Autoimmunity Reviews 14 (2015) 517–527

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Skewing dendritic cell differentiation towards a tolerogenic state for recovery of tolerance in rheumatoid arthritis

Katina Schinnerling, Lilian Soto, Paulina García-González, Diego Catalán *, Juan C. Aguillón *

Programa Disciplinario de Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Santiago, Chile
Millennium Institute on Immunology and Immunotherapy, Santiago, Chile

ARTICLE INFO

Article history:
Received 15 January 2015
Accepted 20 January 2015
Available online 26 January 2015

ABSTRACT

To date, the available options to treat autoimmune diseases such as rheumatoid arthritis (RA) include traditional corticoids and biological drugs, which are not exempt of adverse effects. The development of cellular therapies based on dendritic cells with tolerogenic functions (TolDCs) has opened a new possibility to efficiently eradicate symptoms and control the immune response in the field of autoimmunity. TolDCs are an attractive tool for antigen-specific immunotherapy to restore self-tolerance in RA and other autoimmune disorders. A promising strategy is to inject autologous self-antigen-loaded TolDCs, which are able to delete or reprogram autoreactive T cells. Different protocols for the generation of stable human TolDCs have been established and the therapeutic effect of TolDCs has been investigated in multiple rodent models of arthritis. Pilot studies in humans confirmed that TolDC application is safe, encouraging clinical trials using self-antigen-loaded TolDCs in RA patients. Although an abundance of molecular regulators of DC functions has been discovered in the last decade, no master regulator of tolerogenicity has been identified yet. Further research is required to define biomarkers or key regulators of tolerogenicity that might facilitate the induction and monitoring of TolDCs.

Contents

Abbreviations: RA, rheumatoid arthritis; DCs, dendritic cells; TolDCs, tolerogenic dendritic cells; NSAIDs, non-steroidal anti-inflammatory drugs; GC, glucocorticoids; DMARDs, disease-modifying anti-rheumatic drugs; TLRs, toll-like receptors; CLRs, cell surface C-type lectin receptors; NOD, nucleotide-binding oligomerization domain; NRLs, (NOD)-like receptors; RIG, retinoid acid-inducible gene; RLRs, (RIG) I-like receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; CXCR4, C-X-C motif chemokine receptor 4; CCR7, C-C motif chemokine receptor 7; MHC, major histocompatibility complex; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; TCR, T cell antigen receptors; Tregs, natural occurring regulatory T cells; Tr1, IL-10-secreting type 1 regulatory T cells; TGFβ, transforming growth factor-beta; IFNγ, interferon-gamma; Th1, IFNγ-producing type 1 T helper cells; Th2, IL-4-producing type 2 T helper cells; Th17, IL-17-producing type 17 T helper cells; RANK, receptor activator of nuclear factor κB; RANKL, ligand of RANK; TNF, tumor necrosis factor; BAFF, B-cell-activating factor of the TNF family; IDO, indoleamine 2,3-dioxygenase; LPS, lipopolysaccharide; Dex, dexamethasone; VD3, vitamin D3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; MPLA, monophosphoryl lipid A; GMP, good manufacturing practice; CIA, collagen-induced arthritis; CII, type II collagen; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; EAE, experimental autoimmune encephalomyelitis; PPAR, peroxisome-proliferator activated receptor; GILZ, glucocorticoid-induced leucine zipper; ILT3, immunoglobulin-like transcript 3; PD-L1, programmed death ligand 1; AhR, aryl hydrocarbon receptor; BLIMP-1, B lymphocyte-induced maturation protein-1; ITIM, immunoreceptor tyrosine-based inhibitory motifs; RALDH2, retinaldehyde dehydrogenase type 2; TAM, Tyro3/Axl/Mer family receptor tyrosine kinases; IFNAR, type I interferon receptor; TNFAIP3, TNF alpha-induced protein 3 gene; RIP1, receptor interacting protein-1; TRAF6, TNF receptor associated factor 6; MFG-E8, milk fat globule-epidermal growth factor 8; HO-1, heme oxygenase-1; CO, carbon monoxide; SHP-1, Src homology region 2 domain-containing phosphatase-1; ID3, inhibitor of DNA binding 3; DCIR, DC immunoreceptor; DC-SIGN, DC-specific intercellular adhesion molecule-3-grabbing non-integrin; ERK, extracellular signal-regulated kinase; FcγRIIB, low affinity immunoglobulin gamma Fc region receptor II-B; FICZ, 6-formylindolo [3,2-b] carbazole; Gas6, growth arrest-specific gene 6; IRF-3, interferon regulatory factor 3; ISRE, interferon-stimulated response element; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TZD, thiazolidinediones.

* Corresponding authors at: Programa Disciplinario de Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Independencia 1027, Santiago, Chile. Tel.: +56 2 2978 6347; fax: +56 2 2978 6979.
E-mail addresses: dfcatalan@med.uchile.cl (D. Catalán), jaguillo@med.uchile.cl (J.C. Aguillón).

http://dx.doi.org/10.1016/j.autrev.2015.01.014
1568-9972/

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, resulting from an autoimmune response to synovial antigens, and leading to cartilage and bone destruction that causes pain and disability [1]. The treatment for RA is based on a wide variety of therapeutic tools that include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents [2]. While NSAIDs constitute only a symptomatic relief and therefore they are not recommended as monotherapy, GC and DMARDs are immunosuppressive drugs with a wide spectrum of action, which are able to arrest the disease progression, but causing severe long-term adverse effects [3]. To overcome this issue, biologic agents intended to block specific pathways or targets involved in RA pathology have been introduced in the last decade. At present, biologic drugs approved for use in RA include cytokines- and cytokine receptor-blocking antibodies or cytokine soluble receptors, chimeric molecules that interfere with T-cell activation [4], B cell-depleting antibodies, and biologic inhibitors of cell signaling [5]. Although these therapies have a lower toxicity profile than DMARDs, they can occasionally cause severe complications, such as infections, autoimmunity or cancer [2]. Moreover, a considerable amount of patients still remain refractory to single or combined therapy with DMARDs and biologic agents, compelling the pharmaceutical industry to develop new members of both families of drugs, which are currently under evaluation in multiple clinical trials [6]. These drugs do not restore self-tolerance and therefore accomplish only a temporary disease remission requiring life-long treatment. Emerging therapeutic approaches focus on strategies to interfere with the generation and amplification of autoimmune responses, to achieve permanent restoration of self-tolerance without affecting protective immune functions [7,8].

Dendritic cells (DCs) are an attractive target of immunotherapy since they efficiently present antigens to T cells and govern the induction of immunity and tolerance dependent on their expression level of stimulatory and inhibitory ligands, receptors and soluble mediators [9]. A promising strategy is to modulate DCs in such a way, that they are able to silence or reprogram autoreactive T cells to a regulatory phenotype *in vivo*.

This article discusses the role of DCs in immune homeostasis and RA pathogenesis, the strategies for their modulation to a tolerogenic state (TolDCs), as well as the effects that TolDCs exert in pre-clinical models of autoimmune diseases and clinical trials in patients. Additionally, putative molecular regulators of DC tolerogenicity are reviewed.

2. Dendritic cells command T cell immunity and tolerance

2.1. Dendritic cell biology

Under steady state conditions, different subtypes of immature DCs residing in peripheral and lymphoid tissues or circulating in the blood, act as sentinels for incoming antigens. DCs become activated after recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular pattern molecules (DAMPs), either directly through pattern recognition receptors, such as toll-like receptors (TLRs), cell surface C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and the retinoid acid-inducible gene (RIG) I-like receptors (RLRs) [10], or indirectly by capturing apoptotic or necrotic cells through a DAMP-mediated TLR activation mechanism [11,12]. Alternatively, DCs can be activated through inflammatory cytokines secreted by cells of the innate immune system, epithelial cells, or fibroblasts, among others [13]. Activation by such “danger signals” induces a complex and coordinated process of maturation and migration in DCs. This differentiation process comprises: morphologic changes, endorsing high cellular motility [14]; loss of phagocytic receptors while endocytic receptors are retained [15]; secretion of specific chemokines, depending on the immune cells that need to be recruited [16]; upregulation of costimulatory (CD80, and CD86) and functional activator (CD40) molecules [17], and chemokine receptors CXCR4 and CCR7, among others [18,19]; synthesis of MHC molecules and translocation of peptide-MHC class II complexes to the cell surface [20]; and finally, the secretion of a specific cytokine profile that promote differentiation and polarization of effector immune cells [21].

