Immune Network
http://dx.doi.org/10.4110/in.2015.15.1.1
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Regulation of Intestinal Immune System by Dendritic Cells

Hyun-Jeong Ko[1] *and Sun-Young Chang*[2]*

[1]Laboratory of Microbiology and Immunology, College of Pharmacy, Kangwon National University, Chuncheon 200-701, [2]Laboratory of Microbiology, College of Pharmacy, Ajou University, Suwon 443-749, Korea

Innate immune cells survey antigenic materials beneath our body surfaces and provide a front-line response to internal and external danger signals. Dendritic cells (DCs), a subset of innate immune cells, are critical sentinels that perform multiple roles in immune responses, from acting as principal modulators to priming an adaptive immune response through antigen-specific signaling. In the gut, DCs meet exogenous, non-harmful food antigens as well as vast commensal microbes under steady-state conditions. In other instances, they must combat pathogenic microbes to prevent infections. In this review, we focus on the function of intestinal DCs in maintaining intestinal immune homeostasis. Specifically, we describe how intestinal DCs affect IgA production from B cells and influence the generation of unique subsets of T cell. **[Immune Network 2015;15(1):1-8]**

Keywords: Dendritic cells, Gut, Regulatory T cells, Th17, Secretory IgA

INTRODUCTION

Our body is covered with tight physical barriers of skin and mucosal tissues. Mucosal surfaces are constantly exposed to the external environment, which includes commensal microbes and exogenous antigens. When pathogenic microbes breach the surface barrier, surveillance systems beneath sense the trespassers and send an alarm to defense headquarters. Mucosal immune tissues comprise lymphoid organs associated with the gastro-intestinal tract (e.g., intestine, oral cavity and pharynx), respiratory tract, and urogenital tract, as well as the glands associated with these tissues, such as the salivary glands and lacrimal glands (1). The lactating breast is also a mucosal immune tissue. Mucosal immunity can maintain peaceful body surface by generating secretory IgA (sIgA) from B cells as well as priming specific T cell immunity. The intestine, especially, harbors an enormous community of commensal microorganisms that may contribute to host defense by enforcing the host's barrier function (2) or by competing against other microorganisms metabolically (3,4). Dendritic cells (DCs) or other phagocytic cells continuously survey the mucosal environment by using innate pattern recognition receptors and sample antigens prior to integrate adaptive immune system. These cells also can adjust suppressive regulation to innocuous antigens by inducing Tregs and keep distance to commensals by producing sIgA. Moreover, these cells protect against pathogenic invasion by generating various kinds of helper T (T_H) and $CD8^+$ T cells as well as helping to produce sIgA antibodies. Here, we provide an overview of the gut immune response, focusing on unique functional features of intestinal DCs and other phagocytic cells.

Received on November 25, 2014. Revised on January 5, 2015. Accepted on January 8, 2015.

*Corresponding Author. Sun-Young Chang, Laboratory of Microbiology, College of Pharmacy, Ajou University, 206, World cup-ro, Yeongtong-gu, Suwon, Korea. Tel: 82-31-219-3454; Fax: 82-2-219-3435; E-mail: sychang@ajou.ac.kr

Abbreviations: DC, dendritic cell; sIgA, secretory IgA; SI, small intestine; FcRn, neonatal Fc receptors; iNOS, inducible nitric oxide synthase; Tip DC, TNF-α/iNOS producing DC; pDC, plasmacytoid DC; Treg, regulatory T cell; GAP, goblet cell associated antigen passage; MLN, mesenteric lymph node; RALDH2, retinaldehyde dehydrogenase type 2; RA, retinoic acid; ILF, isolated lymphoid follicle; SFB, segmented filamentous bacteria; APRIL, a proliferation-inducing ligand; BAFF, B cell-activating factor belonging to the TNF family; CSR, class-switch DNA recombination

INTESTINAL DCs AND MACROPHAGE SUBSETS

Lamina propria DCs in the small intestine (SI) haves been well studied as one of the intestinal DC subsets. $CD11c^+$ major histocompatibility (MHC) class II^+ cells in the gut comprise DCs as well as phagocytic macrophages. Genuine DCs are a $CD11c^{high}$ MHC class II^{high} population, whereas macrophages are a $CD11c^{low}$ MHC class II^{low} population (5). Lamina propria phagocytic cells in the gut have different origins and functions (6). CD103-expressing DCs are widely present in non-lymphoid tissues. $CD103^+$ DC subsets are differentiated by Flt3 ligand-dependent manner whereas CX3CR1-expressing phagocytic cells are dependent on CSF-1R (6). Peripheral $CD103^+CD11b^-$ DCs are developmentally dependent on Batf3 and are related to CD8α^+ conventional DCs (7). DC migration is tightly controlled by the expression of CCR7, and it can be largely classified as non-migratory and migratory (8,9). Non-migratory DCs are generally tissue-resident macrophage-like cells. Migratory DCs travel into draining lymph nodes with sampled antigen and can be infiltrated under inflammation. DC and phagocytic cells in the gut and their functions therein are listed in Table I. In the gut, $CD103^+$ $CD11b^+$ DCs has been well reported by the function to induce lymphocytes. Gut $CD103^+$ DCs comprise two major subsets, $CD103^+CD11b^+$ and $CD103^+CD11b^-$ DCs (10). $CD103^+$ $CD11b^-$ DCs are the dominant population of $CD103^+$ DC in the Peyer's patches and colon lamina propria (11). In contrast, $CD103^+CD11b^+$ DCs are the major DC subset in the SI lamina propria (12). In addition, recent reports regarding resident $CX3CR1^+$ phagocytic cells are increasing. TNF-α/iNOS-producing DCs (Tip DCs) were initially reported in the spleen, where they released large amounts of nitric oxide (NO) after recognizing commensal bacteria through toll-like receptors (TLRs) (13). Several TLR-expressing DCs are reported to induce IgA production. Gut plasmacytoid DCs (pDCs) can induce IgA production and repress inflammation. The detailed function of each subset will be discussed later.

