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REVIEW

Mucosal dendritic cell diversity in the gastrointestinal tract

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Abstract The discovery of dendritic cells (DCs) in skin by Paul Langerhans in 1868 identified a cell type which has since been recognized as a key link between innate and adaptive immunity. DCs originate from bone marrow and disseminate through blood to all tissues in the body, and distinct DC subpopulations have been identified in many different tissues. DC diversity is apparent throughout all mucosal surfaces of the body, but the focus of this review article is DC diversity throughout the gastro-intestinal tract (GIT). DC subpopulations have been well characterized in the oral cavity and small intestine, but DC characterization in other regions, such as the esophagus and stomach, is limited. Substantial research has focused on DC function during disease, but understanding the regulation of inflammation and the induction of acquired immune responses requires combined phenotypic and functional characterization of individual DC subpopulations. Furthermore, little is known regarding mucosal DC subpopulations in the GIT of the neonate and how these DC populations change following colonization by commensal microflora. The current review will highlight mucosal DC diversity and discuss factors that may influence mucosal DC differentiation.

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Introduction

In 1868, a German medical student named Paul Langerhans working in Berlin viewed, perhaps for the first time in history, a dendritic cell. He obtained human skin and stained tissue sections with Cohnheim's gold chloride stain (Egeler et al. 1994). Based on cellular morphology, he concluded these cells had a nervous function (Birbeck et al. 1960/1961). The cells he discovered would become known as Langerhans Cells (LCs) and were actually skin DCs. It would be nearly 100 years before another scientist would be able to build on Langerhan's observations, when Birbeck granules were discovered in 1961, and in 1962 were proven to be unique to LCs (Birbeck et al. 1960/1961; Becker 2003).

In 1973, Ralph Steinman and Zanvil Cohn discovered a new type of cell in the mouse spleen based on morphology and tissue distribution. Using a phase-contrast microscope, Steinman observed cytoplasmic processes emanating from the cell and thus called it a DC (Steinman and Cohn 1973). Over the next few years, this group continued to characterize DCs based on morphological and functional abilities and subsequently other attributes were used to define DCs as a distinct cell type (Steinman and Cohn 1974). Initially, it was thought DCs lacked pinocytotic ability (Steinman et al. 1975), although this was later refuted (Sallusto et al. 1995). An important discovery made in 1974 was that DCs were derived from precursor cells in the bone marrow (Steinman et al. 1974). Cells with properties similar to mature DCs were absent in bone marrow, which suggested DCs must originate from a bone marrow precursor cell. DCs were identified that

exhibited responses similar to lymphoid cells, and another significant step forward came in 1979 when splenic DCs were isolated and purified (Steinman et al. 1979), which created the opportunity to perform phenotypic and functional studies. Subsequently, DC research rapidly expanded to include the analysis of DC phenotype and function in a variety of other organs and species.

DC lineage

DCs are phenotypically and functionally diverse, which has complicated investigations of cell lineage (Shortman and Liu 2002). Causing even more confusion is the use of phenotype and function, either separately or in combination, to define DC subsets, and both these questions are important when investigating cell lineage. Once cell lineage is established, it is then important to determine from where the cells originate and how cells are recruited to a specific tissue. Finally, it is important to determine if specific DC subpopulations are recruited to a tissue or if immature DCs (iDCs) are recruited and then differentiate under the influence of the local microenvironment.

Like all leukocytes, DCs are derived from common hematopoietic stem cells (HSCs). What makes DCs distinct from other leukocytes is their lineage commitment, which is determined by a number of growth factors. Expression of the hematopoietic growth factor receptor, Csf-1r, is important for the generation of most leukocytes (MacDonald et al. 2005). However, the Flt3 receptor and Flt3 ligand play an important role in the generation of both pre-DCs and plasmacytoid DCs (PDCs) (D'Amico and Wu 2003). In lymphoid tissues, there are two known DC progenitor cells: monocyte/macrophage and DC precursor cells (MDP) and common DC precursor cells (CDP). Both these precursors have the ability to produce PDCs and conventional (c)DCs (Varol et al. 2007); however, only MDP have the ability to produce monocyte/macrophages (Naik et al. 2007). In the bone marrow, CDPs give rise to preclassical DCs (pre-cDCs) and PDCs (Liu et al. 2009). PDCs and pre-cDCs then traffic through the blood and are recruited to various tissues. PDCs differentiate from CDPs just as pre-cDCs do in the bone marrow and then traffic to target tissues (Geissmann et al. 2008). Pre-DCs are also recruited to various tissues and then differentiate into a variety of phenotypically and functionally distinct DC subsets.

