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Brief Reviews

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The Importance of Dendritic Cells in Maintaining Immune Tolerance

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Immune tolerance is necessary to prevent the immune system from reacting against self, and thus to avoid the development of autoimmune diseases. In this review, we discuss key findings that position dendritic cells (DCs) as critical modulators of both thymic and peripheral immune tolerance. Although DCs are important for inducing both immunity and tolerance, increased autoimmunity associated with decreased DCs suggests their nonredundant role in tolerance induction. DC-mediated T cell immune tolerance is an active process that is influenced by genetic variants, environmental signals, as well as the nature of the specific DC subset presenting Ag to T cells. Answering the many open questions with regard to the role of DCs in immune tolerance could lead to the development of novel therapies for the prevention of autoimmune diseases. ***The Journal of Immunology*****, 2017, 198: 2223–2231.**

Antigen-presenting cells, namely B cells, macrophages, and dendritic cells (DCs), initiate both protective and autoimmune T cell responses, and DCs bear the highest Ag presentation potential, as shown by stronger induction of naive T cell activation (1). DCs play a nonredundant role in the initiation of immune responses and the control of some pathogens. For instance, *IRF8* mutations in humans cause defects in DCs, resulting in opportunistic infections and an increase in anergic T cells (2). Additionally, DCs also play a key role in maintaining immune tolerance, as we discuss in this review.

The importance of DCs in maintaining immune tolerance was shown by using mouse models to manipulate the number of DCs in vivo. For one, the CD11c–Cre/ROSA-diphtheria toxin A (CD11c-DTA) transgenic mouse model allows for specific depletion of $CD11c^+$ cells (3). CD11c is an integrin expressed at high levels by DCs and at much lower levels by many cellular subsets, namely neutrophils, macrophages, NK cells, as well as activated monocytes and T cells. Selective depletion of $CD11c^+$ cells induces an increase in effector Th1 and Th17 cells and strong autoimmune symptoms, such as lymphadenopathy, splenomegaly, and infiltration of nonlymphoid organs (3–5). Elimination of DCs in mice thus is sufficient to break immune tolerance and lead to autoimmune pathology, suggesting that DCs play a central role in the maintenance of immune tolerance. Notably, these findings were recently confirmed in a model that permits more selective elimination of DCs. Indeed, within the hematopoietic system, the *Zbtb46* transcription factor is exclusively expressed in DCs (6). The specific depletion of DCs in Zbtb46–diphtheria toxin receptor (DTR) adult mice via diphtheria toxin injection causes lymphoangiogenesis and myeloproliferative disorders, thus confirming the importance of DCs in the maintenance of immune tolerance (7, 8). Interestingly, the autoimmune pathology was less severe in the Zbtb46-DTR mice when compared with the CD11c-DTA mice, possibly because of either the more selective nature of the Zbtb46-DTR model or the timing of DC deletion. The CD11c-DTA model continuously deletes DCs from early development, but the deletion of DCs in Zbtb46-DTR mice is transiently induced in adult mice. Nevertheless, both experimental settings show that elimination of DCs in mice is sufficient to break immune tolerance and lead to autoimmune pathology, suggesting that DCs play a central role in the maintenance of immune tolerance.

If depletion of DCs leads to autoimmune phenotypes, one could postulate that increasing the prevalence of DCs would strengthen immune tolerance and prevent autoimmune disease occurrence. To this effect, Flt3 ligand injection increases the

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Abbreviations used in this article: cDC, conventional DC; CD11c-DTA, CD11c–Cre/ROSA-diphtheria toxin A; DC, dendritic cell; DTR, diphtheria toxin receptor; EAE, experimental autoimmune encephalitis; GVHD, graft-versus-host disease; MHC-I, MHC class I; MHC-II, MHC class II; pDC, plasmacytoid DC; RTOC, reaggregate thymus organ culture; tol-DC, DC with tolerogenic properties; Treg, regulatory T cell.

