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Natural and Induced Tolerogenic Dendritic Cells

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Abstract

Dendritic cells (DCs) are highly susceptible to extrinsic signals that modify the functions of these crucial antigen presenting cells. Maturation of DCs induced by diverse pro-inflammatory conditions promotes immune responses, but certain signals also induce tolerogenic functions in DCs. These “induced tolerogenic DCs” help moderate immune responses such as those to commensals present at specific anatomical locations. However, also under steady state conditions, some DCs are characterized by inherent tolerogenic properties. The immunomodulatory mechanisms constitutively present in such “natural tolerogenic DCs” help to promote tolerance to peripheral antigens. By extending tolerance initially established in the thymus, these functions of DCs help to regulate autoimmune and other immune responses. Here we will discuss the mechanisms and functions of natural and induced tolerogenic DCs and offer further insight into how their possible manipulations may ultimately lead to more precise treatments for various immune-mediated conditions and diseases.

Dendritic cells in peripheral tolerance

Dendritic cells (DCs) are antigen presenting cells (APCs) critical for the initiation and regulation of T cell immune responses to foreign and self-antigens and for the maintenance of peripheral immune homeostasis first established in the thymus. Together with other types of cells in the thymus, DCs have important roles in mediating central tolerance, combining thymic deletion of self-reactive T cells and a production of thymically derived regulatory T cells (tTreg cells) in a cumulative process aimed at preventing overt anti-self responses (1). However, due to differing efficiencies of antigenic presentation in the thymus and the periphery, and to a cross-reactivity of T cell receptors (TCRs), the mature peripheral T cell repertoire still contains T cells that may be reactive to self (2, 3). These self-reactive peripheral T cells can then be primed in the periphery, even by low-affinity peptides that are below their original thresholds for negative selection in thymus (2, 4), ultimately increasing the risk of autoimmune responses against self-antigens (2, 4–7).

The priming of self-reactive peripheral T cells is controlled by tTreg cells (8). However, the functions of tTreg cells may be overwhelmed by specific pro-inflammatory autoimmune activation; also, in some individuals, the development of tTreg cells may be compromised (2,

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4, 9, 10). Various animal models of autoimmune diseases initiated in healthy animals after immunization with specific self-antigens either in the presence of adjuvants or in the context of an introduced infectious agent have demonstrated that specific priming of pre-existing self-reactive T cells mediates an autoimmune process (2, 4–7). Therefore, pathways of thymic tolerance need to be extended by the specific mechanisms operating in the peripheral immune system. Particularly, autoimmune responses can be ameliorated or even completely prevented by the antigen specific peripherally-formed Treg cells (pTreg cells) that are induced extrathymically by DCs (7, 11).

The roles of DCs in peripheral tolerance have been established by multiple lines of independent experimental evidence. The disturbance of tolerance and immune homeostasis caused by the absence of DCs and their subsets was observed in various experimental systems that relied on a specific *in vivo* killing of DCs expressing diphtheria toxin receptor (DTR) or DT A subunit (DTA) or by other means such as a chemical depletion of DCs (12–16). These results are in agreement with other early studies that identified the roles of DCs in the induction of peripheral tolerance by employing methods of specific delivery of defined antigens to DCs *in vivo,* tracking the uptake of proteins to DCs, and the transgenic expression of ectopic antigens as cytosolic proteins in DCs (17–20). The combination of specific antigen targeting methods with various genetic models of DCs has allowed for further advances in our understanding of the importance of DCs in governing peripheral tolerance, as we also recently discussed in (11).

The specific functions of DCs depend, in part, on the developmentally-determined diversity of DC subsets reviewed extensively by Murphy and Merad and their colleagues (21, 22). Both human and murine DCs consist of two main populations, conventional (cDC or DC) and plasmacytoid (pDC), both of which develop from progenitors in the bone marrow (BM) and then differentiate into various subsets present throughout multiple tissues (23, 24). The (conventional) DC population can be further divided into the DC1 and DC2 subsets, as defined by the transcription factors required for their development. The DC1 subset, which requires the transcription factors Irf8, Id2, and Batf3 for development, is distinguished by the expression of XCR1 and further characterized by the expression of additional cell surface molecules including BTLA, CD8α, and DEC-205. In contrast, the development of DC2s is governed by the transcription factors Irf4 and Notch2, and these DCs are distinguished by cell surface expression of CD172a (SIRPα) as well as DCIR2 and CD11b (11, 23, 24). Though not a main focus of this review, pDCs, characterized by the expression of cell surface molecules including B220, DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN), and Siglec-H, are primarily involved in antiviral responses but also have some roles in tolerance (11, 25). Importantly, $CD141^+$ ($BDCA\text{-}3^+$) $XCR1^+$ $BTLA^+$ human DC1s and $CD1c^+$ $CD172a^+$ $CD11b^+$ human DC2s share many developmental, phenotypical, and functional similarities with their murine counterparts (21, 26).

