Review Article

Immunity and Tolerance Induced by Intestinal Mucosal Dendritic Cells

Julio Aliberti

Division of Immunobiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA

Correspondence should be addressed to Julio Aliberti; julio.aliberti@cchmc.org

Dendritic cells present in the digestive tract are constantly exposed to environmental antigens, commensal flora, and invading pathogens. Under steady-state conditions, these cells have high tolerogenic potential, triggering differentiation of regulatory T cells to protect the host from unwanted proinflammatory immune responses to innocuous antigens or commensals. On the other hand, these cells must discriminate between commensal flora and invading pathogens and mount powerful immune response against pathogens. A potential result of unbalanced tolerogenic versus proinflammatory responses mediated by dendritic cells is associated with chronic inflammatory conditions, such as Crohn's disease, ulcerative colitis, food allergies, and celiac disease. Herein, we review the dendritic cell population involved in mediating tolerance and immunity in mucosal surfaces, the progress in unveiling their development in vivo, and factors that can influence their functions.

1. Introduction

The digestive tract is in direct contact with foreign antigens and microorganisms. The ability of the immune system to keep tolerance to commensals while remaining capable of responding to injury or infection with pathogenic microorganisms is essential for tissue homeostasis. Any disturbances in this balance either by genetic, environmental, or infectious causes can lead to chronic inflammatory and/or autoimmune diseases. The mucosal immune system should sense pathogens versus innocuous dietary antigens or commensal microorganisms. While a strong and protective response is required to eliminate pathogens, tolerance is essential for harmless antigens or nutrients, thus avoiding inflammatory responses.

During oral tolerance systemic immune effector function including delayed type hypersensitivity response and IgE antibody production are affected [1, 2]. Furthermore, intestine-resident effector cells also undergo tolerance. Impairment of oral tolerance seems to be associated with coeliac disease, characterized by an aberrant Th1-mediated DTH triggered by dietary gluten [1, 3]. Similarly, IgE-mediated food allergies can be derived from the break of tolerance to food antigens [1, 4].

Along the same lines, break of tolerance at the large intestine is thought to trigger hyperreactivity to commensal bacteria resulting in inflammatory bowel diseases, including Crohn's disease [5]. Interestingly, tolerance to commensal flora does not exert a systemic effect [6, 7]. Moreover, IgA production is maintained, thus supporting commensalism, because of the noninflammatory properties of IgA [8, 9].

The induction of oral tolerance has been the object of several studies. It is well accepted that clonal deletion and/or T cell anergy are components of the mechanism of action of oral tolerance, however induction of regulatory T cells (Treg's) has become widely known as its central component [10]. The induction of FoxP3+ Treg cells requires CD103+ dendritic cells (DCs). Herein, we will review the development/differentiation of mucosal resident DC subsets and their relative contribution to tolerance and immunity.

2. Subsets and Function

Intestinal DCs are located throughout the villus lamina propria and in intestinal lymphoid tissue (Peyer's Patches, solitary isolated lymphoid tissue, and mesenteric LN), where they play a central role in sampling and processing luminal as well as peripheral self-antigen for presentation to
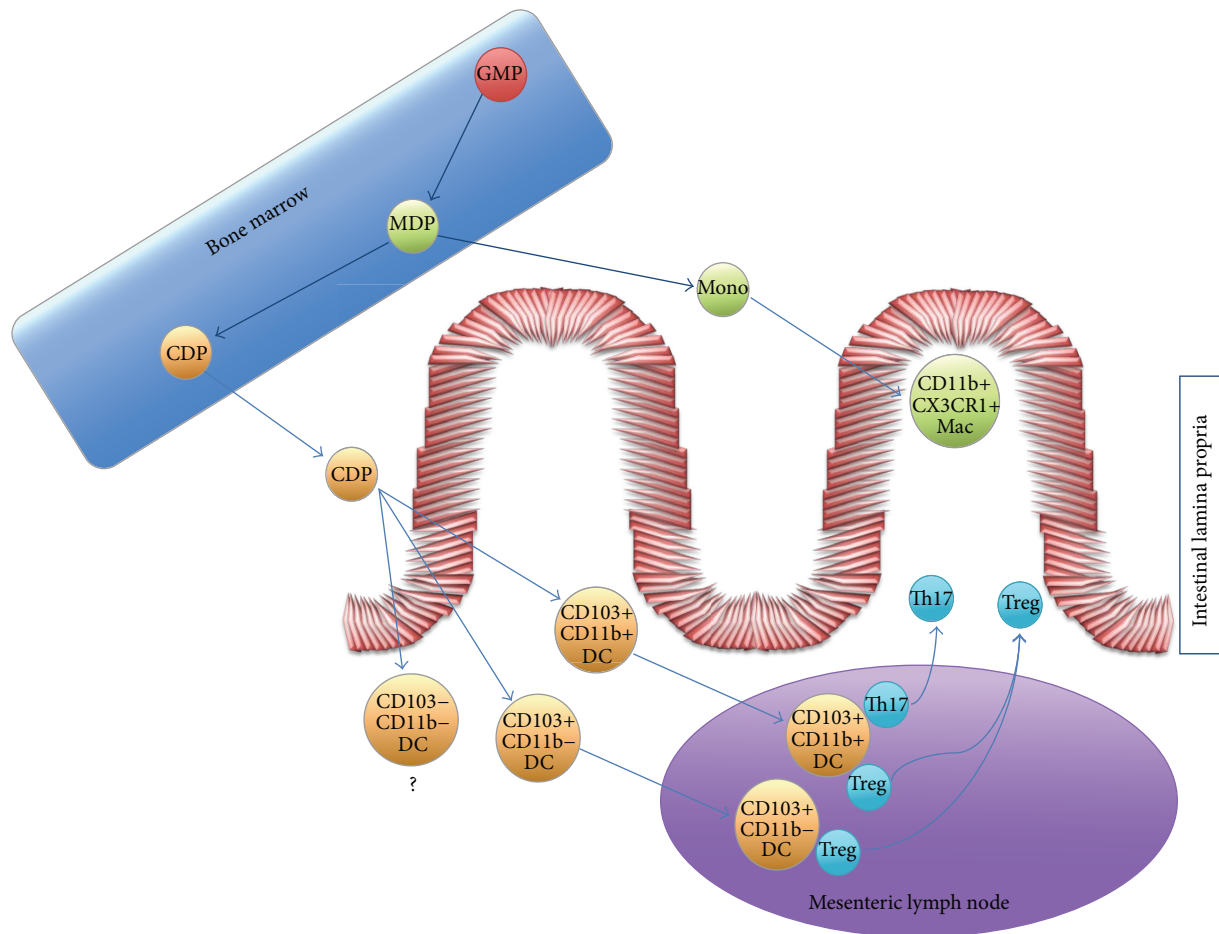
FIGURE 1: Intestinal mucosal dendritic cell and macrophage development and function. Bone marrow resident Granulocyte Macrophage Progenitors (GMP) give rise to Macrophage DC Precursors (MDP). In turn, CDP give rise to peripheral blood monocytes (Mono) and Common DC Progenitors (CDP). Monocytes will migrate to the lamina propria differentiating into CD11b+CX3CR1+ macrophages that directly sample antigens from the intestinal lumen. On the other hand, CDP will give rise to three subpopulations of intestinal lamina propria DCs: CD11b+CD103+, CD11b−CD103+, and CD11b−CD103−. The former two subsets are responsible for sampling antigen and priming naïve T cells into regulatory T cells (Treg) or IL17-producing T cells (Th17).

