

Review Article



The Role of Plasmacytoid Dendritic Cells in Gut Health

Hye-Yeon Won , Ju-Young Lee, Dahye Ryu, Hyung-Taek Kim , Sun-Young Chang *

Research Institute of Pharmaceutical Science and Technology (RIPST), Ajou University College of Pharmacy, Suwon, 16499, Korea



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*Correspondence to Sun-Young Chang

Laboratory of Microbiology, Research Institute of Pharmaceutical Science and Technology (RIPST), Ajou University College of Pharmacy, 206 Worldcup-ro, Yeongtong-gu, Suwon 16499, Korea.
E-mail: sychang@ajou.ac.kr

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ORCID iDs

Hye-Yeon Won <https://orcid.org/0000-0002-3290-2733>
Hyung-Taek Kim <https://orcid.org/0000-0003-4430-2492>
Sun-Young Chang <https://orcid.org/0000-0001-7336-9245>

Conflict of Interest

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ABSTRACT

Plasmacytoid dendritic cells (pDCs) are a unique subset of cells with different functional characteristics compared to classical dendritic cells. The pDCs are critical for the production of type I IFN in response to microbial and self-nucleic acids. They have an important role for host defense against viral pathogen infections. In addition, pDCs have been well studied as a critical player for breaking tolerance to self-nucleic acids that induce autoimmune disorders such as systemic lupus erythematosus. However, pDCs have an immunoregulatory role in inducing the immune tolerance by generating Tregs and various regulatory mechanisms in mucosal tissues. Here, we summarize the recent studies of pDCs that focused on the functional characteristics of gut pDCs, including interactions with other immune cells in the gut. Furthermore, the dynamic role of gut pDCs will be investigated with respect to disease status including gut infection, inflammatory bowel disease, and cancers.

Keywords: Plasmacytoid dendritic cell; Gut; Type I interferon; Immune tolerance; Host defense

INTRODUCTION

At intestinal tissues, an interplay between antigen-presenting cells (APCs) including dendritic cells (DCs) and macrophages can be critical for the maintenance of immune homeostasis (1). Classical dendritic cells (cDCs) are found throughout the gut-associated lymphoid tissues (GALTs) including the lamina propria (LP), Peyer's patches (PPs), and isolated lymphoid follicles (ILFs), as well as intestinal draining lymph nodes (LNs) such as the mesenteric lymph nodes (MLNs) (2). The cDCs fully express MHC class II and CD11c, and can be derived from committed cDC progenitors in the bone marrow (BM) and differentiate into mature cDCs in the periphery (3). When mapping the human DC lineage through 2 unbiased high-dimensional technologies, single-cell messenger RNA sequencing and cytometry by time-of-flight, pre-DCs are a group of heterogeneous populations consisting of 1 early uncommitted CD123^{high} pre-DC subset and 2 CD45RA⁺CD123^{low} lineage-committed subsets (4). Most subsets of gut cDCs can synthesize retinoic acid by expressing retinaldehyde dehydrogenase 2, which imprint gut-homing capacity for lymphocytes (5), and result in the production of mucosal IgA from B cells (6,7). Pre-cDCs, but not monocytes, can be differentiated into both CD103⁺CD11b⁺ and CD103⁺CD11b⁻ cDCs in the intestinal LP (8). Differentiation of intestinal CD103⁺CD11b⁻ cDCs is dependent on Batf3, IFN regulatory factor

Abbreviations

APC, antigen-presenting cell; BM, bone marrow; cDC, classical dendritic cell; CDP, common dendritic cell progenitor; CSR, class-switching recombination; DC, dendritic cell; GALT, gut-associated lymphoid tissue; HSV, herpes simplex virus; IBD, inflammatory bowel disease; ICOS, inducible co-stimulatory receptor; IDO, indoleamine 2,3 dioxxygenase; ILC, innate lymphoid cell; ILF, isolated lymphoid follicle; IRF, IFN regulatory factor; LN, lymph node; LP, lamina propria; MDSC, myeloid-derived suppressor cell; MLN, mesenteric lymph node; pDC, plasmacytoid dendritic cell; PGE2, prostaglandin E2; PP, Peyer's patch; PSA, polysaccharide A; TI, T cell-independent; UC, ulcerative colitis

Author Contributions

Conceptualization: Chang SY; Data curation: Won HY, Lee JY, Ryu D, Kim HT; Formal analysis: Won HY, Lee JY, Ryu D, Kim HT; Investigation: Chang SY; Supervision: Chang SY; Writing - original draft: Won HY, Lee JY, Ryu D, Kim HT, Chang SY; Writing - review & editing: Won HY, Lee JY, Ryu D, Kim HT, Chang SY.