In addition to their roles in tolerance, DCs have crucial functions in the initiation of immune responses. The efficient priming of immune responses by specific DC subsets requires additional signals from the pro-inflammatory environment that can be sensed through specific pattern recognition receptors (PRRs) (27–29). These signals lead to the DC acquisition of enhanced properties to induce immune responses in a process referred to as a

"maturation." Overall, the model of such "pro-immunogenic" DC maturation postulates increased pro-inflammatory cytokine production and increased cell surface expression of costimulatory and major histocompatibility complex (MHC) molecules and chemokine ligands or receptors in response to microbial and other pro-inflammatory stimulation (28, 30). In addition to this maturation process resulting in increased immune responses, specific extrinsic signals were also proposed to induce tolerogenic differentiation of DCs. The experiments utilizing bone marrow-derived DCs (BMDCs), monocyte-derived DCs (moDCs), and DCs obtained *ex vivo* showed that some PRR agonists, as well as various other physiological and pharmaceutical agents, can allow for the induction of DCs with tolerogenic functions. Further, the experiments *in vivo* revealed that, in response to certain signals in specific anatomical sites including the intestines and airways, some DCs help to maintain immune homeostasis toward commensal organisms and other antigens, even under partially pro-immunogenic conditions (28, 31–33). We propose to refer to such DCs that acquire tolerogenic properties either *in vitro* or *in vivo* as "induced tolerogenic DCs," or "itDCs," as partially based on the terminology first introduced by Maldonado and von Adrian (34).

However, even in the absence of specific extrinsic signals, generally referred to as "steady state" conditions, many DCs that are present in the spleen and other lymphoid organs do not necessarily remain as "immature" immunological bystanders but instead have important roles in initiating and maintaining tolerance to available peripheral antigens (11). These DCs inherently promote in T cells various mechanisms of tolerance including T cell anergy, T cell deletion, and a conversion of pTreg cells (11). We therefore propose to refer to such DCs as "natural tolerogenic DCs," or "ntDCs" (Fig. 1).

Establishing peripheral tolerance by natural tolerogenic functions of DCs

The physiological steady state can be defined by the undisturbed expression of cytokines and other molecules contributing to the baseline conditions that, together with stromal cells of the secondary lymphoid tissues, provide a framework for the interactions between DCs and T cells (35, 36). Initially, it was postulated that, in the steady state, DCs remain "immature" akin to BMDCs or moDCs that are characterized by lower expression of MHC and costimulatory molecules when cultured in the absence of maturation signals (35). However, the available experimental evidence has clearly shown that, even in the steady state, DCs can constitutively initiate active mechanisms of tolerance in T cells, such as the conversion of pTreg cells (7, 11). These general contradictions were recognized early by Lutz and Schuler, who proposed that the division between "immature DCs" and "mature DCs" (as defined by DC phenotypes) did not necessarily correspond with "tolerogenic DCs" and "immunogenic DCs," respectively. Instead, divisive tolerogenic and immunogenic maturation processes were proposed (31), further supported by the identification of transcriptional determinants of certain tolerogenic and immunogenic maturation states in DCs as well as the emerging concept of "homeostatic maturation" of DCs under steady state conditions (37–40). For example, a decrease in E-cadherin-mediated cell-to-cell contact results in specific increases in expression of MHCII and costimulatory molecules (39). The concept of DC maturation in the steady state was additionally defined by other observations of multiple specific gene expression changes comparable in scope to those observed under Toll-like receptor (TLR)

agonist-mediated maturation (30). This process of maturation under homeostatic conditions has also been proposed to result in functions of DCs necessary to induce active mechanisms of tolerance (38). While the specific mechanisms governing DC functions *in vivo* under steady state conditions following their initial development from the BM precursors are being uncovered, it is clear that these processes are continuous and some possibly cell-autonomous, resulting in the stable numbers and phenotypes of DCs expressing crucial molecules involved in tolerance ((Fig. 2) and as discussed below).

In the steady state, DCs can induce multiple mechanisms of tolerance in T cells including anergy, but a *de novo* conversion of pTreg cells bestows a dominant and long-lasting tolerance to peripheral antigens (7, 11, 41–44). Although in the steady state antigens initially acquired by all conventional DCs can induce tolerance, DC1s are more prone to induce tolerogenic effects as compared to DC2s (7, 11, 42). The specialization among DCs can be attributed to different localization of DCs within a local architecture of immune organs, differences in the efficiencies of processing and presentation of antigens to T cells, and the specific immunomodulatory mechanisms in DC1s and DC2s (11, 45–48). The immunomodulatory pathways are of particular importance in the mediation of a tolerogenic partnership of DCs and T cells (49). Importantly, the engagement of immunomodulatory axes including PD-L1/PD-1, CD80/CD86/CTLA-4, and B7h/ICOS can promote *Foxp3* expression, pTreg cell induction, and tolerance (7, 11, 49). Specifically, the “programmed death ligand-1/programmed death-1” (PD-L1/PD-1) axis promotes immune tolerance via PD-L1’s competition with costimulatory CD28 for binding with B7–1 as well as by the recruitment of inhibitory SHP phosphatases by PD-1, which negatively impacts TCR signaling (50). Moreover, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4, CD152) expressed on the T cell surface competes with the costimulatory molecule CD28 for binding with CD80/CD86 (B7–1 and B7–2) present on the surface of the DC. While CTLA-4 can remove CD80/CD86 from the DC surface, it also directly negatively regulates $CD4^+$ and $CD8^+$ T cell activation by dampening TCR signaling, hindering IL-2 production, and preventing cell cycle progression (51–53). Finally, B7h (ICOS-L or B7RP-1) is constitutively expressed on DCs, and expression of its receptor, inducible T cell costimulator (ICOS), is induced upon T cell activation (49). Related to other members of the aforementioned CD28 immunoglobulin superfamily, ICOS (together with its binding partner B7h) has proven important in the development of regulatory T cells, and a deficiency in ICOS signaling has rendered mice more susceptible to various autoimmune pathologies, even though ICOS functions are required for the progression of some autoimmune processes (54–58).