T cells [10]. A seminal study by Rescigno et al. [11] showed that CD11c+ cells send transepithelial dendrites from the lamina propria that penetrate through tight junctions and capture *Salmonella* from the lumen. Lamina propria contains two major populations of CD11c+ mononuclear phagocytes: CD11c^{hi}CD103+CD11b+CX3CR1− cells (DCs) and CD11c^{int}CD103−CD11b+CX3CR1+ cells (macrophages) [6, 9, 12–15]. CX3CR1+ macrophages, rather than the CD103+ DCs, are sampling the intestinal luminal content by extending transepithelial dendrites [11, 13, 16–18]. Exposure to TLR-ligands [13] and microbes [18] induces transepithelial dendrites formation [17]. CD103+ DCs have not been observed extending transepithelial dendrites [17].

DCs (CD11c+CX3CR1− cells) can be further subdivided into three major subsets based on the expression of CD11b and CD103, with CD11b+CD103+, CD11b−CD103+, and CD11b−CD103− [19, 20] (Figure 1). Lymphoid tissue resident DCs include plasmacytoid DCs (pDCs) and CD8α+ and CD11b+ conventional DCs (cDCs). They can be found along

the lymphoid organs associated with the intestine, including PPs, isolated lymphoid follicles, and MLNs. Nonlymphoid tissue DCs, found in the parenchyma of tissues, are also known as migratory DCs. Under steady-state conditions, migratory DCs promote the expansion of regulatory T cells, required for tolerance to self-antigens [21, 22] (Figure 1). On the other hand, during inflammatory response to infection, these cells promote protective T cell responses [23, 24]. The expression of the chemokine receptor CCR7 and its ligands CCL21 and CCL19 control whether migratory DCs move into draining LNs [25].

Classic process of DC maturation occurs upon exposure to microbial stimuli or proinflammatory cytokines. Typically, morphological, phenotypic, and functional changes are observed. Such modifications are essential for effective naïve T cells priming and activation. On the other hand, migratory DC maturation is associated with tolerance induction rather than activation and proliferation, despite upregulation in MHC II and CD40 [20]. Importantly, the signals that

trigger and modulate such maturation processes are poorly understood.

Induction of tolerance versus immunity by intestinal DC is, at least in part, mediated by retinoic acid receptors (RAR) signaling [26–29]. Thus, exposure to RA triggers expression of gut-homing receptors along with enhancing expansion of FoxP3+ T cell and IgA B cell differentiation. On the other hand, antagonists of RAR inhibit expansion of such cells [30–32]. Induction of gut-homing receptors on primed T cells as well as FoxP3+ T cell differentiation in vitro is best achieved in the presence of migratory (CD103+CD11b− or CD11b+) DCs among other DC subsets [4, 5, 7]. RALDH2 is one of the enzymes that metabolize retinal to RA, CD103+ DCs express high levels of the gene encoding it – *aldh1a2*. Consistently, CD103+ DCs triggered RAR-dependent signaling in responding T cells [33]. Small intestine-lamina propria and MLN resident CD103+ DCs trigger RAR signals and induce expression of CCR9 in responding T cells [34]. All DCs trigger limited RAR signaling in T cells; however high levels of CCR9 induction are a key function associated with small intestine-lamina propria and MLN CD103+ DCs. On the other hand, the CD103+CD11b+ subset seems critical for the induction of proinflammatory Th17 cells [19, 20] given its high induction of IL6 in response to microbial stimulation [35].

3. Mucosal Dendritic Cell Precursors and Homing Markers

The interaction of FMS-like tyrosine kinase 3 (Flt3) with its ligand (Flt3-L) is critical for the generation of CD103+ DCs [36], both in mice and humans [37, 38]. Pre-B cells as well as myeloid and monocytic lineages show upregulated Flt3 mRNA, while Flt3-L mRNA expression is ubiquitous [39]. Both Flt3 and Flt3-L show high conservation in mice and humans. Treatment of mice with human Flt3-L leads to activation of mouse Flt3 [40] triggering bone marrow hyperplasia along with hematopoietic stem and progenitor cell proliferation. Interestingly, FLT3-L showed a positive bias in the expansion of CD103+ DCs [13].

