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TOPIC HIGHLIGHTS

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Role of mucosal dendritic cells in inflammatory bowel disease

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Abstract

The gastrointestinal innate and adaptive immune system continuously faces the challenge of potent stimuli from the commensal microflora and food constituents. These local immune responses require a tight control, the outcome of which is in most cases the induction of tolerance. Local T cell immunity is an important compartment of the specific intestinal immune system. T cell reactivity is programmed during the initial stage of its activation by professional presenting cells. Mucosal dendritic cells (DCs) are assumed to play key roles in regulating immune responses in the antigen-rich gastrointestinal environment. Mucosal DCs are a heterogeneous population that can either initiate (innate and adaptive) immune responses, or control intestinal inflammation and maintain tolerance. Defects in this regulation are supposed to lead to the two major forms of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC). This review will discuss the emerging role of mucosal DCs in regulating intestinal inflammation and immune responses.

Key words: Dendritic cells; Commensal; Inflammatory bowel disease; Mucosal immunity; Host defence

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INTRODUCTION

The intestinal innate and adaptive immune system has evolved in response to potent stimuli derived from constituents of the commensal microflora. In most cases these local immune responses achieve tolerance to the intestinal microflora and food antigens. Defects of the tightly regulated mucosal immune responses are assumed to result in inflammatory bowel disease (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC)[1,2]. Local T cell immunity is an important compartment of the specific intestinal immune system. T cell reactivity is programmed during the initial stage of its activation by dendritic cells (DCs) that can either initiate (innate and adaptive) immune responses, or control intestinal inflammation and maintain tolerance[3-5]. DCs reside in mucosal tissues or recirculate in the blood and lymphoid tissues[6]. The lamina propria of the small and large intestine are effector sites of mucosal tissues. Inductive sites are Peyer's patches (PP), intestinal lymph follicles (iLFs), DC aggregates and mesenteric lymph nodes (MLNs) (Table 1). The local microenvironment influences the phenotype of DCs, a heterogeneous population that can be divided into conventional DCs ($CD8\alpha^+CD11b^-$, $CD4^+CD11b^+$, $CD4^-CD11b^+$)[7,8] and plasmacytoid DCs ($B220^+CD11c^{low}$) (Table 2) and are characterized by a remarkable plasticity between DCs[9]. In the lamina propria of the small and large intestine, DCs are ideally situated to survey the constituents of the commensal microflora and monitor food antigens[10]. After antigen recognition at peripheral sites DCs migrate to regional draining lymph nodes to initiate (innate and adaptive) immune responses[11]. This review will discuss the emerging role of mucosal DCs in regulating intestinal inflammation and immune responses.

DCs IN THE SMALL INTESTINE

The lamina propria of the small intestine is populated by $CD4^-CD8\alpha^-$ cDCs. Only 2%-5% plasmacytoid DCs reside in the small intestinal lamina propria[12]. Mucosal DCs can be discriminated into DCs that express CX3CR1 (the receptor for fractalkine/

Table 1 Anatomic compartments of GALT

Compartment			Gut segment		
Inductive/effector sites	Structure	Abbreviation	Small intestine		Large intestine[3]
			Upper[1]	Lower[2]	
Effector	Lamina propria	LP	+++	+++	+++
	Intraepithelial lymphocytes	IEL	+++	+++	+++
Inductive	Peyer´s patch	PP	+	+++	-
	Intestinal lymph follicle	iLF	+	+++	-
	Intestinal lymph aggregate	iLA	+	++	++
	Mesenteric lymph node	MLN	-	-	-

[1]Distribution of the described structures in the upper small intestine (duodenum and jejunum); [2]Distribution of the described structures in the upper small intestine (ileum); [3]Distribution of the described structures in the upper small intestine (ileum). "+++": Very frequent; "++": Frequent; "+": Randomly; "-": Not present.

