Dendritic Cell-Based Approaches in Autoimmunity

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Dendritic cells (DCs) dictate the outcomes of tissue-specific immune responses. DCs instruct T cells to respond to antigens (Ags), including self-Ags, leading to organ damage in the context of autoimmune diseases, or to becoming regulatory T cells (Tregs) promoting and perpetuating immune tolerance. DCs can acquire tolerogenic properties in vitro and in vivo in response to several stimuli, a feature that opens the possibility to generate or to target DCs to restore tolerance in autoimmune settings.

Keywords: dendritic cells ; autoimmune diseases ; tolerance

1. Autoimmune Diseases: Breakdown of Tolerance

Breakdown of immunological tolerance can lead to unwanted and detrimental activation of immune responses against self Ags that causes autoimmune diseases, such as Type 1 Diabetes (T1D), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), and Inflammatory Bowel Disease (IBD) [1]. These pathologies, usually involving genetic predisposition and poorly defined environmental factors, are widespread. It is estimated that worldwide almost 1 in 10 individuals (7.6–9.4%) suffer from autoimmune diseases [2].

Organ destruction in autoimmune diseases is associated with the dysregulation of the immune system with hyper-reactive effector cells that escape the immune control mediated by the tolerogenic arm of the immune system, leading to hyperactivation of adaptive immune responses and chronic inflammation. Studies, in autoimmune patients, demonstrated that aberrant activation of immune cells, including lymphoid and myeloid cells, leads to inflammation in the target organs of autoimmunity [3][4][5][6]. Currently, approved therapies for autoimmune diseases involve lifelong administration of immunomodulatory and immunosuppressant drugs that can efficiently improve the outcomes of the disease but, on the other side, are often associated with severe side effects. Specifically, the drugs used in these treatments are non-specific and non-curative, and can induce a systemic, generalized, and persistent immunosuppression leading to the risk of chronic infections or cancer development [7]. The increased knowledge on the unique ability of DCs, able to induce primary immune responses bridging innate and adaptive immunity, revealed their central role in maintaining tissue homeostasis and tolerance. Further improvements in understanding how DCs promote immunological tolerance and the development of protocols for the manipulation of DC activity *in vitro* and *in vivo* will lead to actively explore the possibility of identifying effective and specific approaches based on DCs to cure autoimmune diseases. In this context, the use of DCs rendered tolerogenic by different means represents an attractive therapeutic approach for restoring permanent Ag-specific tolerance. Tolerogenic (tol)DCs can be used to specifically target the detrimental immune response against disease associated Ags, while they maintain the retention of the capacity of the immune system to be functional and reactive against other pathogens and malignancies [8]. In this review, we briefly introduce the different subsets of human DCs, and we review the involvement of DCs in the induction of tissue-specific autoimmunity. Furthermore, we present current approaches using tolDC-based therapies or targeting DCs in vivo for the treatment of tissue-specific autoimmunity.

2. Dendritic Cells Are Central Players in Promoting Immune Responses in Autoimmunity

DCs in the immature state (iDCs) predominantly reside in the peripheral tissues and in secondary lymphoid organs [9][10][11] and serve as sentinels of the immune system, continuously patrolling the extracellular milieu. iDCs can recognize a plethora of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through the innate pattern-recognition receptors (PRRs), Toll-like receptors (TLRs) or c-type-lectin receptors. iDCs express high levels of PPRs and low levels of major histocompatibility complex (MHC) class II, CD80 and CD86, and their lysosomal activity is attenuated (reviewed in [12]). During classical immune responses, iDCs process the encountered Ags into smaller peptides, which can be presented on the cell surface in the context of MHC class I/II [13][14]. The encountering of the Ag drives the maturation of iDCs that lose their ability to process new peptides and they acquire the capacity to present Ags to T cells. Specifically, DCs upregulate the expression of MHC class II and co-stimulatory molecules (e.g.,

CD40, CD80 and CD86), secrete pro-inflammatory cytokines (e.g., IL-1β, IL-12, IL-6, and tumor-necrosis factor α (TNFα)) [15][16] and upregulate the expression of CCR7 and CXCR4, which enable them to migrate to lymph nodes, where they can present Ags to naïve T cells, driving their polarization toward pro-inflammatory Th1, Th2 or Th17 cells or CTLs (reviewed in [17]). For effective activation of T cells, three signals are required: (i) interaction between TCR and Ag/MHC complex; (ii) engagement of CD28 with co-stimulatory molecules (CD80 or CD86); and (iii) secretion of cytokines and chemokines.