2.2. Dendritic cell populations in humans

DCs are a heterogeneous group of cells, comprising BDCA2 + CD123 + plasmacytoid DCs, CD1c+ and CD141+ myeloid DCs, as well as CD14 + CD1c + inflammatory DCs [22]. Plasmacytoid DCs produce large amounts of type I interferons upon activation [23], and induce B cell differentiation into antibody-producing cells [24]. Initially, myeloid DCs were characterized by CD11c expression and subdivided into CD1c+, CD141+ and CD16+ subsets, however, assignment of the latter subset to DCs or monocytes is controversial [25,26]. Upon activation, myeloid CD1c + DCs secrete T lymphocyte-recruiting chemokines [27], and are potent stimulators of allogeneic T cells [25]. Myeloid CD141 + DCs ingest necrotic cells *via* CLEC9A, and are able to efficiently crosspresent antigen to CD8+ T cells [28]. Inflammatory DCs have been found in murine models of inflammatory diseases [29] and affected tissues from patients with atopic dermatitis, psoriasis, and RA [30,31]. In contrast to myeloid and plasmacytoid DCs which originate from a common DC precursor, inflammatory DCs differentiate from CD14+ monocytes recruited from the blood to sites of inflammation [30]. The ability of monocytes to differentiate into DCs was first described by Sallusto and Lanzavecchia, who reported the generation of DCs from human peripheral blood monocytes after *in vitro* culture with granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-4 for 7 days [32]. The close relation between *in vitro* generated monocyte-derived DCs and inflammatory DCs found *in vivo* was confirmed by transcriptome analyses [30]. During the past two decades, the generation of monocyte-derived DCs has enabled numerous functional studies on human DCs that were previously hampered because of the small number of DCs present in human peripheral blood, and has henceforth become a promising tool for cell-based immunotherapies [33].

2.3. Dendritic cells as key players in central tolerance and peripheral tolerance

A pivotal role of DCs in the control of central (thymic) tolerance and peripheral tolerance was underscored by the fact that the absence of DCs leads to the development of spontaneous autoimmunity in mice [34]. In the thymus, DCs are involved in negative selection and clonal deletion of autoreactive thymocytes with high affinity T cell antigen receptors (TCR) [35,36]. Epithelial cells in the Hassall's corpuscles of the thymus express thymic stromal lymphopoietin which instructs thymic DCs to convert self-reactive thymocytes into natural occurring CD4 + CD25 + FOXP3 + regulatory T cells (Treg) [37], which constitutively express the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), an essential protein for the prevention of aberrant activation and expansion of conventional T cells [4]. However, autoreactive T cells with low-affinity TCRs are still released to the periphery, thus relying on well-organized mechanisms to prevent autoimmunity. In this sense, both Treg and CD8 + suppressor T cells play crucial roles in hindering the appearance of autoimmune diseases [38].

Several studies provide evidence on the tolerance-inducing properties of plasmacytoid DCs. Plasmacytoid DCs stimulated through CD40 have been shown to induce IL-10-secreting type 1 CD4 + regulatory T cells (Tr1) [39] as well as CD8 + Treg [40], Moreover, the depletion of plasmacytoid DCs exacerbated airway hypersensitivity in a mouse asthma model [41].

Under steady state conditions, tissue-resident immature and migratory semi-mature DCs of the myeloid lineage continuously present self-antigens to autoreactive T cells and, due to deficient costimulation, induce anergy or deletion of potentially harmful T cells [42]. Steady-state migratory DCs acquire antigens in non-inflamed tissues and carry these antigens to the draining lymph nodes where they convert naïve T cells into Treg or autoantigen-specific Tr1 [43]. In the guts and lungs, CD103 + DCs are responsible for retinoic acid and transforming growth factor beta (TGFβ)-dependent induction of Treg [44,45]. Dermis-derived DCs that trigger the generation of Treg are CD103 −, including the langerin-CD11b + retinoic acid-producing DC subset in mice [46], and the CD141 + CD14 + IL-10-producing DC population in human skin [47]. Dermal RelB + langerin + DCs use TGFβ/latency associated protein (LAP) complexes on their surface to convert CD4 + T cells into Treg [48]. Epidermal Langerhans cells of the skin are also potent inducers of T cell hyporesponsiveness and Treg conversion [49]. In human liver, an IL-10-secreting CD1c + DC subset has been shown to induce the differentiation of Treg and IL-4-producing type 2 T helper (Th2) cells in hyporesponsive CD4 + T cells, contributing to hepatic tolerance [50]. Recently, a population of IL-10-producing CD1c − CD141 − CD14 + DCs has been detected in human peripheral blood, and functional assays using their *in vitro* analogues point to their immunoregulatory capabilities [51]. Nevertheless it is likely that tolerogenic features of naturally occurring steady-state DC subsets can be easily overcome by inflammatory signals [52].

3. Dual role of dendritic cells in rheumatoid arthritis

3.1. Dendritic cells in the pathogenesis of rheumatoid arthritis

Synovial fluid and tissue of RA patients are infiltrated by immature and mature DCs that accumulate in perivascular regions closely associated with T cells and B cell follicles [53,54]. It has been suggested that DCs might either migrate to the joint in response to cytokines and chemokines, or differentiate locally from myeloid progenitors in response to growth factors present in synovial fluid [55]. There is strong evidence that DCs contribute to the initiation and/or perpetuation of inflammation through the presentation of synovial autoantigens and activation of T cells [56,57]. Synovial DCs are highly activated in RA patients, including enhanced expression of MHC and costimulatory molecules, RelB, receptor activator of nuclear factor κB (RANK) and its ligand, RANKL [54,57,58].

Both myeloid and plasmacytoid DCs populations are increased in synovial fluid from RA patients compared with peripheral blood [59]. Myeloid CD1c + DCs appear to play a key role in promoting synovial inflammation by producing large amounts of T cell-attracting chemokines and the pro-inflammatory cytokines IL-12 and IL-23, which promote T cell differentiation towards IFNγ-producing type 1 (Th1) and IL-17-producing type 17 (Th17) cells, respectively [60,61]. Plasmacytoid DCs recruited to RA synovial tissue and capable of producing interferon (IFN)α, IFNβ, IL-18, and IL-23 could contribute to the local inflammatory environment [61]. Furthermore, plasmacytoid DCs expressing of B-cell-activating factor of the tumor necrosis factor (TNF) family (BAFF) might promote B cell survival within RA synovial tissue [61]. This is supported by the particular increase of synovial plasmacytoid DCs in RA patients who display anti-citrullinated protein antibodies, and the positive correlation between autoantibody levels in serum and plasmacytoid DC numbers in synovium [61]. It has been reported that TGFβ-treated plasmacytoid DCs promote the differentiation of naïve T cells into Th17 cells with arthritogenic features [62]. In contrast, some investigators attributed plasmacytoid DCs a protective role in RA. For instance, a population of plasmacytoid DCs expressing indoleamine 2,3-dioxygenase (IDO) and capable of generating Tr1 cells *in vitro*, increase in peripheral blood of RA patients after therapy-induced remission [63]. In an animal model of RA, selective depletion of this plasmacytoid DC population aggravated severity of disease and enhanced autoreactive responses [64].

A population of monocyte-derived inflammatory DCs has been recently identified in synovial fluid of RA patients [30,65]. These inflammatory DCs were characterized by the production of the pro-inflammatory cytokines TNF, IL-6 and IL-1β, and the capacity to drive Th17 responses [30]. Human monocyte-derived DCs have been previously shown to promote cartilage destruction *in vitro* through a TNF-dependent mechanism [66]. The prominent role of DC-derived TNF in early autoimmune lesions has previously been shown in the mouse model [67], and is supported by the effective suppression of joint damage in RA patients who receive anti-TNF therapy [68].

3.2. Tolerogenic dendritic cells as therapeutics for rheumatoid arthritis

In the last two decades, researchers have made intensive efforts in developing innovative therapies based on conditioned DCs for the treatment of RA [69–72] and other autoimmune diseases [7,8]. The main therapeutic approach is to differentiate patient's precursor cells (such as monocytes and bone marrow-derived stem cells) *ex vivo* into DCs with tolerogenic properties, which are then loaded with appropriate autoantigens and re-infused in the patient with the goal of restoring T cell tolerance to specific autoantigens and achieving long-term remission (Fig. 1).

3.3. Experimental approaches for in vitro generation of tolerogenic dendritic cells

There is a multitude of experimental procedures to induce stable tolerogenic features in DCs derived from monocytes [69,72] or bone marrow-derived stem cells [73]. These include DC modulation with cytokines, such as IL-10 [74], TGFβ [75], IL-21 [76], hepatocyte growth factor [77], IL-6 [78], TNF [79], and combination of IL-10 with TGFβ or IL-6 [80]; short stimulation with microbial products like lipopolysaccharide (LPS) [81] or *Aspergillus oryzae* protease [82]; immunosuppressive drugs, such as dexamethasone (Dex) [83], rapamycin [84], aspirin [85], cyclosporine A [86], mycophenolic acid [87], and the Janus kinase inhibitor tofacitinib [88]; natural compounds like resveratrol [89], curcumine [90], sulforaphane [91], 1α,25-dihydroxyvitamin D3, the active form of vitamin D3 (VD3), either alone [92], or in combination with Dex [93]; the hormone vasoactive intestinal peptide [94]; protein kinase