Among various cytokines governing immune responses, the presence of TGF-β is often correlated with maintaining immune homeostasis. The absence of TGF-β leads to spontaneous lymphoproliferation and inflammatory disease, and TGF-β also influences the expression of IL-10, an important pro-tolerogenic cytokine (34, 49, 59, 60). By acting directly on T cells, TGF-β promotes differentiation of both regulatory and some effector T cells (43, 61–65). Metabolites such as retinoic acid (RA) enhance tolerogenic properties of cytokines including TGF-β, further promoting the induction of *Foxp3* expression and the amelioration of autoimmune disease (66–70).

In addition to the immunomodulatory pathways described above, which can directly contribute to inducing *Foxp3* expression in pTreg cells, recent results identified the roles of the immunoglobulin superfamily member B and T lymphocyte associated (BTLA) and CD5 in promoting pTreg cell homeostasis via the modulation of the sensitivity of the developing pTreg cells to effector-differentiating cytokines (7, 42, 71, 72). Among the DC populations, BTLA is expressed specifically in DC1s (72). During the interactions between the $BTLA^{hi}$ DC1s and T cells in the steady state, BTLA signals through HVEM in naïve $CD4^+$ T cells to activate MEK and subsequently ETS1 to increase expression of *Cd5* (42, 72). High CD5 expression then allows for a conversion of these T cells to $Foxp3^+$ pTreg cells by interfering with mammalian target of rapamycin (mTOR) activation in response to effector-differentiating cytokines such as IL-4, IL-6, and IFNγ (7, 42, 71).

$BTLA^{hi}$ DC1s reside in lymphoid organs including the spleen, and these resident lymphoid-tissue DCs are ideally positioned to capture systemic self-antigens including those derived from apoptotic cells (20, 73, 74). Although the specific roles of BTLA in governing tolerance among $CD8^+$ T cells remain unclear, DC1s can maintain tolerance to self-antigens by presenting endogenous antigens to both $CD4^+$ and $CD8^+$ T cells (73, 75). DC1s also have important roles in eliciting Th1 responses as well as in cross-priming $CD8^+$ cytotoxic T cells (23). Such versatile functions of some DC1s may reflect complex mechanisms mediated by BTLA and HVEM (76–79), yet it is also interesting to speculate that at least some of these pro-immune functions may be performed by DC1s characterized by low expression of BTLA.

Nevertheless, it is clear that apoptotic materials are an abundant source of tissue self-antigens crucial for the maintenance of immune tolerance (20, 80, 81). The relationship between the uptake, processing, and presentation of apoptotic materials and the functional characteristics of DCs is complex. The phagocytic scavenger receptor CD36 has long been recognized for its role in facilitating the uptake of apoptotic materials via recognition of phosphatidylserine found on the outer leaflets of the membranes of apoptotic cells (74, 82). Consistent with the notion that DC1s are primarily responsible for the constitutive uptake of apoptotic materials, CD36 is expressed highly on DC1s compared to DC2s and pDCs (83, 84). In addition to being a source of antigens, an exposure to apoptotic materials may also enhance the tolerogenic properties of some DCs. An engagement of CD36 can inhibit maturation of moDCs induced by pro-immunogenic stimuli and can induce tolerogenic BMDCs that resist lipopolysaccharide (LPS) stimulation and induce $Foxp3^+$ pTreg cell development (85, 86), also discussed later in the text.

In contrast, necrotic-type materials derived from injured cells can be recognized by Clec9a (DNGR-1), a C-type lectin expressed by some DC1s, resulting in inflammation and maturation of DCs (87, 88). However, under steady state conditions, the resident lymphoid-tissue $BTLA^{hi}$ DC1s (as well as some migratory DCs) exhibit inherent tolerogenic properties (11). The ability of DC1s to uptake, process, and present antigens to T cells in the steady state has been demonstrated by using multiple methods, including a direct targeting of antigens to such DCs by using chimeric antibodies specific for DEC-205 and other surface receptors (11, 17, 89). Importantly, the combination of genetic models including a DC-specific deletion of *Irf4* (resulting in an increased DC1:DC2 ratio) or a deletion of *Batf3*

(resulting in decreased numbers of DC1s) and targeted antigen delivery to CD11c, DEC-205, and other DC-specific molecules have helped to further clarify the specific functions of DC subsets (11, 17, 42, 49).

In addition to the tolerance promoted by resident lymphoid-tissue DCs, tolerance to self-antigens is also promoted by migratory DCs that transport antigens from the non-lymphoid tissue to the lymph nodes (LNs). Such migratory DC1s, especially those found in skin and parenchymal organs, undergo homeostatic maturation in the steady state and have tolerogenic functions (40, 90–92). However, the tolerogenic functions of many migratory DCs are also induced at certain anatomical locations (such as the intestines) upon exposure to specific extrinsic stimuli (as discussed below).

Inducing tolerogenic DCs for the maintenance of homeostasis

In contrast to resident lymphoid-tissue DCs and DCs migrating from the parenchymal organs in the steady state, many DCs that are exposed to various environmental stimuli present in the intestines, airways, and skin are constantly at risk of undergoing immunogenic maturation. However, as discussed earlier in the text, these DCs do not induce detrimental immune responses and instead induce tolerogenic functions. The specific tolerogenic mechanisms employed by itDCs remain an area of active investigation, but it is clear that, despite the presence of pro-inflammatory mediators, these DCs are typically characterized by an elevated production of various anti-inflammatory cytokines and other regulatory molecules (11, 93–99).

