Immunomodulatory Bonds of the Partnership between Dendritic Cells and T Cells

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Abstract

By acquiring, processing, and presenting both foreign and self-antigens, dendritic cells (DCs) initiate T cell activation that is shaped through the immunomodulatory functions of a variety of cell-membrane-bound molecules including BTLA-HVEM, CD40-CD40L, CTLA-4-CD80/CD86, CD70-CD27, ICOS-ICOS-L, OX40-OX40L, and PD-L1-PD-1, as well as several key cytokines and enzymes such as interleukin-6 (IL-6), IL-12, IL-23, IL-27, transforming growth factor-beta 1 (TGF-β1), retinaldehyde dehydrogenase (Raldh), and indoleamine 2,3-dioxygenase (IDO). Some of these distinct immunomodulatory signals are mediated by specific subsets of DCs, therefore contributing to the functional specialization of DCs in the priming and regulation of immune responses. In addition to responding to the DC-mediated signals, T cells can reciprocally modulate the immunomodulatory capacities of DCs, further refining immune responses. Here, we review recent studies, particularly in experimental mouse systems, that have delineated the integrated mechanisms of crucial immunomodulatory pathways that enable specific populations of DCs and T cells to work intimately together as single functional units that are indispensable for the maintenance of immune homeostasis.

Keywords

dendritic cell; T cell; immunoregulation; T cell differentiation; regulatory T cell; effector T cell

I. INTRODUCTION

Dendritic cells (DCs) are antigen-presenting cells (APCs) that initiate and regulate T cell responses to foreign and self-antigens. DCs patrol various tissues and internalize such antigens, which they then process and present as peptides on major histocompatibility complexes (MHCs) to T cell receptors (TCRs) that are reactive to specific peptide:MHC complexes. In addition to activating T cells to combat various pathogens, DCs have a well-established role in the induction and regulation of tolerance in the absence of pro-inflammatory stimuli, known as the steady state.[1] DCs can also sense the presence of various environmental signals, including materials from dead cells, microbial products, and specific

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pro-inflammatory conditions, allowing them to discern what the appropriate immune response for the surrounding environment should be.[2–5] Some of these environmental signals may also promote the tolerogenic functions of DCs.[3,6–17] However, the molecular mechanisms by which DCs induce different immunological outcomes remain a subject of active investigation.

Depending on the cytokines secreted and the immunomodulatory molecules present on the surface of both the DCs and T cells, T cells differentiate to acquire various effector or regulatory functions. Moreover, DCs can modulate T cell functions through the production of metabolites by specific immunomodulatory enzymes. However, the interactions between DCs and T cells are not unidirectional because T cells can also influence certain aspects of DC biology. Overall, multiple immunomodulatory pathways enable DCs and T cells to work together as functional units that carry out diverse functions in order to promote an appropriate immune response (Fig. 1). Increasing our understanding of the various mechanisms utilized by different subsets of DCs to help shape T cell responses in order to maintain immune homeostasis is vital for the design of new therapies for a variety of diseases, including cancer, autoimmunity, and infections.

II. IMMUNOMODULATORY PATHWAYS

A. CTLA-4–CD80/86

A crucial example of an immunomodulatory molecule that facilitates a dynamic partnership between DCs and T cells in the maintenance of immune homeostasis is cytotoxic T-lymphocyte antigen 4 (CTLA-4). This molecule, with its multi-faceted tolerogenic capabilities, is a member of the CD28 family that is expressed in activated T cells, particularly regulatory T (Treg) cells, in a cell-membrane-bound form.[18–22] Additionally, CTLA-4 has been shown to be expressed and secreted by DCs.[23,24] In T cells, CTLA-4 competes with CD28 for binding of CD80 or CD86 expressed on DCs.[25,26] Although the precise molecular signals are still unclear, signaling by membrane-bound CTLA-4 in T cells can result in tolerant CD4$^+$ T cell responses, including clonal anergy or transforming growth factor-beta 1 (TGF-β1) production.[27,28] In CD8+ T cells, CTLA-4 promotes DC-mediated T cell tolerance, although the mechanism by which this occurs is also unclear.[29]

In addition to T cell-intrinsic effects mediated by CTLA-4, studies by several groups have shown that Treg cells exert tolerogenic effects by modulating DC biology through several different mechanisms mediated by Treg cell-expressed CTLA-4. Foxp3$^+$ Treg cells can inhibit autophagy in DCs by signaling with CTLA-4 to CD80 and CD86 on DCs, activating the phosphoinositide 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway, which downregulates transcription of *Lc3b* and induces nuclear exclusion of Foxo1, thus reducing autophagy in these cells.[30] Additionally, Treg cells upregulate expression of CTLA-4 following TCR engagement, which then leads to the downregulation of CD80 and CD86 on DCs through a mechanism that is at least in part mediated by the *trans*-endocytosis of these costimulatory molecules.[31–35] Another group has shown that CD80 on DCs binding to CTLA-4 expressed by *in vitro*-induced Treg cells or the fusion protein (CTLA-4-Fc) leads to the phosphorylation of STAT3 and subsequent nuclear factor-kappa beta (NF-κB)-dependent downregulation of CD80 and CD86 gene transcription in

DCs.[36] Furthermore, human DCs can secrete CTLA-4, which binds to and downregulates CD80 and CD86 molecules on bystander DCs, resulting in decreased $CD8^+$ T cell activity.[24] This finding further illustrates the complex nature of interactions between DCs and T cells while also raising the possibility that a similar secretory mechanism may be additionally carried out by CTLA-4 expressed by Treg cells to influence DCs.

B. Indoleamine 2,3 Dioxygenase

Another important immunomodulatory mechanism facilitated by CTLA-4-CD80/86 axis is the induced expression of the tolerogenic enzyme indoleamine 2,3 dioxygenase (IDO) in DCs that is triggered through the engagement of CD80/86 by CTLA-4 expressed in $Foxp3^+$ $CD25^+$ Treg cells.[37–39] IDO is the rate-limiting enzyme for tryptophan catabolism that is expressed by DCs and it exerts tolerogenic effects on T cell responses by producing pro-apoptotic tryptophan metabolites and depleting the tryptophan available for surrounding T cells.[37,40–42] Mice with a conditional deletion of CTLA-4 in $Foxp3^+$ cells were found to have a 50% reduction of IDO-expressing $CD11c^+$ DCs.[43] This pathway is also important in humans because CTLA-4 expressed in human Treg cells signals to human monocyte-derived DCs through CD80 and CD86, resulting in the expression of the active form of IDO.[44] When $CD8^+$ T cells are cultured with IDO^+ DCs, the combination of tryptophan deprivation and the presence of tryptophan metabolite kynurenine promotes downregulation the TCR ζ-chain, leading to decreased functionality of T cells.[45] This downregulation is dependent on the stress-response kinase GCN2 because this effect is not seen in $CD8^+$ T cells from $Gcn2^{-/-}$ mice.[45] Furthermore, IDO can lead to the direct conversion of Foxp3-expressing peripheral Treg (pTreg) cells through the production of kynurenine, which can activate the transcription factor aryl hydrocarbon receptor (AHR) and thus induce expression of Foxp3 in T cells.[46] Furthermore, activation of AHR in DCs by other ligands can induce IDO expression and retinoic acid (RA) production by DCs, thus promoting their tolerogenic functions.[47–49] IDO-derived tryptophan metabolites can also act on the DCs to increase their expression of the immunomodulatory molecules ILT3 (LILRB4) and ILT4 (LILRB4), which themselves play a role in the induction of Treg and IL-10-producing regulatory type 1 T (Tr1) cells.[50–53] Expression of these molecules by DCs can also be increased upon interactions with $CD8^+$ Treg cells, leading to the induction of $CD4^+$ T cell anergy.[54]