Macrophage and DC bone marrow precursors give rise to monocytes and common DC progenitor [41]. Common DC progenitors are comprised within lineage (lin)- negative, Flt3-L+ cell subset [42, 43] (Figure 1). PDCs and cDCs are both derived from the common DC precursor within this lin-Flt3+ compartment [44, 45]. The common DC precursor is GM-CSF receptor α+ [45]. The transcription factor IRF8 is required for development and activation of pDCs and CD8α+ DCs [46–48] and PU.1 is important for all conventional (nonplasmacytoid) DCs [49, 50]. The expression of PU.1 is induced by Flt3 signaling [51]. Intestinal CD103+CD11b− DCs are developmentally related to the CD8α+ lymphoid DC subset, since both subsets are dependent on the presence of the transcription factors IRF8, Id2, and BATF3 [52].

Most CD103+ small intestine-lamina propria DCs have been shown to develop directly from a circulating FLT3+ common DC precursor and not from CD103− small intestine-lamina propria DCs [53] (Figure 1). Interestingly, a great proportion of MLN resident CD103+ DCs are thought to be derived from a migratory population arriving from small intestine-lamina propria that plays a critical role in presenting orally derived soluble antigen to T cells (Figure 1). Presumably, these cells seize antigens locally in the small intestine and subsequently migrate into the MLN. On the other hand, CD103− MLN DCs appear to be derived from a blood population that populate and expand the MLN and is involved in the T cell priming to systemic antigens [53]. Importantly, CD103+ DCs are present in normal and inflamed human MLN and display similar phenotypic and functional properties to their murine counterparts [6].

CCR7, a chemokine receptor which is required for DC migration from peripheral tissues into the draining LN, is required for accumulation of CD103+ DC in the MLN, as CCR7-deficient hosts have reduced numbers of MLN CD103+ DCs [54–56].

4. Intestinal Mucosal Dendritic Cell Responses to Infection

Intestinal flora is composed of trillions of resident bacteria that can provide beneficial effects to the host [57]. For example, bacterial metabolites including vitamins and short chain fatty acids are relevant for the host development, including lymphoid populations in the intestine. Moreover, resident bacteria mediate resistance against pathogen infection [58]. Several host immune-regulatory mechanisms have evolved to prevent inappropriate activation of inflammatory responses in response to the commensal flora, including the hyporesponsiveness of intestinal epithelium and resident macrophages to bacterial Toll-like receptor ligands [59, 60]. However, intestinal microbiota can potentially trigger (or enhance) an inflammatory response. Chemically induced and spontaneous colitis are reduced or abolished in antibiotic-treated mice and germ-free mice [61–65] and *Bacteroides* species and members of the Enterobacteriaceae family including *Klebsiella pneumoniae* and *Proteus mirabilis* can promote colitis [66, 67].

Activation of inflammatory responses by flora is mediated by host pattern-recognition receptors [68]. Inflammasome, a multiprotein complex that leads to caspase-1 initiated proteolytic processing of pro-interleukin-1β and pro-IL18 into their active forms [69]. In the intestine, *Salmonella* triggers resident phagocytes to produce IL-1β in an NLRC4-dependent manner leading to neutrophil recruitment [70].

The role of the NLRP3 inflammasome in intestinal inflammation is controversial. On one hand, mice lacking NLRP3 or caspase-1 were shown to be less susceptible to chemically induced colitis [71, 72]. On the other hand, it was shown that these same animals had increased susceptibility and worsened pathology [73, 74]. Along the same lines, the role of IL-1β in colitis is also controversial. While IL-1β blockage improves intestinal inflammation in different animal colitis models [75, 76], another study showed that genetic deficiency of IL-1β leads to increased susceptibility to experimental colitis [8]. Although it is not clear what the reasons for such differences in results are, one potential explanation is the composition of gut flora [71]. For instance,

Escherichia coli trigger NLRP3 inflammasome in bone marrow derived macrophages to produce IL-1β [77, 78].

5. Mucosal Tolerance and Dendritic Cells

Several commensal *Bacteroides* and Bifidobacteria strains can directly induce monocyte-derived DCs to acquire a tolerogenic phenotype [79]. Polysaccharide A from *Bacteroides fragilis*, a Gram-negative anaerobic commensal bacterium, can also associate with CD11c+ cells in MLNs and drive a mixture of Th1 systemic responses and IL10-producing Treg cells in the colonic LP [80]. Segmented filamentous bacteria induce differentiation of both mucosal Th17 and FoxP3+ Treg cell. These effects are associated with the modulation of APC function in the lamina propria [19, 81, 82]. Antigen presentation by CD103+ DCs can be tolerogenic [5, 7] or immunogenic [83], dictated by the microenvironment [83–85]. Those conditions should be crucial for the development of novel therapeutic approaches using CD103+ DCs in triggering mucosal immunity or tolerance.

Under steady-state conditions, lamina propria-resident CD103+ DCs are tolerogenic. However, inflammation induces MLN CD103+ DCs into a proinflammatory phenotype. For instance, MLN CD103+ DCs purified from colitic mice triggered Th1 responses along with high levels of IL6 production [83, 86]. During intestinal inflammation, MLN CD103+ DC acquires these proinflammatory properties with no phenotypical and ontogenetic changes.

Naturally occurring CD4+CD25+Foxp3+ Treg cells are thymus-derived and are important to modulate a wide range of immune-mediated pathologies, including autoimmunity, colitis, and chronic infection. However, inducible Treg cells arising from the naïve pool are particularly beneficial in the intestine. The balance of triggering protective immunity to invading pathogens while retaining tolerance to dietary antigen and the commensal flora is critical. These cells can be generated in the periphery from the naive T cell pool after, for example, the oral administration of antigen or the targeting of peptide ligands to DCs in vivo [87].