(IRF) 8, and Id2, which is developmentally associated with lymphoid tissue resident CD8 α ⁺ cDCs (9-11). CD103⁺CD11b⁺ intestinal cDCs are dependent on IRF4 and Notch2 (12,13).

Plasmacytoid dendritic cells (pDCs) are a rare type of immune cell that is known to secrete large quantities of type I IFNs in response to a viral infection, or self-nucleic acids through innate recognition receptors such as TLRs (14). Human pDCs lack expression of CD11c but selectively expressed BDCA2 (CD303), one of the type II C-type lectins (15). In contrast to human pDCs, mouse pDCs express intermediary CD11c and specifically express B220, Ly6C, BM stromal Ag 2, and Siglec-H (16). The functional characteristics of gut pDCs are different from typical pDCs found in the blood circulation and periphery. Gut pDCs are unable to produce type I IFNs (17), and pDCs from the liver and MLNs also suppress T cell responses and induce oral tolerance rather than produce type I IFN (18).

THE ROLE OF pDCS IN THE GUT

Gut pDCs in mucosal environments

Although both cDCs and pDCs are derived from BM cells, pDCs can be differentiated from common dendritic cell progenitors (CDPs) via a unique pathway by the constitutive expression of E2-2, which is a pDC-specific transcription factor (19). FLT3-ligand-STAT3 signaling can promote the expression of E2-2 (20). The pDC can be originated from IL-7R⁺ lymphoid precursor cells and the amount of IRF8 is associated with pDC commitment (21). The transcription factor Zeb2 regulates commitment to pDCs by repressing Id2 (22,23). The cDC precursors migrate from the BM to lymphatic or peripheral tissues, existing as a resident or migratory DCs. Upon microbial stimuli, these immature cDCs migrate to the LNs to develop activated phenotypes. On the other hand, pDCs are fully developed in the BM and then migrate into the thymus and secondary lymphoid organs via the blood circulation (24). Furthermore, the pDCs migrated from the BM to the small intestine via C-C chemokine receptor type 9 chemokine receptors (25). Several factors including mucosal vascular addressin cell adhesion molecule 1, β 7 integrin, and CD103 are also involved in pDC trafficking to the gut (26). The pDCs can act as APCs as well as effector cells that secrete type I and type III IFNs. Once infected, pDCs secrete type I IFN, underwent morphological and functional changes, and then acted as an APC to prime naïve T cells (27). The pDCs selectively express TLR2 (28), TLR7 (29), TLR9 (30), TLR11, and TLR12 (31). The recognition of the microbial pathogen by pDC is mainly mediated by the endosomal sensors TLR7 and TLR9. TLR7 recognizes RNA viruses such as influenza, and TLR9 recognizes unmethylated CpG-rich sequences of DNA viruses such as herpes simplex virus (HSV)-1 and HSV-2 (32). Once recognized via these receptors, pDCs secrete type I IFNs through the myeloid differentiation primary response 88-IRF7 pathway and produce pro-inflammatory cytokines through the NF- κ B pathway. The pDCs also detect *Toxoplasma gondii* profilin (31) and bacterial polysaccharide A (PSA) (28) via TLR12 and TLR2, respectively.

In addition, pDCs can also detect cytosolic DNA by the cyclic GMP-AMP synthase stimulator of interferon genes pathway to induce the production of type I IFN (33). Lastly, pDCs also express various vitamin D receptors, and vitamin D signaling can act as a natural inhibitory mechanism on pDCs (34).