C. TGF-β

There are also several secreted factors that mediate the diverse functions carried out by DCs, such as the cytokine TGF-β1, which is produced in an inactive form. Integrin $α_vβ_8$ activates TGF-β1 by binding to the propeptide of TGF-β1 (LAP-β1) and associating with membrane-type 1- matrix metalloprotease (MT1-MMP) in order to cleave the pro-peptide into its active form.[55] Mice lacking expression of integrin $α_vβ_8$ in DCs develop inflammatory bowel disease and autoimmunity, further demonstrating the *in vivo* importance of this immunomodulatory molecule.[56] In the canonical signaling pathway, binding of mature TGF-β1 to either TGF-βRIII or the heterodimeric receptor consisting of the TGF-βRI and TGF-βRII subunits results in the dimerization of SMAD2 and SMAD3, which subsequently form a complex with SMAD4 that can translocate to the nucleus and induce gene transcription.[57] Non-canonical signaling is mediated by various kinase pathways, including the Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and extracellular

signal-regulated kinase (ERK) pathways.[57] TGF-β1 signaling is critical for Treg cell differentiation due to its ability to induce Foxp3 gene expression.[58,59]

In addition to influencing Treg cell differentiation, TGF-β1 is also important for the development of Th17 cells *in vivo*. Analogous to its function of activating TGF-β1 to its active form to allow the development of Treg cells, integrin $\alpha_v\beta_8$ is also required to activate TGF-β1 to promote the development of Th17 cells. Mice lacking integrin $\alpha_v\beta_8$ expression in CD11c^{+} DCs do not develop experimental autoimmune encephalomyelitis (EAE), a well-established mouse model of multiple sclerosis, due to an impairment in the development of Th17 cells, which play a pathogenic role in EAE.[60] Additionally, mice lacking integrin $\alpha_v\beta_8$ expression in DCs are protected against infection with the helminth *Trichuris muris* due to increased expression of IL-13 as a result of more efficient differentiation of Th2 cells that are protective against helminth infection.[61] Mice with a DC-specific conditional knockout of the β_8 integrin subunit are also unable to generate $CD4^+CD8\alpha\alpha^+$ intra-epithelial lymphocytes.[62] These studies provide further evidence that DC-expressed integrin $\alpha_v\beta_8$ plays an important role in controlling the balance of T cell subsets by activating TGF-β1 in order to fight infections or maintain tolerance by promoting the differentiation of Th17 or Treg cells.[63]

D. Retinaldehyde Dehydrogenase

In addition to TGF-β1, another important soluble factor shown to modulate the differentiation of Treg cells is RA, which is generated during the metabolism of vitamin A by several related aldehyde dehydrogenase enzymes, including retinaldehyde dehydrogenase type 2 (Raldh2). In splenic DCs, TLR2 signaling can induce expression of Raldh2 and consequently the metabolism of RA through the enzyme's actions. Together with IL-10, RA is able to promote the development of Foxp3^{+} Treg and Tr1 cells.[13] RA can inhibit Th17 cell differentiation and also promote Treg cell differentiation in combination with TGF-β1.[64] The precise mechanism by which RA enhances Foxp3 expression in differentiating T cells is still unclear, although it has been shown to be independent of IL-2, STAT3, and STAT5.[65] RA also helps to promote Treg cell development by promoting Foxp3 expression that would normally be inhibited in the presence of CD28 co-stimulation from CD80/86 on DCs or an agonistic αCD28 antibody.[66] RA further enhances the tolerogenic gut environment by inducing the expression of the gut-homing molecules integrin $\alpha_4\beta_7$ and CCR9 on the developing Treg cells, an effect mediated by lamina propria DCs.[67,68] This immunomodulatory axis demonstrates that multiple regulatory mechanisms are in place to allow DCs and T cells to maintain the appropriate level of tolerance, depending on the environmental context.

E. BTLA–HVEM

In addition to the crucial signaling axes described above, another immunomodulatory pathway that is critical for the partnership between DCs and T cells involves the molecules B and T lymphocyte associated (BTLA) and herpesvirus entry mediatory (HVEM), which have also been shown to have bidirectional signaling capabilities. BTLA is a receptor of the immunoglobulin superfamily that was first identified as an inhibitory receptor due to its three immunoreceptor tyrosine-based inhibition motifs (ITIMs) which, when

phosphorylated, can recruit Src homology domain 2 (SH2)-containing protein tyrosine phosphatases, SHP-1 and SHP-2, which generally exert inhibitory effects within the cell. [69–71] BTLA was originally shown to be a negative regulator of T cell activation, but its functions have since proven to be more varied with roles in B cells and DCs.[71,72] BTLA interacts with the tumor necrosis factor receptor superfamily (TNFRSF) member HVEM, which is expressed in naive T cells and downregulated following activation.[73–75] HVEM has also been shown to be expressed on DCs.[76,77] HVEM can additionally interact with HSV-1 glycoprotein D (gD), lymphotoxin α (LTα3), LIGHT (TNFSF14), and CD160.[71,78–80] Upon binding to BTLA, HVEM induces NF-κB RelA expression via TNF receptor associated factor 2 (TRAF2) and pro-survival signals within activated T cells.[73,81] The functional results of the interactions between BTLA and HVEM can be either inhibitory or activating, depending on the conditions and type of cell that expresses BTLA and HVEM. Such interactions have been shown to influence $CD8^+$ T cell survival, memory formation, Treg cell functions, and DC homeostasis[77,82–88] For example, $CD8^+$ T cells transferred into $Btla^{-/-}$ mice fail to expand and survive in response to infection with either *Listeria monocytogenes* or vaccinia virus.[82,86] The memory formation of these $CD8^+$ T cells is dependent on HVEM signaling within the T cells that is induced by BTLA-expressing DCs. [86] Conversely, BTLA signaling in $CD8^+$ T cells, presumably induced by HVEM-expressing DCs (although this was not directly examined), reduces their ability to expand and form memory responses.[85] The HVEM–BTLA pathway also regulates DC homeostasis through an unclear mechanism, but due to ability of these molecules to signal in both directions, it is possible that this effect is mediated by T cells expressing either molecule, which can bind to its partner on DCs.[77]

BTLA and HVEM have both been shown to play an important role in protection from autoimmunity. Mice deficient in either BTLA or HVEM are susceptible to EAE.[69,89] Recently, BTLA–HVEM signaling has been shown to be critically important for pTreg cell differentiation.[72] To do so, BTLA signals through HVEM in naive T cells to increase phosphorylation of mitogen-activated protein kinase (MAPK) kinase (MEK) and expression of ETS1, which in turn increases transcription of *Cd5*. The specific functions of CD5 in these $CD5^{hi}$ T cells then enable induction of Foxp3 expression and conversion into pTreg cells by opposing mTOR activation mediated by effector differentiating cytokines.[72,90] Such DC-induced pTreg cells have crucial functions in mitigating autoimmunity, as shown in an EAE model.[91,92] The diverse functions mediated by these molecular partners allow for fine-tuning of immune responses by DCs and T cells in multiple immune settings, something that must be appreciated in the design of immunotherapies targeting BTLA and HVEM.

