Peripheral immune tolerance requires a controlled balance between the maintenance of self-tolerance and the capacity to engage protective immune responses against pathogens. Dendritic cells (DCs) serve as sentinels of the immune system by sensing environmental and inflammatory signals, and play an essential role in the maintenance of immune tolerance. To achieve this, DC play a key role in dictating the outcome of immune responses by influencing the balance between inflammatory or Foxp3\(^+\) regulatory T (T\(_{reg}\)) cell responses. At the heart of this immunological balance is a finely regulated DC and T\(_{reg}\) cell crosstalk whereby T\(_{reg}\) cells modulate DC phenotype and function, and DC drive the differentiation of Foxp3\(^+\) T\(_{reg}\) cells in order to control immune responses. This review will focus on recent advances, which highlight the importance of this bidirectional DC and T\(_{reg}\) cell crosstalk during the induction of tolerance and organ-specific autoimmunity. More specifically, we will discuss how T\(_{reg}\) cells modulate DC function for the suppression of inflammatory responses and how DC subsets employ diverse mechanisms to drive differentiation of T\(_{reg}\) cells. Finally, we will discuss the therapeutic potential of tolerogenic DCs for the induction of tolerance in autoimmune diseases.

**Keywords:** Foxp3, immunity, suppression, tolerance, tolerogenic DC

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**INTRODUCTION**

Immune tolerance consists of two main processes, namely central and peripheral tolerance. Central tolerance takes place in the thymus where most of the self-reactive T cells are deleted at an immature stage of their development (Bluestone, 2011). Despite negative selection, self-reactive T cells can escape thymic clonal deletion, and subsequently provoke autoimmune diseases such as type 1 diabetes (T1D), multiple sclerosis (MS), and inflammatory bowel disease (IBD) unless they are controlled by one of many peripheral mechanisms (Sakaguchi et al., 1995).

**REGULATORY T CELLS ARE MAJOR MEDIATORS OF PERIPHERAL SELF-TOLERANCE**

In order to ensure tolerance induction of such auto-reactive T cells in the peripheral immune system, a number of mechanisms including a network of regulatory T (T\(_{reg}\)) cells exist to achieve this function. T\(_{reg}\) cells constitute 1–10% of thymic and peripheral CD4\(^+\) T cells in humans and mice, and arise during a thymic selection (Sakaguchi, 2000). They are characterized by the constitutive expression of the IL-2Ra chain (CD25) and expression of the forkhead winged helix transcriptional regulator Foxp3 (Hori et al., 2003). The importance of Foxp3 has been demonstrated by natural mutations of the foxp3 gene that result in a loss of T\(_{reg}\) cell function and the development of severe autoimmune diseases, including T1D, in scurfy mice and IPEX patients (Bennett et al., 2001; Chang et al., 2006; d’Hennezel et al., 2009). T\(_{reg}\) cell population can be divided into the naturally occurring Foxp3 T\(_{reg}\) population (here defined as T\(_{reg}\)) and any of many inducible T\(_{reg}\) cell populations (here defined as iT\(_{reg}\)), that are derived in the periphery from CD4\(^+\) Foxp3\(^-\) precursors upon activation in presence of differentiating signals like TGF-\(\beta\) and IL-10 (e.g. Th3, Tr1 cells) (Haribhai et al., 2011; Pot et al., 2011).

**DENDRITIC CELLS DICATE THE BALANCE BETWEEN TOLERANCE AND IMMUNITY**

Numerous studies show that different cell populations of the innate immune system such as dendritic cells (DCs), macrophages, and natural killer cells, and \(\gamma\delta\) T cells can regulate tolerance induction (Lueben et al., 2010). DCs represent a heterogeneous population of bone marrow-derived cells and are the most potent antigen presenting cells (APCs) (Banchereau and Steinman, 1998; Shortman and Naik, 2007). DCs are derived from multiple lineages, have a distinct stage of development, activation, and maturation state (Banchereau and Steinman, 1998; Steinman et al., 2003). DCs exist as a distinct subset and differ in their ontology, surface molecule expression, and biological functions (Banchereau and Steinman, 1998; Steinman and Nussenzweig, 2002). These factors seems to determine the T cells polarizing signals and type T cells responses induced by DCs namely Th1, Th2, Th17, or T\(_{reg}\) cells. Although all DCs are able to prime T cells, they differ in their in vivo niches, migration, function, and requirements.
from the environment for their generation and activation (Shortman and Naik, 2007). DCs are divided into conventional, myeloid, or plasmacytoid DC (pDC) subsets. In mice, three main subsets of conventional CD11c+ DCs have been identified in the spleen and lymph nodes, namely the CD8+, CD4+CD8−, and CD4−CD8+ DCs (Vremec et al., 2000). Lymph nodes contain two additional DCs subsets; skin-derived Langerhans cells and tissue interstitial DCs that arrive from the periphery through the lymphatic circulation (Vremec et al., 2000).