proportion of DCs in vivo and prevents autoimmune diabetes onset in NOD mice (9). However, a break in immune tolerance is observed in mouse models where DC number is increased by inhibiting DC apoptosis. Specifically, transgenic mice with CD11c promoter-driven p35, a caspase inhibitor that blocks apoptosis, present with an accumulation of DCs in lymphoid organs over time (10). Consequently, CD11c-p35 transgenic mice exhibit lymphocytic infiltration in nonlymphoid organs, activation of both T and B cells, and production of anti-DNA Ab (10). Also, DC-specific knockout of *Bim* decreases DC apoptosis, which leads to an increase in DCs and results in inflammation (11). Therefore, depending on the context, an increase in the number of DCs can either increase or decrease T cell tolerance. This is perhaps due to distinct impacts on the DC phenotype, such that expansion of DCs either by stimulating hematopoiesis or by blocking DC apoptosis may yield different outcomes in the maintenance of immune tolerance. Still, because DCs are capable of both immunity and tolerance, manipulation of numbers alone may not be a consistent way to alter the balance of immunity and tolerance.

Induction of stable tolerogenic DCs could provide a powerful platform for Ag-specific treatment of autoimmune diseases. In vitro protocols to induce DCs with tolerogenic properties (tol-DCs) include the differentiation of DC precursors in media complemented with agents such as dexamethasone, IL-10, or TGF-β (12). These tol-DCs can then be loaded with specific Ags and, upon injection in vivo, are expected to provide Ag-specific immune tolerance through different means, such as by promoting Ag-specific regulatory T cell (Treg) differentiation or by producing IDO and/or NO (13). Various DC populations that facilitate immune tolerance have also been identified in vivo (14). For example, spleen $CD11c^{low}CD45RB^{+}$ DCs induce Ag-specific differentiation of Tregs via Ag presentation and IL-10 production (15, 16). Additionally, $CD11c^{low}CD11b^{high}I\text{-}A^{low}$ DCs create a tolerogenic environment by secreting high levels of IL-10 and NO (17). Therefore, understanding the mechanisms by which DCs can induce and maintain both central and peripheral immune tolerance may inform treatments for autoimmunity. In this review, we discuss the mechanisms by which DC subsets can induce steady-state immune tolerance, and how an inflammatory/autoimmune disease context can change DC-mediated tolerance.

Thymic tolerance

The process of central tolerance in the thymus eliminates potentially autoreactive thymocytes by negative selection and promotes T cell differentiation into various Treg subsets via additional selection processes (18–22). Central tolerance is, in fact, highly dependent on the presentation of self-antigens to T cells by both thymic epithelial cells and APCs (23–25). Early work showed that MHC expression on thymic bone marrow–derived APCs contributes to central tolerance induction (26). Among these APCs, DCs clearly contribute to elimination of maturing autoreactive thymocytes, as DC-specific expression of MHC class II (MHC-II) I-E is sufficient to negatively select thymocytes specific for endogenous superantigens in a manner comparable to that of mice expressing the I-Eα transgene on all APCs (27). MHC expression on DCs thus appears sufficient, at least in the context of superantigens, to induce effective central tolerance (27). In comparison with macrophages and B cells, only DCs were able to induce negative selection of thymocytes in reaggregate thymus organ cultures (RTOCs) (25), showing the dominant role of DCs in central tolerance. More recently, it was shown that DCs are not simply bystanders in the thymocyte selection process. They actively attract postpositive selection thymocytes by producing CCR4 ligand to facilitate the negative selection process (28). Interestingly, and likely due to the experimental challenges associated with separating central and peripheral tolerance processes, the general outcome of a defect in DC-mediated central tolerance on the potential development of an autoimmune phenotype has yet to be clearly defined.