F. PD-1–PD-L1/2

Other cell-membrane-bound molecules also contribute to promotion of tolerance via Treg cell induction, such as programmed death ligand-1 (PD-L1). PD-L1 is a member of the B7 family that is constitutively expressed in DCs, macrophages, mast cells, B cells, T cells, and some tumor cells that can bind to B7–1 (CD80) and programmed death-1 (PD-1) on activated T cells.[93–96] PD-1 is a member of the Ig superfamily and contains both an ITIM and ITSM (immunoreceptor tyrosine-based switch motif) that contribute to its inhibitory functions by recruiting SHP-1 and SHP-2 phosphatases.[95,96] PD-L1 signaling through PD-1

reduces the phosphorylation of Akt, mTOR, S6, and ERK2 while upregulating PTEN expression, the combination of which allows for efficient Treg differentiation.[97] PD-L1 signaling can lead to the formation of iTreg cells in combination with TGF-β1.[97,98] PD-1 signaling has been shown to be an important mechanism for pTreg cells development *in vivo* as well.[99] To enhance this process, CD11c^{+} DCs can upregulate PD-1 in naive T cells during priming by signaling with PD-L1 and the related molecule PD-L2, promoting the development of Foxp3^{+} Treg cells that are protective against autoimmunity such as in an EAE model.[100] However, the efficient induction of such anti-autoimmune pTreg cells also requires signals mediated by HVEM engaged by BTLA expressed on DCs.[72] As already discussed above, the resulting increase in the functions of CD5 in T cells inhibits mTOR, thereby limiting T cell sensitivity to effector cytokines and promoting pTreg cell differentiation.[90] Overall, the interactions between DCs and T cells are a dynamic process, allowing them to collaborate in order to promote tolerance.

The immunomodulatory functions of DCs can also regulate the balance of effector T cell subsets in order to refine the immune response to better protect against infections. A key example of this type of functionality is PD-L2, which binds to PD-1 with higher binding affinity than PD-L1 and has more limited expression that can be upregulated during inflammation on DCs, macrophages, mast cells, peritoneal B1 and memory B cells.[101–103] In a recent study, it was observed that patients infected with malaria had a decrease in the number of PD-L2[+] DCs and that patients with a higher ratio of PD-L2[+] to PD-L1[+] DCs had reduced parasitemia.[104] Using a murine model of malaria infection, they went on to show that PD-L2 on DCs played a protective role by outcompeting PD-L1 for PD-1 expressed by T cells, thus preventing T cell exhaustion and controlling the infection. They additionally used *in vitro* DC: T cell co-cultures to show that PD-L2 can increase the expression of CD3 and ICOS by T cells, an opposite effect of that observed to be mediated by engagement of PD-1 through PD-L1. This combination of effects led to more effective Th1 responses, which are critical for effective immunity against malaria.[104] That study highlights the idea that immunomodulatory molecules have varied context-dependent functions, some of which may still be unknown.

As its name implies, PD-L1 signaling can additionally induce programmed cell death, specifically apoptosis, of PD-1^{+} T cells.[105] The pro-apoptotic function of DC-expressed PD-L1 is likely mediated by the pro-apoptotic molecule Bim, although this mechanism has not been directly examined for interactions between DCs and T cells.[106] PD-L1–PD-1 interactions have also been shown to shorten the time of interaction between DCs and T cells, which prevents disease in a model of autoimmune diabetes.[107] PD-L1^{+} DCs can also downregulate TCR expression in CD8^{+} T cells by signaling through PD-1 to upregulate Cbl-b E3 ubiquitin ligase in CD8^{+} T cells, preventing hyperactivation and autoimmunity.[108] Furthermore, conditional deletion of PD-L1 in DCs limits EAE severity by reducing antigen-specific CD4^{+} T cell activation in the early stages of EAE in addition to inhibiting differentiation of T follicular helper and regulatory (T$_{FH}$ and T$_{FR}$) cells.[109]

G. OX40–OX40L

An additional member of the TNFRSF with diverse immunomodulatory functions is OX40 (CD134, TNFRSF4), which is expressed in a cell membrane form in activated CD4^{+} and CD8^{+} T cells.[110–112] Its ligand, OX40L (CD252, TNFSF4), is expressed in DCs and also macrophages, B cells, and endothelial cells.[113–116] OX40 signaling can influence several aspects of T cell biology, including proliferation, survival, and memory, by activating the PI3K and NF-κB pathways through TRAF molecules.[116] Although OX40 has been shown to skew T cells toward the Th2 phenotype by signaling through NFATc1 to upregulate expression of IL-4, its signaling can also help Th1 responses in the presence of certain cytokines.[116,117] OX40 signaling has also been shown to suppress Foxp3 expression in naive T cells, preventing their conversion to pTreg cells in the presence of TGF-β1.[118,119] However, OX40 signaling can also induce the proliferation of Treg cells, although the precise molecular mechanism by which this occurs still needs to be characterized.[120,121]

H. ICOS–ICOS-L

Similar to the OX40–OX40L axis, interactions between the cell-membrane-bound molecule inducible T cell costimulator (ICOS), which is a member of the CD28 family that is expressed in activated T cells, and its ligand, ICOS-L (B7RP-1, CD275, B7h, B7-H2), which is expressed in DCs, B cells, and macrophages, can result in functionally diverse responses.[122–124] Although other signaling molecules may be involved, ICOS signals in T cells are mostly mediated by PI3K and TBK1, which is a member of the inhibitor of NF-κB kinase (IKK) family.[125–127] In addition to its role in driving differentiation and cytokine production of Th1 and Th2 cells, this interaction can also promote tolerance by increasing the development of antigen-specific Treg and Tr1 cells.[17,128–133] Although the majority of research investigating the functions of ICOS signaling in T cells does not specify the cell type expressing ICOS-L, it has been shown that DC-expressed ICOS-L promotes the development of effective T cell-dependent antibody responses as well as IL-10-producing Tr1 cells.[134–136] ICOS–ICOS-L interactions may also be bidirectional because ICOS-L signaling induced by ICOS-Fc or ICOSIg in monocyte-derived DCs (moDCs) and bone marrow-derived dendritic cells (BMDCs) alters cytokine secretion and antigen presentation by these cells.[137,138]

