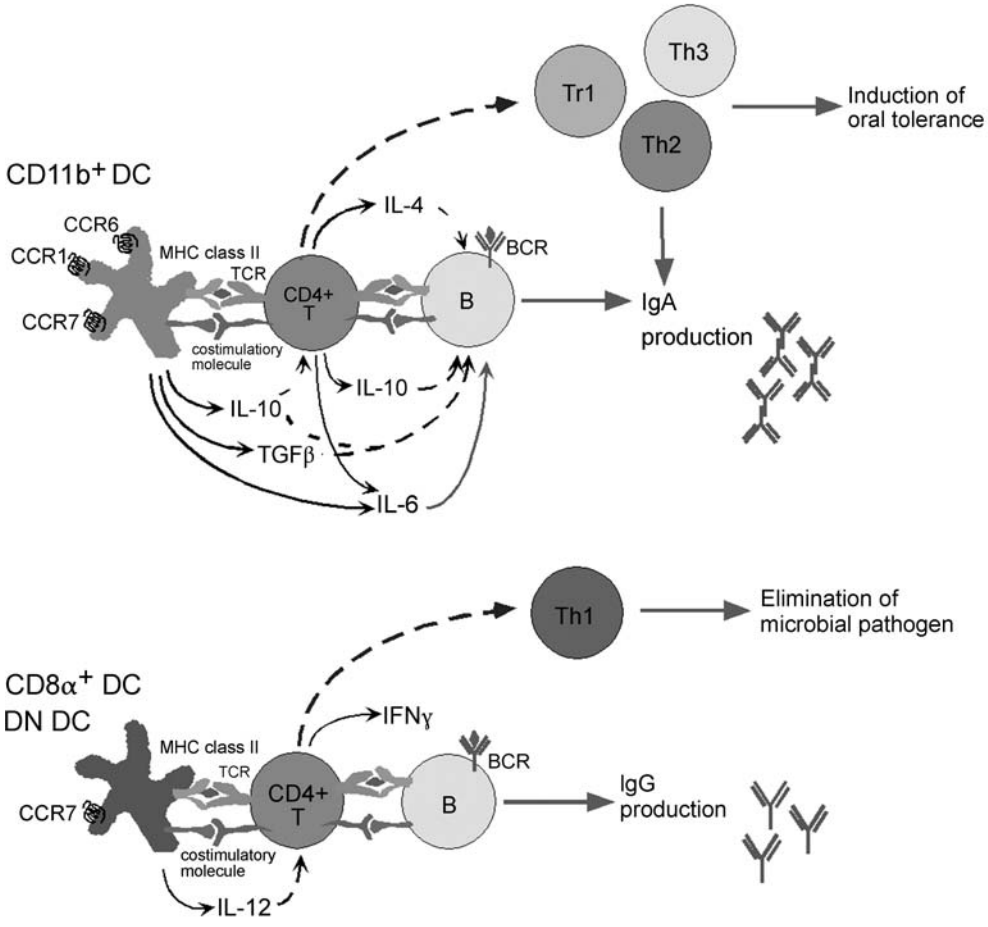

Figure 2. Proposed mechanisms of immune induction by Peyer's patch dendritic cell (DC) subsets. $CD11b^+$ DCs secrete transforming growth factor β (TGF-β) and interleukin (IL)-6 and induce IgA production. These cells may also induce oral tolerance by inducing regulatory T cells. $CD8\alpha^+$ and double negative (DN) DCs induce the T cell differentiation to T helper (Th) 1 cells by secreting IL-12 and lead to the elimination of microbial pathogens. TCR, T cell receptor; BCR, B cell receptor; CCR, CC chemokine receptor; IFNγ, interferon γ.

In support of this hypothesis, CD11b$^+$ PP DCs, unlike their splenic counterpart, were found to produce higher levels of IL-6 and promote the induction of IgA production ex vivo [44]. In this study, we compared IgA levels in an in vitro culture system in which DCs from the PP and SP were used as the antigen-presenting cells (APCs). Freshly isolated PP or SP DCs were co-cultured with naïve sIgD$^+$ B lymphocytes isolated from the SP of BALB/c mice and with naïve T cells from the SP of ovalbumin (OVA) TCR-transgene mice in the presence of OVA. Table 1 depicts the levels of IgA secreted in these B-DC-T co-culture systems. Higher IgA production was observed when PP DCs were used as the APCs compared with the wells containing SP DCs, consistent with previous reports [30–32]. To investigate the role of IL-6, a critical factor for the development of IgA-producing B cells [40, 42, 43], we measured IgA production levels in culture in the presence of either anti-mouse IL-6 monoclonal antibody (mAb) or exogenous recombinant IL-6 (rIL-6). We found that IgA production induced by PP DCs was substantially decreased in the presence of neutralizing anti-mouse IL-6 mAb (table 1). In the presence of additional rIL-6, IgA levels were found to be enhanced in cultures containing SP DCs as the APCs. In contrast, there was no further enhancement of IgA secretion by addition of rIL-6 in the PP DC-B-T co-culture. These data suggest that PP DCs have the capacity to induce IgA production and that IL-6 is important for DC-induced IgA secretion. Yamamoto et al. reported that PP-deficient mice induced IgA production in MLNs [45]. Thus, it is possible that the PP CD11b$^+$ DCs induce differentiation IgA producing B cells within the PP or MLNs in vivo.

An important contribution of the PP DCs in the induction of IgA responses to gut commensal bacteria was recently demonstrated. A study by Macpherson and Uhr showed that PP DCs captured and retained small numbers of commensal bacteria and selectively induced IgA [46]. The IgA helped protect against mucosal penetration by commensals. The commensal-loaded DCs migrated to the MLNs but were confined within this lymphoid tissue, preventing systemic spread of the commensal bacteria. Therefore, PP DCs play a critical role in the generation of IgA responses to both commensal and pathogenic microbes.

Future directions

Although various functions of the three subsets of PP DCs have been revealed in recent years, many questions remain as to how these DC subsets coordinate initiation to distinct types of immune responses to oral antigens in vivo. Immature CD11b$^+$ DCs within the SED region of the PP that encounter soluble antigens, such as innocuous food proteins, may generate Th2/Th3 responses through secretion of high levels of IL-10 and TGF-β. In contrast, upon recognition of pathogen-associated molecular patterns (PAMPs), maturation of DCs and secretion of Th1-promoting cytokines are triggered by the CD8α^+ and DN DC subsets (fig. 1). Microbial stimulation of SED DCs leads them to migrate toward the IFR by upregulating CCR7 expression, which could cause IFR-resident DCs to induce Th1 responses via cross-priming (fig. 2). Moreover, other types of DCs, such as the plasmacytoid DCs, in the PP, may play a key role during intestinal viral infection. It is well known that DCs recognize PAMPs through TLRs [47, 48]. Whether TLR-mediated signals play a role in the induction of positive and negative immune responses by PP DCs remains to be determined. Finally, PP DCs can direct T cell homing to other mucosal tissues. Investigating the role of PP DCs in homing antigen-specific memory T cells and B cells to the lamina propria will be important in deciphering the mechanism behind the notion of the common mucosal immune system.

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