Although all thymic DCs contribute to central tolerance, they do so through different means (Fig. 1). Three thymic DC subsets contribute to central tolerance, namely resident DCs ($CD8\alpha^{+}SIRP\alpha^{-}$), migratory DCs ($CD8\alpha^{-}CD11b^{+}SIRP\alpha^{+}$), and plasmacytoid DCs (pDCs; $CD11c^{int}CD45RA^{int}$) (29–32). Resident DCs that develop from thymic lymphoid precursors are the most abundant subset and are primarily localized in the medulla (29, 31, 33, 34). They contribute to the elimination of autoreactive thymocytes by presenting a wide array of self-antigens, and by cross-presenting both blood-derived Ag and tissue-specific Ags from medullary thymic epithelial cells (35–37). Migratory $SIRP\alpha^{+}$ DCs also contribute to central tolerance. They develop in the periphery and, as shown in parabiosis experiments, migrate to the thymus via CCR2/α_4 integrin where they mostly localize to the corticomedullary junction to present peripheral self-antigens to developing thymocytes (34, 38, 39). pDCs also develop in the periphery and use CCR9/α_4 integrin signals to migrate to the thymus and contribute to the maintenance of immune tolerance (32). Interestingly, in RTOC experiments, pDCs were shown to only minimally contribute to the induction of negative selection (25). The reason for this discrepancy is not clear, but it may be due to the different localization of cells in RTOCs. Still, all of the DC subsets contribute to immune tolerance by presenting self-antigens and inducing negative selection of developing thymocytes that present with a high affinity to self-ligands. Whereas pDCs and migratory DCs specialize in the presentation of peripheral Ags, resident DCs provide immature T cells with a distinct self-antigenic repertoire. Additionally, although thymic resident and migratory conventional DCs (cDCs) can uptake MHC class I (MHC-I) and MHC-II from thymic epithelial cells in a cell contact–dependent manner, this process is dependent on the PI3K pathway only for $CD8\alpha^{+}$ resident cDCs (40), further supporting the view that each DC subset provides a nonredundant role in Ag presentation to T cells and in the maintenance of central tolerance.

In addition to inducing negative selection, thymic DCs are also important for the selection of natural Tregs during thymocyte differentiation. Proietto et al. (41) constructed mixed bone marrow chimeric mice, with T cells specific to a given Ag (from OT-II.$Rag2^{-/-}$ mice) and DCs as the only source of APCs presenting this Ag (from CD11c-OVA mice). In these mice, DCs successfully induced the differentiation of natural Ag-specific Tregs in the thymus. Specifically, both resident and migratory DCs, but not pDCs, are able to induce Tregs in vitro (25, 41, 42), but the mechanisms by which they

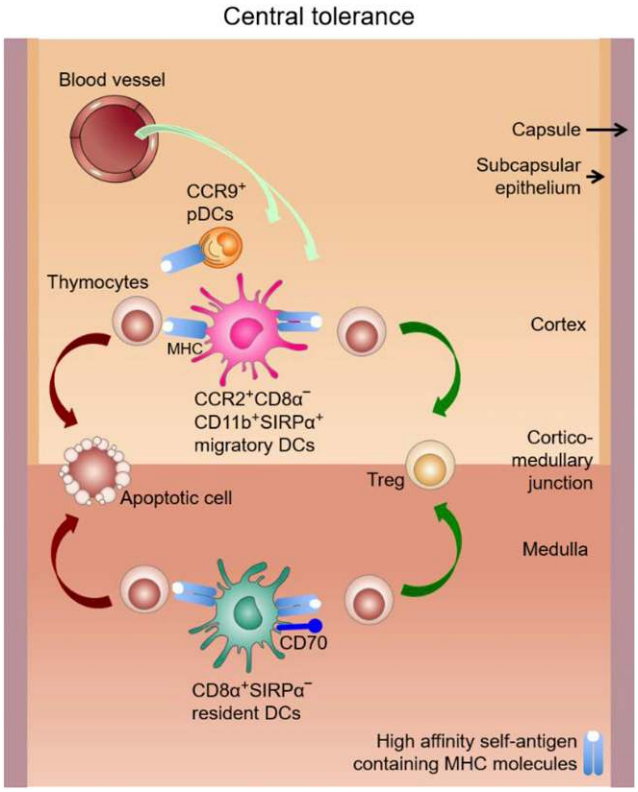

FIGURE 1. DC-mediated central tolerance. Migratory $CD11b^+CCR2^+$ DCs and $CCR9^+$ pDCs migrate from periphery to the thymic cortex and induce tolerance to peripheral self-antigens by inducing apoptosis of autoreactive thymocytes. Migratory DCs also promote Treg differentiation. $CD8a^+$ resident DCs induce apoptosis of thymocytes reactive to self-antigens and promote Treg differentiation and survival.