Apart from the induction of efficient immune responses against invading pathogens and foreign Ags, DCs are critical modulators of both central and peripheral tolerance. During T cell development in the thymus, DCs play a critical role in the depletion of autoreactive T cells. DCs localized in the medulla, together with thymic epithelial cells, present self-Ags to thymocytes, and when the TCR/MHC interaction is strong, they promote self-reactive T cell apoptosis [18]. However, this mechanism does not fully assure the selection of T cell unresponsive to self and innocuous foreign Ags since: (i) self-reactive lymphocytes can escape negative selection; (ii) many innocuous environmental Ags, including those deriving from commensal microbiota, are not expressed in the thymus; and (iii) TCRs specific for foreign Ags can recognize MHC-self-Ag complexes. To overcome these events, in the periphery there are tolDCs which, by exploiting several immunosuppressive mechanisms, modulate the activity of potentially pathogenic T cells and promote the expansion or/and the differentiation of several subtypes of regulatory T cells, including classical CD4 + CD25 hi Foxp3 + Tregs [19][20][21] and CD49b + LAG-3 + type 1 T regulatory (Tr1) cells [22][23].

Four main mechanisms of peripheral tolerance have been described: induction of clonal anergy, metabolic modulation, secretion of anti-inflammatory cytokines and clonal deletion. TolDCs express low co-stimulatory molecules and high inhibitory receptors such as programmed cell death ligand (PDL)-1 [24] and inhibitory Ig-like transcripts (ILTs) [25][26]. These characteristics lead to T cell clonal anergy and T cell unresponsiveness due to Ag presentation in the presence of low co-stimulation, [27], or by the engagement of inhibitory receptors with their ligands expressed on the T cells. The latter include: PDL-1/PDL-2 interaction with programmed death 1 (PD-1) [28][29], the interaction between ILTs and classical and non-classical HLA class I molecules [30][31] and CD80/CD86 binding to the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). CTLA-4/CD80-CD86 interaction mediates CD80 and CD86 trans-endocytosis and degradation [32] or the induction of indoleamine 2,3-dioxygenase (IDO) [33][34], an enzyme that catabolizes tryptophan, an essential amino acid for T cell proliferation. IDO upregulation in tolDCs leads to: (i) T cell starvation by physical depletion of tryptophan from the local environment [35]; (ii) production of immune-toxic kynurenines that promote T cell apoptosis [36]; and (iii) accumulation of kynurenine, which, upon interaction with the aryl hydrocarbon receptor (AhR) on CD4 + T cells, promotes their polarization into Tregs [37]. TolDCs can also alter T cell responses by modulating the metabolic milieu through the expression of heme oxygenase-1 (HO-1), which catabolizes hemoglobin and promotes the production of carbon monoxide, overall reducing DC immunogenicity [38]. Moerover, tolDCs, by secreting anti-inflammatory cytokines (i.e., IL-10, TGF-β, and IL-35), are involved in promoting Treg differentiation. TolDC-derived IL-10 suppresses effector T cell responses and induces Tr1 cells [39]. IL-35, which can be secreted by DCs [40], promotes the differentiation of IL-35-producing FOXP3 + Tregs and suppress Th17 cell induction [41][42]. Also TGF-β can promote the induction of FOXP3 + Tregs [15]. In a preclinical model of MS, retinoic acid, a metabolite of vitamin A, has been used to modulate DCs that acquire the ability to induce Tregs and to inhibit Th17 cell polarization [43]. Finally, tolDCs by the expression of FasL and TNF-Related Apoptosis-Inducing Ligand (TRAIL) promote T cell clonal deletion [44][45].

3. Strategies to Generate Ex Vivo Tolerogenic Dendritic Cells

Several naturally occurring subtypes of TolDC have been identified in humans and the tolerogenic properties of DCs prompt researchers to set-up different protocols to generate *ex vivo* tolDCs for the treatment of autoimmune diseases (**Figure 1**).