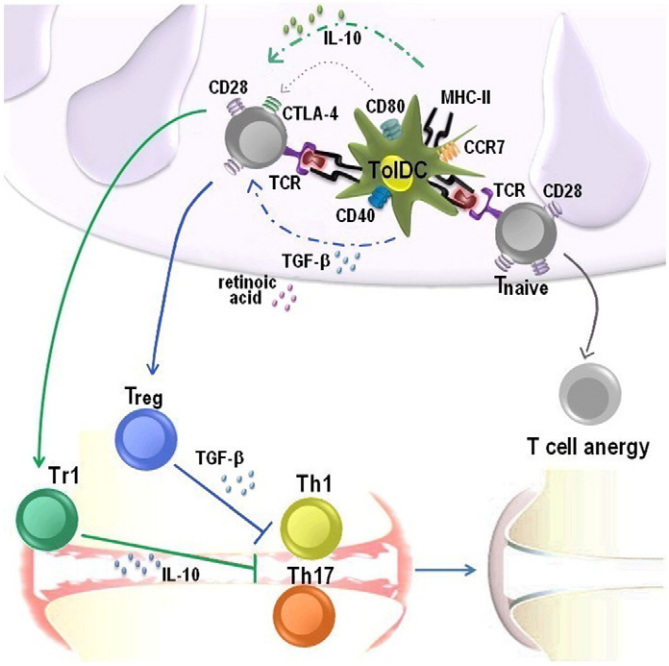

Fig. 1. Tolerogenic dendritic cells as therapeutic tools to restore self-tolerance in rheumatoid arthritis. Tolerogenic dendritic cells (TolDCs) can establish antigen-specific tolerance by presenting autoantigen peptides to CD4+ T cells in the context of low or inhibitory costimulation (CD80/CTLA-4 signals dominate), and anti-inflammatory cytokines IL-10 and TGFβ. Contact with these TolDCs induces anergy in naïve autoantigen-specific T cells and promotes the generation of IL-10 and TGFβ producing Tr1 and Treg, which suppress effector T cell responses and joint inflammation.

C inhibitors [95]; modulators of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity, such as BAY11-7082 [96], rosiglitazone and andrographolide [97]; and the CTLA4-Ig fusion protein abatacept [98], among others. Alternatively, TolDCs have been obtained through genetic modifications such as transduction of the IL-10 or IL-4 genes [99,100], and knockdown of costimulatory molecules using RNA interference [101]. Partial maturation of TolDCs, induced by additional stimulation with LPS [102], the non-toxic LPS analogue monophosphoryl lipid A (MPLA) [103], or a cytokine cocktail, containing TNF, IL-1β and prostaglandin E2 [104], enhances antigen presentation, acquisition of lymph node homing capacity, and stability of the tolerogenic phenotype [105,106], features which are all desirable when thinking in a potential therapeutic use of TolDCs.

Though the properties of TolDCs may vary dependent on the protocol used for their generation, there are fundamental similarities, such as (i) reduced expression of co-stimulatory molecules, (ii) low production of pro-inflammatory cytokines, *i.e.* IL-12, and high levels of anti-inflammatory cytokines IL-10 and/or TGFβ, and (iii) the ability to induce T cell hyporesponsiveness or IL-10-producing Tr1 cells. In recent years, protocols have adapted Good Manufacturing Practice (GMP) requirements for therapeutic application in patients [103–105].

3.4. Tolerogenic dendritic cells in pre-clinical models of rheumatoid arthritis

Several studies in mice suggest that TolDCs are able to modulate arthritogenic autoimmune responses *in vivo*. In a mouse model of adjuvant-induced arthritis, provoked by the intra-articular injection of methylated bovine serum albumin, BAY 11-7082-treated bone-marrow-derived DCs induced antigen-specific immune suppression, associated with increased IL-10 production and antibody isotype switching from IgG2b to IgG1 and IgA [96].

Collagen-induced arthritis (CIA) is the most studied mouse model of RA, which develops in susceptible strains after immunization with type II collagen (CII), the major component of articular cartilage, and shares many pathophysiological features with human RA, such as mononuclear cell infiltration, *pannus* development, and cartilage and bone erosion [107]. The development of CIA can be prevented by administration of DCs modulated with TNF, Dex, or IL-10 [108]. A recent study demonstrates that CII-pulsed DCs treated with the calcineurin inhibitor FK506/Tacrolimus act as cellular drug delivery system that targets antigen-specific T cells and inhibits CIA [109]. Interestingly, FK506-treated DCs exhibited a mature phenotype and continuously released the drug over several days, causing activation induced cell death in encountered T cells [109].

Established CIA can be reduced by CII-pulsed TolDCs treated with Dex and VD3 [110]. The decline in disease severity and progression is accompanied by a decreased proportion of Th17 cells and an increase in IL-10-producing T cells [110]. Recently, our group demonstrated that short-term LPS-modulated TolDCs loaded with CII inhibit CIA in an IL-10 and TGFβ dependent manner [111]. Another report demonstrates that allogeneic murine bone-marrow-derived DCs, modulated with IL-10 plus TGFβ and loaded with CII, reduce Th17-driven inflammation and CIA progression [112]. Even human monocyte-derived TolDCs, modulated by FK506/Tacrolimus, exhibited a therapeutic effect in CIA mice [113].

Despite similarities between RA-like disease in mice and human RA, studies in mice are limited by differences between murine and human immune systems [114], the diversity of genetic and environmental factors predisposing to human RA [115], and the multitude of T cell autoantigens involved in the development and perpetuation of chronic RA, requiring more sophisticated preclinical models, as humanized mice, to validate the therapeutic effect of TolDCs before their application in patients.

3.5 . Tolerogenic dendritic cells in clinical trials of rheumatoid arthritis and other autoimmune diseases

The use of TolDCs as tolerance-inducing therapeutics was inspired by a visionary study from Dhodapkar and colleagues, who injected autologous immature DCs pulsed with influenza matrix peptide into healthy individuals [116]. As a result, the effector function of antigen-specific CD8+ T cells was inhibited, while antigen-specific IL-10-secreting T cells emerged, pointing to a tolerizing effect of immature DCs [116]. More than ten years passed from this pioneer study until Giannoukakis and colleagues published the first clinical trial using TolDCs in type 1 diabetic patients [117]. In a randomized, double-blind, phase I study, seven insulin-requiring type 1 diabetic patients received four intradermal administrations of autologous TolDCs, generated from monocytes and treated with a mixture of antisense oligonucleotides targeting the primary transcripts of CD40, CD80 and CD86 [117]. The trial proved that administration of TolDCs was not only safe and well tolerated, but also increased the frequency of a B220 + CD11-B cell population [117]. Further *in vitro* studies and *in vivo* experiments in non-obese diabetic mice indicated that the TolDCs used in the clinical trial convert and expand IL-10-producing regulatory B cells with suppressive properties through the production of retinoic acid [118,119].

At present, two phase I clinical trials with TolDCs are conducted in RA patients. An approach published by J. Isaacs and C. Hilkens uses autologous DCs modulated with Dex, VD3, and MPLA, and pulsed with synovial fluid, which were injected into inflamed joints [69]. The setup of Thomas and co-workers is based on the intradermal administration of autologous DCs, modulated by the NF-kB inhibitor BAY11-7082 and pulsed with a mixture of four different citrullinated peptides, to patients displaying “shared epitope” alleles and anti-citrullinated protein antibodies [120]. Both strategies, using different protocols for DC generation and antigen loading, highlight the emergence of TolDC therapy as a new approach to treat autoimmune diseases.

4. Molecular regulators of tolerogenicity in dendritic cells

An important point to consider when translating TolDCs to clinical application is the definition of specific tolerance-inducing features as quality control parameters of the *ex vivo* differentiated cells. The multitude of modulation strategies, interfering with different signaling pathways and evoking a particular DC phenotype, makes it a challenging task to identify unique intrinsic factors that confer tolerogenic properties to DCs (Table 1).

4.1. Transcription factors and adaptor proteins

To date, no master regulator of DC tolerogenicity is known. Approaches to identify biomarkers for TolDCs, either by transcriptional profiling [80,91] or 2D gel electrophoresis and mass spectrometry [121], showed inconsistent results and failed to identify a universal molecular regulator of tolerogenic function. However, studies in knockout mice revealed several transcriptional regulators, which exert tolerizing effects [122].

Table 1
Intrinsic regulators of dendritic cell tolerogenicity.