The production of type I IFN from gut pDCs can be affected by the mucosal microenvironment. IL-10 expressed by activated LP DCs and macrophages, prostaglandin E2

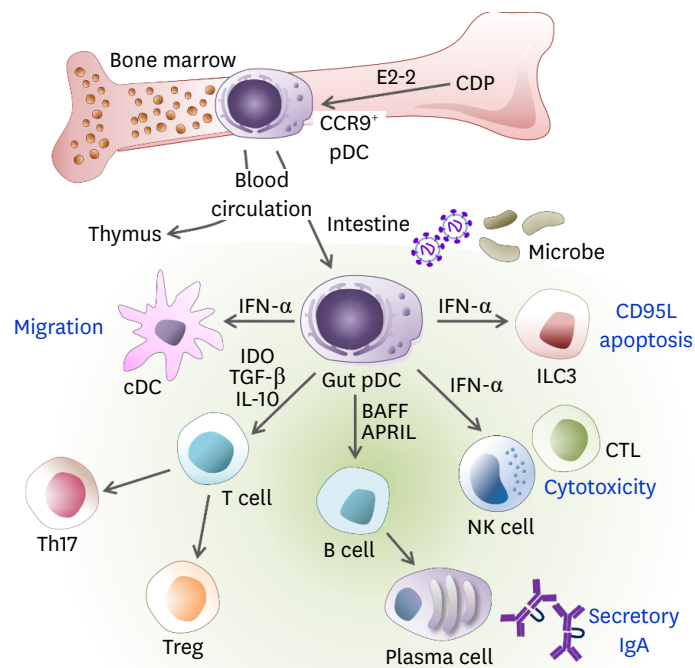


Figure 1. The role of pDCs in gut immunity. The pDCs can be differentiated from CDPs and IL-7R⁺ lymphoid precursor cells in an E2-2-dependent manner in the BM and distributed via the blood circulation to lymphoid organs such as the thymus, spleen, LNs, and peripheral tissues such as the intestine. The pDCs are recruited to the lamina propria of the small intestine in a CCR9-dependent manner. While pDCs do not migrate from the intestinal periphery to the draining MLNs, they can mobilize the lamina propria cDCs toward MLN via the production of type I IFN. During viral infections, type I IFN produced by gut pDCs induces CD95L expression on ILC3, which reduces IL-22 and then impairs barrier permeability. The pDCs activate NK cells and CD8⁺ T cells to enhance cytotoxicity via IFN- α . Activated pDCs produce BAFF and APRIL, which induce secretory IgA production from B cells. The pDCs are poor APCs to naive T cells. However, the gut pDCs conditioned by microbial ligands such as PSA or TLR9 induce the generation of Tregs and Th17 cells via IDO, IL-10, and/or TGF- β . APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; CCR9, C-C chemokine receptor type 9.

(PGE2) by stromal cells, and TGF- β by intestinal epithelial cells can prevent PP pDCs from producing significant amounts of type I IFN by inhibiting primary signaling via TLR9 (17). In fact, the production of type I IFN from the spleen pDCs can be inhibited by IL-10, PGE2, and TGF- β in response to a treatment of CpG oligodeoxynucleotides. Furthermore, pDCs are generally resident DC subsets in the gut (35). However, pDCs can mobilize LP cDCs to the MLNs in response to TLR stimuli via TNF and type I IFN-dependent mechanisms (36).

Gut pDCs are known for the induction of oral tolerance (18) rather than the production of type I IFN (17). Mucosal factors that are expressed from GALT can inhibit type I IFN secretion by pDCs, while maintaining the ability of pDCs to prime naive T cells and triggering differentiation into Tregs (37) and Th17 cells (38). Gut pDCs are effective in causing mucosal B cell responses to induce IgA production independently of T cells (39). As studies regarding the interaction between the mucosal immune system and microbiome are rapidly progressing, pDCs in GALT are also becoming the focus of increasing interest (32). The roles of gut pDCs are summarized in Fig. 1.