Table I. Representative subsets of DCs and phagocytes in the intestine

Name	Phenotype	Characteristic features	Functions	References
$CD103^+$ $CD11b^+$ DCs	$CD103^+$ $CD11b^+$	CCR7 expression : migration into LN	$CD4^+Foxp3^+$ Treg generation	(17-19, 51)
		RALDH2 expression : RA production	IgA class switching	(41)
			Imprinting of lymphocyte gut homing	(43, 52)
		Antigen uptake by extending long dendrite or goblet cell associated antigen passage (GAP)	by expression of CCR9	(28)
		TLR stimulation: IL-6 production	T_H17 generation	(33)
		TLR5 stimulation: IL-23, IL-22 production	RegIIIγ induction	(34)
$CD103^+$ $CD11b^-$ DCs	$CD103^+$ $CD11b^-$ $CD8\alpha\alpha^+$	Expression of TLR3, TLR7, and TLR9	T_H1 response and CTL activity	(36)
		Production of IL-6 and IL-12p40		
$CX3CR1^+$ cells	$CX3CR1^+$ $F4/80^+$ $CD11b^+$	No CCR7 expression: tissue-resident	Bacteria clearance	(22)
		Antigen uptake by extending long dendrite from luminal antigen and bacteria	Generation of regulatory $CD8^+$ T cells ($CD8\alpha\beta^+TCR\alpha\beta^+$)	(23)
		Uptake of circulatory antigen		
		IL-10 production	Treg expansion	(21)
		IL-22 induction by ILC3	Enhanced barrier integrity	(24)
Tip DCs	TNF-α^+iNOS$^+$ $CD11b^+$	TGF-β	IgA production	(13)
		APRIL and BAFF production		
$TLR5^+$ DCs	$TLR5^+CD11c^{hi}$ $CD11b^{hi}F4/80^+$ $CD103^+$	IL-6 production	Differentiation of T_H17 and T_H1 cells	(35)
		RALDH2 expression : RA production	Generation of IgA–producing cells	
		Expression of TLR5 and TLR9		
pDCs	$CD11c^{int}B220^+$ mPDCA1$^+$	Type I IFN receptor expression	T cell-independent IgA production	(39)
		APRIL and BAFF production		
		IL-10 induction by $CD4^+$ T cells	Immune suppression	(25)

REGULATORY T CELLS AND INTESTINAL DCs

The SI shows a strong propensity for immune suppression in response to exogenous antigens. The presentation of innocuous food antigens by antigen-presenting cells induces oral tolerance by generation of inducible regulatory T (Treg) cells (14). $CD103^+CD11b^+$ DCs can sample soluble antigens from the intestinal lumen through a process termed goblet cell-associated antigen passages (GAPs) (15) (Fig. 1). These DCs can also patrol among enterocytes while extending dendrites toward the lumen (16). These intraepithelial $CD103^+$ DCs are recruited to sample bacterial antigens for presentation. In the SI lamina propria as well as mesenteric lymph node (MLN), these DCs express retinaldehyde dehydrogenase type 2 (RALDH2) which can convert retinal to retinoic acid (RA), a metabolic derivative of vitamin A found in food. This DC subset can induce regulatory $Foxp3^+CD4^+$ T cells dependent on RA and TGF-β (17-19); Alternatively, $CD11b^+F4/80^+CD11c^-$ macrophages in the lamina propria has been reported as more potent inducers of Treg cells than DCs (20). $CX3CR1^+$ phagocytic cells in the lamina propria support expansion of the $Foxp3^+CD4^+$ Treg cell population by producing IL-10 to harness immune tolerance (21). $CX3CR1^+$ phagocytic cells can capture *Salmonella* by extending dendrites across epithelium in a CX3CR1-dependent manner (22). Antigens captured by $CX3CR1^+$ phagocytic cells can be transferred through gap junctions to $CD103^+$ DCs in the lamina propria to establish oral tolerance (23). In addition to luminal antigen, lamina propria $CX3CR1^+$ cells facilitate the surveillance of circulatory antigens from blood vessels (24). These cells fail to prime naïve $CD4^+$ T cells; however, cross-presentation by these cells can induce priming of and differentiation into $CD8^+$ T cells that express IL-10, IL-13, and IL-9. These $CD8^+$ T cells can suppress pathogen-specific $CD4^+$ T cell activation through IL-10 (24). Finally, these $CD8^+$ T cells act as a regulatory $CD8\alpha\beta^+TCR\alpha\beta^+$ T cell population in the epithelium. $CX3CR1^+$ cells regulate colonic IL-22 producing group 3 innate lymphoid cells (ILC3) to promote mucosal healing and maintain barrier integrity (25). Therefore, $CD103^+$ DCs and $CX3CR1^+$ phagocytic cells can generate two distinct regulatory T cell subsets by different mechanisms to maintain gut immune homeostasis at steady state (Fig. 1). pDCs may me-