Dendritic cells receive the maturation signals through the pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) receptors that detect certain microbial and tissue damage signals via activation of nuclear factor-κB (NF-κB) and interferon regulatory factors (IRF) families (Maldonado and von Andrian, 2010). Upon activation, DCs up-regulate a wide variety of gene products involved in antigen presentation and costimulation such as MHC II, CD86, CD80, OX40-L, inducible co-stimulator (ICOS) ligand as well cytokines involved in the modulation of effector function such as IL-1β, IL-2, IL-6, IL-8, IL-12, and IL-18 (Maldonado and von Andrian, 2010). These changes are required for DCs to initiate a three-step T cell activation process: MHC molecules displaying cognate peptide (signal 1), co-stimulatory signal expression (signal 2), and cytokine production by DCs (signal 3).

While potentially capable to initiate inflammatory responses, DCs also play an important role in modulating tolerance induction. Tolerogenic DCs are characterized by high antigen uptake and processing capabilities in order to present antigen to antigen-specific T cells, but fail to deliver proper co-stimulatory signal for effector T (T Eff) cells activation and proliferation (Steinman et al., 2003). This results in T cell death, T cell anergy, or induction and expansion of Treg cells subsets. As such, tolerogenic DCs have been shown to suppress experimental autoimmune disease and play an important role in allostimuny (Morelli and Thomson, 2007).

SUBSETS OF TOLEROGENIC DCs: DIVISION OF LABOR IN TOLERANCE INDUCTION

Different DCs subsets are specialized in tolerance vs. inflammatory immune response decisions. Specific markers capable of discriminating tolerogenic from inflammatory DCs are still ill-defined. However, CD8+ DCs expressing CDPRL and DEC205 often possess tolerogenic properties (Mahnke et al., 2002; Yamazaki et al., 2008). Expression of inhibitory immunoglobulin-like transcript (ILT) receptors is also frequently observed in some subsets of tolerogenic DCs, where ILT-3 and ILT-4 mediated signals on DCs inhibits expression of co-stimulatory molecules and induce a tolerogenic state (Manicassamy and Pulendran, 2011). In humans, ILT-3 and ILT-4 expressing tolerogenic DCs can promote antigen-specific unresponsiveness in CD4+ T cells and induce Treg cells. Recent studies have shown that Indoleamine 2,3-dioxygenase (IDO) and IL-10 can induce the expression of ILT-3 and ILT-4 on DCs and promote tolerogenic response (Manicassamy et al., 2013). Activation of ILT-3 receptor on DCs leads to the recruitment of protein phosphatase SHP-1 and SHIP-1 to the immunoreceptor tyrosine-based inhibitory motif (ITIM) resulting in the inhibition of NF-κB and p38MAPK pathways that are critical for inflammatory responses (Cella et al., 1997; Staiger et al., 2008).

While immature DCs appear to be good indicators for DC tolerogenicity, mature DCs might not always induce immunity. Hence, other factors such as exposure to certain differentiation signals or cues from the local environment might condition DCs beyond their expression of co-stimulatory molecules. Therefore, tolerance is not only a consequence of T cells receiving insufficient signals 2 and 3, but additional tolerance inducing factors might be in play.

GENERATION OF TOLEROGENIC DCs

Treg CELLS, THROUGH VARIOUS MECHANISMS, PROMOTE THE GENERATION OF TOLEROGENIC DCs

While several environmental factors and cytokines can promote the tolerogenic phenotype of DCs, there is accumulating evidence that Treg cells can also induce a tolerogenic phenotype in DCs by modulating their maturation and function. Several studies indicate that Treg cells can suppress the capacity of DCs to activate T Eff cells by down-regulating CD80/CD86 expression on bone marrow-derived or splenic DCs in vitro (Cederbom et al., 2000). Depletion of Treg cells from asthma susceptible mice resulted in DCs with higher expression levels of MHC II, CD80, CD86 and displayed a increased T cell stimulatory activity (Mahnke et al., 2007). Although the mechanism by which Treg cells achieve this is unknown, this might be mediated through cell surface molecules such as IL-10, CTLA-4, and TGF-β (Figure 1).