Some specific nutrients are known to have notable effects on the modulation of mucosal immunity. Moreover, mucosal DCs are constantly exposed to dietary antigens. Vitamin A, whose only source in mammals is through the diet, mediates several functions of CD103+ DCs. Its depletion from the diet inhibits Treg differentiation induced by MLN CD103+ DCs as well as inducing gut-homing receptors on T cells [88, 89].

Tryptophan is another example of dietary element that is required for the IDO-dependent tolerogenic effects of mucosal DCs [90] and for generation of ligands of the aryl hydrocarbon receptor (AhR), such as L-kynurenine that regulates the balance between Th17 and Treg cell differentiation [91–93] and has powerful direct anti-inflammatory activity on DCs [94].

Diet-derived lipid mediators can activate anti-inflammatory peroxisome proliferator-activated receptor (PPAR)γ [95]. Short chain fatty acids (including acetate, butyrate, and propionate) are among the most abundant metabolites derived from microbiota-mediated digestion of dietary fiber [96]. Exposure of monocyte-derived DCs to butyrate and propionate prevented proinflammatory cytokine release induced after LPS incubation [97]. In fact, animals deficient for butyrate receptor, GPR109a, are susceptible to the development of colitis and colon cancer [98].

Curcumin is a spice historically used as a medicine in India and Southeast Asia. Exposure of curcumin triggers a tolerogenic activity in DCs, including upregulation of *aldh1a2* and IL10 while promoting FoxP3+ Treg cells [99].

The mucosal neural anatomy is disrupted in inflammatory bowel diseases [100]; intestine is permeated by a complex nervous system. On the other hand, hematopoietic cells are responsive to neurotransmitters and mediators from the enteric nervous system exert immune-regulatory effects [100]. Vasoactive intestinal peptide (VIP) is produced by intestinal enteroendocrine and immune cells and has vasodilator and regulator of epithelial permeability activities [101]. VIP suppresses lipopolysaccharide-induced DC maturation [102] while promoting differentiation of IL10- and TGF-β-secreting Treg cells [103–105]. In agreement with these observations, DCs exposed to VIP to prevent chemically induced colitis [105]. Taken together, these studies revised here point to the complexity of interactions between mucosal DCs, nonimmune cells, the microbiota, and ingested nutrients. All these factors contribute to promoting and maintaining tolerance mediated by intestinal DCs under steady-state conditions. While no single mediator plays a dominant role, redundancy among several pathways and components is evolutionary advantageous to ensure that homeostasis is maintained.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

References

[1] A. L. Hart, H. O. Al-Hassi, R. J. Rigby et al., "Characteristics of intestinal dendritic cells in inflammatory bowel diseases," *Gastroenterology*, vol. 129, no. 1, pp. 50–65, 2005.

[2] B. Kelsall, "Recent progress in understanding the phenotype and function of intestinal dendritic cells and macrophages," *Mucosal Immunology*, vol. 1, no. 6, pp. 460–469, 2008.

[3] J. L. Coombes and F. Powrie, "Dendritic cells in intestinal immune regulation," *Nature Reviews Immunology*, vol. 8, no. 6, pp. 435–446, 2008.

[4] B. Johansson-Lindbom, M. Svensson, O. Pabst et al., "Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing," *Journal of Experimental Medicine*, vol. 202, no. 8, pp. 1063–1073, 2005.

[5] J. L. Coombes, K. R. R. Siddiqui, C. V. Arancibia-Carcamo et al., "A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-β− and retinoic acid-dependent mechanism," *The Journal of Experimental Medicine*, vol. 204, no. 8, pp. 1757–1764, 2007.

[6] E. Jaensson, H. Uronen-Hansson, O. Pabst et al., "Small intestinal CD103+ dendritic cells display unique functional properties that are conserved between mice and humans," *Journal of Experimental Medicine*, vol. 205, no. 9, pp. 2139–2149, 2008.

[7] C.-M. Sun, J. A. Hall, R. B. Blank et al., "Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid," *Journal of Experimental Medicine*, vol. 204, no. 8, pp. 1775–1785, 2007.

[8] M. Bersudsky, L. Luski, D. Fishman et al., "Non-redundant properties of IL-1α and IL-1β during acute colon inflammation in mice," *Gut*, vol. 63, no. 4, pp. 598–609, 2014.

[9] M. Bogunovic, F. Ginhoux, J. Helft et al., "Origin of the lamina propria dendritic cell network," *Immunity*, vol. 31, no. 3, pp. 513–525, 2009.

[10] D. V. Ostanin, K. P. Pavlick, S. Bharwani et al., "T cell-induced inflammation of the small and large intestine in immunodeficient mice," *American Journal of Physiology—Gastrointestinal and Liver Physiology*, vol. 290, no. 1, pp. G109–G119, 2006.

[11] M. Rescigno, M. Urbano, B. Valzasina et al., "Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria," *Nature Immunology*, vol. 2, no. 4, pp. 361–367, 2001.

[12] O. Schulz, E. Jaensson, E. K. Persson et al., "Intestinal CD103^{+}, but not CX3CR1^{+}, antigen sampling cells migrate in lymph and serve classical dendritic cell functions," *Journal of Experimental Medicine*, vol. 206, no. 13, pp. 3101–3114, 2009.

[13] C. Varol, A. Vallon-Eberhard, E. Elinav et al., "Intestinal lamina propria dendritic cell subsets have different origin and functions," *Immunity*, vol. 31, no. 3, pp. 502–512, 2009.

[14] E. K. Persson, E. Jaensson, and W. W. Agace, "The diverse ontogeny and function of murine small intestinal dendritic cell/macrophage subsets," *Immunobiology*, vol. 215, no. 9-10, pp. 692–697, 2010.

[15] C. Varol, E. Zigmond, and S. Jung, "Securing the immune tightrope: mononuclear phagocytes in the intestinal lamina propria," *Nature Reviews Immunology*, vol. 10, no. 6, pp. 415–426, 2010.

[16] J. H. Niess, S. Brand, X. Gu et al., "CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance," *Science*, vol. 307, no. 5707, pp. 254–258, 2005.