Table 2 Mucosal DCs and their proposed function

DC[1]		Intestinal compartment[2]					Comment[3]	Ref.
Lineage	Phenotype	MLN	siLP	cLP	PP	iLF		
cDC	$CD4^-CD8^-$ $CD11b^+CD11c^+$	+++	+++	+++	+++	+++	Express CD103 or CX3cR1. Mediate intestinal antigen acquisition. Involved in the RA dependent T_{reg} conversation. Permitting homing of conventional T cells to intestinal tissues by inducing CCR9 and $\alpha_4\beta_7$.	12-14, 47, 86, 99
	$CD4^+CD8^-$ $CD11b^+CD11c^+$	+++	-	-	++	+	Prime CD4 T cell responses.	8, 28
	$CD4^-CD8^+$ $CD11b^-CD11c^+$	++	-	-	++	++	Prime CD8 T cell responses.	8, 28
pDC	$B220^+PDCA1^+CD11c^+$	+	+/-	+/-	+	+	Produce type I interferons	10

cDC: Conventional DC; pDC: Plasmacytoid DC; MLN: Mesenteric lymph node; PP: Peyer´s patch; cLP: colonic lamina propria; siLP: small intestinal lamina propria; iLF: intestinal lymph follicle. [1]DC lineage; [2]Phenotype of the described DC lineage; [3]Distribution of the described DC lineage in distinct intestinal compartments.

CX3CL1)[12] and into DCs that express the integrin αE chain CD103[13,14]. $CD103^+$ DCs originate from Ly-$6C^{high}CCR2^{high}$ monocytes. Conversely Ly-$6C^{low}CCR2^{low}$ monocytes repopulate $CX3CR1^+CD11b^+$ mucosal DCs[15]. $CX3CR1^+CD11b^+$ DCs directly access the intestinal lumen by extending transepithelial dendrites in a CX3CR1-dependent manner to survey the intestinal lumen[12], whereas $CD103^+$ DCs induce the expression of CCR9 and $\alpha_4\beta_7$ integrin on cognate CD4 and CD8 T cells to facilitate homing of T cells to small intestinal tissues[13,16] and induce the differentiation of regulatory T cells (T_{regs}) in the absence of exogenous cytokines.

DCs IN THE LARGE INTESTINE

The cLP is populated by $CD4^-CD8^-$ DCs which endocytose and process antigens and induce T cell proliferation. Compared to their splenic counterparts TLR-4, -5 and -9 expression by colonic $CD4^-CD8^-$C DCs is low[17]. Only few $CD8^+$ and plasmacytoid DCs are found in the cLP[17]. In human biopsies from colonic tissues, $CD3^-CD14^-CD16^-CD19^-CD34^-$ DCs with an immature state with low TLR-2 and -4 expressions were observed[18]. In addition the presence of $CD83^+$ and DC^-SIGN^+ DCs was described[19]. Human and mouse mucosal DCs are assumed to be less responsive to microbial-derived TLR-ligands compared to spleen or blood born DCs[17] Despite the functional subspecifications of DCs, DCs are characterized by a remarkable plasticity between DCs which is influenced by the local environment, the antigen itself or the activation state of the DC[9,20].

DCs IN PPs

PP, iLF, CP and DC clusters of the small and large intestine belong to the gut associated lymphoid tissues (GALTs)[6], secondary lymphoid structure, which lack in contrast to lymph nodes the afferent lymph and are located in close proximity to the intestinal epithelium. In PP the subepithelial dome regions beneath the follicle-associated epithelium can be discriminated from follicular and interfollicular regions, which serve as inductive sites where immune responses are primed. Specialized epithelial cells, the M cells, deliver luminal antigens to DCs located in the subepithelial dome regions beneath the follicle associated epithelium[21]. The subepithelial dome regions are populated with $CD8\alpha^-$ $CD11b^+B220^-$ DCs and with $CD8\alpha^-CD11b^-B220^-$ DCs[22,23]. By expressing high concentrations of the chemokines CCL20, CXCL16 and CCL9, the follicle-associated epithelium creates a specific micromilleu that allows DCs to selectively migrate towards the follicle associated epithelium[24,25]. Upon pathogen challenge