Regulator	Targets or affected signaling pathways in DCs	Inducing stimuli or agonist	Reference
NF-κB1 p50 (homodimer)	Suppression of TLR-induced inflammatory cytokines; induction of IL-10 transcription and expression of TGF-β and retinoic acid	IL-10, TLR signals, commensals?	[124,125,183]
PPAR-γ	Inhibition of NF-κB nuclear localization	TZD, *e.g.* rosiglitazone	[97,137]
BLIMP-1	Suppression of *Il6* and *Ccl2* transcription	TLR ligands	[144,145]
STAT3	Inhibition of NF-κB activation; induction of SOCS3 expression; reduction of LPS-induced maturation and pro-inflammatory cytokine production	IL-10, IL-6, CTLA-4	[132,133,184]
GILZ	Blockage of NF-κB, MAPK, and AP-1 signal transduction pathways; induction of Tr1-promoting features	GCs, IL-10, TGF-β, VD3	[82,139,140]
AhR	Promotion of *Il8*, *Baff*, *Irf3* and *Cyp1a* expression when partnering with NF-κB subunit RelB; induction of indoleamine 2,3-dioxygenase expression	Toxins (*e.g.* TCDD), tryptophan metabolites (FICZ, kynurenine)	[143,185,186]
SOCS-1	Blockage of TLR-induced STAT-1 activation; impairment of Th1-inducing capacity	GCs, TLR ligands	[128,130]
SOCS-3	Blockage of p38/MAPK activation; overexpression induces Th2 polarizing features	Retinoic acid, IL-6, TLR ligands	[135,152]
ERK	Decrease of NF-κB DNA-binding activity and inhibitor of κBα levels	Mitogens, growth factors	[169]
SHP-1	Recruitment to cytoplasmic domains of inhibitory receptors; inhibition of NF-kB, AP-1, ERK, and JNK activity, while enhancing p38 activity; inhibition of pro-survival signals through AKT activation; inhibition of CCR7 expression	Cytokines, growth factors, binding to inhibitory receptors (*e.g.* ILT3, FcγRIIB)	[171,172]
Lyn	Src family tyrosin kinase; phosphorylating of ITIM motifs (*e.g.* of FcγRIIb); negative regulation of MyD88 signaling pathway; recruitment of inhibitory phosphatases SHP1/2	Integrins, growth factors, binding to FcεRI	[173,187]
HO-1	Heme oxygenase, degradation of heme into biliverdin, CO and free iron; inhibition of NF-κB p65 and IRF-3 activation	IL-10, cobalt protoporphyrin	[165–167]
A20/TNFAIP3	Deubiquitinase, degradation of intermediate NF-κB signaling molecules, *e.g.* RIP1, TRAF6; interference with TLR, NOD2, CD40, IL-1R and TNFR signals	TNF	[162,163]
TAM	Action *via* type I interferon receptor (IFNAR)-STAT1 pathway; induction of SOCS1 and SOCS3, inhibition of TRAF3/6	Gas6/ProS	[160]
RALDH2	Retinaldehyde dehydrogenase, conversion of retinal to retinoic acid which induces SOCS3 expression; suppresses MAPK p38 activation and prevents expression of proinflammatory cytokines	Dex	[82,152]
IDO	Indoleamine 2,3-dioxygenase: degradation of tryptophan to kynuric acid; tryptophan deprivation induces stress response pathway mediated by the GCN2 kinase	Dex, AhR agonists	[82,143,148]
CD39	Ecto-ATPDase, hydrolysis of ATP and ADP to AMP reduces extracellular concentration of pro-inflammatory ATP and decreased ATP-triggered activation of NLRP3 inflammasome	TGF-β, IL-27	[80,174]
PD-L1	Interaction with PD-1 on T cells favors induction of Treg responses and triggers IL-10 production	VD3 + LPS	[102]
ILT3	Inhibition of cell activation by transmitting negative signals through cytoplasmic ITIM, recruitment of SHP-1 and inhibition of NF-κB signaling	Resveratrol, IL-10, IFN-α, Dex, VD3, rapamycin	[89,148,149]
ILT4	Inhibition of cell activation by transmitting negative signals through cytoplasmic ITIM, recruitment of SHP-1 and inhibition of NF-κB signaling	Resveratrol, IL-10, IFN-α, rapamycin, HLA-G	[51,89,148]
TLR2	Induction of RALDH2 expression *via* activation of ERK	Dex, VD3, IL-10 + LPS	[152,188]
FcγRIIB (CD32b)	Inhibition of cell activation by transmitting negative signals through cytoplasmic ITIM, recruitment of SHP-1 and inhibition of NF-κB signaling	IgG immune complexes	[157,159]
DEC-205	Delivery of endocytosed protein for MHC class II presentation and MHC class I crosspresentation, leading to induction of regulatory CD4+ and CD8+ T cells, expression of B7H1 molecules, and TGF-β secretion	Modified extracellular proteins (of apoptotic cells)	[153,154,189]
DCIR	C-type lectin antigen uptake and signaling receptor; inhibition of cell activation by transmitting negative signals through cytoplasmic ITIM, recruitment of SHP-1 and SHP-2, leading to downregulation of TLR8-induced IL-12 and TNF production	Glycoproteins from pathogenic and endogenous origin	[155,190,191]
DC-SIGN	C-type lectin antigen uptake and signaling receptor; modulates TLR signals through ERK1/2 and Akt phosphorylation, thereby favoring IL-10 production and Th2/Tr1 responses	Mannose-containing glycoconjugates from pathogenic and endogenous origin	[192–194]
Wnt5a	Stimulation of intracellular Ca2+ mobilization and triggering of Calmodulin-dependend protein kinase II, leading to upregulation of inhibitor of DNA binding 3 (ID3) and SOCS3 expression; induction of STAT3 and IL-6 production	Inflammation, sepsis	[176,177,195]
C1q	Complex formation with gC1qR and DC-SIGN; increase of ERK, p38 and p70S6 kinase activity	TLR ligands, IL-6, Dex	[181,182]
MFG-E8	Phosphatidylserine-binding protein; suppression of ISRE and NF-κB activity; activation of STAT-3 and A20	GM-CSF	[178,179]

Abbreviations used: BLIMP-1: B lymphocyte-induced maturation protein 1; CO: carbon monoxide; DCIR: DC immunoreceptor; DC-SIGN: DC-specific intercellular adhesion molecule-3-grabbing non-integrin; Dex: dexametahasone; ERK: extracellular signal-regulated kinase; FcγRIIB: Low affinity immunoglobulin gamma Fc region receptor II-B; FICZ: 6-formylindolo [3,2-b] carbazole; Gas6: growth arrest-specific gene 6; HO-1: heme oxygenase 1; IRF-3: interferon regulatory factor 3; ISRE: interferon-stimulated response element; ITIM: immunoreceptor tyrosine-based inhibitory motifs; MFG-E8: milk fat globule-epidermal growth factor 8; PD-L1: programmed death ligand 1; PPAR: peroxisome-proliferator activated receptor; RALDH2: retinaldehyde dehydrogenase type 2; RIP: receptor interacting protein; SHP-1: SH2-containing protein tyrosine phosphatase 1; SOCS: suppressor of cytokine signaling; STAT: signal transducer and activator of transcription; TAM: Tyro3/Axl/Mer (TAM) family receptor tyrosine kinases; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; TRAF6: tumor necrosis factor receptor associated factor 6; TZD: thiazolidinediones; VD3: Vitamin D3.

NF-κB is known to play a central role in DC activation. A detailed analysis of the different NF-κB family members revealed that heterodimers of NFκ-B1 p50 and RelA or NF-κB2 p52 and RelB promote inflammatory responses, while NF-κB1 p50 homodimers act as transcriptional repressors [123–125]. Self-antigen-pulsed unstimulated DCs deficient for NF-κB1 induced CD8 + T cell responses and triggered autoimmunity *in vivo* [126]. Moreover, DCs lacking NF-κB1 have shown an increased secretion of pro-inflammatory cytokines and an extended lifespan [127].

Differentiation, maturation and functions of DCs are tightly controlled by the counterregulation of the signal transducer and activator of transcription (STAT) and suppressor of cytokine signaling (SOCS) family protein members. TLR-mediated STAT1 activation is attenuated by GCs through the induction of SOCS1 [128]. SOCS1-deficient DCs induce hyperactivation of Th1, promote B cell proliferation, autoantibody production and the development of lupus-like autoimmune disease [129,130]. STAT3 directs the anti-inflammatory effects of IL-10, IL-6 and CTLA-4 [131–133], and the activation of STAT3 reduces LPS-induced DC maturation [131]. STAT3-deficiency in DCs leads to enhanced pro-inflammatory cytokine production, antigen-dependent T-cell activation and resistance to IL-10-mediated suppression [132]. Mice with conditional knockout of STAT3 in CD11c + DCs develop intestinal inflammation [132]. SOCS3-deficiency in DCs resulted in constitutive activation of STAT3, and decreased expression of MHC class II, costimulatory molecules, and IL-12 [134]. SOCS3-deficient DCs promoted TGFβ-mediated Treg expansion, and reduced the severity of experimental autoimmune encephalomyelitis (EAE) [134]. Interestingly, transduction with SOCS3 also decreased expression of MHC class II, CD86, IL-12 and IL-23, while enhancing IL-10 production [135]. Adoptive transfer of DCs overexpressing SOCS3 suppressed EAE and skewed differentiation of myelin antigen-specific T cells towards Th2 [135].

Peroxisome-proliferator activated receptor (PPAR)-γ is highly expressed in immature human monocyte-derived DCs [136]. Activation of PPAR-γ by thiazolidinediones/glitazones hampers nuclear localization of the RelB subunit of NF-κB, thereby affecting LPS-induced maturation, IL-12 secretion, expression of CCR7 and its ligand CCL19, and the capacity to prime antigen-specific CD4 + and cytotoxic T cell responses [136,137]. Moreover, PPAR-γ ligation induces the expression of TGFβ and retinoic acid in murine bone-marrow-derived DCs and endows them with the capacity to generate Treg [138]. DCs that were treated with the PPAR-γ agonist rosiglitazone and pulsed with myelin antigens prevented the development of EAE in mice [97].