[17] M. Chieppa, M. Rescigno, A. Y. C. Huang, and R. N. Germain, "Dynamic imaging of dendritic cell extension into the small bowel lumen in response to epithelial cell TLR engagement," *The Journal of Experimental Medicine*, vol. 203, no. 13, pp. 2841–2852, 2006.

[18] A. Vallon-Eberhard, L. Landsman, N. Yogev, B. Verrier, and S. Jung, "Transepithelial pathogen uptake into the small intestinal lamina propria," *Journal of Immunology*, vol. 176, no. 4, pp. 2465–2469, 2006.

[19] T. L. Denning, Y.-C. Wang, S. R. Patel, I. R. Williams, and B. Pulendran, "Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses," *Nature Immunology*, vol. 8, no. 10, pp. 1086–1094, 2007.

[20] T. L. Denning, B. A. Norris, O. Medina-Contreras et al., "Functional specializations of intestinal dendritic cell and macrophage subsets that control Th17 and regulatory T cell responses are dependent on the T cell/APC ratio, source of mouse strain, and regional localization," *Journal of Immunology*, vol. 187, no. 2, pp. 733–747, 2011.

[21] H. Azukizawa, A. Döhler, N. Kanazawa et al., "Steady state migratory RelB^{+} langerin^{+} dermal dendritic cells mediate peripheral induction of antigen-specific CD4^{+}CD25^{+}Foxp3^{+} regulatory T cells," *European Journal of Immunology*, vol. 41, no. 5, pp. 1420–1434, 2011.

[22] M. Guilliams, K. Crozat, S. Henri et al., "Skin-draining lymph nodes contain dermis-derived CD103^{−} dendritic cells that constitutively produce retinoic acid and induce Foxp3^{+} regulatory T cells," *Blood*, vol. 115, no. 10, pp. 1958–1968, 2010.

[23] S. Bedoui, P. G. Whitney, J. Waithman et al., "Cross-presentation of viral and self antigens by skin-derived CD103^{+} dendritic cells," *Nature Immunology*, vol. 10, no. 5, pp. 488–495, 2009.

[24] S. Henri, L. F. Poulin, S. Tamoutounour et al., "CD207^{+} CD103^{+} dermal dendritic cells cross-present keratinocyte-derived antigens irrespective of the presence of Langerhans cells," *The Journal of Experimental Medicine*, vol. 207, no. 1, pp. 189–206, 2010.

[25] L. Ohl, M. Mohaupt, N. Czeloth et al., "CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions," *Immunity*, vol. 21, no. 2, pp. 279–288, 2004.

[26] J. A. Hall, J. R. Grainger, S. P. Spencer, and Y. Belkaid, "The role of retinoic acid in tolerance and immunity," *Immunity*, vol. 35, no. 1, pp. 13–22, 2011.

[27] C. H. Kim, "Roles of retinoic acid in induction of immunity and immune tolerance," *Endocrine, Metabolic & Immune Disorders-Drug Targets*, vol. 8, no. 4, pp. 289–294, 2008.

[28] J. W. Fluhr, M.-P. Vienne, C. Lauze, P. Dupuy, W. Gehring, and M. Gloor, "Tolerance profile of retinol, retinaldehyde and retinoic acid under maximized and long-term clinical conditions," *Dermatology*, vol. 199, supplement 1, pp. 57–60, 1999.

[29] R. Kurzrock, E. Estey, and M. Talpaz, "All-trans retinoic acid: tolerance and biologic effects in myelodysplastic syndrome," *Journal of Clinical Oncology*, vol. 11, no. 8, pp. 1489–1495, 1993.

[30] J. R. Mora, M. Iwata, B. Eksteen et al., "Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells," *Science*, vol. 314, no. 5802, pp. 1157–1160, 2006.

[31] M. Iwata, A. Hirakiyama, Y. Eshima, H. Kagechika, C. Kato, and S.-Y. Song, "Retinoic acid imprints gut-homing specificity on T cells," *Immunity*, vol. 21, no. 4, pp. 527–538, 2004.

[32] S. G. Kang, H. W. Lim, O. M. Andrisani, H. E. Broxmeyer, and C. H. Kim, "Vitamin A metabolites induce gut-homing FoxP3^{+} regulatory T cells," *The Journal of Immunology*, vol. 179, no. 6, pp. 3724–3733, 2007.

[33] M. Svensson, B. Johansson-Lindbom, F. Zapata et al., "Retinoic acid receptor signaling levels and antigen dose regulate gut homing receptor expression on CD8^{+} T cells," *Mucosal Immunology*, vol. 1, no. 1, pp. 38–48, 2008.

[34] H. Takeuchi, A. Yokota, Y. Ohoka et al., "Efficient induction of CCR9 on T cells requires coactivation of retinoic acid receptors and retinoid X receptors (RXRs): exaggerated T cell homing to the intestine by RXR activation with organotins," *The Journal of Immunology*, vol. 185, no. 9, pp. 5289–5299, 2010.

[35] A. Harusato, K. L. Flannigan, D. Geem, and T. L. Denning, "Phenotypic and functional profiling of mouse intestinal antigen presenting cells," *Journal of Immunological Methods*, vol. 421, pp. 20–26, 2015.

[36] S. D. Lyman, L. James, J. Zappone, P. R. Sleath, M. P. Beckmann, and T. Bird, "Characterization of the protein encoded by the flt3 (flk2) receptor-like tyrosine kinase gene," *Oncogene*, vol. 8, no. 4, pp. 815–822, 1993.

[37] O. Rosnet, S. Marchetto, O. deLapeyriere, and D. Birnbaum, "Murine Flt3, a gene encoding a novel tyrosine kinase receptor of the PDGFR/CSF1R family," *Oncogene*, vol. 6, no. 9, pp. 1641–1650, 1991.