induce Tregs are distinct (Fig. 1). Resident DCs promote Treg survival via their expression of CD70, whereas CD70-deficient migratory DCs effectively induce Tregs through an undefined pathway (42). However, the capacity to induce Tregs is not restricted to DCs. When high concentrations of self-antigens are present, Tregs can differentiate in RTOCs devoid of APCs, suggesting that epithelial cells can sometimes induce Tregs (25). As such, thymic Treg numbers are normal in mice that only express MHC-II on epithelial cells (43). Therefore, both thymic epithelial cells and DCs play an active role in the induction of central tolerance through both the elimination of potentially autoreactive thymocytes and in facilitating the generation of Tregs. As thymic epithelial cells and DCs bear distinct immunopeptidomes, one can presume that these roles are not fully redundant. Indeed, both have the capacity to uptake Ags from different sources and exploit different proteolytic pathways resulting in distinct peptide repertoires, with each contributing toward effective induction of central tolerance (20).

DC-mediated peripheral tolerance mechanisms

Although thymic selection efficiently eliminates many self-reactive T cells, some remain and must be kept in check with additional peripheral tolerance mechanisms to avoid autoimmunity. In the absence of inflammation, DCs can present self-antigens to T cells, providing transient T cell activation that can lead to either anergy or deletion of these T cells (44). DC-mediated tolerance is thus an active process that requires TCR signaling (45). T cell clonal deletion is mediated by the activation of Fas-, Bim-, or TNF-dependent apoptosis and inhibition of NF-κB signaling (46–48). Many DC factors contribute to the balance of tolerance and immunity, including maturation states defined by their gene signature, and the level of Ag presentation; therefore, it is necessary to understand the conditions under which DCs remain immature or become activated (37, 49, 50).

Steady-state DCs that normally express low levels of DC maturation markers and promote tolerance induction are termed immature DCs (51). Once activated by pathogen or damage-associated molecular patterns, DCs turn on different metabolic, cellular, and gene transcription programs that initiate increased DC migration out of peripheral tissue into draining lymph nodes where Ag presentation to T cells occurs (52–54). DC maturation is marked by increased expression of molecules relevant for T cell activation, including MHC-II, costimulatory proteins such as CD40, CD80/CD86, and inflammatory cytokines or chemokines (55–57). However, functional capacity of DCs to induce T cell activation does not always directly correlate with common maturation markers, in part because Tregs use some of the same signals, including CD80/CD86 (58–60). Therefore, tolerogenic and immunogenic DCs should ideally be defined based on the signals they give to conventional T cells or Tregs (37).

Steady-state DCs are exposed to commensal microorganisms and other tonic inflammatory signals that can induce the expression of maturation markers at low levels, which are not sufficient to break self-tolerance in most individuals. The ability of steady-state DCs to remain in an immature/nonactivated form likely depends on the timing, dose, and signal strength of the factors interacting with DCs. Steady-state DC migration is associated with considerable transcriptional changes, suggesting that immunoregulatory function of steady-state DCs is an active process (37). Indeed, regulators such as A20 can modulate NF-κB signaling and contribute to maintaining tolerance (61–64). Upregulation in DCs of IDO synthesis, a rate-limiting enzyme of tryptophan catabolism, contributes to tolerance by depleting tryptophan and causing apoptosis of effector T cells (65–67). Negative costimulation via CTLA4-CD80/CD86 or PD-1–PD-L1/PD-L2 is also implicated in the induction of tolerance, but these proteins display minimal expression on steady-state DCs, suggesting that these inhibitory signals may be more important for dampening activation in the context of inflammatory signals (68–70).