Among such specific anatomical sites, the skin represents a crucial barrier that is in constant contact with foreign antigens and commensal microbes and requires intricately regulated immune responses orchestrated by DCs (93, 100). The lungs are another crucial anatomical site that is continually exposed to commensals and pathogens, therefore also requiring active immunoregulation. Correspondingly, DCs obtained from patients with chronic obstructive pulmonary disorder (COPD) were shown to produce IL-10, leading to the induction of Tr1 regulatory cells (95, 101, 102). The intestines are yet another key organ that remains in constant contact with a large number of commensal bacteria and that can also be exposed to potentially-pathogenic microbes. Oral administration of antigens is well-established to lead to the induction of $Foxp3^+$ Treg cells, thereby helping to maintain homeostasis (103).

It has recently been suggested that the specific anatomical organization of gut-draining lymph nodes (gLNs) may play a role in the balance of tolerance and immunity, as proximal and distal gLNs supported primarily tolerogenic and immunogenic responses, respectively (47). In addition to such anatomic specialization, other studies have demonstrated that the presence of commensal microbes from the human gut, dietary metabolites, and some other biologically-active molecules results in the formation of itDCs that can differentiate $Foxp3^+$ Treg cells and regulatory Tr1 cells and decrease the numbers of effector T cells (33, 104–107). Accordingly, the pTreg cell-inducing functions of IRF8/Batf3-dependent $CD103^+CD11b^-$ DC1s help maintain a local immune homeostasis within the gut associated lymphoid tissues (GALT), as well as at other mucosal surfaces and also some immuneprivileged sites such as the eye (12, 13, 32, 108–110). Although DC2s are generally

less efficient at inducing pTreg cells, some itDC2s in the intestines still promote both Treg cell-independent and Treg cell-dependent tolerance (111, 112).

Recent work identified that stimulation through certain PRRs and the presence of specific cytokines and metabolites can actively divert DCs towards tolerogenic functions ((34, 47, 93, 101, 113) and (Fig. 3)). In contrast to their pro-immunogenic roles, some PRRs may contribute to a tolerogenic sensitization (33, 114–118). However, the impact of individual PRRs on the induction of tolerogenic DCs is likely to be context dependent. For example, BMDCs differentiated in the presence of splenic stroma were found to produce high amounts of IL-10 and to dampen naïve $CD4^+$ T cell responses in culture (36). Paradoxically, an additional stimulation with TLR-2, −3, −4, and −9 agonists of DCs co-cultured with splenic stromal cells further enhances their tolerogenic state, resulting in heightened production and secretion of CXCR3 chemokine IFNγ-inducible protein 10 (IP-10) and a corresponding decrease in Th1 proliferation (119). Nevertheless, certain TLRs such as TLR-2 appear to be more tolerogenic than other TLRs. In a murine disease model of arthritis, the microbial commensals' stimulation of TLR-2 on APCs promotes Treg cell suppressive functions and dampens IFNγ production, whereas stimulation of TLR-4 promotes Th17- and IL-17-driven pathology (120). Various TLRs may also physically associate as heterodimers to promote contrasting responses depending on the specific composition of each heterodimer. Studies using the *Yersinia pestis* virulence factor LcrV showed that recognition of LcrV by a TLR-2/TLR-6 heterodimer could lead to itDC induction, complete with IL-10 production and Tr1 induction, whereas recognition of LcrV by a TLR-2/TLR-1 heterodimer resulted in IL-12 production and induction of effector Th1 cells (121).

A particular agonist may also lead to divergent immune responses by stimulating different PRRs. Early reports suggested that zymosan, a glucan derived from yeast cell walls, promotes IL-10 production and tolerance by concomitant engagement of TLR-2 and dectin-1 (122). However, later reports from *ex vivo* and *in vivo* experimental systems suggested that divergent responses may arise from zymosan's stimulation of these PRRs. It was found that TLR-2 ligation by zymosan increases the expression of Raldh2 by DCs, leading to the production of RA and the eventual promotion of Treg cells via the suppression of effector differentiation. In contrast, ligation of dectin-1 increases Th1 and Th17 differentiation and exacerbates autoimmunity (117). In some instances, the concomitant signaling of specific combinations of other PRRs (such as TLR-2 and TLR-4 or TLR-3, −4, or −5 and DC-SIGN) may result in tolerogenic profiles, including increased IL-10 production and lower costimulatory molecule expression by DCs (123, 124).

In addition to TLRs, signaling via G-protein coupled receptors (such as GPR109a and GPR81) extends DC-mediated tolerance in the gut. The G-protein coupled receptor GPR109a is a receptor for commensal bacteria-produced butyrate and niacin that induce production of IL-10 and Aldh1a1 in DCs (125). The deficiency of GPR109a (genetically modeled in *Niacr1*$^{-/-}$ mice) results in an increased susceptibility to colonic inflammation and colon cancer in azoxymethan- (AOM) and dextran sulfate sodium- (DSS) treated mice, respectively (125). Similarly, the G-protein coupled receptor GPR81 is expressed on intestinal DCs and macrophages and has been shown to be activated by lactate, a product of

microbial fermentation that is present in abundance in the colon (126, 127). The genetic deletion of GPR81 results in a decrease in tolerance protecting from colitis, as evidenced by an increase in pro-inflammatory cytokine production, a decrease in regulatory factors such as IL-10, and a decrease in indoleamine 2,3-dioxygenase 1 (IDO1) expression; correspondingly, pharmacological activation of GPR81 has been shown to lessen murine colitis severity (127). Also, other molecules, such as DC-SIGN, play a specific role in itDC induction, as well as in the induction of tolerogenic functions in macrophages, by promoting specific mechanisms of tolerance (such as the production of IL-10) in response to various microorganisms (118, 128, 129). However, the binding of DC-SIGN (possibly in concert with the binding of TLRs) to various ligands including cell wall components and modified oligosaccharides derived from bacterial LPS results in divergent tolerogenic or immunogenic DC-mediated immune responses and may also lead to Th1 responses (123, 130–132).