Role of Treg cell-derived IL-10 in induction of tolerogenic DCs

The production and activity of the immunomodulatory cytokine IL-10 is often associated with tolerogenic responses. IL-10 inhibits multiple aspects of DC function including MHC/II and CD80/CD86 co-stimulatory molecules expression and a release of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and IL-12 (Mahnke et al., 2002, 2007; Alexander, 2005). Interestingly, IL-10 mediated effects could be only observed when immature DCs were exposed to IL-10 (Read et al., 2000), as mature DCs were insensitive to IL-10 stimulation and displayed stable, mature phenotype (Read et al., 2000). In addition, DCs cultured in presence of Treg cells has been shown to secrete of IL-10, TGF-β, and IL-27 cytokines (Awasthi et al., 2007). IL-27 cytokine plays an important role in suppressing production of Th17 polarizing cytokines, such as IL-1β, IL-6, IL-23 derived from DCs and act on naïve T cells to induce Th1 differentiation (Pot et al., 2009). IL-10 treated DCs have also been shown to promote tumor growth, and prevent transplant rejection and ameliorate MS (Mahnke et al., 2007).

CTLA-4 is a potent inducer of tolerogenic DCs

CTLA-4 plays an important role in Treg cell-mediated suppression (Salomon et al., 2000). Treg cells constitutively express high levels of CTLA-4 and conditional deficiency of CTLA-4 in Treg cells results in lymphoproliferation and variety of autoimmune disease, an outcome analogous to global CTLA-4 deficient mice (Wing et al., 2008). Monoclonal antibody blockade of CTLA-4 exacerbates T1D in non-obese diabetic (NOD) mice and induce EBD (Read et al., 2000; Wing and Sakaguchi, 2010). CTLA-4 mediates suppression through down regulation of CD80 and CD86 expression on DCs. Treg cells from CTLA-4 deficient mice or
Kornete and Piccirillo DC-Treg crosstalk in immune tolerance

**FIGURE 1** | Major mechanisms by which Treg cells induce tolerogenic DCs and inhibit T eff cell activation. Treg cells can inhibit the function of DCs through various mechanisms. CTLA-4 expression on Treg cells down-regulates up-regulation of CD80 and CD86 co-stimulatory molecules on DCs. LAG3 binding to MHCII-expressing immature DCs results in inhibitory signals that suppress DCs maturation and co-stimulatory capacity. Nrp-1 expression on Treg cells promotes sustained interactions between Treg cells and DCs, and limits the access of T eff cells to DCs. Expression of LFA-1 on Treg cells promotes aggregate formation around DCs, and inhibit the up-regulation of CD80 and CD86 on DCs. IL-10 inhibits up-regulation of MHCII and B7 co-stimulatory molecule expression, suppresses release of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IL-12, and up-regulates of B7-H4 and B7-H1 inhibitory molecules.

**FIGURE 2** | Major mechanisms of immune modulation by tolerogenic DCs. DCs modulate the immune system by promoting Treg cell generation through various mechanisms. Upon stimulation, DCs are able to increase production of various cytokines and inflammatory mediators such as IL-10, RA, vitamin D, TGF-β, IL-2, TSLP, TNF-α and down-regulate expression of inflammatory cytokines such as IL-12p70. BCs, by down-regulating co-stimulation and antigen presentation, can favor induction of Treg cells. Various signaling pathways program DCs to induce tolerogenic responses. Administration of CTLA-4 blocking antibodies results in reduced down-modulation of B7 molecules and increased T cell proliferation (Oderup et al., 2006). IDO, a potent regulatory molecule that is known to induce the production of pro-apoptotic metabolites from the catabolism of tryptophan, results in the suppression of Treg cells through a mechanism dependent on interaction between CTLA-4 and CD80/CD86 (Fallarino et al., 2003). Baban et al., 2009). Baban et al. (2019) recently demonstrated that IDO is a critical molecular switch that stimulates potent Treg cells suppression while simultaneously block IL-6 driven reprogramming of Treg cells into Th17 cells and production pro-inflammatory cytokines such as IL-17, IFN-γ, TNF-α, and IL-2. Interestingly, it has also been demonstrated that Treg cells can modulate DCs to express IDO and more specifically CTLA-4 immunoglobulin.
A number of other mechanisms have been proposed by which Treg cells can either abrogate the antigen presenting capacity of DCs or promote the secretion immunomodulatory cytokines. In addition, Treg cells are able to induce the expression of B7-H and B7-H4, a ligands responsible for negative regulation of cell-mediated immunity in peripheral tissues (Mahlke et al., 2007). Recently, Treg cells have also been shown to trigger high levels of IL-10 production by APCs and in turn stimulate B7-H4 expression in an autocrine fashion and render these APCs immunosuppressive (Kryczek et al., 2006).