The transcription inhibitor GC-induced leucine zipper (GILZ) is a key mediator of the anti-inflammatory effects exerted by GCs, IL-10, and TGFβ [139]. GILZ interacts with and inhibits NF-κB, STAT, AP-1, Ras and Raf-1, thereby preventing the upregulation of costimulatory molecules, inflammatory cytokines and chemokines in DCs [140]. Additionally, GILZ stimulates immunoglobulin-like transcript 3 (ILT3) and programmed death ligand 1 (PD-L1) expression, IL-10 production, and induction of antigen-specific Tr1 cells [139,141]. In the EAE model, GILZ expression in transferred TolDCs was indispensable for the inhibition of Th1 and Th17 responses, Treg induction and reduction of disease severity [142].

The expression of the ligand-activated transcription factor aryl hydrocarbon receptor (AhR) equips DCs with the capacity to express IL-10 and IDO [143]. IDO degrades tryptophan to kynurenin, which inhibits T cell proliferation due to amino acid starvation, and promotes the generation of FOXP3 + Treg [143].

An important role of the transcriptional repressor B lymphocyte-induced maturation protein-1 (BLIMP-1) in the regulation of DC function has been discovered recently [144,145]. The expression of BLIMP-1 is upregulated upon DC activation and negatively regulates the expression of IL-6 and CCL2 genes [144]. BLIMP-1 deficient DCs exhibit elevated expression of MHC II and increased secretion of pro-inflammatory cytokines upon exposure to TLR agonists, and conditional knockout of Blimp-1 in DCs induced a lupus-like disease in mice [145].

4.2. Membrane inhibitory receptors

Several surface molecules have been suggested as TolDC markers. Inhibitory receptors ILT3 and ILT4 transmit negative signals through cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIM) [146]. While ILT4 binds to classical MHC class I and non-classical MHC human leukocyte antigen (HLA)-G, the ligand of ILT3 is unknown [147]. Expression of ILT3 has been shown to be required for the induction of Treg by TolDCs [148]. TolDCs derived from ILT3-transduced human hematopoietic stem/progenitor cells exhibited decreased expression of costimulatory molecules, downregulation of NF-κB, and the capacity to induce allogeneic T cell hyporesponsiveness and functional Treg [149]. Gregori and co-workers found that both, ILT4 and HLA-G are required for the induction of Tr1 cells by IL-10-derived TolDCs [51].

The inhibitory receptor PD-L1, constitutively expressed on murine and human T and B cells, macrophages and DCs, upon interaction with PD-1 on T cells, blocks the CD28-CD80/CD86-mediated T cell activation [150]. This CD80/CD86 co-inhibitory molecule, linked to the development and function of Tregs, could be considered as an alternative biomarker for cytokine- or LPS-activated VD3-induced DCs given its high expression on this type of TolDCs [102,151]; on the contrary, LPS-activated Dex-induced DCs displayed a low PD-L1 expression [102]. Our recent study, with partial maturated TolDCs, induced by additional stimulation with MPLA, did not find a differential expression of PD-L1 when compared to mature DCs [103].

Interestingly, TolDCs that were modulated with GCs, VD3, or IL-10 plus LPS showed a markedly elevated TLR2 expression in comparison to immature and mature DCs [93,103]. Activation of TLR2 has been shown to induce the expression of retinaldehyde dehydrogenase type 2 (RALDH2) in DCs *via* activation of extracellular signal-regulated kinase (ERK) [152]. RALDH2 converts retinal to retinoic acid, which promotes the *de novo* generation of Treg [44], but also acts in an autocrine manner on DCs, inducing the expression of SOCS3, which suppresses mitogen-activated protein kinase (MAPK) p38 activation and the production of proinflammatory cytokines [152].

C-type lectin receptors (CLRs), such as DEC-205, DC immunoreceptor (DCIR), and DC-SIGN, recognize glycosylated endogenous tissue antigens and play an important role as negative regulators of DCs. *In vivo* targeting of antigen to DEC-205 generates tolerance against the antibody-coupled antigen [153,154]. Mice deficient for DCIR spontaneously developed autoimmune sialadenitis and enthesitis, accompanied by elevated serum autoantibodies [155]. Activation of SIGN-R1, a murine DC-SIGN homolog, has been shown to induce IL-10 expression in lamina propria DCs promoting the generation of Tr1 cells [156].

Engagement of the inhibitory FcγRIIB (CD32B) by IgG-bearing immune complexes modulates DC function increasing IL-10 production, induces CD4 + and CD8 + T cell tolerance and promotes the generation of antigen-specific Tr1 cells [157–159].

TLR- and cytokine-induced DC maturation can also be inhibited by the Tyro3/Axl/Mer (TAM) receptor tyrosine kinases family, which forms a complex with type I interferon receptor (IFNAR), and uses the associated transcription factor STAT1 to trigger the production of SOCS1 and SOCS3 [160]. TAM triple gene-deficient mice exhibited DC hyperactivation and developed systemic autoimmunity [161].

4.3. Enzymes and signaling pathways-associated molecules

Recent studies have identified the ubiquitin-editing enzyme A20, the product of the TNF alpha-induced protein 3 gene(TNFAIP3), as a molecular checkpoint for the control of DC activation [162,163]. A20 deubiquitinate intermediate NF-κB signaling molecules, such as receptor interacting protein-1 (RIP1) and TNF receptor associated factor 6 (TRAF6) and thereby interferes with TLR, NOD2, CD40, IL-1R and TNFR signals in DCs [123,163]. DCs lacking A20 were resistant to apoptosis and show increased NF-κB signaling which leads to elevated expression of costimulatory molecules, MHC class II, and inflammatory cytokines

[163]. Mice with specific deletion of A20 in DCs are prone to develop autoimmune disease [162]. Single-nucleotide polymorphisms in the human TNFAIP3 locus are associated with increased susceptibility to multiple autoimmune disorders including RA, multiple sclerosis, and systemic lupus erythematosus [164].

The stress-inducible heme oxygenase-1 enzyme (HO-1) is also exclusively expressed in immature DCs [165] and catalyzes the degradation of heme into biliverdin, carbon monoxide (CO) and free iron [166]. The expression of HO-1 can be induced by IL-10 or cobalt protoporphyrin, and prevents LPS-induced maturation and secretion of pro-inflammatory cytokines in DCs through inhibition of NF-κB p65, while preserving IL-10 production [165]. Both induction of HO-1 expression and treatment with CO inhibit the IFN regulatory factor 3 pathway, thereby affecting maturation and T cell stimulatory capacity of DCs [165,167]. Gaseous CO-treated DCs pulsed with pancreatic β cell peptides showed reduced IL-12 production and protected mice from autoimmune diabetes [168].

MAPK p38 and ERK signaling pathways differentially regulate the maturation of monocyte-derived DCs [169]. Opposite to MAPK p38, ERK signal transduction negatively regulates LPS- and TNF-induced DC maturation by decreasing the NF-κB DNA-binding activity and levels of inhibitor of κBα [169]. Lentiviral transfer of an ERK activator to DCs induced TGFβ production and conveyed the ability to induce functional Treg [170].

The Src homology region 2 domain-containing tyrosine phosphatase-1 (SHP-1) has been suggested as another intrinsic regulator of DC function. Specific inhibition or deletion of SHP-1 in DCs enhanced production of the pro-inflammatory cytokines IL-6, IL-12, and IL-1β, promoted survival, migration to draining lymph nodes, and Th1 activation resulting in glomerulonephritis and autoantibody production in aged mice [171,172].

A recent report demonstrated that DC-specific deletion of the Src family tyrosine kinase Lyn, a negative regulator of the MyD88 pathway, induced spontaneous T and B cell activation leading to lupus-like autoimmune disease [173].

Ecto-ATPDase CD39, which reduces the extracellular concentration of pro-inflammatory ATP, has been shown to be upregulated in TolDCs generated with TGFβ or IL-27 [80,174]. *In vivo*, CD39 expression by TolDCs prevented pathogenic Th1 and Th17 responses and the development of EAE [174].

4.4. Soluble regulators

The activation of β catenin signaling pathways by the binding of Wnt ligands to its Frizzled (Fzd) receptor programs tolerogenic functions in DCs [175]. The Wnt proteins Wnt5a and Wnt3a induce the secretion of IL-10 and TGFβ, respectively, and inhibit TLR-induced production of pro-inflammatory cytokines while supporting the generation of Treg [176]. Exogenous Wnt5a reduces the expression of HLA-DR and CD86, and increases DC-SIGN, PD-L1, and PD-L2 levels as well as IL-10 secretion in DCs [177]. Blocking experiments and transcriptional profiling revealed that Wnt5a acts through a non-canonical pathway, stimulating intracellular Ca^{2+} mobilization and triggering calmodulin-dependent protein kinase II, leading to an upregulation of inhibitor of DNA binding 3 (ID3) and SOCS3 expression [177].

Milk fat globule EGF VIII (MFG-E8) has also been shown to be linked to DC tolerogenicity [178,179]. The expression of MFG-E8 can be induced by GM-CSF, and confers the ability to suppress Th1 and Th17 responses and to induce Treg upon engulfment of apoptotic cells [178]. Immature, but not mature DCs, express high levels of MGF-E8, which restrains the co-stimulatory capabilities and pro-inflammatory cytokine production in response to necrotic cells *via* activation of STAT-3 and A20 [179].