Peripheral DCs are subdivided into functional subsets with various locations and roles in both immunity and tolerance, namely pDCs, monocyte-derived DC (moDCs), and cDCs. The latter are further subdivided into two populations, that is, $CD8\alpha^+/CD103^+$ and $CD11b^+$ (71). moDCs ($CD11c^+$ $CD11b^{high}MHC\text{-}II^+$) are usually inflammatory and separated from the cDCs by higher CD11b expression and lack of cDC-specific markers such as CD4 and DCIR2 (54, 72). Because many studies do no separate cDCs from moDCs in their analyses, it is not yet clear whether moDCs can contribute to tolerance induction, whereas strong evidence supports a clear role for both cDCs and pDCs in the maintenance of immune tolerance.

cDCs prime T cells via Ag presentation and other signals, leading to immunogenicity or tolerance (49, 70, 73–75). Delivering Ag to particular cDC subsets via chimeric Abs

specific for lectin cell surface receptors can elucidate the role of these subsets in T cell tolerance induction (Fig. 2). CD8α$^+$ cDCs express DEC205 and are located in the T cell zone in the spleen where they can cross-present exogenous Ag to CD8$^+$ T cells via MHC-I. DCIR2, another DC lectin receptor, is expressed by murine CD11b$^+$ cDCs and some human DCs (76–78) In mice, CD11b$^+$DCIR2$^+$ DCs located in the red pulp and marginal zone area of the spleen can migrate to the edge of the T cell zone where they primarily stimulate CD4$^+$ T cells (79–82). Both DEC205 and DCIR2 are efficiently internalized upon receptor–ligand interaction, and these receptors are directed to endosomal/lysosomal compartments for Ag presentation (79, 83). In mice that have been challenged with anti-DEC205– or anti-DCIR2–mediated Ag delivery to cDCs during steady-state, Ag-specific T cells are rapidly deleted and the remaining Ag-specific T cells become unresponsive upon in vitro stimulation (65, 75, 79). Some studies have proposed that natural ligands for DEC205 such as apoptotic, necrotic materials or CpG may stimulate CD8α$^+$ cDCs and possibly contribute to their maturation (84, 85). Still, many lectins can impart maturation or inhibitory signals upon binding ligand or Ab (86, 87), and recent evidence points to DCIR2 in providing a negative signal to cDCs, further adding to the role of DCIR2 in the cDC-mediated maintenance of steady-state tolerance (88).

cDCs not only induce tolerance by deleting Ag-specific T cells or by inducing anergy, but they can also promote Treg differentiation or function (Fig. 2). Whereas CD8α$^+$ cDCs are more efficient in providing TGF-β for de novo Foxp3$^+$ Treg generation, likely potentiated by BLTA expression (89), CD11b$^+$ cDCs enhance activation and proliferation of existing CD4$^+$Foxp3$^+$ Tregs (90). Interestingly, Tregs play a very important role in steady-state cDC-mediated tolerance. Depletion of Foxp3$^+$ Tregs increases cDC numbers as well as the surface expression of costimulatory molecules, resulting in enhanced T cell responses (91). This strongly suggests that Tregs also contribute to peripheral tolerance by maintaining cDCs in the immature state (91, 92).

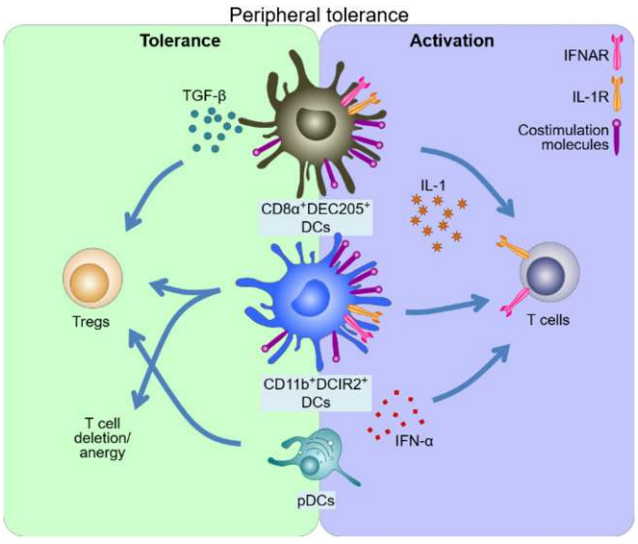

FIGURE 2. DC-mediated peripheral tolerance. cDCs and pDCs induce tolerance by promoting Treg differentiation or function. cDCs can also induce peripheral tolerance by inducing T cell anergy or T cell deletion. In inflammatory conditions, cDCs and pDCs promote T cell activation.