[38] O. Rosnet, C. Schiff, M.-J. Pébusque et al., "Human FLT3/FLK2 gene: cDNA cloning and expression in hematopoietic cells," *Blood*, vol. 82, no. 4, pp. 1110–1119, 1993.

[39] K. Brasel, S. Escobar, R. Anderberg, P. de Vries, H.-J. Gruss, and S. D. Lyman, "Expression of the flt3 receptor and its ligand on hematopoietic cells," *Leukemia*, vol. 9, no. 7, pp. 1212–1218, 1995.

[40] S. D. Lyman, L. James, L. Johnson et al., "Cloning of the human homologue of the murine flt3 ligand: a growth factor for early hematopoietic progenitor cells," *Blood*, vol. 83, no. 10, pp. 2795–2801, 1994.

[41] D. K. Fogg, C. Sibon, C. Miled et al., "A clonogenic bone marrow progenitor specific for macrophages and dendritic cells," *Science*, vol. 311, no. 5757, pp. 83–87, 2006.

[42] A. D'Amico and L. Wu, "The early progenitors of mouse dendritic cells and plasmacytoid predendritic cells are within the bone marrow hemopoietic precursors expressing Flt3," *The Journal of Experimental Medicine*, vol. 198, no. 2, pp. 293–303, 2003.

[43] H. Karsunky, M. Merad, A. Cozzio, I. L. Weissman, and M. G. Manz, "Flt3 ligand regulates dendritic cell development from Flt3⁺ lymphoid and myeloid-committed progenitors to Flt3⁺ dendritic cells in vivo," *The Journal of Experimental Medicine*, vol. 198, no. 2, pp. 305–313, 2003.

[44] S. H. Naik, P. Sathe, H.-Y. Park et al., "Development of plasmacytoid and conventional dendritic cell subtypes from single precursor cells derived in vitro and in vivo," *Nature Immunology*, vol. 8, no. 11, pp. 1217–1226, 2007.

[45] N. Onai, A. Obata-Onai, M. A. Schmid, T. Ohteki, D. Jarrossay, and M. G. Manz, "Identification of clonogenic common Flt3⁺M-CSFR⁺ plasmacytoid and conventional dendritic cell progenitors in mouse bone marrow," *Nature Immunology*, vol. 8, no. 11, pp. 1207–1216, 2007.

[46] J. Aliberti, O. Schulz, D. J. Pennington et al., "Essential role for ICSBP in the in vivo development of murine CD8α⁺ dendritic cells," *Blood*, vol. 101, no. 1, pp. 305–310, 2003.

[47] H. Tsujimura, T. Tamura, C. Gongora et al., "ICSBP/IRF-8 retrovirus transduction rescues dendritic cell development in vitro," *Blood*, vol. 101, no. 3, pp. 961–969, 2003.

[48] G. Schiavoni, F. Mattei, P. Sestili et al., "ICSBP is essential for the development of mouse type I interferon-producing cells and for the generation and activation of CD8α⁺ dendritic cells," *The Journal of Experimental Medicine*, vol. 196, no. 11, pp. 1415–1425, 2002.

[49] K. L. Anderson, H. Perkin, C. D. Surh, S. Venturini, R. A. Maki, and B. E. Torbett, "Transcription factor PU.1 is necessary for development of thymic and myeloid progenitor-derived dendritic cells," *The Journal of Immunology*, vol. 164, no. 4, pp. 1855–1861, 2000.

[50] A. Guerriero, P. B. Langmuir, L. M. Spain, and E. W. Scott, "PU.1 is required for myeloid-derived but not lymphoid-derived dendritic cells," *Blood*, vol. 95, no. 3, pp. 879–885, 2000.

[51] N. Onai, A. Obata-Onai, R. Tussiwand, A. Lanzavecchia, and M. G. Manz, "Activation of the Flt3 signal transduction cascade rescues and enhances type I interferon-producing and dendritic cell development," *The Journal of Experimental Medicine*, vol. 203, no. 1, pp. 227–238, 2006.

[52] K. M. Murphy, "Transcriptional control of dendritic cell development," *Advances in Immunology*, vol. 120, pp. 239–267, 2013.

[53] F. Ginhoux, K. Liu, J. Helft et al., "The origin and development of nonlymphoid tissue CD103⁺ DCs," *The Journal of Experimental Medicine*, vol. 206, no. 13, pp. 3115–3130, 2009.

[54] N. S. Wilson, D. El-Sukkari, G. T. Belz et al., "Most lymphoid organ dendritic cell types are phenotypically and functionally immature," *Blood*, vol. 102, no. 6, pp. 2187–2194, 2003.

[55] S. Uematsu, K. Fujimoto, M. H. Jang et al., "Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5," *Nature Immunology*, vol. 9, no. 7, pp. 769–776, 2008.

[56] A. Iwasaki and B. L. Kelsall, "Unique functions of CD11b⁺, CD8α⁺, and double-negative Peyer's patch dendritic cells," *Journal of Immunology*, vol. 166, no. 8, pp. 4884–4890, 2001.

[57] N. Kamada, S.-U. Seo, G. Y. Chen, and G. Núñez, "Role of the gut microbiota in immunity and inflammatory disease," *Nature Reviews Immunology*, vol. 13, no. 5, pp. 321–335, 2013.

[58] N. Kamada, G. Y. Chen, N. Inohara, and G. Núñez, "Control of pathogens and pathobionts by the gut microbiota," *Nature Immunology*, vol. 14, no. 7, pp. 685–690, 2013.

[59] M. Lotz, D. Gütle, S. Walther, S. Ménard, C. Bogdan, and M. W. Hornef, "Postnatal acquisition of endotoxin tolerance in intestinal epithelial cells," *The Journal of Experimental Medicine*, vol. 203, no. 4, pp. 973–984, 2006.

[60] L. E. Smythies, M. Sellers, R. H. Clements et al., "Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity," *The Journal of Clinical Investigation*, vol. 115, no. 1, pp. 66–75, 2005.