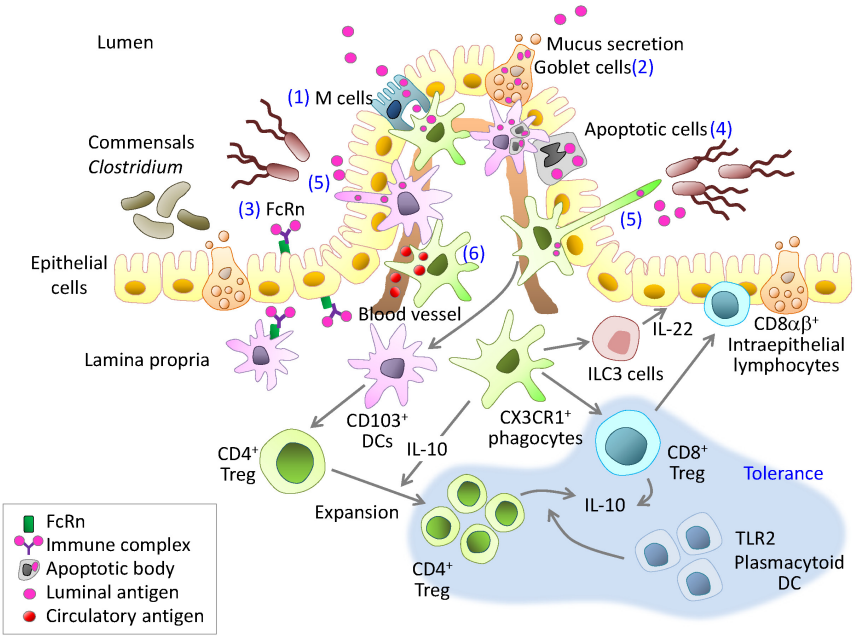

Figure 1. Regulatory T cells induced by intestinal DCs. Intestinal DCs can take up antigen indirectly through M cell-dependent (1), Goblet cell-dependent (2), and neonatal Fc receptor (FcRn)-dependent (3), and apoptosis-dependent manner (4). Alternatively, intestinal DCs can sample luminal antigen using intraepithelial dendrites (5). $CX3CR1^+$ phagocytes facilitate the surveillance of circulatory antigens (6). Under steady-state conditions, $CD103^+$ DCs induce $Foxp3^+CD4^+$ Tregs using retinoic acid by delivering luminal innocuous antigen. $CX3CR1^+$ phagocytes can induce $CD8^+$ Tregs to both luminal and circulatory antigens. These cells can expand the $Foxp3^+CD4^+$ Treg populations by IL-10 secretion in the intestinal lamina propria. Plasmacytoid DCs can produce IL-10 in response to TLR2.

diate anti-inflammatory responses following TLR2-polysaccharide A signaling (26) and Type I interferon supports Treg function and regulates colitis (27,28).

T CELL DIFFERENTIATION AND INTESTINAL DCs

After DCs sample antigen in the lamina propria, they can present antigenic epitope to naïve T cells in the isolated lymphoid follicles (ILF) or draining MLN. Distinct DCs subset instructs T cell differentiation (Fig. 2). $CD103^+CD11b^+$ DCs, one of the major DC subset in the SI lamina propria, are primarily a migratory population that responds to CCR7 expression and can be infiltrated under inflammatory conditions (29,30). Segmented filamentous bacteria (SFB), murine commensal bacteria, are shown to be sufficient for T_H17 differentiation (31). MHC II-dependent presentation of SFB antigens by intestinal DCs is crucial for T_H17 cell induction (32). Most T_H17 cells recognize antigenic repertoires derived from SFB (33). $CD103^+$ $CD11b^+$ DCs produce IL-6 with TLR stimuli which enable to induce T_H17 cell differentiation (34). Several studies suggest the possibility that $CD103^+CD11b^+$ DCs might interact with SFB and link signals to induce T_H17. $CD103^+$ $CD11b^+$ DCs can express high amounts of IL-23 following TLR5 stimuli and then drove IL-22-dependent RegIII γ production from Paneth cells (35). $TLR5^+$ DCs promote the differentiation of antigen-specific T_H17 and T_H1 cells following stimulation by flagellin, a TLR5 ligand (36). $CD103^+CD11b^-CD8\alpha^+$ DCs expressing TLR3, TLR7, and TLR9 can produce IL-6 and IL-12p40 following stimulation of the respective TLR ligands (37). These DCs induce a T_H1 response and cytotoxic T lymphocytes (CTL). $CX3CR1^+$ phagocytic cells contribute to intestinal clearance of intracellular bacteria. While their function under conditions of inflammation or infection remains unclear, their suppressive functions are well described at steady state.