Immature DCs, derived from monocytes or CD34+ stem cells, produce early complement component 1q (C1q), whose expression is completely downregulated following maturation [180]. C1q renders DCs tolerogenic, inducing IL-10, while reducing IL-12 and IL-23 production, and impairing the capacity to stimulate Th1 and Th17 responses [181]. C1q and its receptor C1qR were suggested to associate with DC-SIGN and might thereby regulate DC differentiation and function through DC-SIGN–mediated intracellular signaling pathways [182]. In clinical responders to allergen immunotherapy, levels of C1q were shown to be associated with the *in vivo* generation of TolDC [82].

5. Conclusions

The therapeutic effect of *ex vivo* generated TolDCs has been confirmed in animal models of RA and other autoimmune diseases, and the development of GMP-compliant protocols for the generation of stable human TolDCs has made a considerable progress in the recent years. Pilot studies on safety of the administration of TolDCs demonstrated promising results, which led to the conduction of the first phase I/II clinical trials using autoantigen-loaded TolDCs.

Further research is required to: (i) define immunodominant autoantigen peptide candidates for loading of TolDCs; (ii) establish preclinical humanized models for the characterization of TolDC effects on multiple cell types *in vivo*, and determination of optimal dose, time interval and route of TolDC application; and (iii) identify biomarkers or key regulators of tolerogenicity that would facilitate the quality control of TolDC preparations before administration to the patient, and enable monitoring of therapeutic success. Finally, the knowledge about proteins that control the differentiation and maintenance of the tolerogenic state could provide novel therapeutic targets for the development and application of reagents that specifically modulate DC functions.

Take-home messages

- DCs contribute substantially to the pathogenesis of RA and are thus target of novel therapeutic approaches.
- DCs with tolerance-inducing features can be generated *in vitro* from RA patient's peripheral blood monocytes.
- Hallmarks of TolDCs are (i) reduced expression of costimulatory molecules, (ii) an anti-inflammatory cytokine profile, and (iii) modulation of T cell responses.
- The efficacy of TolDCs has been demonstrated in mouse models of autoimmunity.
- First studies in humans confirmed safety of TolDCs administration; clinical phase I/II trials using autologous TolDCs in RA are in progress.
- A master regulator of TolDC function has not been yet identified.

Acknowledgments

The authors thank to Dr. Karina Pino-Lagos for critical revision of the manuscript, and Dr. Natalia Silva and Mrs. Jaxaira Maggi for figure design. Supported by FONDECYT-Chile 1140553, REDES140041, FONDECYT-Postdoctorado 3150453, Millennium Institute on Immunology and Immunotherapy-P09-016-F and Fundación Ciencia Translacional from Chile.

References

[1] Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376(9746):1094–108.
[2] Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73(3):492–509.
[3] Quan LD, Thiele GM, Tian J, Wang D. The development of novel therapies for rheumatoid arthritis. Expert Opin Ther Pat 2008;18(7):723–38.
[4] Romo-Tena J, Gomez-Martin D, Alcocer-Varela J. CTLA-4 and autoimmunity: new insights into the dual regulator of tolerance. Autoimmun Rev 2013;12(12):1171–6.