pDCs are a specialized subset of DCs that rapidly make a large amount of type 1 IFN in response to signals such as viral infections (Fig. 2). In the steady-state, pDCs express very low levels of MHC-II and costimulatory molecules and may contribute to T cell unresponsiveness. Although pDCs are not as efficient as cDCs for Ag presentation to T cells, pDCs can upregulate MHC-II molecules on their surface and migrate to the T cell area and induce T cell proliferation and Treg generation (93, 94). Activated pDCs can have enhanced MHC-II expression (95, 96), allowing for prolonged T cell activation that may contribute to Treg development, as increased MHC-II on pDCs is required for Treg homeostasis (97). Type 1 IFN and IL-10 produced by pDCs may also contribute to Treg generation (98). pDCs can produce IDO and express PD-L1 that correlate with an increased Treg frequency (99, 100). Tolerogenic pDCs have been reported in many inflammatory disorders, including acute graft-versus-host disease (GVHD), autoimmune arthritis, and oral tolerance, where they promote tolerance by modulating Treg function or by maintaining Ag-specific T cell tolerance (101–103).

The local environment also plays an important role in modulating DC tolerogenic function. For example, migratory dermal DCs and Langerhans cells present in both the skin and skin-draining lymph nodes appear to play a central role in Treg differentiation. DCs in skin-draining lymph nodes are particularly effective at inducing Tregs, as Tregs converted from naive CD4 T cells display enhanced immunoregulatory properties when isolated from the skin-draining lymph nodes rather than the spleen of mice (104). In mice where langerin$^+$ migratory DCs are depleted using diphtheria toxin injections in Lang-DTR transgenic mice, anti-DEC205–mediated Ag-specific delivery to DCs is no longer able to induce Ag-specific Tregs in the spleen and skin-draining lymph nodes and results in a loss of immune tolerance (105, 106). Importantly, langerin$^+$ migratory DCs may, in fact, uniquely contribute to the induction of Tregs and the maintenance of peripheral tolerance, as the specific depletion of langerin$^+$ DCs has no effect on the initiation of antiviral responses (107). This latter finding suggests that specific DC subsets found in unique environments may have specialized roles in immune tolerance. Further investigation of the role of langerin$^+$ DCs in the modulation of various immune responses is needed to clarify their contribution in pathogenic settings.

DCs found in the gut-associated lymphoid tissues can also promote immune tolerance. As in the skin, CD103$^+$ DCs in the gut tissue express high levels of the enzyme aldehyde dehydrogenase, which converts vitamin A into retinoic acid, which in turn promotes the conversion of naive T cells into Tregs (108, 109). A second mechanism by which gut DCs induce tolerance is through the production of IDO, which itself facilitates induction of Tregs (110). In fact, selective elimination of CD103$^+$CD11b$^-$ DCs results in a decrease in IDO levels and an increased susceptibility to dextran sodium sulfate–induced colitis (111). Finally, CD103$^+$CD11b$^+$ DCs also significantly contribute to immune tolerance through the expression of acyloxyacyl hydrolase, an enzyme able to inactivate LPS and thus to prevent effective TLR4 activation that induces the differentiation of naive T cells into effector Th17 cells (112). Collectively, these data support the view that DCs found in the gut microenvironment are geared to promote immune tolerance, likely because of the perpetual exposure to microflora and to food Ags (113).

How do DCs maintain/adjust tolerance against self-antigens in the context of inflammatory signals? Although activated DCs acquire strong phenotypic changes linked with enhanced effector T cell function and inflammatory cytokine production, DCs can also exert regulatory function under inflammatory situations. For example, pDCs promote persistence of viral infection in the liver (114). Even under strong activation due to allergen exposure, pulmonary DCs can stimulate the development of $CD4^+$ T regulatory 1–like cells (115). Immunoregulatory DCs in the context of infection have been defined based on the net sum of inhibitory versus stimulatory signals. Induction of inhibitory molecules, including PD-1, TGF-β, or IDO, and downregulation of costimulatory molecules or cytokines are important correlates of regulatory DC function (116, 117). For example, upon infection with *Listeria monocytogenes*, DCs induce both stimulatory and regulatory molecules (118). Infected DCs suppress T cell activity mainly by IL-10 and cyclooxygenase 2–mediated mechanisms (118, 119). In certain contexts, signals associated with inflammation, such as TLR2, TNF-α, and PG receptor, can induce immunoregulatory DC phenotypes (118). In chronic viral infection, DCs can become immunosuppressive, losing their surface expression of MHC-I and MHC-II and costimulatory molecules (120). DCs also upregulate PD-L1 during chronic viral infections such as HIV and hepatitis C virus (121–123). PD-L1 interacts with PD-1 on T cells, which can induce T cell deletion and also increase Treg generation and function by enhancing FOXP3 expression, in humans (124).