PDCs arise from HSCs in the bone marrow similar to all leukocytes and comprise 1–2% of all cells in that region (Reizis 2010). PDCs are classed as DCs because they are very similar in function and development to other types of DCs. PDCs are defined as a distinct subpopulation based on an atypical DC morphology, recirculation and homing patterns, a prolonged survival time, and they share common properties with B cells (Reizis 2010). PDCs are also unique in their capacity to respond to viral infections by secreting large amounts of type 1 interferon (Zuniga et al. 2004).

Murine mucosal DCs appear to arise from monocytes by first expressing Ly-6C^{+} and then traffic through the bloodstream to become CX3CR1^{+} lamina propria (LP) DCs. Another possible pathway for LP DC development is by differentiating from pre-cDCs, arising from CDPs. These cells are thought to eventually become CD103^{+} LP DCs (Geissmann et al. 2008). In cattle, we have observed a variety of distinct DC subsets in the LP which are absent or rare in blood (Table 1). For example, CD11c^{hi}CD13^{+} are absent in the blood of calves, but approximately 10% of ileal and jejunal LPLs are CD11c^{hi}CD13^{+} (Fries and Griebel, unpublished observations). These observations support the conclusion that iDCs are recruited to mucosal surfaces and differentiate into phenotypically distinct subsets under the influence of the local microenvironment.

DC function

DCs are an important component of the innate immune system and are found throughout the body. The main function of DCs is to interact with pathogens and present their antigens to cells of the adaptive immune system, such as T cells and B cells (Iwasaki 2007). This initiates effector responses to enhance pathogen clearance and establish immune memory specific to individual pathogens. For this reason, it is said that DCs are the bridge between the innate and adaptive immune system. DCs also have the ability to secrete cytokines depending on their location in the body and their state of differentiation and activation. For example, PDCs have potent anti-viral effects

Table 1 Monocyte and DC subpopulations present in the blood and small intestine of 6 month old calves

Phenotype	Blood	Intestine (jejunum)
CDllc^{hi}MHC Class II^{+}	Present[a]	Present
CDllc^{hi}MHC Class II^{-}	Rare[b]	Rare
CDllc^{hi}CD11b^{+}	Present	Present
CDllc^{hi}CD11b^{-}	Minor[c]	Present
CDllc^{hi}CD13^{+}	Absent	Present
CDllc^{hi}CD13^{-}	Present	Rare
CDllc^{hi}CD14^{+}	Present	Minor
CDllc^{hi}CD14^{-}	Present	Present
CDllc^{hi}CD26^{+}	Minor	Present
CDllc^{hi}CD26^{-}	Present	Present
CDllc^{hi}CD205^{+}	Present	Present
CDllc^{hi}CD205^{-}	Present	Present

[a] Present = 10–90%

[b] Rare = 0–2%

[c] Minor = 2–10%

because of their ability to secrete type 1 interferon, whereas myeloid DCs secrete vast amount of IL-12 in response to antigenic stimulation (Zuniga et al. 2004; Kalinski et al. 1997). Based on location, DCs can be divided into two broad categories: blood DCs and tissue DCs. Blood DCs circulate in the bloodstream searching for antigen and have been extensively studied because of their ease of isolation. Tissue DCs reside throughout the body, including mucosal surfaces, and DC populations are specialized for the tissue in which they reside.

Mucosal DC diversity

The surface molecules used to define DC phenotype vary among species. Some molecules have been conserved across species and provide a basis for interspecies comparison. For example, CD11b and CD11c molecules are found on murine, human and bovine DCs (Table 1). In contrast, some molecules are species-specific and no functional orthologue may be known. Despite these limitations, it has been possible, within individual species, to begin appreciating the diversity of DC subsets identified at specific mucosal surfaces.