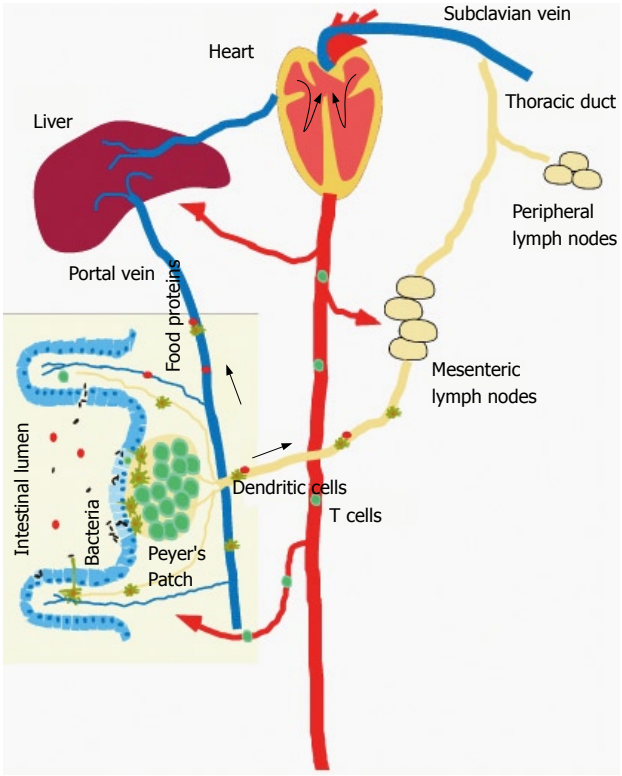

Figure 1 Bacterial and food antigens are continuously surveyed by the mucosal immune system, processed and transported *via* the lymph to mesenteric lymph nodes or *via* the portal vein to the liver. DCs present processed luminal antigens to naïve T cells to achieve tolerance or to initiate host defence to pathogens.

CCR6$^+$ DCs which are located in the interfollicular regions are recruited towards the follicle-associated epithelium to process microbial antigens, and to facilitate rapid local adaptive immune responses[23]. In the absence of CCR6 in CCR6$^{GFP/GFP}$ mice CX3CR1$^+$ DCs that lack CCR6 expression reside in the follicle-associated epithelium[23,26]. In the interfollicular regions CD11b$^-$ CD8α^- and CD11b$^-$ CD8α^+ DCs as well as plasmacytoid DCs are found that produce IL-12 and IL-10, and induce the differentiation of IFN-γ secreting TH1 cells, whereas the CD11b$^+$ subsets produce low IL-12 and high IL-10 levels and prime IL-10 producing T cells[22,27]. CD8$^-$33D1$^+$ DCs, but not CD8α^+DEC205$^+$ DCs are specialized to present processed antigens in a MHC class Ⅱ dependent manner to CD4 T cells[28]. Reoviral antigens are sampled and processed by CD11b$^-$CD8α^- DCs to initiate TH1 adaptive immune responses likely resulting in protective host defence to viral antigens[29].

DCs IN INTESTINAL LYMPHOID TISSUES

Intestinal lymphoid aggregates (iLAs) can be discriminated from PP, which comprises iLF and CP that are closely associated with the epithelial lining in the small and large intestine[30]. CP were defined as tiny aggregates of c-Kit$^+$IL-7R$^+$ cells[31], whereas iLFs are constituted by solitary B follicles that are localized in the anti-mesenteric regions of the intestinal wall, and contain small numbers of mature T lymphocytes, but also c-Kit$^+$ and IL-7R$^+$ cells[32-34]. By analyzing large numbers of such aggregates, the classification of iLA into CP and iLF was recently challenged showing that most of them display properties intermediate between CP and iLF and were termed small intestinal lymphoid tissues (siLT)[35]. In the large intestine, subepithelial DC aggregates locate in the regions of cLP where inflammation develops[36]. DC aggregates are formed by CD8α^+, CD8α^- and B220^{lo} DCs. DCs with high MHC Ⅱ expression, but low expression of the costimulatory molecules CD40, CD80 and CD86 extend transepithelial dendrites into the intestinal lumen[37]. During colitis induced by adoptive transfer of CD45RB^{hi} CD4 T cells into immunocompromised RAG mice, FoxP3 regulatory T cells accumulate in colonic DC aggregates producing TGF-β suggesting that DC aggregates are important structures to regulate inflammation[37].