I. CD27–CD70

Another pathway with varied functions that are crucial for the functional partnership between DCs and T cells involves CD70 and CD27. CD70, which can be expressed by DCs in response to signals from CD4^{+} T cells or the environment, is a cell-membrane-bound TNF superfamily (TNFSR) member that engages TNFRSF member CD27, which is expressed on T cells.[139–141] CD27 signals in T cells are mediated by TRAF2 and TRAF6, which in turn activate NF-κB and JNK.[142–144] Downstream, this signaling can increase expression of IL-12Rβ2 and T-bet in naive T cells and thus promote the differentiation of Th1 cells.[145] CD27 signaling also represses Th17 differentiation in developing T cells by suppressing expression of IL-17 and CCR6 at the transcriptional level via the JNK pathway as well as through epigenetic modifications.[146] Additionally, thymic medullary DCs that express CD70 signal to CD27^{+} thymocytes and promote survival of thymus-derived Treg

(tTreg) cells by inhibiting the mitochondrial apoptotic pathway.[147] In addition to mediating intracellular signaling upon engagement with CD70, CD27 expressed by B, T, or tumor cells has also been shown to reciprocally induce signals into CD70+ NK and B cells through the P13K/Akt and MEK pathways, raising the possibility that similar reverse signaling may occur in CD70+ DCs during their interactions with T cells.[148,149] For example, CD27+ tTreg cells inhibit Th1 responses by downregulating expression of CD70 in DCs.[150] The expression of CD70 by DCs can also be downregulated once it binds to CD27 through transcriptional regulation.[151]

In addition to its crucial roles in CD4+ T cell biology, the CD27–CD70 immunomodulatory axis is also vital for effective CD8+ T cell responses. DC-expressed CD70 has been implicated in the direct priming of CD8+ T cells as well as the expansion and survival of primed CD8+ T cells by signaling through CD27 in these T cells.[152–156] Furthermore, this pathway plays a critical role in the process that allows DCs to mediate CD4+ T cell help of CD8+ T cell responses. Expression of CD70 by DCs has been shown to be necessary for CD4+ T cell-helped CD8+ responses by instilling a specific gene transcription profile in developing CD27+ CD8+ T cells.[157]

J. CD40–CD40L

In addition to increasing expression of CD70 by DCs, CD4+ T cells help CD8+ T cell responses via CD40–CD40L interactions to modulate other aspects of DC biology. CD40 is TNFRSF member that can be expressed on DCs, where it is engaged by TNFSF member CD40L (CD154), which is pre-dominantly expressed by activated CD4+ T cells.[158–161] Like the other TNFSF members, CD40 signaling is mediated by the TRAF molecules, especially TRAF6, resulting in MAPK and JNK activation and subsequent changes in gene expression of various immunomodulatory molecules, such as CD80, CD86, and IL-12.[161] CD40–CD40L interactions are also important in the thymus, where CD40L+ CD4 single-positive thymocytes interact with CD40+ thymic DCs to promote upregulation of surface molecules CD40, PD-L1, CD86, CD200, and MHCII, as well as several other genes associated with DC functions to promote the formation of tTreg cells by CD40+ DCs.[162] CD40 and CD70-mediated signaling cooperate to promote clonal expansion of CD8+ T cells in response to CD40 engagement, an effect that is diminished when interaction between CD70 and CD27 are blocked.[163] T cells can further refine the Th1 response by increasing expression of CD70 in DCs expression by engaging DC-expressed CD40 during a concomitant treatment with poly I:C.[164,165]

K. IL-12 Family Cytokines

CD40 signaling can additionally induce the production of different cytokines by DCs. An important example of such cytokines is IL-12, the namesake member of the IL-12 family of cytokines that is composed of two subunits, IL-12p35and IL-12p40, that together form IL-12p70. Upon binding to its receptor, which consists of the IL-12Rβ1 and IL-12Rβ2 subunits, TYK2 (tyrosine kinase 2) and JAK2 (Janus kinase 2) are recruited, allowing for the activation of STAT4 and subsequent induction of interferongamma (IFN-γ) expression in Th1-differentiating T cells.[166] Expression of heterodimeric IL-12p70 is induced in response

to cross-linking of DC-expressed CD40 *in vitro*, but a microbial stimulus must be administered to achieve the same effect *in vivo*.[167]

Although not necessarily induced by CD40 signaling, DCs can also express other members of the IL-12 family of cytokines that carry out important immunomodulatory functions. One of these is IL-23, which is composed of the IL-12p40 and IL-23p19 subunits. Its receptor consists of the IL-12Rβ1 and IL-23R subunits and, after recruitment of TYK2 and JAK2, its signals are mediated by STAT2 and STAT4.[166] IL-23 plays an important role in Th17 cell biology by helping to maintain IL-17 expression.[168–170] Another IL-12 family member is IL-27, which is composed of the IL-27p28 and EBV-induced gene 3 (Ebi3) subunits. Its receptor (IL-27R) is also composed of two subunits: gp130 and WSX-1/TCCR (IL-27Rα), which recruit JAK1, JAK2, and TYK2 in order to activate STAT1 and STAT3.[166] IL-27 is produced by a variety of cells, including DCs in response to poly I:C.[171] IL-27 signaling can promote Th1 cell differentiation by inducing expression of T-bet and IL-12Rβ2 in a STAT1-dependent manner.[172,173] Furthermore, Foxp3+ Treg cells can induce the production of IL-27 and TGF-β1 by DCs, which synergistically promote the differentiation of Tr1 cells.[174] Specifically, IL-27 signals in T cells to induce expression of c-Maf, IL-21, and ICOS in order to promote differentiation of Tr1 cells.[175–177] Moreover, IL-27 signaling in DCs induces the expression of the ectonucleotidase CD39, an enzyme that degrades extracellular ATP to ADP and thus promotes a tolerogenic environment for developing T cells.[178] Tumor-infiltrating DCs also express CD39, which mediates their ability to inhibit T cell activation when cultured *in vitro*.[179] Another soluble factor that increases the tolerogenic capacity of DCs is vasoactive intestinal peptide (VIP), a neuropeptide secreted by T cells that can increase the ability of DCs to induce Treg cells.[180] These pathways highlight how DCs and T cells can work together using multiple interconnected immunomodulatory pathways to maintain immune homeostasis in a tightly regulated manner.

III. FUNCTIONAL SPECIALIZATION OF DC SUBSETS

Over the past few years, our knowledge about the development of various DC subsets has greatly expanded.[181–183] Briefly, DCs are divided into two main groups: conventional DCs (cDCs) and plasmacytoid DCs (pDCs). The cDC population can be further delineated into the cDC1 and cDC2 subsets on the basis of the transcription factors required for their development. The cDC1 subset, which requires the transcription factors Irf8, Id2, and Batf3 for development, can be distinguished by expression of XCR1 as well as CD8α, CD103, DEC205, CD24, and DNGR-1/CLEC9A.[181,182,184,185] The cDC2 lineage, which requires the transcription factor Irf4 for development, can be distinguished by expression of CD172a (SIRPα) in addition to CD11b, CD4, and DCIR2.[181,182,184,185] pDCs depend on the transcription factors Irf8 and E2–2 for their development and can be distinguished by their expression of B220, Siglec-H, and Bst2.[181,182,184,185] In addition to the rapid progress made in DC subset classification in recent years, our understanding of the functional importance of such delineations has also improved.