Mucosal surfaces can be divided into two distinct functional groups: type I and type II mucosa. Mucosal surfaces covered by simple columnar epithelium are classified as type I mucosa and include the small and large intestine, the respiratory system, and the upper female reproductive system (oviduct, ovary, uterus, endocervix). Mucosal surfaces covered by noncornified, stratified epithelial layer are classified as type II mucosa and include the mouth, esophagus, cornea and the lower female reproductive system (ectocervix, vagina) (Iwasaki 2007). DC access to surface antigens varies between these two types of mucosal surfaces, and there is emerging evidence that mucosal DC subpopulations also vary among mucosal sites. Understanding the functional and phenotypic differences in mucosal DC subsets is important for understanding the immune regulatory roles DCs play through interactions with commensal microflora, pathogens, and food antigens.

Oral cavity

The oral cavity is the first site of exposure to many pathogens, and oral mucosal DCs (omDCs) are present throughout the mouth. Organized lymphoid tissue is also present in the oral cavity, including the tongue and tonsils, and function as important immune induction sites. Investigation of omDCs has increased with interest in developing sublingual immunotherapy (SLIT), whereby antigen-specific tolerance can be induced by administering antigen under the tongue, a region rich in DCs. In mice, PDCs ($B220^{+}120G8^{+}$), myeloid DCs ($CD11b^{+}CD11c^{+/-}$), and LCs ($CD207^{+}$) (Table 2) have been found in the oral submucosa, the submucosa/mucosa interface, and the mucosa, respectively (Mascarell et al. 2008). The function of omDCs is to ingest, process, and present antigen to $CD4^{+}$ T cells, where they will stimulate the production of either IFNγ or IL-10. The production of IL-10 is linked to immune tolerance and the induction of Th1 regulatory T cell responses.

Phenotype studies of DCs in the human tongue have identified distinct DC subsets which reside in the fungiform papillae (FP) of the tongue. $CD11c^{+}$ myeloid DCs and DC-$SIGN^{+}$ immature DCs are both found in the epithelium and LP, but mainly in the LP (Table 3). $CD83^{+}$ mature DCs are found in both the epithelium and LP, while $CD1a^{+}$ LC DCs are found solely in the epithelium (Feng et al. 2009). The study of DCs and immune cells in the tongue may also have relevance due to their possible contribution to taste dysfunction in patients who suffer from this disease.

Over the past 10 years, research on LCs in the oral mucosa has increased greatly. Oral DCs were discovered to express high levels of high affinity receptor for IgE (FCεRI) (Allam et al. 2003). FCεRI is a receptor on the surface of DCs, among other cell types, responsible for regulating allergic response (Felaco et al. 2009). Oral LC DCs differ from epidermal LC DCs in their expression of FCεRI, which could alter their involvement in allergic responses (Allam et al. 2008). On the other hand, nasal mucosal DCs and oral mucosal DCs both share certain properties, such as a high expression of FCεRI, myeloid markers and costimulatory expression, but display differences when it comes to lineage, phenotype, and function (Allam et al. 2006). Therefore, regional differences in DC phenotype and function are apparent within the oral cavity. Studies investigating age-dependent and species-specific differences among omDC subsets have not yet been undertaken. Studies in fetal sheep, however, confirmed DCs were present in the oral mucosa as early as the second trimester of pregnancy, and effective antigen presentation could occur following exposure to oral antigens (Tsang 2007).