**Lymphocyte activation gene 3 (LAG3)**

Lymphocyte activation gene 3 is a cell surface molecule expressed on Treg cells that can modulate DC phenotype and function (Huang et al., 2004; Workman and Vignali, 2005; Liang et al., 2008). LAG3 is a CD4 homolog that binds MHC II molecules with very high affinity, has a negative regulatory intrinsic function and is required for maximal Treg cells suppression (Huang et al., 2004; Workman and Vignali, 2005). Binding of LAG3 to MHC II molecules on the surface of DCs initiates a receptor tyrosine-based activation motif (ITAM) mediated inhibitor signaling pathway that suppress DC maturation (Liang et al., 2008). These findings provide a novel tolerogenic pathway that may endow Treg cells to enhance tolerance by inhibiting DCs functions.

**Treg–DCs cognate interactions mechanism**

It has been shown that Treg cells are more motile than naive T cells in vitro, in turn out-competing the latter for physical access to DCs (Tsao et al., 2009). This Treg–DC cell aggregation process is antigen-dependent, and the selective advantage of Treg cells over Teff cells for physical interactions with DCs can be attributed, at least in part, to the expression of LFA-1 (Lymphocyte function-associated antigen 1) by Treg cells, as deficiency or blockade of LFA-1 and CTLA-4-dependent antigen in order to exert their suppressive functions in vitro and in vivo (Takahashi et al., 1998), activated Foxp3+ Treg cells can mediate in vitro bystander suppression of Teff cells with different antigen specificities. However, it still remains to be determined whether such mechanism can also apply to other cell types like DCs, and to what extent such bystander suppression occurs in vivo.

Recently it has been shown that neuropilin (Nrp-1) also plays a critical role in mediating Treg–DC interactions (Sarris et al., 2008). Nrp-1 is a ligand binding receptor for a class of semaphorins, and is preferentially expressed by Treg cells. Nrp-1 expression can be induced by ectopic expression of Foxp3 in Foxp3- T cells, and antibody blockade of Nrp-1 reduces the frequency of Treg–DC interactions. Furthermore, retrowial introduction of Nrp-1 endows T helper cells with ability to establish a long interactions with DCs (Sarris et al., 2008). Interestingly, it has been demonstrated that Nrp-1 can confer a high adhesive property of Treg cells in their interaction with DCs under steady conditions; however, this potential by Treg cells is lost under inflammatory conditions (Sarris et al., 2008).

The described results above demonstrate the capacity of Foxp3+ Treg cells, through the expression of LAG3 and Nrp-1 molecules, to influence immature but not mature DCs. Mature DCs, in contrast to immature DCs, produce pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β which can down-regulate Foxp3 expression and abolish Foxp3+ Treg cell-mediated suppression (Ratnala et al., 2006). Although IL-6 production induced by LPS stimulation only slightly reduced Foxp3+ Treg cells-mediated suppression, DC-derived IL-6 may render responder T cells resistant to suppression (Pasare and Medzhitov, 2003). Moreover, IL-6 might also facilitate the reprograming of Foxp3+ Treg cells into Th17 lineage (Rettel et al., 2007).

In other instances, it has been demonstrated that Treg cells, through the expression of LFA-1 and CTLA-4, can suppress TNF and LPS matured DCs by selectively down-regulating CD80, CD86, PDL1, and PD-L2, but not MHCII and CD40, expression on the DC surface. Overall, these findings demonstrate that Treg cells may employ specific mechanism(s) to suppress DCs functions in different microenvironments of antigen priming.