To keep DCs at immature state, Machen and colleagues designed a protocol based on the use of specific antisense oligodeoxyribonucleotide (AS-ODN) targeting CD40, CD80, and CD86 transcripts to suppress these proteins expression in murine bone-marrow derived DCs [46]. A single injection of AS-ODN-treated DCs into prediabetic NOD mice significantly delay the incidence of T1D without affecting the response of T cells to alloAgs [47]. These pre-clinical results lead to the translation of AS-ODNs to human monocyte-derived DCs and their clinical application in T1D patients. Administration of AS-ODN-treated DCs was well-tolerated with no observable adverse events or toxicities. *In vivo* treatment slightly increased the prevalence of FOXP3+ Tregs [48].

Dexamethasone (Dexa), a potent synthetic steroid, has been used to modulate the phenotype of DCs toward a tolerogenic state. Exposure of human CD14 + cells, during monocyte-derived DC differentiation, or murine bone-marrow precursors, to Dexa prevents the differentiation of fully maturated DCs, as evidenced by the altered expression of MHC, CD86, CD80 and CD40 molecules, and by the reduced IL-12 production and T cell stimulatory capacity [49]. RA patients derived Dexa-DCs were administered in knee joints and resulted in a reduced synovitis formation at 3 months after

treatment [50]. In patients of MS, injection of autologous Dexa-DCs loaded with disease relevant Ags demonstrated to be safe and well tolerated. Finally, Dexa was also used in another clinical trial in combination Vitamin A for the treatment of Crohn's Disease. In CD patients Dexa-VitA TolDCs were administered intraperitoneally and treatment was well-tolerated, and a clinical improvement was observed in one-third of the patients based on a CD activity index [51].

The active form of Vitamin-D3 (VitD3), 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), impairs the differentiation of murine and human DCs *in vitro* and *in vivo*, leading to a tolerogenic phenotype characterized by low Ag presentation capacity, downregulation of costimulatory molecules, and inhibition of IL-12 production. VitD3-DCs are unable to fully activate T cells and to initiate an immune response [52]. In a clinical trial for T1D patients the intradermal injection of proinsulin-epitope loaded VitD3-tolDCs coincided with low grade toxicity not likely related to the therapy, with no signs of systemic immune suppression, no induction of allergy to insulin, no interference with insulin therapy, and no accelerated loss of β-cell function in patients with the remaining C-peptide[53] . VitD3-tolDCs loaded with a pool of 7 myelin peptides are used in two coordinated phase I clinical trials in MS patients, to test the safety and tolerability of autologous tolDCs-VitD3 and to compare two routes of tolDC administration, intradermal vs intranodal injection [54]. In an additional clinical trial, VitD3 and Dexa have been used in combination to generate TolDCs from RA patients' monocytes. The cellular product was pulsed with autologous synovial fluid collected from inflamed joints and injected into knee joints of RA patients leading to an improvement of the clinical symptoms without worsening knee flares, or other side effects [50].