[61] W. S. Garrett, G. M. Lord, S. Punit et al., "Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system," *Cell*, vol. 131, no. 1, pp. 33–45, 2007.

[62] T. Hudcovic, R. Štěpánková, J. Cebra, and H. Tlaskalová-Hogenová, "The role of microflora in the development of intestinal inflammation: acute and chronic colitis induced by dextran sulfate in germ-free and conventionally reared immunocompetent and immunodeficient mice," *Folia Microbiologica*, vol. 46, no. 6, pp. 565–572, 2001.

[63] D. Kirkland, A. Benson, J. Mirpuri et al., "B cell-intrinsic MyD88 signaling prevents the lethal dissemination of commensal bacteria during colonic damage," *Immunity*, vol. 36, no. 2, pp. 228–238, 2012.

[64] S. Kitajima, M. Morimoto, E. Sagara, C. Shimizu, and Y. Ikeda, "Dextran sodium sulfate-induced colitis in germ-free IQI/Jic mice," *Experimental Animals*, vol. 50, no. 5, pp. 387–395, 2001.

[65] M. Vijay-Kumar, C. J. Sanders, R. T. Taylor et al., "Deletion of TLR5 results in spontaneous colitis in mice," *The Journal of Clinical Investigation*, vol. 117, no. 12, pp. 3909–3921, 2007.

[66] S. M. Bloom, V. N. Bijanki, G. M. Nava et al., "Commensal *Bacteroides* species induce colitis in host-genotype-specific fashion in a mouse model of inflammatory bowel disease," *Cell Host and Microbe*, vol. 9, no. 5, pp. 390–403, 2011.

[67] W. S. Garrett, C. A. Gallini, T. Yatsunenko et al., "Enterobacteriaceae Act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis," *Cell Host and Microbe*, vol. 8, no. 3, pp. 292–300, 2010.

[68] O. Takeuchi and S. Akira, "Pattern recognition receptors and inflammation," *Cell*, vol. 140, no. 6, pp. 805–820, 2010.

[69] K. Schroder, R. Zhou, and J. Tschopp, "The NLRP3 inflammasome: a sensor for metabolic danger?" *Science*, vol. 327, no. 5963, pp. 296–300, 2010.

[70] L. Franchi, N. Kamada, Y. Nakamura et al., "NLRC4-driven production of IL-1β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense," *Nature Immunology*, vol. 13, no. 5, pp. 449–456, 2012.

[71] C. Bauer, P. Duewell, H.-A. Lehr, S. Endres, and M. Schnurr, "Protective and aggravating effects of Nlrp3 inflammasome activation in IBD models: influence of genetic and environmental factors," *Digestive Diseases*, vol. 30, no. 1, pp. 82–90, 2012.

[72] C. Bauer, P. Duewell, C. Mayer et al., "Colitis induced in mice with dextran sulfate sodium (DSS) is mediated by the NLRP3 inflammasome," *Gut*, vol. 59, no. 9, pp. 1192–1199, 2010.

[73] I. C. Allen, E. M. Tekippe, R.-M. T. Woodford et al., "The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer," *Journal of Experimental Medicine*, vol. 207, no. 5, pp. 1045–1056, 2010.

[74] M. H. Zaki, K. L. Boyd, P. Vogel, M. B. Kastan, M. Lamkanfi, and T.-D. Kanneganti, "The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis," *Immunity*, vol. 32, no. 3, pp. 379–391, 2010.

[75] M. Coccia, O. J. Harrison, C. Schiering et al., "IL-1β mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4$^+$ Th17 cells," *Journal of Experimental Medicine*, vol. 209, no. 9, pp. 1595–1609, 2012.

[76] T. Saitoh, N. Fujita, M. H. Jang et al., "Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1β production," *Nature*, vol. 456, no. 7219, pp. 264–268, 2008.

[77] K. Schaale, K. M. Peters, A. M. Murthy et al., "Strain- and host species-specific inflammasome activation, IL-1β release, and cell death in macrophages infected with uropathogenic *Escherichia coli*," *Mucosal Immunology*, vol. 9, no. 1, pp. 124–136, 2015.

[78] H. Yen, N. Sugimoto, and T. Tobe, "Enteropathogenic *Escherichia coli* uses NleA to inhibit NLRP3 inflammasome activation," *PLoS Pathogens*, vol. 11, no. 9, Article ID e1005121, 2015.

[79] N. Baba, S. Samson, R. L. Bourdet-Sicard, M. Rubio, and M. Sarfati, "Commensal bacteria trigger a full dendritic cell maturation program that promotes the expansion of non-Tr1 suppressor T cells," *Journal of Leukocyte Biology*, vol. 84, no. 2, pp. 468–476, 2008.

[80] S. K. Mazmanian, H. L. Cui, A. O. Tzianabos, and D. L. Kasper, "An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system," *Cell*, vol. 122, no. 1, pp. 107–118, 2005.

[81] I. I. Ivanov, K. Atarashi, N. Manel et al., "Induction of intestinal Th17 cells by segmented filamentous bacteria," *Cell*, vol. 139, no. 3, pp. 485–498, 2009.

[82] K. Atarashi, J. Nishimura, T. Shima et al., "ATP drives lamina propria T_H17 cell differentiation," *Nature*, vol. 455, no. 7214, pp. 808–812, 2008.

[83] S. Laffont, K. R. R. Siddiqui, and F. Powrie, "Intestinal inflammation abrogates the tolerogenic properties of MLN CD103$^+$ dendritic cells," *European Journal of Immunology*, vol. 40, no. 7, pp. 1877–1883, 2010.

[84] C. L. Scott, A. M. Aumeunier, and A. M. Mowat, "Intestinal CD103$^+$ dendritic cells: master regulators of tolerance?" *Trends in Immunology*, vol. 32, no. 9, pp. 412–419, 2011.