[5] Meier FM, McInnes IB. Small-molecule therapeutics in rheumatoid arthritis: scientific rationale, efficacy and safety. Best Pract Res Clin Rheumatol 2014;28(4):605–24.
[6] Chang C. Unmet needs in the treatment of autoimmunity: from aspirin to stem cells. Autoimmun Rev 2014;13(4–5):331–46.
[7] Van Brussel I, Lee WP, Rombouts M, Nuyts AH, Heylen M, De Winter BY, et al. Tolerogenic dendritic cell vaccines to treat autoimmune diseases: can the unattainable dream turn into reality? Autoimmun Rev 2014;13(2):138–50.
[8] Mackern-Oberti JP, Llanos C, Vega F, Salazar-Onfray F, Riedel CA, Bueno SM, et al. Role of dendritic cells in the initiation, progress and modulation of systemic autoimmune diseases. Autoimmun Rev 2015;14(2):127–39.
[9] Pulendran B, Tang H, Manicassamy S. Programming dendritic cells to induce T(H)2 and tolerogenic responses. Nat Immunol 2010;11(8):647–55.
[10] Barber GN. Innate immune DNA sensing pathways: STING, AIMII and the regulation of interferon production and inflammatory responses. Curr Opin Immunol 2011;23(1):10–20.
[11] Rock KL, Lai JJ, Kono H. Innate and adaptive immune responses to cell death. Immunol Rev 2011;243(1):191–205.
[12] Zelenay S, Reis e Sousa C. Adaptive immunity after cell death. Trends Immunol 2013;34(7):329–35.
[13] Ueno H, Klechevsky E, Morita R, Aspord C, Cao T, Matsui T, et al. Dendritic cell subsets in health and disease. Immunol Rev 2007;219(1):118–42.
[14] Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. Annu Rev Immunol 2005;23:975–1028.
[15] Platt CD, Ma JK, Chalouni C, Ebersold M, Bou-Reslan H, Carano RA, et al. Mature dendritic cells use endocytic receptors to capture and present antigens. Proc Natl Acad Sci U S A 2010;107(9):4287–92.
[16] Piqueras B, Connolly J, Freitas H, Palucka AK, Banchereau J. Upon viral exposure, myeloid and plasmacytoid dendritic cells produce 3 waves of distinct chemokines to recruit immune effectors. Blood 2006;107(7):2613–8.
[17] Han TH, Jin P, Ren J, Slezak S, Marincola FM, Stroncek DF. Evaluation of 3 clinical dendritic cell maturation protocols containing lipopolysaccharide and interferon-gamma. J Immunother 2009;32(4):399–407.
[18] Delgado-Martín C, Escribano C, Pablos JL, Riol-Blanco L, Rodríguez-Fernández JL. Chemokine CXCL12 uses CXCR4 and a signaling core formed by bifunctional Akt, extracellular signal-regulated kinase (ERK)1/2, and mammalian target of rapamycin complex 1 (mTORC1) proteins to control chemotaxis and survival simultaneously in mature dendritic cells. J Biol Chem 2011;286(43):37222–36.
[19] Dieu MC, Vanbervliet B, Vicari A, Bridon JM, Oldham E, Ait-Yahia S, et al. Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. J Exp Med 1998;188(2):373–86.
[20] Chow A, Toomre D, Garrett W, Mellman I. Dendritic cell maturation triggers retrograde MHC class II transport from lysosomes to the plasma membrane. Nature 2002;418(6901):988–94.
[21] Tanaka H, Demeure CE, Rubio M, Delespesse G, Sarfati M. Human monocyte-derived dendritic cells induce naive T cell differentiation into T helper cell type 2 (Th2) or Th1/Th2 effectors. Role of stimulator/responder ratio. J Exp Med 2000;192(3):405–12.
[22] Satpathy AT, Wu X, Albring JC, Murphy KM. Re(de)fining the dendritic cell lineage. Nat Immunol 2012;13(12):1145–54.
[23] Jaehn PS, Zaenker KS, Schmitz J, Dzionek A. Functional dichotomy of plasmacytoid dendritic cells: antigen-specific activation of T cells versus production of type I interferon. Eur J Immunol 2008;38(7):1822–32.
[24] Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity 2003;19(2):225–34.
[25] MacDonald KP, Munster DJ, Clark GJ, Dzionek A, Schmitz J, Hart DN. Characterization of human blood dendritic cell subsets. Blood 2002;100(13):4512–20.
[26] Lundberg K, Albrekt AS, Nelissen I, Santegoets S, de Gruijl TD, Gibbs S, et al. Transcriptional profiling of human dendritic cell populations and models—unique profiles of in vitro dendritic cells and implications on functionality and applicability. PLoS One 2013;8(1):e52875.
[27] Piccioli D, Tavarini S, Borgogni E, Steri V, Nuti S, Sammicheli C, et al. Functional specialization of human circulating CD16 and CD1c myeloid dendritic-cell subsets. Blood 2007;109(12):5371–9.
[28] Jongbloed SL, Kassianos AJ, McDonald KJ, Clark GJ, Ju X, Angel CE, et al. Human CD141+ (BDCA-3) + dendritic cells (DCs) represent a unique myeloid DC subset that cross-presents necrotic cell antigens. J Exp Med 2010;207(6):1247–60.
[29] Campbell IK, van Nieuwenhuijze A, Segura E, O'Donnell K, Coghill E, Hommel M, et al. Differentiation of inflammatory dendritic cells is mediated by NF-kappaB1-dependent GM-CSF production in CD4 T cells. J Immunol 2011;186(9):5468–77.
[30] Segura E, Touzot M, Bohineust A, Cappuccio A, Chiocchia G, Hosmalin A, et al. Human inflammatory dendritic cells induce Th17 cell differentiation. Immunity 2013;38(2):336–48.
[31] Zheng X, Vladau C, Shunner A, Min WP. siRNA specific delivery system for targeting dendritic cells. Methods Mol Biol 2010;623:173–88.
[32] Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. J Exp Med 1994;179(4):1109–18.
[33] Leon B, Lopez-Bravo M, Ardavin C. Monocyte-derived dendritic cells. Semin Immunol 2005;17(4):313–8.
[34] Ohnmacht C, Pullner A, King SB, Drexler I, Meier S, Brocker T, et al. Constitutive ablation of dendritic cells breaks self-tolerance of CD4 T cells and results in spontaneous fatal autoimmunity. J Exp Med 2009;206(3):549–59.
[35] Brocker T, Riedinger M, Karjalainen K. Targeted expression of major histocompatibility complex (MHC) class II molecules demonstrates that dendritic cells can induce negative but not positive selection of thymocytes in vivo. J Exp Med 1997;185(3):541–50.
[36] McCaughtry TM, Baldwin TA, Wilken MS, Hogquist KA. Clonal deletion of thymocytes can occur in the cortex with no involvement of the medulla. J Exp Med 2008;205(11):2575–84.
[37] Watanabe N, Wang YH, Lee HK, Ito T, Wang YH, Cao W, et al. Hassall's corpuscles instruct dendritic cells to induce CD4 + CD25+ regulatory T cells in human thymus. Nature 2005;436(7054):1181–5.
[38] Singh RP, Waldron RT, Hahn BH. Genes, tolerance and systemic autoimmunity. Autoimmun Rev 2012;11(9):664–9.
[39] Ito T, Yang M, Wang YH, Lande R, Gregorio J, Perng OA, et al. Plasmacytoid dendritic cells prime IL-10-producing T regulatory cells by inducible costimulator ligand. J Exp Med 2007;204(1):105–15.
[40] Gilliet M, Liu YJ. Generation of human CD8 T regulatory cells by CD40 ligand-activated plasmacytoid dendritic cells. J Exp Med 2002;195(6):695–704.
[41] de Heer HJ, Hammad H, Soullie T, Hijdra D, Vos N, Willart MA, et al. Essential role of lung plasmacytoid dendritic cells in preventing asthmatic reactions to harmless inhaled antigen. J Exp Med 2004;200(1):89–98.
[42] Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. Annu Rev Immunol 2003;21:685–711.
[43] Vitali C, Mingozzi F, Broggi A, Barresi S, Zolezzi F, Bayry J, et al. Migratory, and not lymphoid-resident, dendritic cells maintain peripheral self-tolerance and prevent autoimmunity via induction of iTreg cells. Blood 2012;120(6):1237–45.
[44] Sun CM, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 Treg cells via retinoic acid. J Exp Med 2007;204(8):1775–85.
[45] Khare A, Krishnamoorthy N, Oriss TB, Fei M, Ray P, Ray A. Cutting edge: inhaled antigen upregulates retinaldehyde dehydrogenase in lung CD103+ but not plasmacytoid dendritic cells to induce Foxp3 de novo in CD4+ T cells and promote airway tolerance. J Immunol 2013;191(1):25–9.
[46] Guilliams M, Crozat K, Henri S, Tamoutounour S, Grenot P, Devilard E, et al. Skin-draining lymph nodes contain dermis-derived CD103(−) dendritic cells that constitutively produce retinoic acid and induce Foxp3(+) regulatory T cells. Blood 2010;115(10):1958–68.
[47] Chu CC, Ali N, Karagiannis P, Di Meglio P, Skowera A, Napolitano L, et al. Resident CD141 (BDCA3) + dendritic cells in human skin produce IL-10 and induce regulatory T cells that suppress skin inflammation. J Exp Med 2012;209(5):935–45.
[48] Azukizawa H, Dohler A, Kanazawa N, Nayak A, Lipp M, Malissen B, et al. Steady state migratory RelB+ langerin + dermal dendritic cells mediate peripheral induction of antigen-specific CD4 + CD25 + Foxp3+ regulatory T cells. Eur J Immunol 2011;41(5):1420–34.
[49] van der Aar AM, Picavet DI, Muller FJ, de Boer L, van Capel TM, Zaat SA, et al. Langerhans cells favor skin flora tolerance through limited presentation of bacterial antigens and induction of regulatory T cells. J Invest Dermatol 2013;133(5):1240–9.
[50] Bamboat ZM, Stableford JA, Plitas G, Burt BM, Nguyen HM, Welles AP, et al. Human liver dendritic cells promote T cell hyporesponsiveness. J Immunol 2009;182(4):1901–11.
[51] Gregori S, Tomasoni D, Pacciani V, Scirpoli M, Battaglia M, Magnani CF, et al. Differentiation of type 1 T regulatory cells (Tr1) by tolerogenic DC-10 requires the IL-10-dependent ILT4/HLA-G pathway. Blood 2010;116(6):935–44.
[52] Joffre OP, Sancho D, Zelenay S, Keller AM, Reis e Sousa C. Efficient and versatile manipulation of the peripheral CD4+ T-cell compartment by antigen targeting to DNGR-1/CLEC9A. Eur J Immunol 2010;40(5):1255–65.
[53] Thomas R, Davis LS, Lipsky PE. Rheumatoid synovium is enriched in mature antigen-presenting dendritic cells. J Immunol 1994;152(5):2613–23.
[54] Thomas R, Quinn C. Functional differentiation of dendritic cells in rheumatoid arthritis: role of CD86 in the synovium. J Immunol 1996;156(8):3074–86.
[55] Santiago-Schwarz F, Anand P, Liu S, Carsons SE. Dendritic cells (DCs) in rheumatoid arthritis (RA): progenitor cells and soluble factors contained in RA synovial fluid yield a subset of myeloid DCs that preferentially activate Th1 inflammatory-type responses. J Immunol 2001;167(3):1758–68.
[56] Tsark EC, Wang W, Teng YC, Arkfeld D, Dodge GR, Kovats S. Differential MHC class II-mediated presentation of rheumatoid arthritis autoantigens by human dendritic cells and macrophages. J Immunol 2002;169(11):6625–33.
[57] Page G, Miossec P. RANK and RANKL expression as markers of dendritic cell-T cell interactions in paired samples of rheumatoid synovium and lymph nodes. Arthritis Rheum 2005;52(8):2307–12.
[58] Pettit AR, MacDonald KP, O'Sullivan B, Thomas R. Differentiated dendritic cells expressing nuclear RelB are predominantly located in rheumatoid synovial tissue perivascular mononuclear cell aggregates. Arthritis Rheum 2000;43(4):791–800.
[59] Jongbloed SL, Lebre MC, Fraser AR, Gracie JA, Sturrock RD, Tak PP, et al. Enumeration and phenotypical analysis of distinct dendritic cell subsets in psoriatic arthritis and rheumatoid arthritis. Arthritis Res Ther 2006;8(1):R15.
[60] Moret FM, Hack CE, van der Wurff-Jacobs KM, de Jager W, Radstake TR, Lafeber FP, et al. Intra-articular CD1c-expressing myeloid dendritic cells from rheumatoid arthritis patients express a unique set of T cell-attracting chemokines and spontaneously induce Th1, Th17 and Th2 cell activity. Arthritis Res Ther 2013;15(5):R155.
[61] Lebre MC, Jongbloed SL, Tas SW, Smeets TJ, McInnes IB, Tak PP. Rheumatoid arthritis synovium contains two subsets of CD83-DC-LAMP-dendritic cells with distinct cytokine profiles. Am J Pathol 2008;172(4):940–50.
[62] Bonnefoy F, Couturier M, Clauzon A, Remy-Martin JP, Gaugler B, Tiberghien P, et al. TGF-beta-exposed plasmacytoid dendritic cells participate in Th17 commitment. J Immunol 2011;186(11):6157–64.