The immunomodulatory molecules discussed in section II highlight how DCs and T cells work together in a dynamic partnership, allowing them to control immune responses and maintain homeostasis. However, rather than affecting the functions of the entire population

of DCs, expression of these molecules can be specific to particular DC subsets and therefore can also help to explain the functional specialization attributed to them. Specifically, cDC1s have multiple mechanisms mediating their ability to promote Th1 and Treg cell differentiation (Fig. 2), whereas cDC2s can promote Th2 and Th17 differentiation (Fig. 3).[1,182] Additionally, both cDC1s and cDC2s can exert additional tolerogenic functions through multiple mechanisms (Figs. 2 and 3).[1] pDCs are important for antiviral responses in addition to promoting tolerance through various mechanisms.[186]

A. cDC1s

Various immunomodulatory molecules mediate the ability of cDC1s to promote Th1 responses. cDC1s from the spleen and lymph nodes are the predominant producers of the crucial Th1-polarizing cytokine IL-12 among DC subsets in response to microbial stimuli or to T cell-derived signals mediated through CD40.[167,187–190] Despite this, IL-12 is not the only molecule mediating Th1 differentiation by cDC1s, because *in vivo* targeting of antigen to DEC205$^+$ cDC1s, along with αCD40 and poly I:C, results in the induction of IFN-γ^+ T cells even in IL-12-deficient mice.[164] This is likely due to the signaling of CD70 and CD27 because the ability of cDC1s to induce Th1 differentiation is lost when CD70 is blocked, demonstrating the importance of this molecule in this process.[164,165] Another level of regulation that further refines the Th1 response is mediated by the upregulation of CD70 expression in cDC1s in response to engagement of CD40 and a concomitant treatment with poly I:C.[164,165]

In addition to Th1 responses, DC-mediated CD4$^+$ T cell help of CD8$^+$ T cell responses has recently been shown to specifically depend on XCR1$^+$ cDC1s because mice deficient in this subset have diminished proliferation, effector differentiation, and memory function in CD8$^+$ T cells.[191] As discussed above, CD70 is important for this process, even though cDC1s and cDC2s express similar levels of this molecule in the steady state.[192] With that in mind, another aspect of CD8$^+$ T cell responses is controlled by CD70$^+$ cDC2s, which promote the expansion of CD8$^+$ T cells in response to influenza infection by signaling through CD27 on the CD8$^+$ T cells.[193] Other aspects of CD8$^+$ T cell function are mediated by cDC1s independently of CD4$^+$ T cell help. For example, BTLA$^+$ cDC1s promote survival and memory formation of CD8$^+$ effector T cells in response to vaccinia virus and *Listeria monocytogenes* infections by signaling through HVEM in CD8$^+$ T cells.[82,86]

Although it was originally thought that all DCs were able to induce pTreg cell differentiation in the steady state, increasing evidence has made it clear that cDC1s may be responsible for Treg cell differentiation in the periphery.[1,98,194–196] When antigen is targeted to all CD11c$^+$ DCs *in vivo* in the steady state, pTreg cells are formed at a much lower frequency than when antigen is selectively targeted to DEC205$^+$ cDC1s, even though they comprise only a minor portion of all CD11c$^+$ DCs.[72] This finding was expanded upon to show that this function of DEC205$^+$ cDC1s is due to the specific expression of BTLA, which signals through HVEM in naive T cells to induce pTreg cell conversion.[72] CD8α^+DEC205$^+$ cDC1s also express more TGF-β1 and latent-TGF-β binding protein 2 (Ltbp2) at the transcriptional level.[194] In addition to this, CD103$^+$ and CD8α^+ cDC1s are able to activate TGF-β1 to its active form through the activity of the integrin $\alpha_v\beta_8$, helping to promote the differentiation of Treg cells,

and the β_8 integrin subunit has shown to be specifically expressed by Irf8-dependent cDC1s in mice.[62,197–199] CD103^{+} cDC1s from the mesenteric lymph nodes or small intestine lamina propria are able to more efficiently promote *de novo* differentiation of Treg cells than CD103^{neg} cDC2s through their specific expression of Raldh2, although this subset-specific difference is lost when exogenous TGF-β1 is added to the cultures.[62,67,200,201] Further, thymic medullary CD8α[+] cDC1s promote survival of tTreg cells by inhibiting the mitochondrial apoptotic pathway through CD70–CD27 interactions.[147]

cDC1s are also the predominant source of the tolerogenic enzyme IDO, helping this subset to further promote tolerogenic responses through the multiple effects of tryptophan metabolism discussed in section II.B.[39–41,202] Additionally, cDC1s are also the main source of the cytokine IL-27 in response to poly I:C, which helps them to promote Tr1 cell differentiation.[171] In another tolerogenic function, Batf3-dependent cDC1s in the renal lymph node signal through PD-L1 to induce apoptosis of PD-1^{+} CD8^{+} T cells, promoting cross-tolerance to circulating antigens filtered by the kidneys.[105] Expression of PD-L1 on CD103^{+} cDC1s is also important for successful checkpoint blockade therapy with αPD-L1 monoclonal antibodies.[203] By expanding this population of DCs in the tumor with FMS-like tyrosine kinase 3 ligand (Flt3L) and poly I:C, the investigators showed that tumor-infiltrating CD8^{+} T cells were better able to control tumor growth upon αPD-L1 therapy, showing the importance of this pathway for anti-tumor responses.[203]

B. cDC2s

Irf4-dependent cDC2s have been shown to play a key role in the development of Th17 responses through their production of several different cytokines. Intestinal CD103^{+}CD11b^{+} and lung CD11b^{+} cDC2s are crucial sources of IL-6 and IL-23p19, which promote Th17 differentiation in this environment.[204–206] Additionally, cDC2s can *trans*-present IL-6 in complex with IL-6Rα, allowing them to signal to T cell-expressed gp130 which subsequently induces STAT3 phosphorylation and pathogenic Th17 cell differentiation, a process that is required for the development of EAE.[207] This specialization is shared with other cDC2s that may frequently come in contact with the commensal and pathogenic microorganisms, such as dermal CD301b^{+} cDC2s that also preferentially produce IL-23.[208,209] Consistently, in response to αCD40 or LPS stimulation cDC2s from the mesenteric lymph nodes also express more IL-23p19 and IL-6 at the transcriptional level.[200] This is functionally important during infection because mice lacking cDC2s are unable to mount a successful Th17 response to infection with the fungus *Aspergillus fumigatus*.[206]

cDC2s have clearly been shown to play an important role in Th2 cell differentiation, although specific mechanisms are not always entirely clear. Mice lacking Irf4-dependent cDC2s fail to develop protective Th2 cell responses against infection with *Nippostrongylus brasiliensis*.[210,211] Mice lacking expression of the transcription factor Klf4 in cDC2s fail to mount a protective Th2 cell response to the helminth *Schistosoma mansoni* while remaining unsusceptible to house dust mite (HDM)-induced allergic inflammation.[212] HDM-induced allergic inflammation is mediated by Th2 cell differentiation by Irf4-dependent cDC2s that secrete IL-10 and IL-33.[213,214] In an additional mechanism controlling Th2 cell differentiation, OX40L expression can also be induced in CD11b^{+} intestinal cDC2s in