Certain cytokines and metabolites have crucial roles in inducing and governing the functions of itDCs as well as in shaping the responses of DCs to PRRs ligands. For example, the addition of IL-10 to human DC cultures may lead to decreased expression of MHCII (HLA-DR) and costimulatory molecules, resulting in T cell anergy (133, 134). In the small intestine, RA is locally found at high concentrations due to the metabolism of dietary vitamin A (109, 135). This localized presence of RA then promotes the expression of Raldh2 and production of additional RA by $CD103^+$ DCs in the lamina propria, ultimately resulting in the increased induction of IL-10-producing $Foxp3^+$ Treg cells (as well as in the inhibition of TGF-β-mediated Th17 cell induction and in the imprinting of gut-homing receptors on T cells) (66, 108, 109, 136–138). Consistent with its pro-tolerogenic roles, IL-10 can then downregulate DC expression of MHCII and costimulatory molecules and reverse the effects of pro-inflammatory cytokines such as IL-6 and TNFα (60). Further, IL-10 treatment of human DCs upregulates TLR-2 expression in response to LPS administration, consistent with the pro-tolerogenic functions observed following TLR-2 activation (as discussed above). Such treated DCs also decrease expression of IL-12-related cytokines, possibly further indicating collaborative roles of IL-10 and TLR-2 in the dampening of the immune response (139).

In addition to IL-10, the IL-12 cytokine family member IL-35, predominantly produced by Treg cells, was proposed to dampen T cell responses (140). Similarly, IL-37 decreases the production of pro-inflammatory cytokines induced by LPS stimulation, and the forced expression of IL-37b in murine skin DCs promotes tolerogenic DC induction, thereby affecting contact hypersensitivity challenge (141, 142). Among other cytokines, IL-27 was initially considered to be pro-immunogenic (143). However, other studies indicated the role of IL-27 in suppressing the differentiation of effector T cells in autoimmune models such as experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) (144–146). Still, it remained unknown how IL-27 signaling directly affected DCs and subsequent T cell responses. A more recent report highlighted the role of IL-27 and the immunoregulatory molecule CD39 expressed by DCs. Specifically, CD39, whose expression is induced by IL-27, reduced NLRP3 inflammasome activation in DCs, thereby reducing subsequent Th1 and Th17 effector T cell differentiation (147).

Other extensively studied physiological factors that function in itDC promotion are ligands for the aryl hydrocarbon receptor (AHR), which is important in the regulation of the balance between the formation of regulatory and effector T cells (148). The endogenous ligands of AHR, such as 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), also act directly on DCs by skewing them towards a tolerogenic profile characterized by decreased production of inflammatory cytokines like IL-6 and IL-12 and increased production of suppressive TGF-β and IL-10 (104, 149). In DCs, AHR can induce expression of IDO1, an immunosuppressive enzyme that catabolizes tryptophan into kynurenine (Kyn) and other metabolites (149). Further, the upregulation of IDO1 and Socs2 expression and increased RA production by DCs contributes to a decrease in the pro-inflammatory cytokine milieu and the subsequent induction of $Foxp3^+$ Treg cells (150). Together, these findings indicate a crucial role of ITE and AHR signaling in the induction of itDCs that could have therapeutic roles in multiple types of autoimmune responses (151).

Vitamin D3 represents another key physiological factor that may induce tolerogenic DCs (152–154). The active form of vitamin D3 induces immunoregulatory properties upon binding to the vitamin D receptor (VDR), which is selectively expressed by various cell types including intestinal and skin epithelial cells, osteoblasts, $CD4^+$ and $CD8^+$ T cells, and also multiple APCs including macrophages, monocytes, and DCs (152, 155). VDR agonists increase IL-10 production but decrease expression of IL-12 and CD80/CD86 and CD40 by DCs (156). Additionally, itDCs induced by VDR agonists such as calcitriol and paricalcitol are poor inducers of antigen specific effector T cells but are potent inducers of Treg cells (152–154, 157). It was further demonstrated that DCs may also synthesize the active form of vitamin D3, therefore providing a local source of this crucial immunomodulant, altering immune cell trafficking, and further increasing the DC secretion of the chemokine CCL22, which attracts Treg cells (158–162). Overall, VDR agonists are promising therapeutics for autoimmune diseases, transplantation tolerance, and allergies (152–154, 157).

Other physiological factors may also play a role in itDC promotion. Vasoactive intestinal peptide (VIP) decreases production of pro-inflammatory TNFα and IL-6 and increases production of IL-10 in human DCs despite a pre-exposure to LPS, thereby mediating T cell anergy (163). Also, an addition of seminal plasma to differentiating moDCs yielded high regulatory cytokine and low pro-inflammatory cytokine production profiles in such moDCs (164).

In addition to these physiological factors, 14-dehydroergosterol (14-DHE), an ergosterol analogue-based compound derived from fermented wheat bran, induces tolerogenic properties in DCs, though the exact mechanisms are unclear (165, 166). Similarly, multiple pharmacological agents including chemically modified TLR ligands, Janus kinase (JAK) inhibitors, corticosteroids, cisplatin, antibiotics, probiotics (including bacterial species of the *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* genera), and dietary supplements (such as zinc) have been shown to promote tolerogenic profiles in BMDCs and moDCs. These profiles are characterized by changes at both the transcriptional and translational levels, ultimately leading to decreased production of the inflammatory cytokines TNFα and IL-6, decreased expression of costimulatory molecules, increased expression of co-inhibitory

molecules like PD-L1, and the production of the anti-inflammatory cytokines IL-10 and TGF-β (167–170).