DCs IN MLN

Luminal antigens are sampled by lamina propria DCs and by DCs located in PP, CP, iLF and DC clusters at the base of intestinal villi. The DCs transport the sampled antigens *via* the lymph to MLN, where naïve T cells are primed and adaptive immune responses are induced[38] (Figure 1). In MLN, blood-born DCs and DCs that originate from PP or the lamina propria are present[6]. In MLN, blood-born DCs are assumed to express CD8α^{hi}CD11b$^-$αL^{int}β7^{int} and CD8α^- CD11b^{hi}αL^{lo}β7^{lo} DCs, whereas DCs derived from mucosal sites are characterized by CD8α^{int}CD11b$^-$ αL^{lo}β7^{hi} and CD8α^-CD11b^{hi}αL^{lo}β7^{hi} expression[39], allowing the discrimination of DCs of distinct origins. CCR7 expression guides lamina propria DCs to MLN[40]. Blood-born DCs enter the MLN *via* interactions with mucosal addressin cellular adhesion molecule (MAdCAM-1) and peripheral node adressin (PNAd) expressed by high endothelial venules (HEVs)[41]. Apoptotic cell bodies derived from intestinal epithelial cells (iECs) are phagocytosed and transported to MLN to induce tolerance against self-antigens[42]. The depletion of MLN results in defective oral tolerance. Lamina propria DCs are continuously carrying commensal bacteria to the MLN[43], which can be further potentate by stimulating DCs with TLR-7/8 agonists[44]. IgA production is induced that is supposed to limit the dissemination of commensal bacteria further than the MLN preventing effectively systemic infections[45].

DCs IN INTESTINAL ANTIGEN ACQUISITION PATHWAYS

Intestinal DCs play a key role in monitoring the intestinal lumen by continuously sampling and processing luminal antigens[46,47]. There are different pathways by which luminal antigens can gain access in the lamina propria[48]. In all pathways, mucosal DCs are supposed to play key roles. Restricted to the ileum DCs extend transepithelial dendrites in a CX3CR1 mediated manner to survey the

intestinal lumen to continuously survey the commensal microflora and to monitor food antigens[12,49]. M cells located in the follicle associated epithelium of PP are specialized epithelial cells which gained the ability to translocate luminal antigens *via* the intestinal barrier and deliver luminal antigens to DCs located in the subepithelial dome regions of PP[21]. Upon pathogen challenge, $CCR6^+$ DCs are recruited to the dome regions to process pathogens, and to trigger rapid local adaptive immune responses[23]. As well $CD11b^-CD8\alpha^-$ $CD11c^+$ interfollicular DCs process antigens derived from luminal reovirus[29]. M cells within the small intestinal villous epithelium are able to translocate pathogens *via* the epithelial barrier to DCs located in the lamina propria[50]. The intestinal epithelium by itself plays an important role in sensing the luminal microenvironment. The intestinal epithelium express Toll-like receptors, such as TLR2[51], TLR-4[52], TLR-5[53] and TLR-9[54] to recognize microbial derived pathogen associated molecular patterns (PAMPs) for the regulation of protective innate immune responses. As well upon LPS-stimulation iECs express the intracellular pathogen recognition pattern NOD1[55] and NOD2[56,57], in which mutations are associated with an increased susceptibility for CD[58,59]. IECs directly participate in intestinal antigen uptake pathways by delivering antigens or exosomes to lamina propria DCs. Secreted IgG binds to cognate luminal antigens to form IgG/antigen complexes that are recycled by neonatal FcRn receptors and delivered to lamina propria DCs[60,61]. IECs also express MHC Ⅱ and may present luminal antigens to CD4 T cells. After luminal exposure with ovalbumin (OVA), OVA is taken up at apical and basolateral surfaces of the epithelial cells. Then, it enters the early endosomes and may be delivered to late endosomes where it is processed in the presence of MHC Ⅱ, and presented in the context of class Ⅱ to T cells[62]. It needs to be dissected in future work whether all or specific luminal antigen acquisition routes are linked to the induction and constant renewal of tolerance and to the development of protective immune responses. DCs are assumed to play key roles in all luminal antigen acquisition routes, and are supposed to represent a major factor for the processing and presentation of orally delivered antigens and the induction of tolerance.