SECRETORY IgA AND INTESTINAL DCs

A unique feature of the mucosal immune system is local production of sIgA from plasma cells differentiated from B cells. IgA class switching generally occurs in gut-associated lymphoid tissues including Peyer's patches, MLNs, and ILFs within the lamina propria. SFB stimulates the postnatal develop-

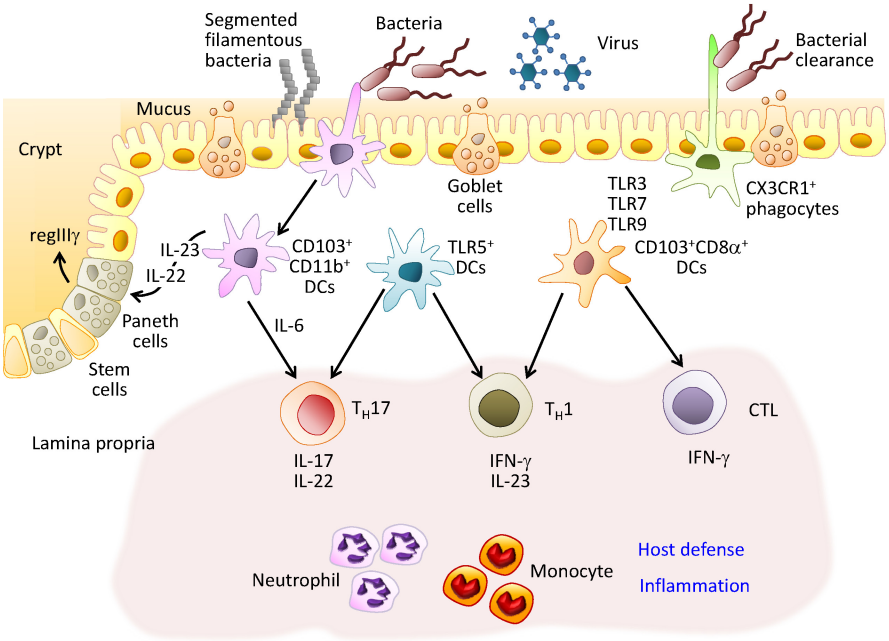

Figure 2. Helper T cell induced by intestinal DCs. $CD103^+CD11b^+$ DCs and $TLR5^+$ DCs induce T_H17 cells. $TLR5^+$ DCs and $CD103^+CD8\alpha^+$ DCs can induce T_H1 cells by means of TLR signaling. $CD103^+CD8\alpha^+$ DCs can also induce CTL. Induced helper T cell and $CD8^+$ T cells confer host defense and further inflammation. Intraepithelial $CD103^+$ DCs and $CX3CR1^+$ phagocytes can sample pathogenic bacteria by extending long dendrites across the epithelium to directly defend against bacterial infection. $CD103^+CD11b^+$ DCs produce IL-23 and IL-22 to promote anti-microbial peptide production from Paneth cells.

ment of ILFs and tertiary lymphoid tissue in the SI lamina propria, which can substitute for Peyer's patches as inductive sites for intestinal IgA (38). Intestinal IgA coating identifies inflammatory commensals that drive intestinal disease like inflammatory bowel disease (33,39). The sIgA within mucus establishes distance with commensals and forms a barrier between invading and commensal microorganisms. Intestinal DCs support IgA isotype class-switching and differentiation into IgA-secreting plasma cells, either together with the assistance of T_H cells or in a T cell-independent manner by expressing B cell-activating factors (BAFFs) and a proliferation-inducing ligand (APRIL) (Fig. 3). Intestinal pDCs, in particular, have been shown to induce IgA production by expressing these factors (40). When commensal bacteria are recognized through TLRs, Tip DCs release large amounts of NO which enhances IgA class-switch DNA recombination (CSR) in B cells by inducing DC expression of BAFF and APRIL (13). Further, RA can be converted by RALDH2 from dietary vitamin A in DCs, and DCs expressing RALDH2 can also induce IgA CSR (41). Lamina propria $CD103^+CD11b^+$ DCs, Tip DCs, and $TLR5^+$ DCs express RALDH2 and produce RA, which in turn can be used for IgA production together with TGF-β (13,36,42). Langerin-expressing DCs in the MLNs that emerge following trans-cutaneous vaccination can also induce RA-dependent antigen-specific IgA production in the SI (43). Moreover, RA confers gut homing signature such as $\alpha_4\beta_7$ integrin and CCR9 on lymphocytes (42,44). Therefore, RA is essential to maintaining the intestinal immune environment (45,46). In normal lamina propria, large numbers of eosinophils are present,accounting for approximately 5% of all lamina propria leukocytes (47). Recently, eosinophils have been found to promote the generation and maintenance of IgA-producing plasma cells by inducing B cell activating factors (48) and supporting the function of $CD103^+$ DCs (49).