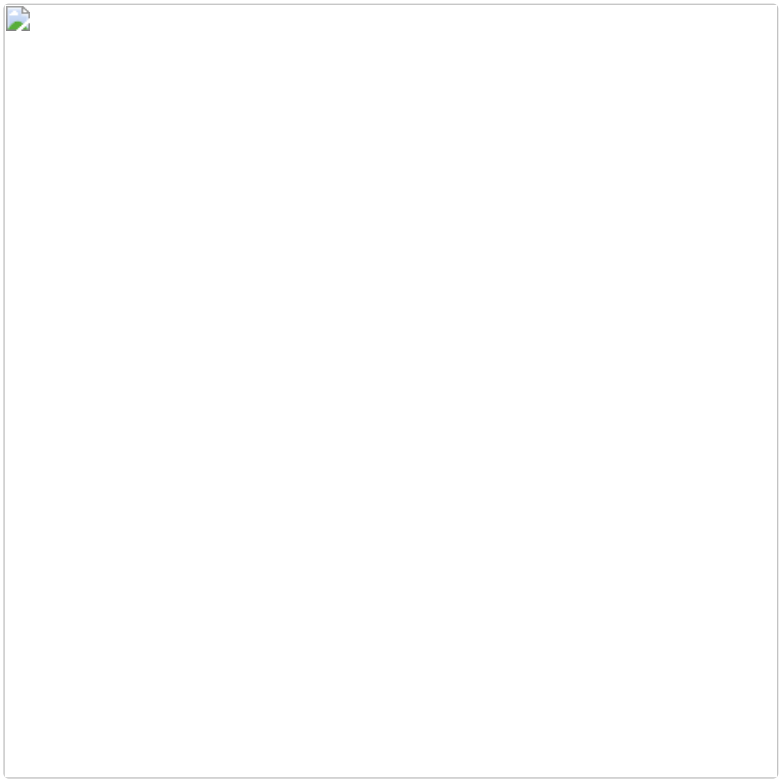

Figure 1. Clinical trials employing ex vivo generated tolerogenic DCs (tolDCs). TolDCs were differentiated starting from patients' $CD14^+$ monocytes in the presence of different tolerogenic agents. The resulting cells have been tested in clinical trials for different autoimmune diseases: Type 1 Diabetes (T1D) (pink panel), Rheumatoid Arthritis (RA) (green panel), Multiple Sclerosis (MS) (blue panel), and Crohn's Disease (CD) (orange panel). Abbreviations: Dexa, Dexametasone; VitD3, 1,25-dihydroxyvitamin D3; VitA, vitaminA; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; AQP4, acquaporin-4; $MBP_{85–99}$, Myelin Basic Protein; $PLP_{139–151}$, proteolipid protein; $MOG_{35–55}$, myelin oligodendrocyte glycoprotein; PAD4, peptidyilarginine deaminase 4; HNRNPA2B, heterogeneous nuclear ribonucleoprotein A2/B1; i.v., intravenous; i.n., intranodal; i.d., intradermal; i.p., intraperitoneal; i.l., intralesional; i.a., intra-articular.

4. In Vivo Dendritic Cell Targeting to Mediate Tolerogenic Responses

The *ex vivo* generation of TolDCs has some drawbacks including the extensive manipulation and the high manufacturing costs that prompted the researchers to exploit new approaches based on *in vivo* Ag-delivery to naturally occurring tolDCs or Ag co-delivered with immunomodulatory factors to polarize DCs toward a tolerogenic phenotype (**Figure 2**).

In the last decades, evidence demonstrated that Nanoparticles (NPs) were widely used in medicine to deliver drugs or molecules to specific cell subsets [55]. In the context of autoimmune diseases, DCs represent an attractive target for nanomedicine to directly promote their tolerogenic activity in an Ag-specific manner. Indeed, the combined delivery of tolerogenic agents and Ags into NPs promote DCs with the ability to present Ag in a tolerogenic manner [56]. To allow

direct phagocytosis from DCs, NPs should have specific characteristics in terms of size, shape, and chemical properties [57]. In pre-diabetic NOD mice, injection of NPs encapsulating InsB and different tolerogenic agents (e.g., Vit D3 MPs + TGF-β1 MPs + GM-CSF) prevented T1D onset in 40% of the treated mice. *Ex vivo* analysis revealed decreased levels of insulitis in mice treated with tolerogenic NPs compared to controls, and an increased percentage of FoxP3 + Tregs [58]. NPs encapsulating antisense oligonucleotides targeting CD40, CD80 and CD86 molecules injected in NOD pre-diabetic mice knocked down the expression of these molecules. Interestingly, treatment with NPs encapsulating antisense nucleotides with or without InsB 9-23 in new onset NOD mice reverted diabetes [59]. Finally, intravenous administration of NPs encapsulated with p31Ag, a mimetope recognized by autoreactive T cells in T1D [60], preserved a normal islet architecture and prevented disease development induced by diabetogenic cells in NOD.SCID mice[61].