**The gut environment promotes development of tolerogenic DCs**

The identification of tolerogenic DC subsets in microenvironments such as gut, skin, and lungs suggest that local signals induce tolerogenic DCs in situ. Given the enormous amount of microbial stimuli in the gut, intestinal DCs represent a key regulatory mechanism to prevent excessive inflammation. Specifically, CD11c+ DCs expressing CD103 have been identified in the gut-associated lymphoid tissue (GALT) and mesenteric lymph node with the...
A recent study demonstrated that antigen-specific T cells and preferential induction of Treg cells through deletion of node derived CD103 MHC II, CD80, and CD86. Interestingly, absence of CD103 on DCs led to the abrogation of Treg cell activity indicating a crucial role for CD103 in maintaining the balance between Treg and Teff cells (Annacker et al., 2005). While mesenteric lymph node derived CD103+ DCs are prone to imprint expression of CCR9 on T cells, an important homing receptor enabling homing to the gut, CD103+ DCs promote the differentiation of CD4+ T cells producing IFN-γ (Jasionowski et al., 2008). Collectively, CD103+ and CD103− DCs represent functional subsets and CD103 is critical to regulate Treg and Teff cells in the gut (Annacker et al., 2005).

APOTOTIC DCs FAVOR FORMATION OF TOLERGENIC DCs

Recent studies show that immature DCs can uptake apoptotic and necrotic DCs without being recognized as an inflammatory event (Kushwah et al., 2010). This uptake results in conversion of mature DCs into tolerogenic DCs that remain resistant to LPS induced maturation and induce the production of TGF-β through the mTOR signaling pathway (Kushwah et al., 2010). TGF-β producing DCs subsequently interact with naive T cells and drive the differentiation of Treg cells (Kushwah et al., 2010; Kushwah and Hu, 2011). Moreover, recent studies showed that α-CD3 mAb treatment transiently depletes large numbers of T cells and induce long term immuno tolerance (Perruche et al., 2008; Esplugues et al., 2011). The mechanism underlying this regulatory outcome is due to increased production of TGF-β by immature DCs after engulfment of apoptotic T cells (Perruche et al., 2008). A recent study demonstrated that α-CD3 mAb treatment resulted in elimination of the inflammatory Th17 cells from intestinal lumen or resulted in acquisition Th17 cells producing a IL-10 (Esplugues et al., 2011). However, it is not known which specific subset of gut-residing DCs is responsible for production of TGF-β and induction of IL-10 producing Th17 cells with regulatory capacity.

IMMUNE MODULATION BY TOLERGENIC DCs

DC EMPLOYS VARIOUS MECHANISMS TO DRIVE THE DIFFERENTIATION OF Treg CELLS

Mature mammalian DCs express high levels of CD80, CD86, and CD40 (Steinman and Nussenzweig, 2002; Steinman et al., 2003; Hubert et al., 2007). Moreover, targeting of antigens to immature DCs via the regulatory receptor DEC205 results in tolerance through deletion of antigen-specific T cells and preferential induction of Treg cells (Hawiger et al., 2001). Interestingly, antibodies bound to DEC205 are efficiently internalized and delivered to antigen processing compartments, however internalization of the antigen by DEC205 does not induce the maturation of the DCs (Mahnke et al., 2000). Immature DCs had been shown to induce Treg cells in vitro and anti-DEC205 targeting of antigens to immature DCs led to anergic T cells in vivo (Mahnke et al., 2003). These data show that the DEC205 receptor is critical for DCs in the steady state to promote tolerance (Mahnke et al., 2003). Moreover, treatment with respective anti-DEC antigen conjugates results in significant improvement of autoimmune disorders such as T1D and MS (Hawiger et al., 2004; Bruder et al., 2005). DCs can also favor tolerance by utilizing ICOS, another CD28 family member, to specifically drive Tr1 cell differentiation (Akbari et al., 2002; Ito et al., 2007).