DC MEDIATE INNATE AND ADAPTIVE IMMUNE RESPONSES TO THE COMMENSAL FLORA

The gastrointestinal immune system faces the tremendous challenge to deal with potent stimuli for the innate and adaptive immune system derived from the commensal microflora and food antigens. DCs are sentinels of the mucosal immune system to survey the constituents of the luminal commensals and to trigger host responses to pathogens[63]. It is thought that gastrointestinal diseases, such as IBDs are results of deregulated immune responses to the commensal microflora[1]. Although germ-free (GF) mice and rats generate alloreactive T cell responses[64] and cellular immunity to certain bacteria (after monocolonization)[65,66], the cellularity of their immune system is greatly reduced[67-69]. In this regard, the numbers of IL-17A producing TH17 cells is reduced in the lamina propria of GF animals[70]. Because commensal flora is a major driving force of the homeostatic proliferation of naïve T cells in the periphery, the reduced cellularity in the immune system of GF mice may be the result of the deficient peripheral expansion of recent thymic T cell emigrants[71,72]. When GF mice are fed bacterial carbohydrate polysaccharide A (PSA) CD4 T cells are activated resulting in a TH1 response imprinted by DCs[72]. After conventionalization of GF rats $OX62^+$ DCs increased, whereas $CD4^+$ DCs located in the follicle associated epithelium decreased indicating that $CD4^+$ DCs phagocytose microbial derived antigens, relocate to the follicular regions, and elicit rapid immune responses to the microflora to achieve tolerance[68]. Furthermore, it has been described that the inducible isoform of nitric oxide synthase (iNOS) expressing DCs is markedly reduced in GF or MyD88-deficient animals indicating that the commensal flora is required for the accumulation of iNOS expressing DCs at mucosal sites[73]. In $iNOS^{-/-}$ animals serum IgA levels are reduced suggesting that iNOS expressing DCs play a role in IgA class switching required to prevent the uncontrolled dissemination of the commensal flora into the host.

HEMATOGENOUS DISSEMINATION OF INTESTINAL ANTIGENS

Although the priming of T cells mainly occurs in draining lymph nodes, antigen-rich blood from the small and large intestine is transported to the liver *via* the portal vein, and pressed through a network of sinusoids and scanned by antigen-presenting cells and lymphocytes in the liver[74,75] (Figure 1). One third of liver cells are constituted by non-parenchymal cells (NPCs), which include liver sinusoidal endothelial cells (LSECs), Kupffer cells, biliary cells, stellate cells (Ito or fat-storing) cells and lymphocytes[74,75]. Resident APCs in the liver are Kupffer cells, LSEC[76], Ito cells[77] and DCs[75]. Plasmacytoid $B220^+CD11c^+$ DCs as well as $B220^-CD11c^+$ DCs are found. The latter can be further divided into major immature ($CD40^{lo}$ $CD80^{lo}$ $CD86^{lo}$ MHC class $Ⅱ^{lo}$) $CD11c^{int}$ and minor mature ($CD40^{hi}$ $CD80^{hi}$ $CD86^{hi}$ MHC class $Ⅱ^{hi}$) $CD11c^{hi}$ DCs[78]. Further, the presence of $CD8\alpha^+CD11b^-$ and $CD8\alpha^-CD11b^+$ DCs has been reported[78]. The continuous exposure of resident APCs with the bacterial cell wall derived LPS promotes the induction of CD4 regulatory T cells and may explain the dominance of IL-10 in the liver[79,80]. If Kupffer cells are depleted by gadolonium chloride treatment, liver tolerance becomes impaired raising the possibility that the liver is increasingly recognized as an innate and adaptive immune organ[81].

DCs IN ORAL TOLERANCE INDUCTION

Mucosal DCs play a key role in the development of oral tolerance, a phenomenon, in which systemic immune responses to a defined peptide/protein are blunted, when the same protein has been orally fed before the rodents were systemically challenged[82]. The triggering of oral tolerance in patients with IBD is impaired[83]; however, the exact mechanism has not been determined. Mucosal DCs are critical for the induction of oral tolerance as shown by studies, in which flt-3 ligand was injected in mice leading to the expansion of DC subsets[84]. After the expansion of the intestinal DC pool, enhanced oral tolerance was observed. Because oral tolerance can be transferred by adoptive transfer of T cells into recipient mice, interactions between DCs and T cells seems to be essential for the development of oral tolerance, in which CD4 CD25 FoxP3 regulatory and IL-10 and TGF-β secreting TH3 cells that suppress systemic immune responses are primed[85]. When spleen DCs are compared to mucosal DCs, the mucosal DCs are more efficient in inducing FoxP3 expression than spleen DCs in the presence of TGF-β[86,87]. Further analyses demonstrated that $CD103^+$ DCs are able to induce the differentiation of T_{reg} cells *via* the production of the Vitamin A metabolite, retinoic acid, in presence of TGF-β, which in addition results in the recruitment of T cells and B cells to intestinal tissues[88-90]. Blocking of TGF-β abrogates the ability of $CD103^+$ DCs to induce T_{reg} cells[91,92]. However, parallel studies have indicated that exogenous TGF-β has not to been added to this system in order to obtain FoxP3 expressing T_{reg} cells[86,87] raising the possibility that gut DCs activates latent TGF-β present in mucosal tissues. In this regard, the integrin $\alpha_v\beta_8$ expressed by DCs is required to activate TGF-β *in vivo*. Mice, in which DCs lack $\alpha_v\beta_8$, develop IBD and autoimmunity[93].