Esophagus

Esophageal DCs are poorly characterized, but it is known that DCs inhabit the LP. DC phenotype in this and other mucosal compartments of the esophagus have, however, been limited to investigations of human disease states, such as Barrett's esophagus. This disease is characterized by chronic inflammation and mucosal epithelial dysplasia following chronic gastric acid reflux (Stein and Siewert 1993). DC-SIGN and $CD83^{+}$ DCs increase in density when comparing adenocarcinoma versus benign Barrett's esoph-

Table 2 Mouse mucosal DC subsets throughout the GIT

Tissue	Subsets	Localization	Reference
Oral cavity (mucosa)	PDCs ($B220^{+}120G8^{+}$)	Submucosa	(Mascarell et al. 2008)
	Myeloid ($CD11b^{+}CD11c^{+}$)	Mucosa	(Mascarell et al. 2008)
	LCs ($CD207^{+}$)		(Mascarell et al. 2008)
Esophagus	Not described		
Stomach	Not described		
Small intestine	$CD11c^{hi}CX3CR1^{-}$ $CD11b^{hi/lo}$ $CD103^{+}$	LP	(Johansson-Lindbom et al. 2005)
	$CD11c^{hi/lo}CX3CR1^{+}CD70^{+}CD11b^{hi}CD103^{-}$	LP	(Atarashi et al. 2008)
Large intestine	$CD40^{lo}$MHC Class $II^{lo}CD80^{+}CD86^{+}$	LP	(Cruickshank et al. 2005)

agus (Bobryshev et al. 2009a), and DC infiltrating the esophagus during disease state have typical morphological features characteristic of DC (Bobryshev et al. 2009b) (Table 3). Studies of DCs in healthy esophagus and comprehensive phenotypic and functional studies are lacking (Table 2).

Stomach

Similar to the esophagus, the analysis of gastric mucosal DCs has been performed primarily within the context of disease. Much of this research has focused on DC responses to *Helicobacter pylori* (*H. pylori*) in the gastroduodenal region. It has been reported that the healthy gastric mucosa of mice is devoid of DCs (Kao et al. 2006) (Table 2). However, a study of the rumen and fore stomach of adult and fetal sheep concluded that LCs were present (Josefsen and Landsverk 1996). DCs are reported to be recruited to the gastric mucosa within 6 h after primary *H. pylori* infection (Necchi et al. 2009). The main site of infiltration for DCs is the LP of the gastric mucosa (Nishi et al. 2003) and recruited DCs express costimulatory markers such as CD54, CD80 and CD86 (Kao et al. 2006) (Table 3). Overall, DCs are thought to contribute to chronic inflammation during *H. pylori* infection through the induction of Th1-biased responses (Khamri et al. 2010). The mechanisms by which DCs contribute to chronic inflammation in *H. pylori* are not completely understood. One theory is that the bacteria replicate in the autophagosome of DCs, impair DC function and induce autophagy (Wang et al. 2010). This internal replication also causes the LC3, LAMP1 and MHC Class II molecules to be held within the vacuole and, as a result, MHC Class II molecules cannot be expressed on the surface of the cell.

Small intestine

Although the ileum and jejunum have physiological and functional differences, the DC subpopulations are often investigated within the small intestine without identifying the specific location (Mutwiri et al. 1999). The most notable immunological difference between ileum and jejunum is the structure of the organized lymphoid tissue known as Peyer's patches (PPs). In ruminants, pigs and many mammalian species, the ileal PP consists of a continuous aggregate of lymphoid follicles while the jejunal PPs consist of multiple discrete lymphoid aggregates (Griebel and Hein 1996). DCs are located in the LP throughout the small intestine, though due to the close proximity of LP and mucosal epithelium, it is difficult to

Table 3 Human mucosal DC subsets throughout the GIT

Tissue	Subsets	Localization	Reference
Oral cavity (tongue)	Immature DCs ($CD11c^{+}$DC-$SIGN^{+}$) Mature DCs ($CD83^{+}$)	Epithelium & LP	(Feng et al. 2009)
	LCs ($CD1a^{+}$)	Epithelium & LP	(Feng et al. 2009)
Esophagus	$CD83^{+}$DC-$SIGN^{+}$	LP	(Bobryshev et al. 2009a)
Stomach	Immature ($CD54^{+}$ $CD80^{+}CD86^{+}$)	LP	(Kao et al. 2006)
Small intestine	$CD11c^{+}CD83^{+}$DC-$SIGN^{+}CCR6^{+}CCR7^{-}$TLR-$4^{+}TNF\alpha^{+}$	Subepithelial dome	(Salim et al. 2009)
Large intestine	$CD83^{+}CD86^{+}CD80^{-}CD25^{-}$	LP	(Bell et al. 2001)
	$CD83^{+}$ and DC-$SIGN^{+}$	LP	(te Velde et al. 2003)