Interaction of pDCs with innate lymphoid cells (ILCs)

The interactions between ILCs and pDCs in healthy and diseased guts have not been well characterized yet. The ILC family includes classic cytotoxic NK cells as well as non-cytotoxic ILC populations consisting of 3 distinct groups (40). The distribution of human ILC subsets

varies in tissues and organs (41). Group 1 ILCs, including NK cells, mostly exist in the fetal intestine and liver. ILC2s are founded in the peripheral blood, lung, and skin. ILC3s are mainly in the skin tissue, thymus, tonsils, BM, and intestine (40). Both cDCs and pDCs can activate NK cells but stimulate different functions of NK cells (42). The cDCs primarily activate NK cells to secrete IFN- γ via the production of IL-12 and IL-18, and to proliferate and survive via the production of IL-15. In contrast, pDCs trigger NK cell cytotoxicity by type I IFN (43). The production of type I IFN from pDCs can be inhibited by activating the NK cell receptor natural cytotoxicity triggering receptor 2 (44), or activated by the inhibitory NK cell receptor IRp60 (45). The ILC2 populations are low in the intestine but prevalent in the lung (40). In the lung, activation of pDCs through TLR7 suppresses ILC2-mediated airway hyper-reactivity and airway inflammation, since IFN- α increased ILC2 apoptosis (46). ILC3s play critical roles in mucosal homeostasis and gut immunity. Gut-resident ILC3s can produce IL-22 that was essential for gut barrier function (47,48). In HIV-1 infections, pDCs can make ILC3s that undergo CD95/FasL-mediated apoptosis via type I IFN (49). Therefore, sustained pDC activation and type I IFN production during chronic viral infection may possibly impair the integrity of the gut mucosal barrier by reducing intestinal ILC3 cells (50).

The pDCs in T cell immunity

Immune tolerance is an important process in the gut because oral tolerance discriminates the latent pathogenic microorganisms from the commensal flora. Failure of oral tolerance may induce mucosal inflammation, resulting in diseases such as inflammatory bowel diseases (IBDs) and food allergies. Gut pDCs have a tendency to induce the differentiation of CD4⁺Foxp3⁺ Tregs instead of CD4⁺ effector T cells via autocrine TGF- β (37). Systemic depletion of pDCs prevents induction of oral tolerance by Ag feeding (18). Unlike cDCs, pDCs are inefficient for phagocytosis and the presentation of exogenous Ags to CD4⁺ T cells because of the sustained MHC class II-peptide complex formation, ubiquitination, and turnover (51). Although pDCs are less efficient for induction of T cells compared to cDCs, they could still activate CD4⁺ helper and Tregs, as well as CD8⁺ cytotoxic T cells (52,53). In response to TLR stimulation, pDCs promote efficient Th17 differentiation (54). In humans, pDCs are inefficient for the activation of Tregs, but are efficient for the induction of effector T cells and support Th17 cell effector function (55,56). T cells that are primed by CD40L-activated pDCs have regulatory phenotypes, resulting in decreased IL-2 and IFN- γ production and increased IL-10 (16). The pDCs exposed to PSA from gut commensal *Bacterioides fragilis* do not produce proinflammatory cytokines, but instead they specifically stimulated IL-10 secretion by CD4⁺ T cells (28). PSA preferentially ligated to TLR2 on pDCs but not on other DC subsets. Ligation of PSA on pDCs cannot directly produce IL-10. Direct secretion of IL-10 by pDCs is dependent on TLR-9, while IL-10 secretion by myeloid DCs is dependent on TLR-2/6 (57). Furthermore, pDCs express indoleamine 2,3 dioxygenase (IDO), which is the rate-limiting step for the degradation of tryptophan into kynurenine and downstream products along the kynurenine pathway (58). IDO is essential for Treg generation by pDCs (59). Interactions of microbiota and pDCs are involved in the regulation of inflammation (60). Feeding of probiotic *Bifidobacterium adolescentis* increases pDCs and Treg frequencies as well as immunity towards pathogenic infections with *Yersinia enterocolitica* (61). Probiotic *Lactobacillus gasseri* increases the population of pDCs that can activate Tregs (62).

The pDCs in B cell immunity

Secretory IgA is continuously produced from the mucosal surface, which forms the first-line barrier along with the mucus to protect the mucosal surface by inhibiting attaching microbes and neutralizing toxic materials (63). B cells undergo a class-switching recombination (CSR)

process to produce IgA via T cell-dependent (TD) or T cell-independent (TI) pathways mainly in the PPs as well as the LP including the ILFs (64,65). The pDCs from the MLN and PP induce a significantly higher production of TI IgA CSR by B cells compared to MLN and PP cDCs (39). However, there is minimal IgA production in pDCs isolated from the peripheral LN. The microbiota activates stromal cells to produce type I IFNs that drove the pDCs to express B cell activating factor and a proliferation-inducing ligand, thereby facilitating IgA responses in the gut. However, a recent study suggests that pDCs are not critical for non-infectious IgA responses (66). Overall, these studies suggest that various gut DC subsets including pDCs may play redundant roles in intestinal IgA homeostasis.