Despite the established role of immature DCs as inducers of Treg cells, recent studies have shown that mature DCs, expressing high levels of CD86, also have the potential to preferentially expand Treg cells in vivo, and prevent T1D development (Yamazaki et al., 2003; Tarbell et al., 2004; Spouridas et al., 2011). Interestingly, DCs isolated from Peyer’s patches, eye, or lungs display a mature phenotype, secrete IL-10, but not IL-12 and drive the development of Tr1 cells (Akbari et al., 2001). Thus, signals derived from the local tissue environment might play a role in conditioning tolerogenic DCs and drive the differentiation of Treg cells. All together, these findings suggest that the previously established paradigm whereby immature DCs leads to Treg cell differentiation and mature DCs drive Teff cell responses might be revisited (Figure 2).

DC- DERIVED CYTOKINES THAT DRIVES DIFFERENTIATION OF Treg CELLS

IL-10

Dendritic cells can secrete high amounts of IL-10 upon stimulation and drive differentiation of naive T cells into IL-10 secreting Tr1 cells (Kushwah and Hu, 2011). DCs of IL-10 transgenic mice display a particularly immature phenotype and Tr1 cells are significantly enriched in spleens of these mice (Wakchach et al., 2003). Langerhans cells in the skin also produce IL-10 and drive differentiation of Tr1 cells (Igarte et al., 2009).

TNF-α

TNF-α can also induce tolerogenic state in DCs (Menges et al., 2002; Mahnke et al., 2007). Despite the fact that TNF-α treated DCs has a mature phenotype, they fail to secrete inflammatory cytokines such as IL-1β, IL-6, TNF-α, and IL-12 (Menges et al., 2002). Moreover, these tolerogenic DCs were able to reverse development of EAE where their suppressive effects were mediated by the induction of IL-10 producing Treg cells (Mahnke et al., 2007). However, there is also a controversial data demonstrating that TNF-α blockade prevented DC maturation and Treg cells were induced in the absence of TNF-α (Mahnke et al., 2007).

TGF-β

TGF-β-producing DCs might preferentially drive differentiation of Treg cells rather than Teff cells. Tumor-bearing mice contains α-CD3+ DC subset characterized by low expression of CD80 and CD86 co-stimulatory molecules and are endowed with the capacity to secrete TGF-β which promotes Treg cells differentiation and proliferation in vivo (Gilchingelli et al., 2005).