discriminate between intraepithelial DCs and DCs present in the LP (Rescigno and Di Sabatino 2009). Approximately 10–15% of LP leukocytes (LPL) in the murine small intestine are thought to be DCs (Sun et al. 2007). $CD11c^+$MHC Class II^+ DCs make up approximately 20% of all $CD45^+$ LPL isolated from the ileum and jejunum of 3-week-old calves. There are, however, age-related decreases in DC frequency, and 5% of ileal and 10% of jejunal LPL are $CD11c^+$MHC Class II^+ DCs in 6-month-old calves (Fries and Griebel, unpublished observations).

Murine DCs in the small intestine are typically categorized into two groups: $CD103^+$ and $CD103^-$ (Table 2). CD103 is integrin α_E and is expressed by 70% of $CD11c^{hi}$ DCs in the murine small intestine LP (Fortin et al. 2009; Johansson-Lindbom et al. 2005). $CD11c^{hi}CD11b^{hi/lo}CD103^+$ DCs are thought to promote differentiation of $Foxp3^+$ Tregs (Sun et al. 2007). These cells are also $CX3CR1^-$ indicating they are unable to extend dendrites into the intestinal lumen since this chemokine receptor has been associated with dendrite formation (Niess et al. 2005). Despite a lack of transmucosal dendrites and a known role in immune tolerance, the $CD103^+$ DCs can induce expression of homing markers CCR9 and $\alpha4\beta7$ on T cells. Another group of DCs identified in the LP are $CD11c^{hi/lo}CX3CR1^+CD70^+CD11b^{hi}CD103^-$, and this DC subset has been implicated in Th17 differentiation from naive T cells (Atarashi et al. 2008). It is also believed that $CD103^-$ DCs perform innate immune functions, such as chemokine-mediated attraction and antigen clearance, which $CD103^+$ cells cannot perform (del Rio et al. 2010). All DCs found in the interfollicular region of the Peyer's patches also express CCR7, which regulates chemotaxis and survival in mature DCs (Escribano et al. 2009). There is research that indicates that the unique functional properties of $CD103^+$ DCs are conserved between humans and mice (Jaensson et al. 2008), but there is no information if this DC subset marker is conserved among other species.

Research in healthy human small intestine is very limited, but investigations into Crohn's Disease (CD) provide some insight into the DC populations present in the ileum. In CD, there is an accumulation of $CD11c^+CD83^+$DC-$SIGN^+$ DCs in the subepithelial dome (Salim et al. 2009). The accumulation of DCs in this region could be a result of the lack of the lymph node migratory receptor CCR7 and the high bacterial load that is found in this region (Keita et al. 2008). These DCs also increase from 0 to 1.6% when comparing healthy ileal wall and CD ileal wall, respectively (Salim et al. 2009). Elevated TLR 4 expression and increased TNFα production may contribute to the inflammatory symptoms that accompany CD. TLR 4 is the receptor on myeloid DCs that recognizes lipopolysaccharide (Taniguchi et al. 2009) and myeloid DCs isolated from the colon of inflammatory bowel disease patients have increased expression of CD83, TLR 4 and TNFα which may contribute to inflammation (Hart et al. 2005; Middel et al. 2006).

Research into small intestine DCs of other species is very limited. We are currently analyzing DC diversity in the ileum and jejunum of young calves and age-related changes that occur in mucosal DC subsets. Our research has also included parallel comparisons of DC/myeloid subsets in blood and the small intestine. This comparison provides information about both leukocyte trafficking and the local differentiation of mucosal DCs. We identified diverse DC subsets located with the LP of small intestine (Table 1). A significant difference in DC subsets was observed when comparing LPL isolate from the ileum and jejunum of 3-week-old calves. $CD11c^{hi}CD14^+$ DCs were significantly more abundant in the LP of the ileum (6.4%) than the jejunum (2.8%). This regional difference in DC subsets was no longer apparent, however, when comparing DCs isolated from the intestine of 6-month-old calves (Fries and Griebel, unpublished observations).

