Regulation of Intestinal Immune System by Dendritic Cells

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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.

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 microorganisms 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 (Th) 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.
INTESTINAL DCs AND MACROPHAGE SUBSETS

Lamina propria DCs in the small intestine (SI) have 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* MHC class II* population, whereas macrophages are a CD11c* MHC class II* 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* DCs   | CD103+    | CCR7 expression : migration into LN | CD4+ Foxp3+ Treg generation (17-19, 51) |
| CD11b+ DCs   | CD11b+    | RALDH2 expression : RA production | IgA class switching (41) |
|               |           | Antigen uptake by extending long dendrite or goblet cell associated antigen passage (GAP) | Imprinting of lymphocyte gut homing by expression of CCR9 (43, 52) |
|               |           | TLR stimulation: IL-6 production | T17 generation (33) |
|               |           | TLR5 stimulation: IL-23, IL-22 production | RegIIIγ induction (34) |
| CD103* DCs   | CD103+    | Expression of TLR3, TLR7, and TLR9 | T1 response and CTL activity (36) |
| CD11b- DCs   | CD11b-    | Production of IL-6 and IL-12p40 |
| CX3CR1+ cells| F4/80+    | No CCR7 expression: tissue-resident | Bacteria clearance (22) |
| CX3CR1* cells| CD11b+    | Antigen uptake by extending long dendrite from luminal antigen and bacteria | Generation of regulatory CD8+ T cells (23) |
|               |           | Uptake of circulariy antigen | Treg expansion (21) |
|               |           | IL-10 production | Enhanced barrier integrity (24) |
|               |           | IL-22 induction by ILC3 |
| Tip DCs      | TNF-α/-iNOS+ | TGF-β | IgA production (13) |
|               | CD11b+    | APRIL and BAFF production |
| TLR5+ DCs    | TLR5+CD11c* | IL-6 production | Differentiation of T17 and T11 cells (35) |
|               | CD11b/F4/80+ | RALDH2 expression : RA production | Generation of IgA-producing cells |
|               | CD103+    | Expression of TLR5 and TLR9 |
| pDCs         | CD11c+B220+ | Type I IFN receptor expression | T cell-independent IgA production (39) |
|               | mPDCA1+   | APRIL and BAFF production |
|               |           | IL-10 induction by CD4+ T cells | Immune suppression (25) |
Regulation of Intestinal Immune System by DCs

Hyun-Jeong Ko and Sun-Young Chang

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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 population by producing IL-10 to harness immune tolerance (21). CX3CR1+ phagocytes can capture Salmonella by extending dendrites across epithelium in a CX3CR1-dependent manner (22). Antigens captured by CX3CR1+ phagocytes 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 CD8αβ+ TCRαβ+ 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-
Regulation of Intestinal Immune System by DCs
Hyun-Jeong Ko and Sun-Young Chang

Figure 2. Helper T cell induced by intestinal DCs. CD103+CD11b+ DCs and TLR5+ DCs induce Th17 cells. TLR5+ DCs and CD103+CD11b+ DCs can express high amounts of IL-23 following TLR5 stimuli and then drove IL-22-dependent RegIIIγ production from Paneth cells (35). TLR5+ DCs promote the differentiation of antigen-specific Th17 and Th1 cells following stimulation by flagellin, a TLR5 ligand (36). CD103+CD11b+CD8α+ 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 Th1 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-
Regulation of Intestinal Immune System by DCs
Hyun-Jeong Ko and Sun-Young Chang

Figure 3. Intestinal DCs support secretory IgA generation. Gut CD103^+CD11b^+ DCs, Tip DCs, and TLRS^+ 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.

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...
Foxp3+ Treg in the colon (50,51), and SFB induce the generation of TGFβ1 cell by IL-6 production from DCs (32). Some pathogens (e.g., Listeria spp.) specifically induce Th1 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.

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CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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