DCs and autoimmune pathologies/diseases

Autoimmune diseases occur, in part, because of changes in DC function that result from genetic and environmental alterations (125–127). Disruption of the tolerance network contributed by each DC subset can promote autoreactive T cell responses and pathology. Therefore, therapies targeting DCs may be effective treatment for autoimmunity. Identifying the DC signaling pathways that are altered in the context of autoimmunity and that can interrupt T cell tolerance induction will help define the signals that allow induction of stable tolerogenic DCs. In addition to the pattern recognition receptors that sense danger signals, host-derived non–pathogen-associated chronic inflammatory signals are also playing a role in autoimmune pathology (75, 128). DC function could be altered under this persistent host-derived inflamed situation (Fig. 2).

One critical inflammatory signal in systemic autoimmunity is type 1 IFN. Patients with systemic lupus erythematosus display an increased IFN gene signature (129, 130), and pDCs from these patients are more prone to induce pathogenic T cell responses (131, 132). The pathogenic role of type 1 IFN in other autoimmune diseases is less clear, but it may also contribute to these pathologies (133, 134). Prior to islet infiltration by autoreactive T cells, autoimmune-prone NOD mice already exhibit increased type 1 IFN and IFN response genes in the islets, and blocking type 1 IFN at this early stage inhibits diabetes pathogenesis (135–137). This suggests that type 1 IFN is critical for the initial break in tolerance. However, the role of chronic innate signals on DCs at later disease stages is less clear. Despite increased chronic type 1 IFN exposure, DCs from older prediabetic NOD mice display impaired type 1 IFN responses due in part to downmodulation of IFN-A receptor (137, 138). However, NOD DCs and other APCs are hyperactive due to increased proinflammatory signals resulting from a defect in NF-κB regulation that enhances Ag presentation to CD8 T cells (139, 140). Therefore, the balance of different types of inflammatory signal is likely important for autoimmune pathogenesis, and type 1 IFN and IL-1 signals can counterregulate each other (141–143). IL-1 and increased NF-κB activation may be the dominant inflammatory signal for type 1 diabetes (144). Autoimmunity may also lead to changes in DC costimulatory molecule expression. DCs from prediabetic NOD mice have increased CD40 expression that is dependent on adaptive immune cells. Increased CD40 expression could be more indicative of inflammation, as blocking CD40 signals blocks NOD autoimmune diabetes pathogenesis (145–148).

The role of particular DC subsets in tolerance induction also differs in autoimmune contexts. Although both $CD8\alpha^+$ $DEC205^+$ and $CD11b^+DCIR2^+$ DCs are tolerogenic in normal mice, only the $CD11b^+DCIR2^+$ DCs are able to induce CD4 tolerance in NOD mice (78). NOD mice have fewer $CD8\alpha^+$ DCs in the spleen, and the function of this DC subset is altered; that is, the cross-presentation capacity of NOD DCs is reduced relative to $CD8\alpha^+$ DC from non–autoimmune-prone mice (149). This significantly reduces the potential for cross-tolerance, a mechanism involved in maintaining immune tolerance (150). This more pathogenic role for $CD8\alpha^+DEC205^+$ DCs in NOD mice was further confirmed by the lack of diabetes development in NOD $Batf3^{-/-}$ mice that cannot develop these cross-presenting DCs (151). NOD mice also exhibit an increased proportion of recently described merocytic DCs (152, 153). This unconventional DC subset is sufficient to break tolerance at steady-state (154). Additionally, the $H2^{g7}$-specific MHC haplotype affects the spectrum of Ag presentation, which has been proposed to contribute to autoimmune susceptibility (155). In experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis, the role of DCs for controlling immune tolerance was demonstrated with two complementary approaches. The lack of MHC-II on APCs using MHC-II–deficient bone marrow chimeric mice reduced EAE symptoms and histopathology scores. Conversely, MHC-II expression restricted to $CD11c^+$ DCs is sufficient to induce EAE pathophysiology in mice bearing myelin oligodendrocyte-specific T cells (156). pDCs are also important in regulating multiple sclerosis susceptibility, but their protective or detrimental role is highly dependent on the timing. Indeed, Ab-mediated depletion of pDCs at the onset of EAE exacerbates the pathophysiological response (157, 158). Similarly, in mice lacking MHC-II expression in pDCs, EAE severity was increased and this was linked to a decrease in Treg proliferation, suggesting that pDCs contribute to immune tolerance by activating Tregs (97). In contrast, pDC depletion during the priming phase decreases the onset and the severity of the disease (158). Therefore, the context and timing in which DCs transmit signals to other immune cells determine whether they will contribute to exacerbating the immunopathology or confer immune tolerance.