As mammals age, marked changes occur within the immune system (Agarwal and Busse 2010; Desai et al. 2010). These age-related changes are also apparent within the LPL of cattle. At 3 weeks of age, $CD3^+$ T cells account for approximately 60% of LPL and DCs account for nearly 20% LPL isolated from both the ileum and jejunum. At 6 months of age, however, $CD3^+$ T cells have increased to 88% of ileal and 77% of jejunal LP. In contrast, DCs have decreased to 5% of ileal and 9% of jejunal LPL. Furthermore, specific DC subpopulations also change with age. In the ileum, LP $CD11c^+CD13^+$, $CD11c^+CD26^+$ and $CD11c^+CD205^+$ DCs become more abundant with age, but $CD11c^+CD14^+$ and $CD11c^+CD172a^+$ decrease in frequency between 3 months and 6 months of age. Similarly, in the jejunum, LP $CD11c^+CD13^+$, $CD11c^+CD26^+$ and $CD11c^+CD205^+$ DCs become more abundant between 3 weeks and 6 months of age (Fries and Griebel, unpublished observations). These observations suggest that developmental differences in mucosal DC subsets may be present at birth, but with exposure to commensal microflora there are substantial changes in mucosal DC subsets.

The interactions between the intestinal epithelial cells (IEC) and DCs are very important for maintaining homeostasis in the intestine and are accomplished through a number of different methods. IEC are the barrier that prevents pathogens from further entering the body. Microorganisms are sampled by IEC and are passed to DCs in the LP and SED through the use of transcytosis (Mowat 2003). $CX3CR1^+$DCs are also able to sample microorganisms in the lumen by extending their dendrities between the tight junctions of the IEC (Rescigno et al. 2001). Specialized IEC known as M cells can also deliver commensal microflora to LP and PP DCs. IEC and DCs also use

cytokines to communicate. IEC express thymic stromal lymphopoietin, which limits IL-12 production by DCs, which in turn inhibits Th1 induction. In vitro assays with monocyte-derived DCs have shown that DCs are conditioned by IEC through 'cross-talk' and, if this is lost, DCs could lose the ability to secrete cytokines and influence immune responses (Rimoldi et al. 2005). The failure of intestinal DCs to not induce an inflammatory response to commensal microflora is not well understood, but one possibility is that anti-inflammatory molecules derived from IEC prevent DCs from initiating such a response (Tezuka and Ohteki 2010). This symbiosis between IEC and mucosal DCs is thought to be critical for maintaining the health of the intestine while inhabited by a diverse community of commensal bacteria.

There have also been studies investigating the role of TLRs on the surface of LP DCs. Murine LP DCs have higher levels of TLR 2, 3, 4, 5, and 9 expression than DCs located in the spleen and mesenteric lymph node, and TLR expression level is lower in DCs located in the proximal small intestine versus the distal small intestine (Monteleone et al. 2008). It has also been reported that $CD11c^{hi}CD11b^{hi}$ LP DCs express high levels of TLR 5. When these cells are stimulated with flagellin, they are able to induce B cells to differentiate into IgA-producing plasma cells and also promote the differentiation of IL-17 Th1 cells (Uematsu et al. 2008). TLR signaling also has the ability to down-regulate intestinal inflammation and is important for maintaining intestinal homeostasis (Rakoff-Nahoum and Medzhitov 2006).