Among the intrinsic signaling pathways involved in sensing specific extrinsic factors that induce tolerogenic properties in DCs, Wnt/β-catenin is a major molecular pathway involved in the promotion of itDCs and the increased production of anti-inflammatory cytokines such as TGF-β, RA, and IL-10, and, conversely, in blocking the production of NFκB-induced pro-inflammatory cytokines (32, 33, 67, 171). Deficiencies in Wnt receptors LRP5/6 and β-catenin signaling mechanisms enhance pro-inflammatory cytokine production and Th1/Th17 effector responses and increase disease severity in mouse models including colitis and MS (67, 172–175). Noncanonical Wnt signaling mediated by Wnt5a is also involved in the promotion of tolerance by modifying DC maturation and IL-10 production in response to TLR agonists (176). In addition to Wnt/β-catenin, mTOR emerges as an important regulator of DC functions that may also affect tolerogenic mechanisms (177, 178).

Harnessing the tolerogenic functions of DCs for therapeutic applications

The functions of DCs as inducers of tolerance represent important therapeutic opportunities. Modulation of such DC-induced tolerance can help block different forms of autoimmunity and also impact other types of immune responses relevant for transplantations as well as tumor immunology (11). Both ntDCs and itDCs are relevant for such therapeutic manipulations, and the targeted delivery of antigens to DEC-205$^+$ and other DCs has proven to be a powerful way to reinforce tolerance against self-antigens implicated in the autoimmune process (89). For example, the spontaneous induction of peripheral tolerance in response to antigens derived from organs insulated from the immune system (such as the central nervous system (CNS)), is likely less efficient (7, 11). This results in an increased potential for autoimmune diseases such as in animal models of MS, which can be readily provoked after an immunization of healthy animals with CNS antigens (7, 179, 180). However, such autoimmune responses can be blocked by tolerance induced by targeted delivery of various tissue-specific antigens to DCs, allowing for efficient antigen presentation to self-reactive T cells (11, 17, 18, 89).

In these initial experiments, DCs were targeted *in vivo* with anti-DEC-205 chimeric antibody to deliver a potentially-encephalitogenic antigen, myelin oligodendrocyte glycoprotein (MOG), which was genetically fused to the antibody molecule, to prevent subsequently-induced EAE (18). These early results were then extended to other EAE models and various encephalitogenic antigens that were delivered through DC-specific molecules, as recently reviewed in (11, 89). The targeting of antigens to DCs has also been successful in mediating tolerance in multiple different models of autoimmunity including diabetes, colitis, and arthritis as well as in a model of graft-versus-host disease (181–184). Overall, this specific delivery of antigens results in tolerogenic mechanisms that prevent autoimmunity.

In addition to the delivery of antigens specifically targeted to DCs, other studies found that certain formulations of antigens (such as nanoparticles or specifically modified cellular material) could lead to their *in vivo* acquisition by DCs and to the amelioration of

autoimmune processes including EAE and diabetes (185–188). Despite generally lacking cell target specificity, these methods showed promise in the treatment of ongoing autoimmune processes, particularly when additionally coupled with agents known to induce the formation of itDCs under pro-inflammatory conditions (150). Some of those methods also incorporated DC-specific antibodies to enhance the specificity of the delivery system (189), although most of such antibody-coupled immunogenic particles have been tested for new vaccine approaches (190). In addition to controlling autoimmunity, DC-mediated tolerance holds promise in mitigating transplant rejection (as recently reviewed by Thomson and colleagues in (191)). Importantly, DCs can cooperate with other types of immune cells such as NKT cells to prevent graft rejections (192).

In human systems, the most available options thus far have been to induce itDCs *ex vivo,* analogous to the induction of itDCs from murine BMDCs, and to treat with agents that can potentially further promote such itDC differentiation *in vivo*. Either murine BMDCs or moDCs derived from humans afflicted with autoimmune disease and then treated *in vitro* with the pharmacologic agents PEGylated-TLR-7 ligand, dexamethasone plus monophosphoryl lipid A, Tofacitinib, or prednisolone were utilized to delay disease onset or ameliorate disease severity in diabetes, rheumatoid arthritis, EAE, and myasthenia gravis (MG), respectively (167, 168, 170, 193–195). Also, treatment with IL-10 leads to the formation of itDCs that likely possess clinical relevance (196). Further, the treatment of BMDCs with the anti-tumor drug cisplatin in conjunction with various TLR agonists results in increased IL-10 production by the BMDCs as well as preventing Th1 and Th17 responses (197).

In contrast to the generally-beneficial functions of tolerogenic DCs in the prevention of autoimmunities as discussed above, the tumor microenvironment can skew DCs toward tolerogenic functions, thereby diminishing tumor rejection (178, 198–203). In an effort to induce anti-tumor immunity, multiple DC-based immunotherapies against cancer have been gaining importance, as recently reviewed by Sancho and colleagues (204). Even more breakthroughs that will determine the contributions of various DCs to tumor immune evasion and allow for the harnessing such DCs for anti-tumor therapies are expected.

Conclusions

The recent years have seen a growing understanding of DC functions in both the initiation and the regulation of immune responses. Overall, whereas functions of induced tolerogenic DCs contribute to the maintenance of homeostasis under potentially pro-inflammatory conditions, natural tolerogenic DCs help to establish tolerance under steady state conditions. Importantly, the new insights are providing us with a framework for exploiting the DC-mediated mechanisms of tolerance for more effective immunotherapies, which will hopefully be burdened by fewer side effects.