THE ROLE OF pDCS IN INTESTINAL DISEASES

The pDCs in gut infections

The pDCs recognize pathogens by microbial nucleic acids via TLR7 or TLR9, then produce large quantities of type I IFN. The production of type I IFN by pDC can be an important key step to protect against viral infections in the acute phase (16). The role of pDCs in enteric rotavirus infections has been relatively well studied. Rotavirus is a common pathogenic virus in children under the age of 5 years and is replicated mainly in small intestinal epithelial cells (67). Recognition of viral dsRNA or DNA by the endosomal receptor TLR7 or TLR9 is important for the production of IFN- α from pDCs. During a rotavirus infection, pDCs play a role in the activation of GALT B cells via type I IFNs (68). However, in some cases such as influenza infections, pDCs cause uncontrolled inflammation or bronchial epithelium apoptosis (69). The activation of pDCs in acute viral infections may induce different results depending on the type of virus and the route of infection (32). The role of pDCs in controlling chronic viral infections also differs depending on the type of virus. Although the level of type I IFN induced by infection of hepatitis B virus, hepatitis C virus, and human papilloma virus is low, type I IFNs appear to play an important role in the control of virus and the survival of anti-viral T cells (70). In human patients with HIV, pDCs are depleted in the circulation but accumulated in the terminal ileum showing upregulation of gut-homing receptor CD103 (71). Excessive production of IFN- α by pDCs is a typical phenomenon of HIV infection. The pDCs can induce T cell apoptosis and promote Treg development (72). In addition to T cells, pDCs can upregulate CD95 expression on ILC3s via type I IFN to induce CD95/FasL-mediated apoptosis (49).

Although pDCs have been shown to play a role in viral infections, the role of pDCs has not been well studied in bacterial infections. The pDCs in the MLN and spleen are expanded after intragastric infection of *Listeria monocytogenes*, which is a gram-positive intracellular bacterium causing severe food-borne gastroenteritis (73). The increased number of pDCs lasts up to 12 days after infection, in which no bacteria were detected, and returns to the basal level at day 19 of infection. In addition, the expressions of costimulatory molecules on pDCs are upregulated, contributing to interactions with T cell. The pDCs in the colon-draining LNs during a *Citrobacter rodentium* infection can be specifically activated, resulting in the production of C-type lectin receptor and proinflammatory cytokines (74).

The pDCs in IBD

IBDs, which includes ulcerative colitis (UC) and Crohn's disease, are chronic inflammatory diseases due to microbial violation or mucosal barrier insults mainly observed in genetically susceptible individuals (75). In patients with IBDs, pDCs significantly accumulate in the

MLN and inflamed colonic mucosa. However, the secretion of IFN- α from peripheral blood pDCs in patients with flaring UC is significantly reduced, suggesting their role as tolerance inducers (76). The roles of pDCs and type I IFN have more complicated features in gut inflammation. In an acute colitis model by a single-cycle administration of dextran sulfate sodium, pDCs accumulate in inflamed areas of acute colitis (77). Selective depletion of pDCs in the pDC-ablated mice that expressed DTR under the control of the Siglec-H gene attenuates acute colitis by decreasing infiltration of inflammatory leukocytes and production of proinflammatory cytokines independent of IFN-I signaling (77). When pDCs are depleted by targeting E2-2, the pDC-specific transcription factor, pDCs are dispensable for the pathogenesis of intestinal inflammation in the experimental IBD model caused by a deficiency of the Wiskott-Aldrich syndrome protein or IL-10 (78). In contrast, several reports support the regulatory roles that type I IFN plays in intestinal injury and inflammation. GM-CSF can ameliorate colitis by increasing type I IFN production of pDC (79). Activation of TLR3 and TLR9 protects mice from experimental colitis via induction of type I IFN (80,81). Recognition of gut resident RNA viruses through TLR3 and TLR7 can regulate acute colitis via IFN- β secretion from pDCs (82). Furthermore, anti-viral drug cocktail treatments exacerbate gut inflammation. In fact, the gut virome exhibits different patterns in patients with IBD compared to healthy individuals, suggesting that the enteric virome may play a role in intestinal diseases (83). Collectively, although the role of pDCs in the intestinal inflammatory disease is controversial, pDCs have a role in gut immune homeostasis by managing the inflammatory or anti-inflammatory response in a case-dependent manner.