CONCLUSION AND FUTURE PERSPECTIVE

In this review, we focused on the integral role of intestinal DCs in shaping the unique intestinal immunity. The advent of advanced experimental techniques for surveying mucosal tissues and analyzing metagenomic data of commensals, along with the wide availability of germ-free mice has facilitated a growing understanding of this unique mucosal immune environment. Diverse microbiota can drive microbe-dependent CD4 effector T-cell programs. For example, *Clostridium* strains provide a rich environment of TGF-β and induce

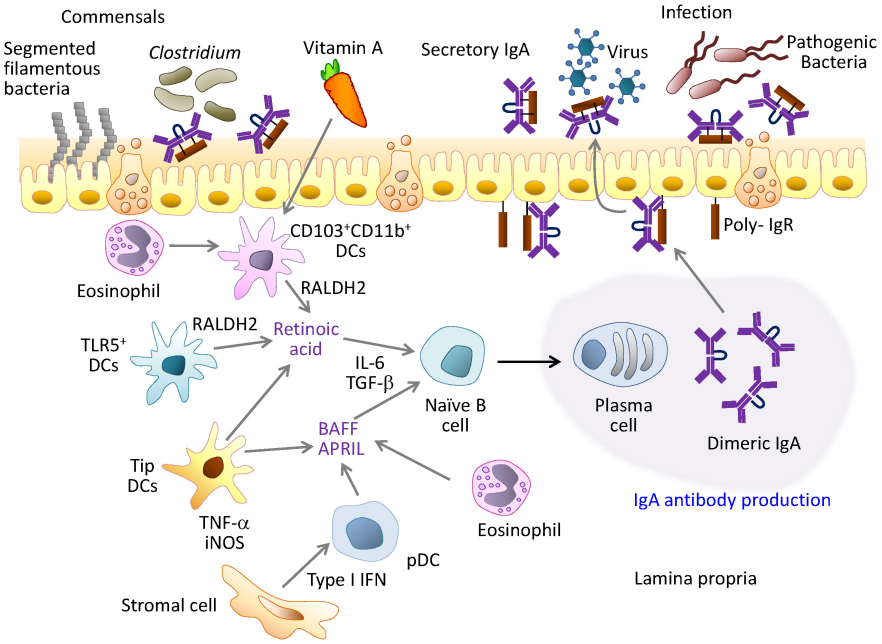

Figure 3. Intestinal DCs support secretory IgA generation. Gut $CD103^+CD11b^+$ DCs, Tip DCs, and $TLR5^+$ DCs express RALDH2 that is converted into retinoic acid from dietary vitamin A and can be used for IgA production. Gut pDCs and Tip DCs induce IgA generation from B cells by expressing BAFF and APRIL. Eosinophils promote IgA production by expressing BAFF and APRIL or support the function of $CD103^+$ DCs.

Foxp3$^+$ Treg in the colon (50,51), and SFB induce the generation of T_H17 cell by IL-6 production from DCs (32). Some pathogens (e.g., *Listeria* spp.) specifically induce T_H1 cells (33). Thus, microbial signals may induce polarizing cytokine secretion from DCs, other innate cells or stromal cells. Assembling combined information, DCs may coordinate to establish gut immune system.

ACKNOWLEDGEMENTS

This work was supported by the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF-2014R1A1A1002129, NRF-2014R1A2A2A01002576).

CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

REFERENCES

1. Murphy, K., P. Travers, M. Walport, and C. Janeway. 2012. Janeway's immunobiology. Garland Science, New York. p. 466-468.
2. Ciorba, M. A., T. E. Riehl, M. S. Rao, C. Moon, X. Ee, G. M. Nava, M. R. Walker, J. M. Marinshaw, T. S. Stappenbeck, and W. F. Stenson. 2012. Lactobacillus probiotic protects intestinal epithelium from radiation injury in a TLR-2/cyclo-oxygenase-2-dependent manner. *Gut* 61: 829-838.
3. Fukuda, S., H. Toh, K. Hase, K. Oshima, Y. Nakanishi, K. Yoshimura, T. Tobe, J. M. Clarke, D. L. Topping, T. Suzuki, T. D. Taylor, K. Itoh, J. Kikuchi, H. Morita, M. Hattori, and H. Ohno. 2011. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 469: 543-547.
4. Pickard, J. M., C. F. Maurice, M. A. Kinnebrew, M. C. Abt, D. Schenten, T. V. Golovkina, S. R. Bogatyrev, R. F. Ismagilov, E. G. Pamer, P. J. Turnbaugh, and A. V. Chervonsky. 2014. Rapid fucosylation of intestinal epithelium sustains host-commensal symbiosis in sickness. *Nature* 514: 638-641.
5. Denning, T. L., B. A. Norris, O. Medina-Contreras, S. Manicassamy, D. Geem, R. Madan, C. L. Karp, and B. Pulendran. 2011. 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. *J. Immunol.* 187: 733-747.
6. Varol, C., A. Vallon-Eberhard, E. Elinav, T. Aychek, Y. Shapira, H. Luche, H. J. Fehling, W. D. Hardt, G. Shakhar, and S. Jung. 2009. Intestinal lamina propria dendritic cell subsets have different origin and functions. *Immunity* 31: 502-512.
7. Edelson, B. T., W. KC, R. Juang, M. Kohyama, L. A. Benoit, P. A. Klekotka, C. Moon, J. C. Albring, W. Ise, D. G. Michael, D. Bhattacharya, T. S. Stappenbeck, M. J. Holtzman, S. S. Sung, T. L. Murphy, K. Hildner, and K. M. Murphy. 2010. Peripheral CD103$^+$ dendritic cells form a unified subset developmentally related to CD8alpha$^+$ conventional dendritic cells. *J. Exp. Med.* 207: 823-836.
8. Forster, R., A. Schubel, D. Breitfeld, E. Kremmer, I. Renner-Muller, E. Wolf, and M. Lipp. 1999. CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. *Cell* 99: 23-33.
9. Jang, M. H., N. Sougawa, T. Tanaka, T. Hirata, T. Hiroi, K. Tohya, Z. Guo, E. Umemoto, Y. Ebisuno, B. G. Yang, J. Y. Seoh, M. Lipp, H. Kiyono, and M. Miyasaka. 2006. CCR7 is critically important for migration of dendritic cells in intestinal lamina propria to mesenteric lymph nodes. *J. Immunol.* 176: 803-810.
10. Persson, E. K., E. Jaensson, and W. W. Agace. 2010. The diverse ontogeny and function of murine small intestinal dendritic cell/macrophage subsets. *Immunobiology* 215: 692-697.
11. Helft, J., F. Ginhoux, M. Bogunovic, and M. Merad. 2010. Origin and functional heterogeneity of non-lymphoid tissue dendritic cells in mice. *Immunol. Rev.* 234: 55-75.
12. Bogunovic, M., F. Ginhoux, J. Helft, L. Shang, D. Hashimoto, M. Greter, K. Liu, C. Jakubzick, M. A. Ingersoll, M. Leboeuf, E. R. Stanley, M. Nussenzweig, S. A. Lira, G. J. Randolph, and M. Merad. 2009. Origin of the lamina propria dendritic cell network. *Immunity* 31: 513-525.
13. Tezuka, H., Y. Abe, M. Iwata, H. Takeuchi, H. Ishikawa, M. Matsushita, T. Shiohara, S. Akira, and T. Ohteki. 2007. Regulation of IgA production by naturally occurring TNF/iNOS-producing dendritic cells. *Nature* 448: 929-933.
14. Mucida, D., N. Kutchukhidze, A. Erazo, M. Russo, J. J. Lafaille, and M. A. Curotto de Lafaille. 2005. Oral tolerance in the absence of naturally occurring Tregs. *J. Clin. Invest.* 115: 1923-1933.
15. McDole, J. R., L. W. Wheeler, K. G. McDonald, B. Wang, V. Konjufca, K. A. Knoop, R. D. Newberry, and M. J. Miller. 2012. Goblet cells deliver luminal antigen to CD103$^+$ dendritic cells in the small intestine. *Nature* 483: 345-349.
16. Farache, J., I. Koren, I. Milo, I. Gurevich, K. W. Kim, E. Zigmond, G. C. Furtado, S. A. Lira, and G. Shakhar. 2013. Luminal bacteria recruit CD103$^+$ dendritic cells into the intestinal epithelium to sample bacterial antigens for presentation. *Immunity* 38: 581-595.
17. Coombes, J. L., K. R. Siddiqui, C. V. rancibia-Carcamo, J. Hall, C. M. Sun, Y. Belkaid, and F. Powrie. 2007. A functionally specialized population of mucosal CD103$^+$ DCs induces Foxp3$^+$ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J. Exp. Med.* 204: 1757-1764.
18. Sun, C. M., J. A. Hall, R. B. Blank, N. Bouladoux, M. Oukka, J. R. Mora, and Y. Belkaid. 2007. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 Treg cells via retinoic acid. *J. Exp. Med.* 204: 1775-1785.
19. Mucida, D., Y. Park, G. Kim, O. Turovskaya, I. Scott, M. Kronenberg, and H. Cheroutre. 2007. Reciprocal TH17 and