response to *Schistosoma mansoni* soluble egg antigens, helping to promote a Th2 response against the antigens.[215] OX40L expression can be upregulated on lamina propria-derived CD103^{+} cDC1s in the mesenteric lymph nodes following administration of cholera toxin in a murine model of allergic sensitization to dietary antigens. This upregulation leads to more efficient Th2 differentiation by increased expression of Th2-differentiating cytokines, showing a compensatory redundancy in subset-specific role depending on different environmental signals.[216] Further, Irf4-dependent cDC2s from skin-draining lymph nodes that are marked by expression of PD-L2 drive Th2 responses from effector and memory CD4^{+} T cells *in vivo*, although this effect does not appear to be dependent on PD-L2 functionality itself.[211]

Although cDC1s play a dominant role in the *de novo* induction of pTreg cells, some pTreg cells can be induced by cDC2s that also have a function in the expansion of existing tTreg cells.[194,196,217,218] This expansion is due to cDC2-mediated proliferation of existing Treg cells through a contact-dependent mechanism that also requires IL-2 provided by CD4^{+} conventional T cells.[194,219] The immunomodulatory molecules controlling this contact-dependent proliferation have not yet been clearly identified, although *in vitro* experiments with BMDCs suggest that OX40L may be required.[120] In addition to expanding existing Treg cells, certain subsets of cDC2s in the skin and oral cavity can directly promote pTreg cell differentiation via RA, which is produced by these DCs through the enzymatic activity of Raldh2.[220,221] Specificity of aldehyde dehydrogenase activity is not seen in lymph-borne DCs derived from the intestine because all subsets have the ability to generate RA, which subsequently induces gut-homing CCR9 expression in T cells.[222] Interestingly, a role for integrin $\alpha_v\beta_8$ in the induction of Treg cells in humans has been shown, although its expression was specifically induced by pro-inflammatory signals in the human intestinal CD1c^{+} cDC2 counterpart, highlighting the more complex possible roles of site-specific DC activation in tolerance.[223]

In addition to their effects on Treg cells, cDC2s also play a tolerogenic role in non-obese diabetic (NOD) mice by increasing *Zbtb32* expression in T cells upon specific delivery of antigen.[218] Zbtb32 is a transcription factor that decreases proliferation and IFN-γ production when overexpressed in T cells from these mice.[218] Although that study shows that cDC2s play an important role in the establishment of tolerance, the conflicting evidence on the specific roles of cDC2s in regard to pTreg cell induction warrants further investigation of these processes and the controlling mechanisms.

C. pDCs

Although they do not present antigen as efficiently as cDCs, pDCs are able to produce large amounts of type I IFNs upon recognition of viral particles by TLR7 or TLR9.[224,225] This production of type I IFN supports the development of effective anti-viral CD8^{+} T cell responses by helping XCR1^{+} cDC1s to more efficiently cross-present antigens to CD8^{+} T cells.[226] pDCs also have important roles in the regulation of tolerogenic T cell responses via multiple immunomodulatory mechanisms.[186] pDCs promote Treg cell differentiation through their expression of multiple immunomodulatory molecules in the steady state or in response to various stimuli, some of which include Raldh, IDO, PD-L1, ICOS-L, and TGF-

β1.[17,135,202,227–233] IDO expression can be induced in pDCs following engagement of pDC-expressed CD200R by CD200, a widely expressed cell surface glycoprotein.[230] Additionally, expression of PD-L1 in pDCs is induced by IL-27.[234] In addition to the tolerogenic functions described in section II.B that are mediated by its enzymatic activity, IDO has also been shown to function as a signaling molecule in pDCs.[229] Upon TGF-β1 signaling, ITIMs on IDO are phosphorylated by Fyn kinase, allowing the molecule to activate the non-canonical NF-κB pathway and recruit SHP proteins, leading to increased expression of IDO, TGF-β1, and type I IFNs.[229] pDCs further contribute to tolerance by promoting the development of IL-10-producing CD4$^+$ and CD8$^+$ T cells that can suppress primary T cell responses.[135,235]

A recently described pathway utilized by pDCs for the maintenance of tolerance utilizes the neuronal guidance molecules Neuropilin-1 (Nrp1) and Semaphorin-4a (Sema4a).[236] Engagement of Treg cell-expressed Nrp1 by Sema4a expressed on intratumoral pDCs results in a PTEN-mediated reduction of Akt phosphorylation and increased nuclear localization of the transcription factor Foxo3a, thus promoting functional stability of Treg cells.[236] Induction of Nrp1 signaling in Treg cells by Sema4aIg in mice with B16 melanoma tumors promotes expression of IFN-γ and IFN-γR in Treg cells, thus reducing their suppressive function and therefore tumor size.[237] Interestingly, Sema4a is also expressed by cDCs and can interact with CD72 and Tim-2 to promote T cell activation.[238,239] This finding further promotes the idea that it is necessary to study the effects of these immunomodulatory pathways mediated by different DC subsets because the functional outcome may differ depending on cell type or environment.

IV. CONCLUSIONS

Our knowledge of immunomodulatory mechanisms has greatly increased in recent years, resulting in a better appreciation of the dynamic and tightly regulated functional partnership between DCs and T cells that govern effective immune responses to pathogens or tumors while also maintaining tolerance. Although the majority of research has focused on how DCs modulate T cell responses, it is clear that T cells can affect DC functionality in turn. Several of the molecules discussed here also have bidirectional signaling capacities or can be expressed on either cell type. Further investigations will be required to determine how these interactions between immunomodulatory molecules on DCs and T cells affect both types of cell in order to fully understand how these cells work together to orchestrate immune homeostasis. This will also help in the development of more precise therapies that target the immunomodulatory functions of DCs to treat cancer, autoimmunity, or infection.