Oral tolerance is not impaired in PP-deficient mice demonstrating that lamina propria DCs play a key role in the development of oral tolerance by sampling the luminal content, and transporting antigens to the MLN[94]. After depletion of the MLN, the development of oral tolerance is reduced indicating that the MLN are a major site for priming tolerance[95]. Interestingly, it has been suggested, that intestinal self antigens can be presented by lymph node stroma cells beyond the MLNs[96]. It also may depend on the presence of certain pathogens within the lumen, because *Heligmosomoides polygyus* infection correlates with DC activation and IL-10 expression[97]. This provides evidence that the studies of intestinal microbial responses not only require the recognition of region- and compartment-specific immune responses, but the consideration of the interplay of different commensals and pathogens in modulating mucosal immune responses.

DC DEPENDENT T_{reg} CELL CONVERSION

T_{reg} cells play a key role for the development of oral tolerance, and the regulation of intestinal inflammation triggered by the intestinal microflora. $CD103^+$ but not $CD103^-$ DCs purified from GALT-induced generation of FoxP3 cells *in vitro*[98]. T_{reg} cells can be distinguished from other T cell populations by the surface expression of the α chain of the high affinity IL-2 receptor (CD25), and the transcription factor FoxP3 that is essential for T_{reg} development. Deadly autoimmunity is prevented by T_{reg} cells as exemplified in X-linked immunodeficiency, polyendocrinopathy, enteropathy (IPEX) syndrome in humans[98]. The conversion of T_{reg} cells in the GALT can be prevented by inhibitors of retinal dehydrogenases, an enzyme that is highly expressed by $CD103^+$ DCs, which converts retinol (vitamine A) into retinoic acid[86,87,91,99]. Retinoic acid binds to nuclear retinoic acid receptors that upon ligation can inhibit the activity of activating protein-1 (AP-1), a transcription factor, which can interfere with nuclear factor of activated T cells (NFAT)-FoxP3 complex[100,101]. However, the exact retinoic acid dependent signal transduction pathways required for the conversion of T_{reg} cells remains to be elucidated. Retinoic acid production by $CD103^+$ DCs also induce the up-regulation of the integrin $\alpha_4\beta_7$, and the CC chemokine receptor CCR9 which binds thymus-expressed chemokine (TECK) permitting the accumulation of T_{reg} cells intestinal tissues[13]. The retinoic acid dependent conversation of T_{reg} cells depends on the presence of TGF-β, a cytokine that, in the presence of IL-6 and IL-23, can also induce the generation of TH17 cells[102] (Figure 2). A small subset of naïve T cells in the small intestine co-express the transcription factors FoxP3 and RORγt[103]. High expression of TGF-β represses IL-23 receptor expression and favours the generation of FoxP3 T_{reg} cells, whereas low TGF-β expression in concert with IL-6, IL-21 and IL-23 relieves FoxP3 mediated RORγT inhibition promoting TH17 cells[103]. TH17 cells accumulate in the lamina propria of patients with IBD indicating that TGF-β can induce regulatory and pro-inflammatory T cell subsets[104].