regulatory T cell differentiation mediated by retinoic acid. *Science* 317: 256-260.
20. Denning, T. L., Y. C. Wang, S. R. Patel, I. R. Williams, and B. Pulendran. 2007. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nat. Immunol.* 8: 1086-1094.
21. Hadis, U., B. Wahl, O. Schulz, M. Hardtke-Wolenski, A. Schippers, N. Wagner, W. Muller, T. Sparwasser, R. Forster, and O. Pabst. 2011. Intestinal tolerance requires gut homing and expansion of Foxp3$^+$ regulatory T cells in the lamina propria. *Immunity* 34: 37-246.
22. Niess, J. H., S. Brand, X. Gu, L. Landsman, S. Jung, B. A. McCormick, J. M. Vyas, M. Boes, H. L. Ploegh, J. G. Fox, D. R. Littman, and H. C. Reinecker. 2005. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science* 307: 254-258.
23. Mazzini, E., L. Massimiliano, G. Penna, and M. Rescigno. 2014. Oral tolerance can be established via gap junction transfer of fed antigens from CX3CR1(+) macrophages to CD103(+) dendritic cells. *Immunity* 40: 248-261.
24. Chang, S. Y., J. H. Song, B. Guleng, C. A. Cotoner, S. Arihiro, Y. Zhao, H. S. Chiang, M. O'Keeffe, G. Liao, C. L. Karp, M. N. Kweon, A. H. Sharpe, A. Bhan, C. Terhorst, and H. C. Reinecker. 2013. Circulatory antigen processing by mucosal dendritic cells controls CD8(+) T cell activation. *Immunity* 38: 153-165.
25. Longman, R. S., G. E. Diehl, D. A. Victorio, J. R. Huh, C. Galan, E. R. Miraldi, A. Swaminath, R. Bonneau, E. J. Scherl, and D. R. Littman. 2014. CX(3)CR1(+) mononuclear phagocytes support colitis-associated innate lymphoid cell production of IL-22. *J. Exp. Med.* 211: 1571-1583.
26. Dasgupta, S., D. Erturk-Hasdemir, J. Ochoa-Reparaz, H. C. Reinecker, and D. L. Kasper. 2014. Plasmacytoid dendritic cells mediate anti-inflammatory responses to a gut commensal molecule via both innate and adaptive mechanisms. *Cell Host Microbe* 15: 413-423.
27. Lee, S. E., X. Li, J. C. Kim, J. Lee, J. M. Gonzalez-Navajas, S. H. Hong, I. K. Park, J. H. Rhee, and E. Raz. 2012. Type I interferons maintain Foxp3 expression and T-regulatory cell functions under inflammatory conditions in mice. *Gastroenterology* 143: 145-154.
28. Kole, A., J. He, A. Rivollier, D. D. Silveira, K. Kitamura, K. J. Maloy, and B. L. Kelsall. 2013. Type I IFNs regulate effector and regulatory T cell accumulation and anti-inflammatory cytokine production during T cell-mediated colitis. *J. Immunol.* 191: 2771-2779.
29. Schulz, O., E. Jaensson, E. K. Persson, X. Liu, T. Worbs, W. W. Agace, and O. Pabst. 2009. Intestinal CD103$^+$, but not CX3CR1$^+$, antigen sampling cells migrate in lymph and serve classical dendritic cell functions. *J. Exp. Med.* 206: 3101-3114.
30. Jaensson, E., H. Uronen-Hansson, O. Pabst, B. Eksteen, J. Tian, J. L. Coombes, P. L. Berg, T. Davidsson, F. Powrie, B. Johansson-Lindbom, and W. W. Agace. 2008. Small intestinal CD103$^+$ dendritic cells display unique functional properties that are conserved between mice and humans. *J. Exp. Med.* 205: 2139-2149.
31. Ivanov, I. I., K. Atarashi, N. Manel, E. L. Brodie, T. Shima, U. Karaoz, D. Wei, K. C. Goldfarb, C. A. Santee, S. V. Lynch, T. Tanoue, A. Imaoka, K. Itoh, K. Takeda, Y. Umesaki, K. Honda, and D. R. Littman. 2009. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 139: 485-498.
32. Goto, Y., C. Panea, G. Nakato, A. Cebula, C. Lee, M. G. Diez, T. M. Laufer, L. Ignatowicz, and I. I. Ivanov. 2014. Segmented filamentous bacteria antigens presented by intestinal dendritic cells drive mucosal Th17 cell differentiation. *Immunity* 40: 594-607.
33. Yang, Y., M. B. Torchinsky, M. Gobert, H. Xiong, M. Xu, J. L. Linehan, F. Alonzo, C. Ng, A. Chen, X. Lin, A. Sczesnak, J. J. Liao, V. J. Torres, M. K. Jenkins, J. J. Lafaille, and D. R. Littman. 2014. Focused specificity of intestinal TH17 cells towards commensal bacterial antigens. *Nature* 510: 152-156.
34. Persson, E. K., H. Uronen-Hansson, M. Semmrich, A. Rivollier, K. Hagerbrand, J. Marsal, S. Gudjonsson, U. Hakansson, B. Reizis, K. Kotarsky, and W. W. Agace. 2013. IRF4 transcription-factor-dependent CD103(+)CD11b(+) dendritic cells drive mucosal T helper 17 cell differentiation. *Immunity* 38: 958-969.
35. Kinnebrew, M. A., C. G. Buffie, G. E. Diehl, L. A. Zenewicz, I. Leiner, T. M. Hohl, R. A. Flavell, D. R. Littman, and E. G. Pamer. 2012. Interleukin 23 production by intestinal CD103(+)CD11b(+) dendritic cells in response to bacterial flagellin enhances mucosal innate immune defense. *Immunity* 36: 276-287.
36. Uematsu, S., K. Fujimoto, M. H. Jang, B. G. Yang, Y. J. Jung, M. Nishiyama, S. Sato, T. Tsujimura, M. Yamamoto, Y. Yokota, H. Kiyono, M. Miyasaka, K. J. Ishii, and S. Akira. 2008. Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5. *Nat. Immunol.* 9: 769-776.
37. Fujimoto, K., T. Karuppuchamy, N. Takemura, M. Shimohigoshi, T. Machida, Y. Haseda, T. Aoshi, K. J. Ishii, S. Akira, and S. Uematsu. 2011. A new subset of CD103$^+$CD8alpha$^+$ dendritic cells in the small intestine expresses TLR3, TLR7, and TLR9 and induces Th1 response and CTL activity. *J. Immunol.* 186: 6287-6295.
38. Lecuyer, E., S. Rakotobe, H. Lengline-Garnier, C. Lebreton, M. Picard, C. Juste, R. Fritzen, G. Eberl, K. D. McCoy, A. J. Macpherson, C. A. Reynaud, N. Cerf-Bensussan, and V. Gaboriau-Routhiau. 2014. Segmented filamentous bacterium uses secondary and tertiary lymphoid tissues to induce gut IgA and specific T helper 17 cell responses. *Immunity* 40: 608-620.
39. Palm, N. W., M. R. de Zoete, T. W. Cullen, N. A. Barry, J. Stefanowski, L. Hao, P. H. Degnan, J. Hu, I. Peter, W. Zhang, E. Ruggiero, J. H. Cho, A. L. Goodman, and R. A. Flavell. 2014. Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease. *Cell* 158: 1000-1010.
40. Tezuka, H., Y. Abe, J. Asano, T. Sato, J. Liu, M. Iwata, and T. Ohteki. 2011. Prominent role for plasmacytoid dendritic cells in mucosal T cell-independent IgA induction. *Immunity* 34: 247-257.
41. Molenaar, R., M. Knippenberg, G. Goverse, B. J. Olivier, A. F. de Vos, T. O'Toole, and R. E. Mebius. 2011. Expression of retinaldehyde dehydrogenase enzymes in mucosal dendritic cells and gut-draining lymph node stromal cells is controlled by dietary vitamin A. *J. Immunol.* 186: 1934-1942.