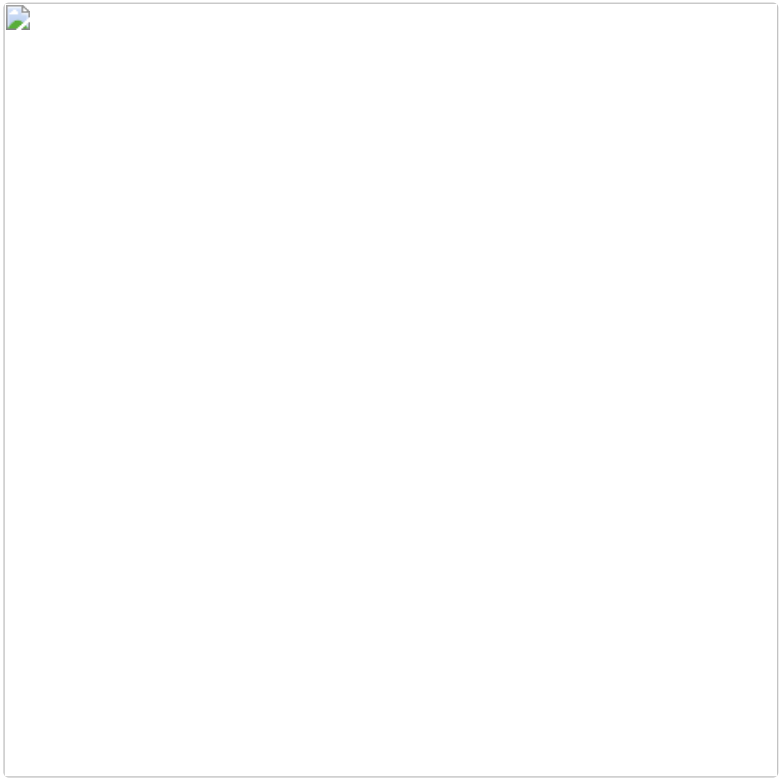

Figure 2. Ex vivo generation of TolDCs vs. in vivo DC targeting. (**A**) Ex vivo generation of TolDCs starts from $CD14^+$ monocyte isolation from peripheral blood of autoimmune disease patients. Monocytes are differentiated into DCs in the presence of tolerogenic agents (i.e., Dexa, VitD3, AS-ODN CD80, CD40, CD86) and then pulsed or not with disease-relevant Ags. The obtained cellular product is infused in patients. (**B**) In vivo targeting of DCs. Nanoparticles encapsulating Ags w/o tolerogenic agents target autologous DCs and skew their phenotype toward a tolerogenic one. Antibodies fused to relevant Ags are generated to recognize surface markers expressed specifically by naturally occurring tolDCs (i.e., DEC205, DCIR2, CLEC9A). Epicutaneous immunotherapy that delivers the Ag to the APCs localized in the superficial layers of the skin.

The use of NPs to target DCs have been exploited also in preclinical models of MS, experimental autoimmune encephalomyelitis (EAE). Maldonado et al. demonstrated that injection of NPs encapsulating PLP, and RAPA inhibited EAE relapse [62]. Moreover, NPs encapsulating IL-10 and MOG injected subcutaneously in mice prior to the induction of EAE showed significant inhibition of EAE development together with a decreased frequency of CD3+ infiltration in the spinal cord of the treated mice compared to controls [63].

Freitag and colleagues demonstrated, in a mouse model of Celiac Disease (CeD), that intravenous infusion of gliadin-encapsulating NPs inhibited the proliferation, IFN-g and IL-17 secretion from gliadin-specific T cells, increased frequency of $FoxP3^+$ Tregs, and decreased anti-gliadin antibody production [64]. Based on these promising results, two clinical trials have been performed to induce gluten-specific tolerance in CeD patients. Results showed that administration of gliadin-encapsulating NPs (TAK-101) was well tolerated, and that Ag-specific T cell response was reduced compared to placebo group. Furthermore, TAK-101 treatment was associated with a reduction in intestinal mucosa damages [65].

An alternative approach to induce Ag-specific tolerance is the use of Ag-delivering antibodies [66]. This system aims to selectively deliver a particular Ag to DCs using the highly specific binding of monoclonal antibodies (mAbs) to cell surface molecules expressed by naturally occurring tolDCs. Once injected *in vivo*, mAbs conjugated to an Ag, bind to their cognate ligand, are internalized and the delivered Ag is processed and presented by DCs to T cells. Since the purpose is to specifically target DCs with tolerogenic properties, the processed Ag will be presented in a pro-tolerogenic context,

leading to the induction/expansion of Tregs, and/or anergy/deletion of Ag-specific effector T cells. Three types of Ag-delivering mAbs have been developed: chemical conjugates between native Abs and Ags; recombinant chimeric Abs; and single-chain fragment variable (scFv) constructs [67].