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ABBREVIATIONS:

APC   antigen-presenting cell

BMDC	bone marrow-derived dendritic cell
BTLA	B and T lymphocyte associated
CTLA-4	cytotoxic T-lymphocyte antigen 4
cDC	conventional dendritic cell
DC	dendritic cell
EAE	experimental autoimmune encephalomyelitis
HVEM	herpesvirus entry mediatory
ICOS	inducible T cell costimulatory
IDO	indoleamine 2,3 dioxygenase
ITIM	immunoreceptor tyrosine-based inhibition motif
iTreg	*in vitro*-induced (or inducible) regulatory T cell
MHC	major histocompatibility complex
moDC	monocyte-derived dendritic cell
mTOR	mechanistic target of rapamycin
PD-1	programmed death-1
PD-L1/2	programmed death ligand-1/2
pDC	plasmacytoid dendritic cell
pTreg	peripheral regulatory T cell
RA	retinoic acid
Raldh	retinaldehyde dehydrogenase
SHP-1/2	Src homology domain 2-containing protein tyrosine phosphatase ½
TCR	T cell receptor
TGF-β	transforming growth factor beta
TNFRSF	tumor necrosis factor receptor super-family
TNFSF	tumor necrosis factor superfamily
Tr1	regulatory type 1 T cell
TRAF	TNF receptor-associated factor
Treg	regulatory T cell
tTreg	thymus-derived regulatory T cell

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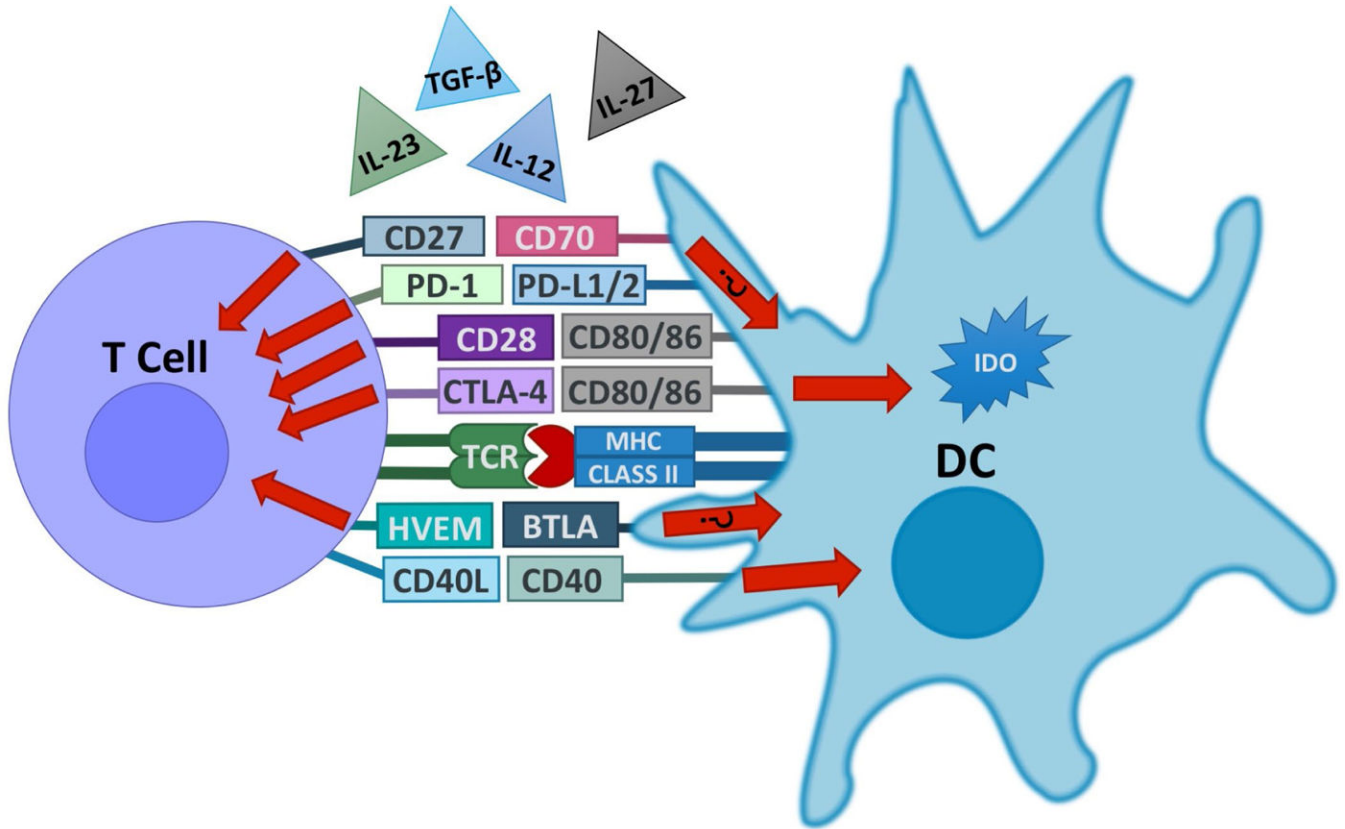
FIG. 1:

DCs and T cells form a functional partnership. DCs and T cells express a variety of surface molecules that work together as ligands and receptors in order to control various aspects of the immune response. Some of these pathways, such as BTLA–HVEM and CD27–CD70, have been shown to induce bidirectional signaling, although the impact of such bidirectional interactions between DCs and T cells remains mostly unclear at this point. In addition, DCs secrete or activate a variety of cytokines that influence T cell differentiation and proliferation. DCs upregulate expression of the CD70 and IL-12 in response to CD40 signaling induced by T cell-expressed CD40L. DCs can also produce the tolerogenic tryptophan-catabolizing enzyme IDO in response to signals mediated by CTLA-4 in T cells.
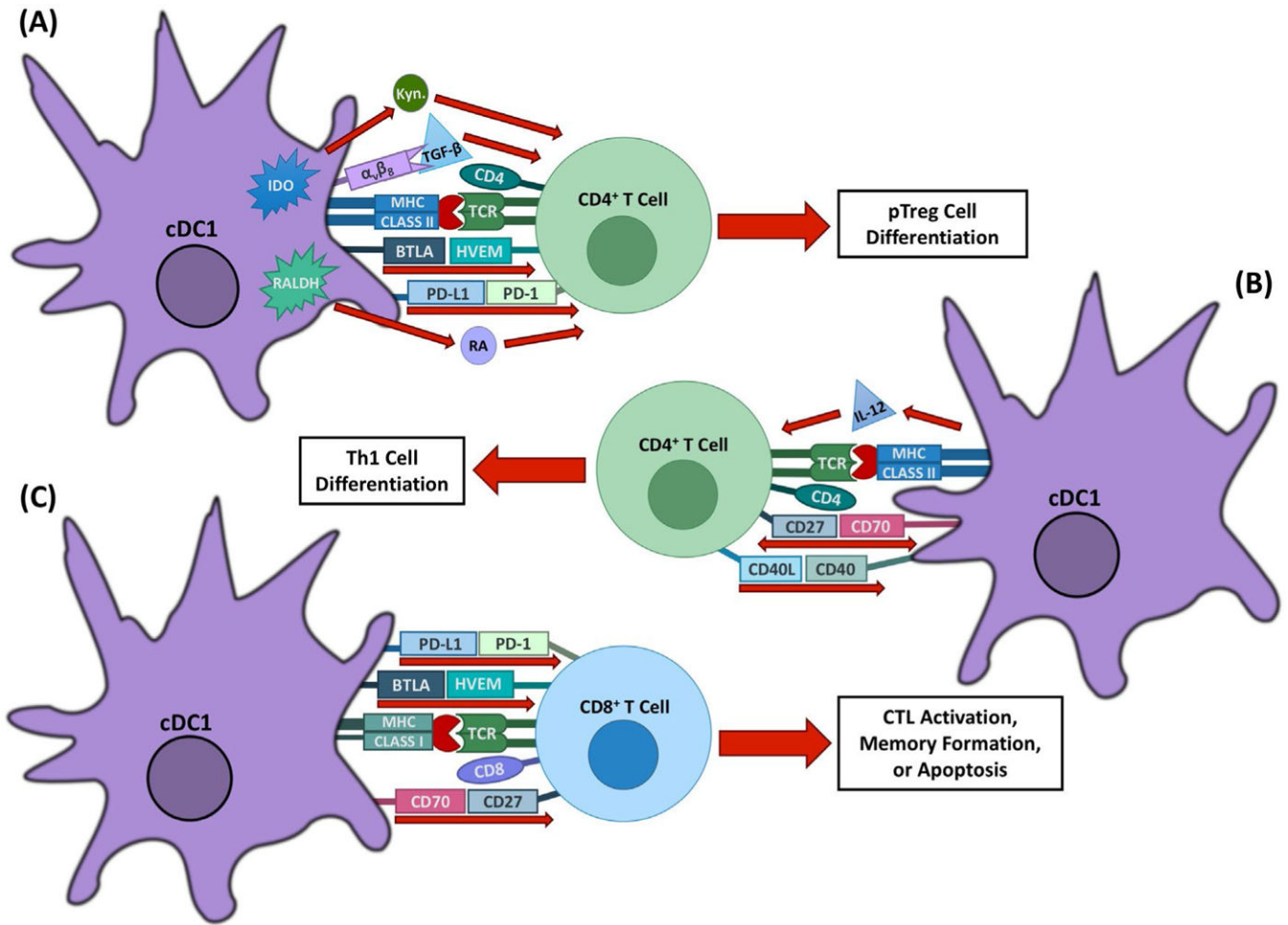
FIG. 2:

Immunomodulatory mechanisms of cDC1s. cDC1s are important for the induction of Th1 and tolerogenic T cell responses through several mechanisms. (A) cDC1s mediate T cell tolerance through several mechanisms, including pTreg induction by BTLA–HVEM, PD-L1–PD-1, RA, and TGF-β signaling. Expression of the enzyme IDO in response to CTLA-4–CD80/86 signaling also promotes tolerance through tryptophan deprivation and the production of metabolites, including kynurenine. (B) cDC1-expressed IL-12 and CD70, which are upregulated in response to CD40 signaling, work together to promote Th1 differentiation from naive CD4+ T cells. (C) cDC1s can promote CD4+ T cell-dependent expansion and effectiveness of CD8+ T cell responses through CD70–CD27 interactions. BTLA–HVEM signaling additionally plays a role in memory formation of CD8+ T cells in response to both viral and bacterial infections. cDC1s can also induce apoptosis of CD8+ T cells through PD-L1–PD-1 signaling.
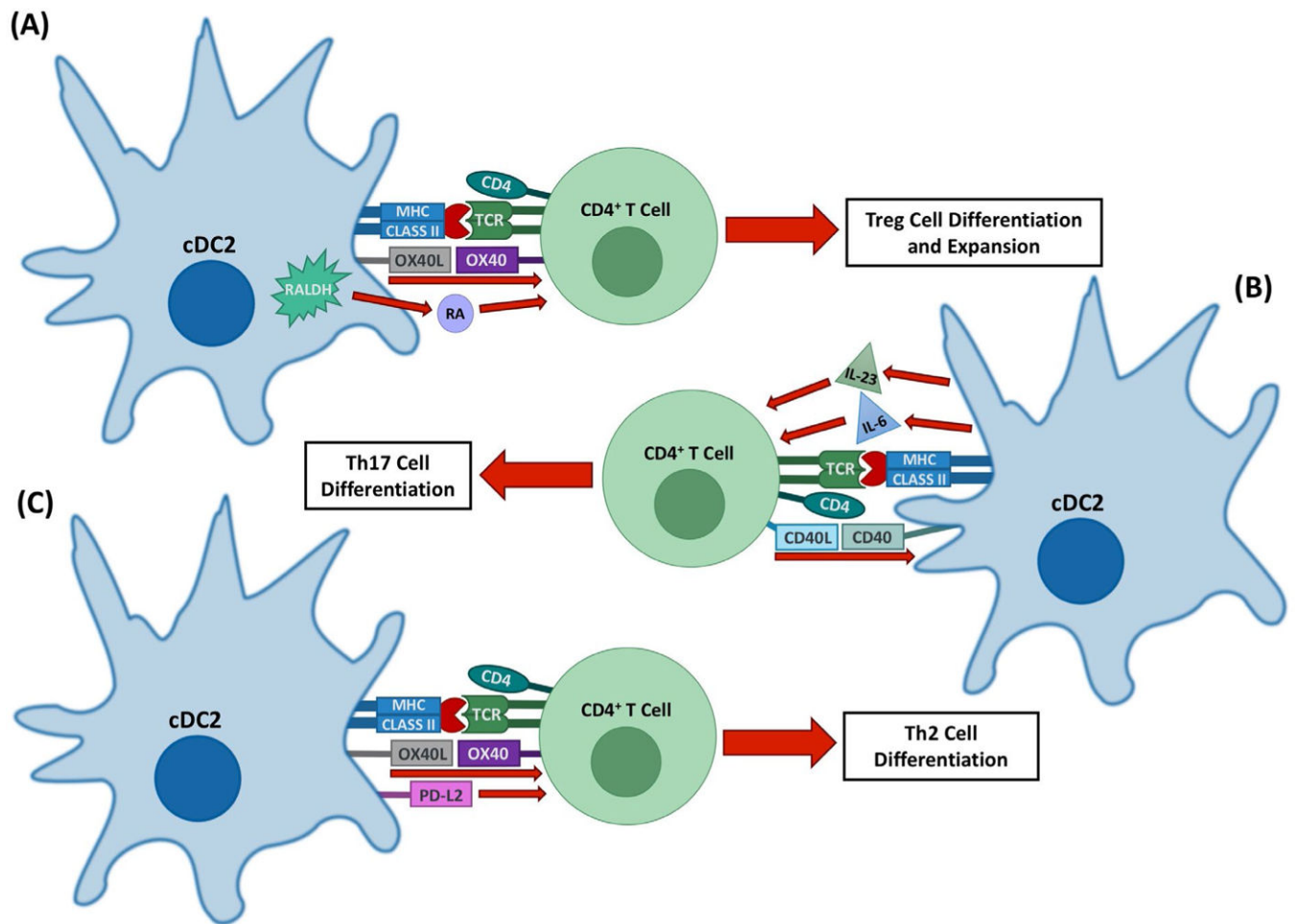
FIG. 3:

Immunomodulatory mechanisms of cDC2s. cDC2s are important for the induction of Th2 and Th17 responses as well as some aspects of tolerogenic T cell responses through several mechanisms. (A) cDC2s can promote the expansion of Treg cells, potentially through OX40 signaling. They also promote pTreg cell formation in some environments through their production of RA by Raldh2. (B) cDC2s are the main source of the Th17-polarizing cytokines IL-23 and IL-6, the expression of which can be upregulated by CD40 signaling. (C) cDC2 promote Th2 responses through OX40-L–OX40 signaling as well as through the production of Th2-polarizing cytokines. PD-L2 may also play a role in Th2 differentiation.