IL-2

We and others have shown that a local deficiency in islets of IL-2, a critical cytokine for the homeostasis/fitness of Treg cells in vivo, compromises Treg cell function in islets, a defect readily
corrected by low dose IL-2 therapy in NOD mice. NOD mice intro-
gressed with a protective IL2 allelic variant from T1D-resistant
C57BL/6 mice (NOD;Idd3BL6) are resistant to autoimmune dia-
betes in contrast to wild-type NOD mice which are susceptible
to the disease. Moreover, T1D-protective IL2 allelic variants in NOD
mice impinge T1D development by bolstering IL-2 production
by CD4+ Treg cells in turn, driving the expansion and homeosta-
sis of CD4+Foxp3+ Treg cells in islets. Recently, we showed that
CD11c+ DCs in NOD;Idd3BL6 have an increased maturation sta-
tus relative to wild-type NOD;CD11c+ DCs. We also showed that
NOD;Idd3BL6 DCs are more potent activators of Treg cells func-
tions in vitro and in vivo, and this increased capacity of congenic
type DCs to prime Treg cells is attributed to their ability to produce
IL-2. Consistently, IL-2 blockade in vivo completely abolished
the proliferative advantage conferred by Idd3BTDCs on Foxp3+
Treg cells (Sgouroudis et al., 2011). Interestingly, CD11c+ MHCII+
DCs isolated from pancreatic LN of NOD;Idd3BL6 mice promoted
Foxp3+Treg cells expansion more efficiently that WT DCs isolated
from similar sites, suggesting that Idd3BL6 DCs display tolerogenic
phenotype specifically in the pancreatic sites to enhance Foxp3+
Treg cells functions (Sgouroudis et al., 2011). Thus, T1D-protective
IL2 allelic variants impinge the development of β-Islet autoim-
unity by bolstering IL-2 mRNA expression and protein secretion by
CD4+ Treg cells and DCs and in turn, driving the functional home-
ostasis of CD4+ Foxp3+ Treg cells in the target organ (Sgouroudis
et al., 2011).
It has been previously shown that CD40/CD40L interaction
regulates Treg cells homeostasis (Kumanogoh et al., 2001; Guiducci
et al., 2005). Mature DCs lacking CD40L are impaired in sustaining
Treg cells proliferation and survival. The underlying mechanism
is mediated by fact that CD40L deficient DCs are not able to pro-
duce IL-2, to as similar extent as wild-type DCs. Administration of
rhIL-2 in vivo restored Treg cells numbers in thymic and peripheral
compartments of CD40L deficient mice, by increasing survival
and homeostatic proliferation of Treg cells (Kumanogoh et al.,
2001; Guiducci et al., 2005). Therefore, CD40 triggering by Treg
DCs contributes to induce IL-2 through CD40L on DCs needed
therefore, several mechanisms have been established by DCs in order to maintain a peripheral pool of Treg
cells through IL-2 production (Kumanogoh et al., 2001; Guiducci
et al., 2005).
IDO EXPRESSION BY DCs DRIVES TREG CELLS DIFFERENTIATION
Dendritic cells populations expressing IDO play a critical role in
immune tolerance by promoting Treg cells differentiation (Mellor
and Munn, 2004; Matteioli et al., 2010). IDO expression by DCs
appears to be dependent on Ahrl hydrocarbon receptor (AHR)
as DCs lacking AHR fail to up-regulate IDO and prime T cells
responses rather than tolerance induction (Nguyen et al., 2010).
Selective inhibition or genetic deletion of IDO affects the de-
velopment of antigen-specific Treg cells while promotes Th1 and
Th17 development and worsens T cells mediated and dextrin
induced enteritis in mice (Baban et al., 2009).
Ido1 expression in vitro and in mice is attributed to their ability to produce
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Foxp3 expression in Treg cells. Interestingly, Zhou et al. (2010) showed that RA maintains the stability of Foxp3+ Treg cells and sustains their suppressive potential in the presence of IL-6, through down-regulation of IL-6 receptor expression and signaling, therefore preventing Treg cells conversion into Th17 cells (Coombes and Powrie, 2008; Zhou et al., 2010). CD103+ DCs from the lamina propria of the small intestine and mesenteric lymph node have been shown to be significantly better than splenic DCs at mediating the conversion of naïve T cells into Foxp3+ T cells in the presence of exogenous TGF-β (Coombes et al., 2007). Moreover, expression of the αβββββ integrin by DCs is important for TGF-β activation, accumulation of Treg cells in the small intestine and prevention of colitis development (Coombes and Powrie, 2008). Overall, gut-derived signals can condition DCs to produce TGF-β for Treg cell generation.

β-Catenin: a novel regulator of intestinal homeostasis

Wnt-β-catenin signaling in intestinal DCs regulates the balance between inflammatory and regulatory responses. Recently, Manicassamy et al. (2009) performed a gene expression profile of lamina propria DCs and demonstrated that several Wnt family genes and β-catenin were constitutively expressed by intestinal DCs, but not by splenic DCs (Manicassamy et al., 2009). Furthermore, they showed that β-catenin signaling promotes the induction of Treg cells while suppress Th1 and Th17 cells in the gut, indicating that β-catenin expression by intestinal DCs is important for maintaining the balance between Treg and Th17 cells in the gut (Manicassamy et al., 2010). In addition, intestinal DCs lacking β-catenin expression produced lower levels of Treg cell-promoting stimuli including RA metabolizing enzymes, IL-10, and TGF-β, but higher levels of Th17-promoting cytokines IL-23 and IL-6 (Manicassamy et al., 2010). Overall, β-catenin signaling is needed to maintain intestinal homeostasis through the induction of Treg cells and the suppression of pro-inflammatory factors.