Maintenance of immune tolerance is also relevant in the context of GVHD where pathogenic alloimmunity develops. Depletion of DCs in the GVHD setting via the utilization of CD11c-DTR bone marrow decreases the expansion of

allogenic T cells, suggesting that donor DCs contribute to the pathogenesis (159). Specifically, the $CD103^+CD11b^-$ DC subset is sufficient to cause GVHD, as exemplified in Irf4-deficient bone marrow chimeras (159). However, pDCs were shown to protect against GVHD by inducing Tregs (101). MHC-II–deficient DCs are also linked with a reduction in Tregs in the context of GVHD (160). These findings support an immunoregulatory role for DCs in GVHD, at least by the induction of Tregs. In addition to immune tolerance, DCs may help prevent GVHD by restoring immune T cell homeostasis, which is severely affected following bone marrow transplants. Although IL-7 treatment facilitates $CD8^+$ T cell homeostatic proliferation, recent evidence suggests that adding either Flt3 or SDF1, two molecules that potentiate DC numbers in vivo, favors homeostatic reconstitution of $CD4^+$ T cells (161). Immunoregulation by DCs is thus relevant for the prevention or treatment of GVHD.

A specific role for pDCs has also been delineated in vascular inflammatory settings. In vascularized grafts, as in GVHD, pDCs promote the development of Tregs and prevent allograft rejection (162). pDCs similarly contribute to prevent atherosclerosis, where specific depletion of pDCs leads to a reduction in Tregs and an exacerbation of atherosclerosis lesions (163). This latter study demonstrates that pDCs induce Ag-specific Tregs via the production of IDO. Taken together, these studies support a tolerogenic role for pDCs through induction of Tregs.

Conclusions

DCs are potent APCs that, depending on the context, can either induce effective immune responses or contribute to immune tolerance. There are many challenges associated with studying the role of specific DC subsets at steady-state, under inflammatory or pathological conditions, to carefully dissect their contrasting immunoregulatory and immunogenic properties. To examine the fundamental tolerogenic function of DCs at steady-state, various mouse models have been engineered to allow manipulation of DCs in an unscathed in vivo setting. Studies exploiting these models have established that DCs contribute to the maintenance of immune tolerance. As DCs efficiently maintain immune tolerance, various protocols have been attempted to effectively produce tol-DCs for the potential treatment of autoimmune diseases. DCs are a rare heterogeneous cellular population, and their phenotype and function are readily modulated by both tissue localization and inflammatory responses. Notably, the context in which a specific DC subset is found can dictate its role. For instance, the $CD8\alpha^+$ cDC subset may exhibit at least three distinct functions depending on its location and activation status. Under homeostatic maturation signals in the thymus, they permit effective induction of T cell central tolerance, whereas in secondary lymphoid organs they induce T cell cross-tolerance (37). In contrast, immunogenic activation of this same cDC subset will initiate effective antiviral responses (37). Recent studies have begun to transpose the role of each murine DC subset to its human equivalent (164–166). This may help lead to the development of new therapeutic strategies for using DCs to establish immune tolerance and treat autoimmune diseases.

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Disclosures

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