Due to the pro-tolerogenic properties of DEC-205 + BTLA hi DCs [68], the first recombinant chimeric Abs were originally designed to target DCs expressing DEC205 (CD205, LY75) [69]. Pioneer studies on this approach led to the establishment of efficient tolerance in different pre-clinical models of autoimmunity. In EAE, treatment with anti-DEC-205 chimeric Abs fused with disease relevant Ags resulted in amelioration of the disease score, prevention of pathogenic T cell accumulation in the CNS, induction of anergy in T effector cells, and reduction in IL-17 secretion[70][71]. Several studies in NOD mice demonstrated that anti-DEC-205 chimeric Ab or anti-DCIR2 chimeric Ab fused with insulin or β-cell-derived Ags induced clonal deletion of CD4 + and CD8 + autoreactive T cells, and conversion of pathogenic CD4 + T cells into FoxP3 + Tregs (reviewed in [67]). Furthermore, administration of anti-DEC205 coupled with a disease-relevant peptide reduced inflammation and symptom severity in models of proteoglycan-induced arthritis and Inflammatory Bowel Disease. At the cellular level, effector T cell deletion/anergy was induced and a portion of the autoreactive CD4 + T cells was converted into FoxP3 + Tregs [72][73]. An alternative target for Ag delivery to DCs is CLEC9A (DNGR1). Ag-coupled anti-DNGR-1 mAb promoted the proliferation of Ag-specific CD4 + T cells and their differentiation into Foxp3 + Tregs [74].

Epicutaneous immunotherapy (EPIT) is a novel immune-therapeutic approach that deliver the Ag to the APCs localized in the superficial layers of the skin *via* repetitive applications of an adhesive dermal patch containing a small amount of Ag (Figure 1). In animal models of food allergy it has been demonstrated that this approach induces desensitization to the given Ag, protects from inflammation and anaphylaxis, and induces Tregs (reviewed in [75]). Moreover, it has been demonstrated that the uptake of the Ag by Langerhans cells plays a central role in the induction of Ag-specific tolerance during EPIT [76]. Several clinical trials of EPIT have recently been completed or are ongoing for pollen, peanuts and milk allergies with encouraging results in terms of safety and tolerability (reviewed in [75]).

The work on the food allergies paved the way for the application of this approach also in autoimmune disease setting. In particular, promising results in preclinical models of MS [77] led to the development of two in-human study for EPIT in Relapsing Remitting MS patients that were treated with an adhesive patch containing a mixture of immunodominant myelin peptides applied to the skin. In the first study, transdermal immunization + promoted Tr1 cells and strongly suppressed myelin-reactive T-cell responses [78]. While in the second study, it was observed that the treatment was well tolerated and significantly reduced both magnetic resonance imaging outcomes (number of Gadolinium^{+} lesions) and clinical symptoms (relapse rate) [79]. The ability of EPIT to induce tolerance has been also tested in animal model of trinitrobenzene sulfonic acid (TNBS) induced ulcerative colitis. In the study the patches containing TNP-conjugated mouse immunoglobulin (TNP-Ig) were applied before the induction of colitis. Results showed that EPIT induced an amelioration of disease signs accompanied by a reduced production of IFNg and IL-17 and an increased production of IL-10 from solenocytes [80]. Finally, EPIT protocol has been also applied to Collagen Induced Arthritis (CIA) model. In this case the patches were soaked with type II collagen (COLL II) before CIA induction and their epicutaneous application was able to reduces disease severity [81].

5. Overall Conclusions

The improved knowledge of tolDCs and the development of protocols to generate cells *ex vivo* leads to the clinical application of these cells in autoimmune diseases. Overall, the generation of tolDCs *ex vivo* from patients' monocytes is feasible and tolDC treatment can be safe and effective for some pathologies. However, there are some limitations that must be considered for improving the development of effective tolDC therapy. In particular, the selection of immune-relevant Ags is crucial, sometimes challenging or not applicable to all autoimmune diseases due to the lack of associated Ags. To overcome this problem, it has been proposed to pulse T cells with pools of different disease associated Ags [82]. Another important aspect to take into consideration is the specific migration of tolDCs to the disease target organ or to the relevant draining lymph nodes to enhance the therapeutic effect. To this end, different routes of administration have been exploited [83], or alternatively, the manipulation of tolDCs by over-expressing specific chemokine receptors to improve tissue-specific homing. Moreover, the generation of autologous ex vivo tolDCs requires the isolation and differentiation of the cells from patients' monocytes, which may bear some alterations that will interfere with the functionality of the final cell product [84]. Finally, the production of ex vivo tolDCs requires extreme manipulation, which leads inevitably to high manufacturing costs. As an alternative to ex vivo manipulation, the development of alternative strategies to induce tolerance by autologous tolDCs *in vivo* can be considered.

Gaining knowledge on the biology of monocytes, the starting population used to generate ex vivo tolDCs, as well as on DCs in autoimmune diseases and on tolDCs, will lead to optimize the manufacturing protocols and to identify new approaches for the generation of innovative tolDCs and possible targets for *in vivo* modulation of DCs in the context of

autoimmunity.

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