DCs IN IBD

Various animal models have provided insights that mucosal DCs play a key role in IBD. However, the specific function of certain DCs are unknown and needs to be determined in future work, which will provide information on mechanisms leading to IBD and limiting intestinal inflammation to achieve protective mucosal immune responses. In agreement with animal models DCs accumulate at sites of inflammation in patients with IBD. It was found that the pathogen recognition receptors TLR-2 and -4 as well as the activation/maturation marker CD40 are upregulated by intestinal DCs derived from patients with CD[18]. Furthermore, increased numbers of TNF-α producing $MDC8^+$ monocytes, which may be precursors of mucosal DC populations, were found in patients with IBD and, hence, the treatment CD patients with anti-TNF-α antibodies resulted in reduced DC activation[105,106]. In inflamed tissues DCs are matured and increased in

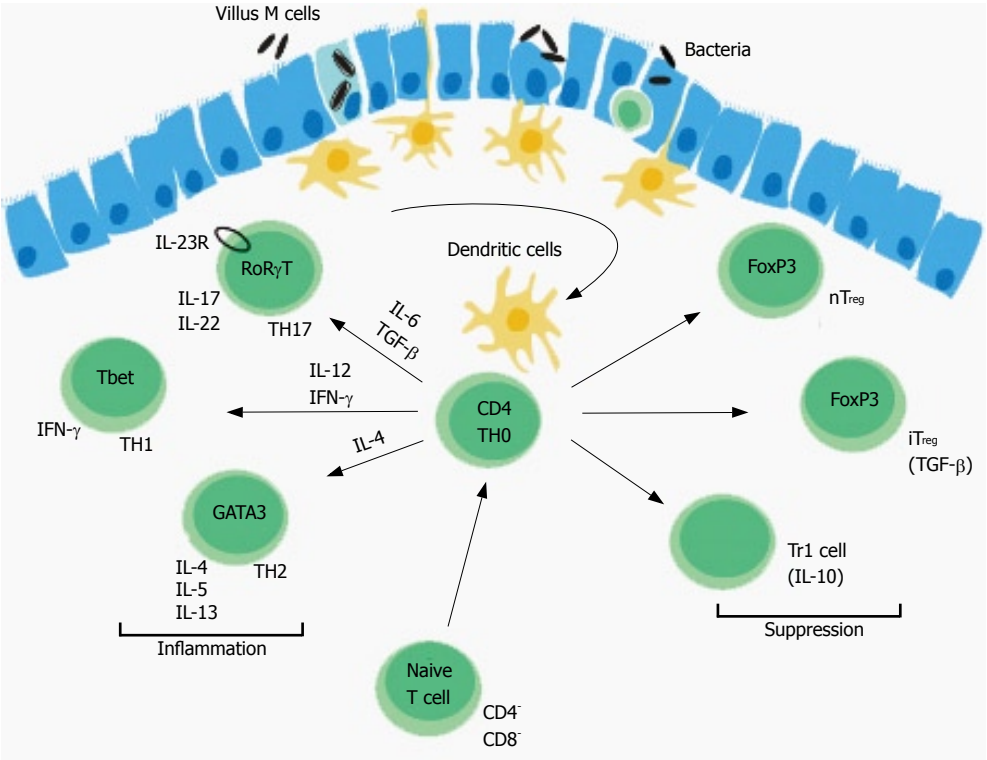

Figure 2 DCs continuously survey the intestinal lumen, phagocytose and process luminal antigens and present them to T cells, which will differentiate in presence of IL-6 and TGF-β to IL-17A and IL-17F producing TH17 cells, in presence of IL-12 and IFN-γ into TH1 cells or in presence of IL-4 into TH2 cells. nTreg, natural occurring regulatory T cell; iTreg, inducible regulatory T cells; Tr1, regulating T cell.