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(Abbreviations used)

AHR	aryl hydrocarbon receptor
BMDC	bone marrow derived dendritic cell
BTLA	B and T lymphocyte associated
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
DC	dendritic cell
EAE	experimental autoimmune encephalomyelitis
HVEM	Herpes virus entry mediator
IDO1	indoleamine 2,3-dioxygenase 1
itDC	induced tolerogenic dendritic cell
moDC	monocyte derived dendritic cell
MS	multiple sclerosis
ntDC	natural tolerogenic dendritic cell
pDC	plasmacytoid dendritic cell
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PRR	pattern recognition receptor
pTreg	peripherally induced regulatory T cell
RA	retinoic acid
tTreg cell	thymically derived regulatory T cell
VDR	vitamin D receptor

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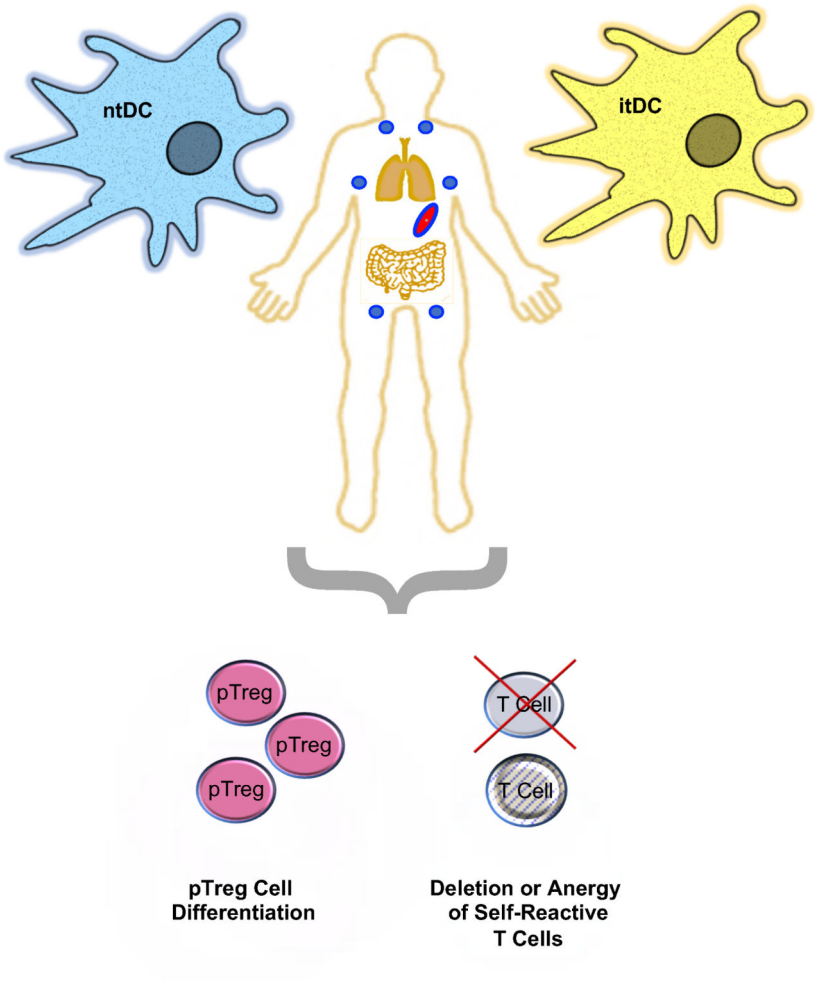

Figure 1.

The role of natural tolerogenic DCs (ntDCs) and induced tolerogenic DCs (itDCs) in extrathymic tolerance. Peripheral tolerance extends tolerance initiated centrally in thymus. The ntDCs and itDCs function to promote the deletion or anergy of self-reactive T cells as well as to induce regulatory T cells in the periphery (pTreg cells). ntDCs are generally tissue-resident DCs found in multiple immune organs including the spleen and lymph nodes (highlighted in blue). itDCs are generally found in various tissues and organs including the lungs, the intestines, and the skin (highlighted in yellow). In these locations, itDCs are in constant contact with a variety of environmental stimuli provided by commensal and pathogenic organisms.