The gut microenvironment influences intestinal DC function

Many of the unique properties of intestinal DCs appear to be a result of environmental conditioning. Activation of NF-κB expression in intestinal epithelial cells, perhaps as a result of microflora signaling through PRRs, enhances TSLP production (Coombes and Powrie, 2008). Recently, important role for TSLP in dictating the quality of immune response has been suggested. TSLP and other epithelial cell factors limit the activation of STAT4 and IRF-8, essential factors for the production of Th1 polarizing cytokine IL-12-23p40 (Arima et al., 2010). In addition, TSLP signaling also induce the activation of STAT6, which programs DCs to secrete chemokines necessary for the recruitment of Th2 cells, and increase IL-10 and TGF-β production (Coombes and Powrie, 2008; Arima et al., 2010). TSLP signaling also induces the activation of STAT5, which programs DCs to secrete chemokines necessary for the recruitment of Th2 cells, and increase IL-10 and TGF-β production (Coombes and Powrie, 2008; Arima et al., 2010). TSLP has also been shown to counteract the inflammatory response of intestinal Th1 and Th17 cells by inhibiting inflammatory cytokines. In vitro generation of tolerogenic DCs in vitro provides significant opportunities for therapeutic interventions. DCs are generated in vitro from bone marrow precursors in rodents or blood monocytes in humans and can be rendered tolerogenic by modulating their culture conditions through exposure to cytokines, growth factors or pharmacologic mediators, or genetic engineering (Morelli and Thomson, 2007). In vitro generation of tolerogenic DC can be achieved through exposure to various anti-inflammatory agents such as vitamin D, as well as clinically approved suppressive drugs such as corticosteroids, cyclosporin, and rapamycin (Morelli and Thomson, 2007). Rapamycin acts as an inhibitor of the Akt-mTOR pathway, increases the number of Foxp3+ Treg cells, and promotes their resistance to apoptosis (Strauss et al., 2007; Basu et al., 2008). Moreover, rapamycin-conditioned myeloid DCs fail to produce IL-12p70 and TNF-α and are resistant to maturation induced by TLR ligands or by CD40 signaling (Turnquist et al., 2007). Advances in gene transfer technology offers the possibility to generate tolerogenic DCs by genetically inducing the expression of immunosuppressive molecules like IL-10, TGF-β, or CTLA-4, or blocking the expression of co-stimulatory molecules (Morelli and Thomson, 2007).

Conversely, it is possible to generate tolerogenic DCs in vivo that drive Treg cells differentiation in a tissue specific manner in order to inhibit inflammation in a particular site (Ressigno, 2010). For example, intestinal epithelial cells release factors that drive the development of mucosal like tolerogenic DCs (Iliev et al., 2007). Incubation of DCs with intestinal, but not mammary or epithelial cell-derived supernatants induces the expression of CD103 on DCs while inhibiting the secretion of inflammatory cytokines. These in vitro generated CD103+ DCs can drive the induction of Treg cells and expression of the gut-associated homing receptor αβββββ (Iliev et al., 2009). Moreover, only intestinal epithelial cell-conditioned DCs are able to protect against colitis development (Iliev et al., 2009). Therefore, DCs conditioned at local environment are...
important for generation of Treg cells that are able to suppress and home to specific sites.

CONCLUSION

Our understanding of the functional and phenotypic plasticity of DCs, as well as the capacity to modulate DC development and maturation in vitro and in vivo, gives opportunity to use these cells for therapeutic purpose in autoimmunity and cancer. Tolerogenic DCs have a dual role, for example in cancer, a profound defect in DC function is associated with accumulation of immature DCs in tumors where DCs are unable to initiate anti-tumor immune responses while contributes to the recruitment, expansion and function of Treg cells. While this has negative outcomes in cancer settings, similar scenarios would be helpful in the case of autoimmunity. Several studies in mice suggest that DCs might be used in the treatment of autoimmunity through their ability to induce Treg cells. For example, repetitive injections of semi-mature DCs results in protection from EAE and thyroiditis (Ueno et al., 2007). In the NOD mice, DC-mediated in vivo generation of Treg cells can inhibit spontaneous T1D development in these mice (Ueno et al., 2007). In the NOD mice, several mechanisms have been identified to explain how tolerogenic DCs mediate their function. For example, IDO expression by intestinal DCs is important for regulating intestinal immune homeostasis by keeping the balance between Treg cells and Th17, Th1 cells. Deregulation of IDO activity results in increased intestinal inflammation, suggesting that IDO could be regarded as a new target for IBD. Therefore, pharmacological targeting of IDO during the chronic inflammation like IBD would be beneficial in dampening the inflammatory process and tissue damage in the gut (Mattoo et al., 2010). Moreover, as IL-6 is often present in inflammatory sites in autoimmune settings, recent findings about ability of RA to stabilize Treg cells in the presence of IL-6 offers the possibility that RA treated Treg cells can be used in many autoimmune settings where achieve such a balance is essential.

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