numbers. The $CD83^{-}CD80^{+}DCSIGN^{+}$ DC subsets produce the cytokine IL-12 and IL-18, which promote TH1 development[19]. Also, in the peripheral blood and in the lamina propria of patients with CD or UC the numbers of $CD86^{+}CD40^{+}$ DCs are increased. In addition, DCs generated *ex vitro* from peripheral blood monocytes of IBD patients show increased abilities to stimulate immune responses[107-109]. Mice studies indicated that DCs isolated from inflamed colonic tissues and DCs located in the terminal ileum, which continuously sample commensal bacteria produce IL-23, but little IL-12[110,111]. It was discovered that IL-10 KO mice that spontaneously develop colitis are protected from colitis when bred on IL12p19, but not on IL-12 p35-deficient mice. In similar studies, *Helicobacter hepaticus* infected immunocompromised $RAG^{-/-}$ bred on IL-12 p19 deficient mice, but not on IL-12 p35 deficient background mice were protected from colitis indicating that DC derived IL-23 plays a major role in intestinal pathology[112,113]. The formation of granulomas, histological characteristics of CD, depends on the release of IL-23 by DC-like cell types that are characterized by CD11c and F4/80 expression[114]. Genome-wide association studies showed associations between CD and UC patients, and a gene encoding a subunit for the IL-23 receptor suggested a major role of IL-23 in the pathogenesis of IBD[115,116]. IL-23 seems to be essential for the expansion and maintenance, but not for the initial induction of IL-17 producing CD4 T cells (TH17) cells[117]. Studies in which TH1 and TH17 cells were generated co-cultures, in which naïve T cells were cultured with fecal extracts pulsed DCs, and in the presence of TH1 or TH17 promoting cytokines indicated that TH17 cells are more pathogenic than TH1 cells[118]. Recent published observations report that colitis induced by transfer of IFNγ-deficient T cells in $RAG^{-/-}$ mice is associated with elevated numbers of TH17 cells in the lamina propria[70]. The adoptive transfer of IL-17F, but not IL-17A deficient CD4 T cells ameliorated the IBD in the transfer model[119,120]. Interesting findings implicated that the IL-1 and IL-23 dependent priming of TH17 effector cells required a NOD2 dependent pathway, and that monocyte derived DCs from CD patients with mutated NOD2 failed to efficiently activate TH17 effector cells[121]. In this regard the TH17 cytokine IL-22 mediates mucosal defence to bacterial pathogens, and ameliorates chronic colitis in the TCRαKO model by stimulating mucus production and globlet cell restitution under inflammatory conditions[122]. In addition IL-22, which is released by T and DCs, act together with IL-17 to clear bacterial infections at mucosal sites[123,124]. When conventional DCs are depleted in a CD11c DTR transgenic animal system by diphtheria toxin applications, the severity of colitis is suppressed in the dextran sodium sulfate (DSS) colitis model[125]. Furthermore, in mice with an iEC specific deletion of IKKβ failed to clear *Trichuris muris* infection characterized by severe intestinal pathology[126]. In these mice an increased accumulation of DCs at mucosal sites was observed that produce IL-12/23 p40 and TNF-α. In addition, an accumulation of IFN-γ producing TH1 and IL-17 producing TH17 cells in the MLN was found. Specific depletion of NEMO (IKKγ) or of both IKKα and IKKβ is essential for the activation of NF-κB activation induce IBD[127]. Constitutive NF-κB activation in IECs by commensal flora may condition DCs to prevent tissue inflammation. Thymic stromal lymphopoietin (TSLP) produced by epithelial cells is involved in the

conditioning of DCs to prime less harmful TH2 and T_{reg} responses[126,128]. Together, these data suggest that DCs are conditioned by iECs to promote immunosuppressive T cell responses. However, DCs and their precursors are sensitive to proinflammatory activation signals, which could help to participate into the long persistence of local T cell activation patterns promoting IBD.

CONCLUSION

Mucosal DCs may have several functions in the mucosal immune system to accomplish tolerance and to maintain homeostasis. Tolerance to intestinal self antigens, oral antigens and the commensal flora is achieved by interactions of DCs with regulatory and effector T cells. DCs are also involved in triggering deleterious T cell responses to the endogenous microflora being the basis of IBD. Mucosal DCs express the integrin alpha E (CD103) or the receptor for fractalkine/CX3CR1. CX3CR1 expressing DCs are involved in luminal antigen recognition pathways, whereas CD103 DCs metabolize vitamin A to retinoic acid and are involved in the conversion of T cells to regulatory T cells. Genetically engineered mouse models, and cellular approaches will be increasingly available to study the biology of CD103 and CX3CR1 DCs in immune responses to the commensal flora, and their role in initiating and regulating intestinal inflammation. DCs maintain intestinal homeostasis allowing the peaceful coexistence with the endogenous microflora. The discovery of specific DCs associated with luminal antigen acquisition and oral tolerance will allow developing strategies for targeting defined antigen acquisition routes to design therapeutic treatments for patients with IBD.

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