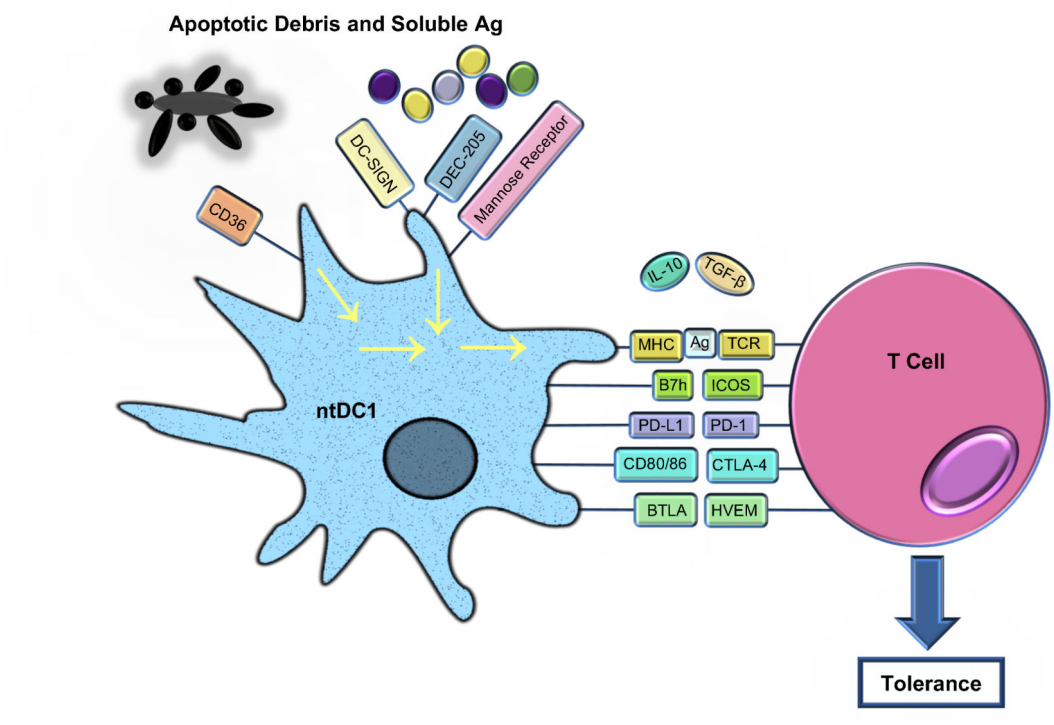

Figure 2.

Natural tolerogenic DCs (ntDCs) promote tolerance in the steady state. ntDCs, which are predominantly DC1s, inherently express immunomodulatory molecules including B and T lymphocyte associated (BTLA), programmed death ligand-1 (PD-L1), B7h, and CD80/CD86 as well as cytokines such as TGF-β and IL-10. Interaction of BTLA with the T cell-expressed receptor Herpes virus entry mediator (HVEM) are necessary for the efficient induction of pTreg cells and long-lasting tolerance. Functionally, using multiple receptors (examples of which are shown), ntDCs constitutively uptake and process tissue-derived antigens (Ag) from apoptotic cells for subsequent presentation to T cells, thereby further enhancing tolerance toward self-tissues. Similarly, ntDCs uptake, process, and present soluble Ag.

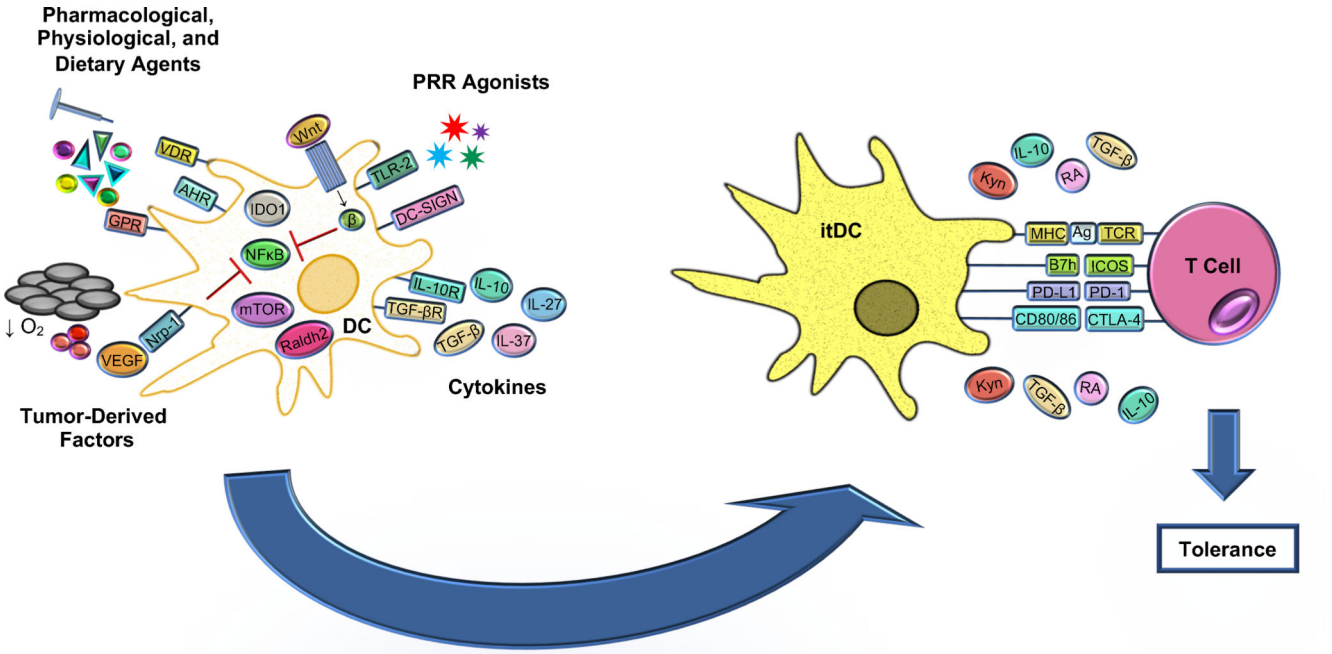

Figure 3.

Induced tolerogenic DCs (itDCs) promote T cell tolerance in response to exogenous signals. itDCs can be induced by multiple types of molecules including: microbial components (that bind to various pattern recognition receptors (PRRs) such as Toll-like receptor 2 (TLR-2)); pharmacological and dietary agents (such as corticosteroids and probiotics) or certain physiological agents that bind to the aryl hydrocarbon receptor (AHR) or the vitamin D receptor (VDR); and also other specific metabolites, cytokines, and growth factors. The downstream diverse immunoregulatory effects are mediated by several different signaling pathways including NFκB, Wnt/β-catenin, and mTOR, ultimately resulting in active mechanisms of tolerance that induce the expression and production of multiple immunomodulatory pathways including IL-10, retinoic acid (RA), and kynurenine (Kyn) (a metabolic product of tryptophan catabolism that is mediated by indoleamine 2,3-dioxygenase 1 (IDO1)).