The pDCs in cancer

The recruitment of pDCs in peri-tumor sites is often associated with poor prognosis (**Fig. 2A**) since the tumor microenvironment converted pDCs into immunosuppressive cells (84). Tumor-derived TGF- β and TNF- α inhibit the production of IFN- α by tumor-associated pDCs (85,86). Tumor-infiltrating pDCs tend to induce Treg cells through the expression of IDO (59) or inducible co-stimulatory receptor ligand (87). Within tumor draining LNs, a small population of IDO⁺ pDCs also creates a suppressive microenvironment via constitutive activation of Tregs (88). Human CD123⁺ pDCs in colorectal tumor tissue and LNs may help developing Tregs and foster tumor tolerance (89). In patients with colorectal cancer, the frequency of pDCs is low, and they tend to be functionally defective (90). The pDCs are also involved in cancer progression via expression of pro-apoptotic granzyme B, which inhibits the proliferation of anti-tumor T cells (91). In contrast to NK cells, pDCs do not release the pore-forming perforin. In tumor-draining LNs, pDCs constitutively express immunosuppressive IDO enzyme (92). The lymphocyte-activation gene 3⁺ pDCs in melanoma produce IL-6 without induction of type I IFN. IL-6 induce the production of CCL2 that can recruit myeloid-derived suppressor cells (MDSCs) at the tumor tissue (93). The number of pDCs in blood is variable depending on the type and progressions of cancer. In patients with melanoma, circulating pDCs are significantly decreased (90). The decrease of circulating pDCs correlates to a more advanced stage of cancer progress, and recovers after complete tumor resection. In gastric carcinoma tissue, Tregs and inducible co-stimulatory receptor (ICOS)⁺ Tregs are the main lineage cells, whereas pDCs are the majority in peri-tumor tissue (94). Under gastric tumor conditions, pDCs may recruit ICOS⁺ Tregs and act as immunosuppressants. Tumor-associated pDCs are poor producers of type I IFN and favor the IL-10 induction from increased Tregs in breast (85) and ovarian cancers (95).

When properly reprogrammed by stimuli such as TLR agonists, tumor promotion by peri- or intra-tumoral pDCs can be reversed (**Fig. 2B**), which can further mediate tumor rejection in a clinical setting (96). Tumor regression can be driven by restored production of type I IFN