Colon

Similar to many other regions of the GIT, the colon LP contains diverse DC subsets (Dellmann and Brown 1987). Most research on the colon involves disease states such as inflammatory bowel disease and ulcerative colitis, but there is some data available for the healthy murine colon (Table 2). The colon LP of healthy mice contains $CD40^{lo}$MHC Class $II^{lo}CD80^{+}CD86^{+}$ DCs in close association with the basement membrane of the villi (Cruickshank et al. 2005). These cells also exhibit high endocytic activity, which suggests they are immature DCs. There are very few PDCs in colonic LP (Takenaka et al. 2007). $IL2^{-/-}$ knockout mice develop spontaneous colitis, and it was observed that $CD40^{lo}$MHC Class $II^{lo}CD80^{+}CD86^{+}$ DCs increased significantly in the colon LP following colitis. A similar increase in $CD40^{lo}$MHC Class $II^{lo}CD80^{+}CD86^{+}$ DCs was observed in the colon of severe combined immunodeficiency (SCID) mice (Malmstrom et al. 2001; Krajina et al. 2003). $CD103^{+}$integrin $\alpha_v\beta_8{}^{+}$ DCs are important for the suppression of colitogenic T cells (Annacker et al. 2005; Travis et al. 2007), and mice lacking this DC subset have fewer Tregs in the colon and are predisposed to develop colitis. DCs in the murine colon have low expression of TLR 4, 5, and 9, while in humans, colonic DCs have low expression of TLR 2 and 4 (Hart et al. 2005; Takenaka et al. 2007; te Velde et al. 2003). However, in mice that suffer from CD or ulcerative colitis, there is up-regulation of TLR 2 and 4 on colonic DCs. A high expression of TLR 2 and 4 may affect microbial recognition and exacerbate the cycle of intestinal inflammation, whereas low level TLR 2 and 4 expression in healthy colon may be protective and prevent excessive interaction with commensal microflora (Hart et al. 2005). Increased TLR 2 and 4 expression is also seen on IEC in CD and ulcerative colitis patients (Hausmann et al. 2002).

Research on human colonic DCs has focused mostly on ulcerative colitis patients (Table 3). Limited description of DCs in healthy human colon has revealed that these cells display an immature phenotype and are $CD83^{+}CD86^{+}CD80^{-}CD25^{-}$ (Bell et al. 2001). Human colonic DCs also express $CD83^{+}$ and DC-$SIGN^{+}$ (te Velde et al. 2003). In ulcerative colitis patients, DCs accumulate in the colon (Niess 2008). DCs isolated from ulcerative colitis patients are $CD83^{-}CD80^{+}$DC-$SIGN^{+}$, produce IL-12 and IL-18, and promote Th1 development (te Velde et al. 2003). A higher number of $CD86^{+}CD40^{+}$ DCs are found in the blood and colon LP of patients with ulcerative colitis (Niess 2008). There have been few descriptions of colonic DCs in other species but it is assumed that they are present.

Peyer's patches

Peyer's patches are prominent mucosal-associated lymphoid tissue (MALT) located in the small intestine and play an important role in the induction of IgA antibody responses. The structure and function of PPs have been studied extensively and several well-defined immune compartments have been identified. Follicle-associated epithelium (FAE) provides a direct interface with the luminal contents and transcytosis of material to the underlying subepithelial dome region and lymphoid follicles. The lymphoid follicles contain primarily B cells and are interspersed among the interfollicular (IF) lymphoid tissue which is rich in T cells and function as sites of T cell trafficking. These structurally defined regions within the MALT perform immunologically distinct functions and are characterized by phenotypically distinct DC subpopulations.

Immature DCs are associated within the FAE of mouse PPs and have been characterized as $CD11b^{-}CD8a^{-}B220^{-}$ (Iwasaki and Kelsall 2001). In contrast, the subepithelial dome region of the follicle contains a mixed population of

$CD11b^-CD8a^-B220^-$ and $CD11b^+CD8a^-B220^-$ DCs (Iwasaki and Kelsall 2000). The IF region is unique in that it contains not only $CD11b^+CD8a^+$ DCs but also PDCs (Asselin-Paturel et al. 2003; Bilsborough et al. 2003). Finally, the lymphoid follicles contain both non-hematopoietically-derived follicular DCs (FDCs) and hematopoietically-derived DCs (Kelsall and Strober 1996). Thus, within murine PPs, there are specific patterns of DC localization but it is not known to what extent these restricted DC subset distribution patterns reflect DC migration and differentiation within each immune compartment.