42. Mora, J. R., M. Iwata, B. Eksteen, S. Y. Song, T. Junt, B. Senman, K. L. Otipoby, A. Yokota, H. Takeuchi, P. Ricciardi-Castagnoli, K. Rajewsky, D. H. Adams, and U. H. von Andrian. 2006. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. *Science* 314: 1157-1160.
43. Chang, S. Y., H. R. Cha, O. Igarashi, P. D. Rennert, A. Kissenpfennig, B. Malissen, M. Nanno, H. Kiyono, and M. N. Kweon. 2008. Cutting edge: Langerin+ dendritic cells in the mesenteric lymph node set the stage for skin and gut immune system cross-talk. *J. Immunol.* 180: 4361-4365.
44. Iwata, M., A. Hirakiyama, Y. Eshima, H. Kagechika, C. Kato, and S. Y. Song. 2004. Retinoic acid imprints gut-homing specificity on T cells. *Immunity* 21: 527-538.
45. Chang, S. Y., H. R. Cha, J. H. Chang, H. J. Ko, H. Yang, B. Malissen, M. Iwata, and M. N. Kweon. 2010. Lack of retinoic acid leads to increased langerin-expressing dendritic cells in gut-associated lymphoid tissues. *Gastroenterology* 138: 1468-1478, e6.
46. Chang, S. Y., and M. N. Kweon. 2010. Langerin-expressing dendritic cells in gut-associated lymphoid tissues. *Immunol. Rev.* 234: 233-246.
47. Sutherland, D. B., and S. Fagarasan. 2014. Gut reactions: Eosinophils add another string to their bow. *Immunity* 40: 455-457.
48. Chu, V. T., A. Beller, S. Rausch, J. Strandmark, M. Zanker, O. Arbach, A. Kruglov, and C. Berek. 2014. Eosinophils promote generation and maintenance of immunoglobulin-A-expressing plasma cells and contribute to gut immune homeostasis. *Immunity* 40: 582-593.
49. Chu, D. K., R. Jimenez-Saiz, C. P. Verschoor, T. D. Walker, S. Goncharova, A. Llop-Guevara, P. Shen, M. E. Gordon, N. G. Barra, J. D. Bassett, J. Kong, R. Fattouh, K. D. McCoy, D. M. Bowdish, J. S. Erjefalt, O. Pabst, A. A. Humbles, R. Kolbeck, S. Waserman, and M. Jordana. 2014. Indigenous enteric eosinophils control DCs to initiate a primary Th2 immune response *in vivo*. *J. Exp. Med.* 211: 1657-1672.
50. Atarashi, K., T. Tanoue, T. Shima, A. Imaoka, T. Kuwahara, Y. Momose, G. Cheng, S. Yamasaki, T. Saito, Y. Ohba, T. Taniguchi, K. Takeda, S. Hori, I. I. Ivanov, Y. Umesaki, K. Itoh, and K. Honda. 2011. Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* 331: 337-341.
51. Atarashi, K., T. Tanoue, K. Oshima, W. Suda, Y. Nagano, H. Nishikawa, S. Fukuda, T. Saito, S. Narushima, K. Hase, S. Kim, J. V. Fritz, P. Wilmes, S. Ueha, K. Matsushima, H. Ohno, B. Olle, S. Sakaguchi, T. Taniguchi, H. Morita, M. Hattori, and K. Honda. 2013. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 500: 232-236.
52. Benson, M. J., K. Pino-Lagos, M. Rosemblatt, and R. J. Noelle. 2007. All-trans retinoic acid mediates enhanced Treg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation1. *J. Exp. Med.* 204: 1765-1774.
53. Mora, J. R., M. R. Bono, N. Manjunath, W. Weninger, L. L. Cavanagh, M. Rosemblatt, and U. H. Von Andrian. 2003. Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. *Nature* 424: 88-93.