[85] M. Semmrich, M. Plantinga, M. Svensson-Frej et al., "Directed antigen targeting in vivo identifies a role for CD103$^+$ dendritic cells in both tolerogenic and immunogenic T-cell responses," *Mucosal Immunology*, vol. 5, no. 2, pp. 150–160, 2012.

[86] F. Powrie, M. W. Leach, S. Mauze, S. Menon, L. B. Caddle, and R. L. Coffman, "Inhibition of Th1 responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RB^{hi} CD4$^+$ T cells," *Immunity*, vol. 1, no. 7, pp. 553–562, 1994.

[87] J.-B. Sun, S. Raghavan, Å. Sjöling, S. Lundin, and J. Holmgren, "Oral tolerance induction with antigen conjugated to cholera toxin B subunit generates both Foxp3$^+$CD25$^+$ and Foxp3$^-$CD25$^-$ CD4$^+$ regulatory T cells," *Journal of Immunology*, vol. 177, no. 11, pp. 7634–7644, 2006.

[88] A. Yokota, H. Takeuchi, N. Maeda et al., "GM-CSF and IL-4 synergistically trigger dendritic cells to acquire retinoic acid-producing capacity," *International Immunology*, vol. 21, no. 4, pp. 361–377, 2009.

[89] S. Bereswill, M. Muñoz, A. Fischer et al., "Anti-inflammatory effects of resveratrol, curcumin and simvastatin in acute small intestinal inflammation," *PLoS ONE*, vol. 5, no. 12, Article ID e15099, 2010.

[90] F. Fallarino, U. Grohmann, S. You et al., "The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor ζ-chain and induce a regulatory phenotype in naive T cells," *The Journal of Immunology*, vol. 176, no. 11, pp. 6752–6761, 2006.

[91] R. Elgueta, F. E. Sepulveda, F. Vilches et al., "Imprinting of CCR9 on CD4 T cells requires IL-4 signaling on mesenteric lymph node dendritic cells," *Journal of Immunology*, vol. 180, no. 10, pp. 6501–6507, 2008.

[92] S. Chmill, S. Kadow, M. Winter, H. Weighardt, and C. Esser, "2,3,7,8-tetrachlorodibenzo-p-dioxin impairs stable establishment of oral tolerance in mice," *Toxicological Sciences*, vol. 118, no. 1, pp. 98–107, 2010.

[93] T. Takamura, D. Harama, S. Fukumoto et al., "*Lactobacillus bulgaricus* OLL1181 activates the aryl hydrocarbon receptor pathway and inhibits colitis," *Immunology and Cell Biology*, vol. 89, no. 7, pp. 817–822, 2011.

[94] C. McBerry, R. M. S. Gonzalez, N. Shryock, A. Dias, and J. Aliberti, "SOCS2-induced proteasome-dependent TRAF6 degradation: a common anti-inflammatory pathway for control of innate immune responses," *PLoS ONE*, vol. 7, no. 6, Article ID e38384, 2012.

[95] T. Varga and L. Nagy, "Nuclear receptors, transcription factors linking lipid metabolism and immunity: the case of peroxisome proliferator-activated receptor gamma," *European Journal of Clinical Investigation*, vol. 38, no. 10, pp. 695–707, 2008.

[96] J. H. Cummings, E. W. Pomare, H. W. J. Branch, C. P. E. Naylor, and G. T. MacFarlane, "Short chain fatty acids in human large intestine, portal, hepatic and venous blood," *Gut*, vol. 28, no. 10, pp. 1221–1227, 1987.

[97] C. Nastasi, M. Candela, C. M. Bonefeld et al., "The effect of short-chain fatty acids on human monocyte-derived dendritic cells," *Scientific Reports*, vol. 5, article 16148, 2015.

[98] N. Singh, A. Gurav, S. Sivaprakasam et al., "Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis," *Immunity*, vol. 40, no. 1, pp. 128–139, 2014.

[99] Y. Cong, L. Wang, A. Konrad, T. Schoeb, and C. O. Elson, "Curcumin induces the tolerogenic dendritic cell that promotes differentiation of intestine-protective regulatory T cells," *European Journal of Immunology*, vol. 39, no. 11, pp. 3134–3146, 2009.

[100] C. T. Taylor and S. J. Keely, "The autonomic nervous system and inflammatory bowel disease," *Autonomic Neuroscience: Basic and Clinical*, vol. 133, no. 1, pp. 104–114, 2007.

[101] Y. Weng, J. Sun, Q. Wu, and J. Pan, "Regulatory effects of vasoactive intestinal peptide on the migration of mature dendritic cells," *Journal of Neuroimmunology*, vol. 182, no. 1-2, pp. 48–54, 2007.

[102] M. G. Toscano, M. Delgado, W. Kong, F. Martin, M. Skarica, and D. Ganea, "Dendritic cells transduced with lentiviral vectors expressing vip differentiate into vip-secreting tolerogenic-like DCs," *Molecular Therapy*, vol. 18, no. 5, pp. 1035–1045, 2010.

[103] M. Delgado, E. Gonzalez-Rey, and D. Ganea, "The neuropeptide vasoactive intestinal peptide generates tolerogenic dendritic cells," *The Journal of Immunology*, vol. 175, no. 11, pp. 7311–7324, 2005.

[104] M. Delgado, A. Chorny, E. Gonzalez-Rey, and D. Ganea, "Vasoactive intestinal peptide generates CD4$^+$CD25$^+$ regulatory T cells in vivo," *Journal of Leukocyte Biology*, vol. 78, no. 6, pp. 1327–1338, 2005.

[105] E. Gonzalez-Rey and M. Delgado, "Therapeutic treatment of experimental colitis with regulatory dendritic cells generated with vasoactive intestinal peptide," *Gastroenterology*, vol. 131, no. 6, pp. 1799–1811, 2006.

Submit your manuscripts at
http://www.hindawi.com