Human PPs have been studied much less, but $CD11c^+$MHC Class II^+ DCs have been identified throughout all immune compartments. There is some evidence for selective DC distribution with $CD11c^-$MHC Class II^+DC-$SIGN^+$ cells restricted to the sub-epithelial dome region of human PPs (Jameson et al. 2002). Studies of porcine PPs also provide evidence for distinct DC subset distribution patterns. Immunohistological (IHC) analysis of jejunal PPs revealed that $CD11b^-CD172a^+$ DCs were located in the subepithelial dome and that $CD11b^-CD172a^-$ DCs predominated in the IF region (Bimczok et al. 2005). Analysis of sheep PPs confirmed that $MgATPase^+$ DCs were present within lymphoid follicles of the fetal ileal PP (Press et al. 1992) and in young sheep $MgATPase^+$ DCs were identified within the FAE, subepithelial dome region and follicles (Halleraker et al. 1990). Neither flow cytometric nor IHC studies have been performed in sheep to determine if DC subsets are differentially distributed either within PPs or among MALT located throughout the GIT.

Conclusions

DCs have been recognized as key cells in the integration of innate and adaptive immunity, and it is hypothesized that the differential capacity of individual DC subsets to recognize and respond to pathogen-associated molecular patterns (PAMPs) directly influences the induction of protective immune responses. This hypothesis is supported by the analysis of human PDC and myeloid DCs isolated from blood (Jarrossay et al. 2001). The analysis of TLR expression on gastro-intestinal DCs is limited, but both the expression and responses to TLR ligands were markedly restricted in mucosal DCs (Monteleone et al. 2008). This same investigation also revealed significant differences in TLR expression when comparing DCs isolated from different regions of the GIT. This is consistent with phenotypic analyses which reveal specific distribution patterns for mucosal DC subsets throughout the gastrointestinal tract of many different species. As the number of surface markers used to identify individual DC subsets increase in complexity, there is a confounding number of possible DC subsets (Varol et al. 2009). It has been a challenge, however, to match DC phenotype characterization with a thorough analysis of DC function. Therefore, it is not known to what extent each DC subset possesses unique functional capacities in terms of PAMP recognition or T cell regulation. Furthermore, it is not known if individual mucosal DC subsets represent immature or mature DCs that are differentiating under the influence of factors unique to each mucosal microenvironment.

Limited functional studies have revealed that individual mucosal DC subsets may possess unique cytokine secretion patterns or functional capacities in terms of T cell activation. Many studies performed with in vitro-derived DCs have been used to define DC function (Caux et al. 1992; Sallusto and Lanzavecchia 1994; Inaba et al. 1992), but it is difficult to extrapolate this information to the myriad of diverse DC subsets identified throughout mucosal tissues. The isolation of splenic DCs opened a new era in the investigation of DC biology. A major challenge that must now be resolved for further investigation of mucosal DC biology is the isolation and purification of sufficient numbers of tissue-derived DCs to perform function assays. These studies are critical to determine if individual DC subsets represent functionally unique populations with a restricted capacity to influence innate and adaptive immune responses. Understanding the link between DC phenotype and function will provide much greater insight when studying DC responses during disease and when using DCs as immune therapy.

The current review of mucosal DC subsets and their distribution throughout the gastrointestinal tract has revealed that little is known for many species. The limited information available for humans and other species supports the observation made in mice that there is a great diversity of mucosal DC subsets with marked regional differences in the tissue distribution of individual DC subsets. Interspecies comparisons are difficult since a wide variety of non-homologous surface proteins are often used to identify individual DC subsets. Mucosal DC diversity, however, raises intriguing questions regarding the link between DC activation and differentiation and the role of the local mucosal microenvironment in this process. Furthermore, in view of the key role DCs play in immune regulation, it is critical to further investigate the function of individual mucosal DC subpopulations. This will be a major challenge, since access to mucosal tissues is often limited and isolating relatively rare mucosal DC subsets presents major technical challenges. Animal models, such as pigs or cattle, which provide access to blood, lymph, and mucosal tissue, may provide sufficient DCs to perform function assays and to study DC function in a variety of disease models. To explore the full potential of these alternative animal models, however, it will be important to

identify monoclonal antibodies and other reagents to select the diverse array of DC subsets identified in the mouse model.

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