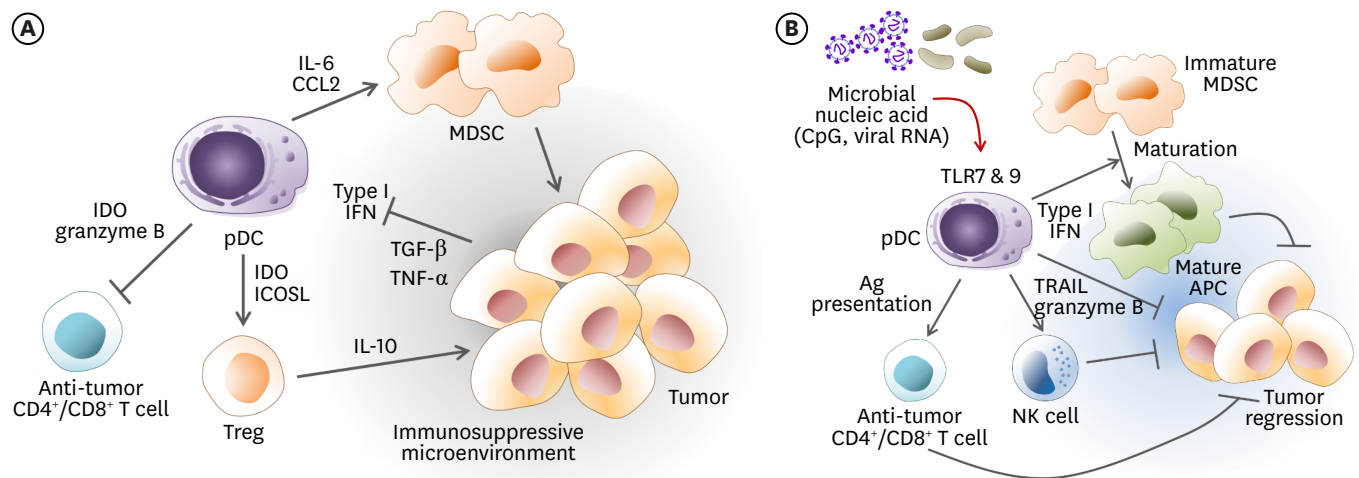


Figure 2. The role of pDCs in the cancer microenvironment. (A) Peritumoral pDCs confer tumor promotion by immunosuppression. Tumors can inhibit the production of type I IFN from pDCs via secretion of TGF-β and TNF-α, which confer pDCs with an immunosuppressive capacity. The pDCs derived IL-6 induces MDSCs recruitment via CCL2 and MDSCs reinforce the tumor immunosuppressive microenvironment. The pDCs directly induce the generation of Treg by expression of IDO and ICOSL. Inversely, pDCs can inhibit anti-tumor effector CD4⁺ T cells and cytotoxic CD8⁺ T cells by expression of IDO or granzyme B. (B) The immunosuppressive tumor microenvironment supported by intratumoral pDCs can be reversed. In the presence of strong stimuli by microbial ligands such as CpG or viral RNA, pDCs can be activated to produce a large amount of type I IFN via TLR7 or TLR9 signaling. Type I IFN produced by pDCs can induce the maturation of immature immunosuppressive MDSCs into mature antigen-presenting cells, which then contribute to initiate anti-tumor immunity. Activated pDCs can exert direct cytotoxicity to tumor cells by expression of TNF-related apoptosis inducing ligand and granzyme B. Alternatively, activated pDCs stimulates NK cells to kill tumor cells. The pDCs can also act as an APC to prime anti-tumor T cells. ICOSL, inducible costimulator ligand.

along with a cross-talk with other immune cells. Finally, pDCs can act as an APC to prime anti-tumor T cells. The pDCs isolated from human colon carcinomas have epithelial cell adhesion molecules (97). Despite deficiencies in phagocytosis, there exists an alternative mechanism of exchange for exogenous Ags between pDCs and tumor cells, which is a cell contact-dependent mechanism. This may enable pDCs to present Ag to tumor Ag-specific T cells. Furthermore, the pDCs can regulate myelopoiesis, especially CD11b^{high}Gr-1⁺ MDSCs in the BM (98). When pDCs are activated by TLR9 stimulation, the production of IFN-α induces MDSC maturation and then blocks MDSC suppressive capacity (99). Activated pDCs can exert direct cytotoxicity to tumor cells by expression of TNF-related apoptosis inducing ligand and granzyme B (100). Alternatively, activated pDCs stimulate NK cells to kill tumor cells (101). Although still limited to several types of cancers besides colon cancer, modulation of pDCs by TLR ligand treatment can be a promising strategy for cancer immunotherapy.

CONCLUSION

Blood circulating peripheral pDCs are one of the main type I IFN producers in response to microbial signals to protect against viral infections. In addition, pDCs also constitute a unique cell subset that participates in the activation of autoreactive T cells via sensing of self-nucleic acids. In the intestine, however, the production of type I IFN by the gut pDCs can be regulated by interactions with the commensal microbes and mucosal environmental factors. Gut pDCs are critically involved in the maintenance of immune tolerance via generation of Tregs and secretory IgA from B cells. In intestinal diseased conditions, pDCs have contradictory roles for immune regulation or initiation of inflammation. This role of pDCs can be modulated by TLR stimuli. Further information for the role of gut pDCs can suggest novel therapeutic paradigms to control infection, inflammatory disease, and cancer in the gut.

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