[63] Kavousanaki M, Makrigiannakis A, Boumpas D, Verginis P. Novel role of plasmacytoid dendritic cells in humans: induction of interleukin-10-producing Treg cells by plasmacytoid dendritic cells in patients with rheumatoid arthritis responding to therapy. Arthritis Rheum 2010;62(1):53–63.
[64] Jongbloed SL, Benson RA, Nickdel MB, Garside P, McInnes IB, Brewer JM. Plasmacytoid dendritic cells regulate breach of self-tolerance in autoimmune arthritis. J Immunol 2009;182(2):963–8.
[65] Segura E, Amigorena S. Identification of human inflammatory dendritic cells. Oncoimmunology 2013;2(5):e23851.
[66] Lakey RL, Morgan TG, Rowan AD, Isaacs JD, Cawston TE, Hilkens CM. A novel paradigm for dendritic cells as effectors of cartilage destruction. Rheumatology (Oxford) 2009;48(5):502–7.
[67] Leung BP, Conacher M, Hunter D, McInnes IB, Liew FY, Brewer JM. A novel dendritic cell-induced model of erosive inflammatory arthritis: distinct roles for dendritic cells in T cell activation and induction of local inflammation. J Immunol 2002; 169(12):7071–7.
[68] Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50(5): 1400–11.
[69] Hilkens CM, Isaacs JD. Tolerogenic dendritic cell therapy for rheumatoid arthritis: where are we now? Clin Exp Immunol 2013;172(2):148–57.
[70] Thomas R. Dendritic cells and the promise of antigen-specific therapy in rheumatoid arthritis. Arthritis Res Ther 2013;15(1):204.
[71] Reynolds G, Cooles FA, Isaacs JD, Hilkens CM. Emerging immunotherapies for rheumatoid arthritis. Hum Vaccin Immunother 2014;10(4):822–37.
[72] Thomas R. Dendritic cells as targets or therapeutics in rheumatic autoimmune disease. Curr Opin Rheumatol 2014;26(2):211–8.
[73] Coleman MA, Steptoe RJ. Induction of antigen-specific tolerance through hematopoietic stem cell-mediated gene therapy: the future for therapy of autoimmune disease? Autoimmun Rev 2012;12(2):195–203.
[74] Steinbrink K, Wolfl M, Jonuleit H, Knop J, Enk AH. Induction of tolerance by IL-10-treated dendritic cells. J Immunol 1997;159(10):4772–80.
[75] Fogel-Petrovic M, Long JA, Misso NL, Foster PS, Bhoola KD, Thompson PJ. Physiological concentrations of transforming growth factor beta1 selectively inhibit human dendritic cell function. Int Immunopharmacol 2007;7(14):1924–33.
[76] Brandt K, Bulfone-Paus S, Foster DC, Ruckert R. Interleukin-21 inhibits dendritic cell activation and maturation. Blood 2003;102(12):4090–8.
[77] Rutella S, Danese S, Leone G. Tolerogenic dendritic cells: cytokine modulation comes of age. Blood 2006;108(5):1435–40.
[78] Hegde S, Pahne J, Smola-Hess S. Novel immunosuppressive properties of interleukin-6 in dendritic cells: inhibition of NF-kappaB binding activity and CCR7 expression. FASEB J 2004;18(12):1439–41.
[79] Menges M, Rossner S, Voigtlander C, Schindler H, Kukutsch NA, Bogdan C, et al. Repetitive injections of dendritic cells matured with tumor necrosis factor alpha induce antigen-specific protection of mice from autoimmunity. J Exp Med 2002; 195(1):15–21.
[80] Torres-Aguilar H, Aguilar-Ruiz SR, González-Pérez G, Munguía R, Bajaña S, Meraz-Ríos MA, et al. Tolerogenic dendritic cells generated with different immunosuppressive cytokines induce antigen-specific anergy and regulatory properties in memory CD4+ T Cells. J Immunol 2010;184(4):1765–75.
[81] Salazar L, Aravena O, Abello P, Escobar A, Contreras-Levicoy J, Rojas-Colonelli N, et al. Modulation of established murine collagen-induced arthritis by a single inoculation of short-term lipopolysaccharide-stimulated dendritic cells. Ann Rheum Dis 2008;67(9):1235–41.
[82] Zimmer A, Bouley J, Le Mignon M, Pliquet E, Horiot S, Turfkruyer M, et al. A regulatory dendritic cell signature correlates with the clinical efficacy of allergen-specific sublingual immunotherapy. J Allergy Clin Immunol 2012; 129(4):1020–30.
[83] Xia CQ, Peng R, Beato F, Clare-Salzler MJ. Dexamethasone induces IL-10-producing monocyte-derived dendritic cells with durable immaturity. Scand J Immunol 2005; 62(1):45–54.
[84] Hackstein H, Taner T, Zahorchak AF, Morelli AE, Logar AJ, Gessner A, et al. Rapamycin inhibits IL-4-induced dendritic cell maturation in vitro and dendritic cell mobilization and function in vivo. Blood 2003;101(11):4457–63.
[85] Buckland M, Jago C, Fazekesova H, George A, Lechler R, Lombardi G. Aspirin modified dendritic cells are potent inducers of allo-specific regulatory T-cells. Int Immunopharmacol 2006;6(13–14):1895–901.
[86] Lee JI, Ganster RW, Geller DA, Burckart GJ, Thomson AW, Lu L. Cyclosporine A inhibits the expression of costimulatory molecules on in vitro-generated dendritic cells: association with reduced nuclear translocation of nuclear factor kappa B. Transplantation 1999;68(9):1255–63.
[87] Lagaraine C, Lemoine R, Baron C, Nivet H, Velge-Roussel F, Lebranchu Y. Induction of human CD4+ regulatory T cells by mycophenolic acid-treated dendritic cells. J Leukoc Biol 2008;84(4):1057–64.
[88] Kubo S, Yamaoka K, Kondo M, Yamagata K, Zhao J, Iwata S, et al. The JAK inhibitor, tofacitinib, reduces the T cell stimulatory capacity of human monocyte-derived dendritic cells. Ann Rheum Dis 2014;73(12):2192–8.
[89] Svajger U, Obermajer N, Jeras M. Dendritic cells treated with resveratrol during differentiation from monocytes gain substantial tolerogenic properties upon activation. Immunology 2010;129(4):525–35.
[90] Rogers NM, Kireta S, Coates PT. Curcumin induces maturation-arrested dendritic cells that expand regulatory T cells in vitro and in vivo. Clin Exp Immunol 2010; 162(3):460–73.
[91] Geisel J, Bruck J, Glocova I, Dengler K, Sinnberg T, Rothfuss O, et al. Sulforaphane protects from T cell-mediated autoimmune disease by inhibition of IL-23 and IL-12 in dendritic cells. J Immunol 2014;192(8):3530–9.
[92] Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 2000;164(5):2405–11.
[93] Harry RA, Anderson AE, Isaacs JD, Hilkens CM. Generation and characterisation of therapeutic tolerogenic dendritic cells for rheumatoid arthritis. Ann Rheum Dis 2010;69(11):2042–50.
[94] Chorny A, Gonzalez-Rey E, Fernandez-Martin A, Pozo D, Ganea D, Delgado M. Vasoactive intestinal peptide induces regulatory dendritic cells with therapeutic effects on autoimmune disorders. Proc Natl Acad Sci U S A 2005;102(38): 13562–7.
[95] Matsumoto T, Hasegawa H, Onishi S, Ishizaki J, Suemori K, Yasukawa M. Protein kinase C inhibitor generates stable human tolerogenic dendritic cells. J Immunol 2013;191(5):2247–57.
[96] Martin E, Capini C, Duggan E, Lutzky VP, Stumbles P, Pettit AR, et al. Antigen-specific suppression of established arthritis in mice by dendritic cells deficient in NF-kappaB. Arthritis Rheum 2007;56(7):2255–66.
[97] Iruretagoyena MI, Sepulveda SE, Lezana JP, Hermoso M, Bronfman M, Gutierrez MA, et al. Inhibition of nuclear factor-kappa B enhances the capacity of immature dendritic cells to induce antigen-specific tolerance in experimental autoimmune encephalomyelitis. J Pharmacol Exp Ther 2006;318(1):59–67.
[98] Ko HJ, Cho ML, Lee SY, Oh HJ, Heo YJ, Moon YM, et al. CTLA4-Ig modifies dendritic cells from mice with collagen-induced arthritis to increase the CD4 + CD25 + Foxp3+ regulatory T cell population. J Autoimmun 2010;34(2):111–20.
[99] Henry E, Desmet CJ, Garzé V, Fiévez L, Bedoret D, Heirman C, et al. Dendritic cells genetically engineered to express IL-10 induce long-lasting antigen-specific tolerance in experimental asthma. J Immunol 2008;181(10):7230–42.
[100] Kim SH, Kim S, Evans CH, Ghivizzani SC, Oligino T, Robbins PD. Effective treatment of established murine collagen-induced arthritis by systemic administration of dendritic cells genetically modified to express IL-4. J Immunol 2001;166(5): 3499–505.
[101] Zheng X, Suzuki M, Ichim TE, Zhang X, Sun H, Zhu F, et al. Treatment of autoimmune arthritis using RNA interference-modulated dendritic cells. J Immunol 2010;184(11):6457–64.
[102] Unger WW, Laban S, Kleijwegt FS, van der Slik AR, Roep BO. Induction of Treg by monocyte-derived DC modulated by vitamin D3 or dexamethasone: differential role for PD-L1. Eur J Immunol 2009;39(11):3147–59.
[103] Garcia-Gonzalez P, Morales R, Hoyos L, Maggi J, Campos J, Pesce B, et al. A short protocol using dexamethasone and monophosphoryl lipid A generates tolerogenic dendritic cells that display a potent migratory capacity to lymphoid chemokines. J Transl Med 2013;11:128.
[104] Naranjo-Gomez M, Raich-Regue D, Onate C, Grau-Lopez L, Ramo-Tello C, Pujol-Borrell R, et al. Comparative study of clinical grade human tolerogenic dendritic cells. J Transl Med 2011;9(1):89.
[105] Boks MA, Kager-Groenland JR, Haasjes MSP, Zwaginga JJ, van Ham SM, ten Brinke A. IL-10-generated tolerogenic dendritic cells are optimal for functional regulatory T cell induction — a comparative study of human clinical-applicable DC. Clin Immunol 2012;142(3):332–42.
[106] Anderson AE, Swan DJ, Sayers BL, Harry RA, Patterson AM, von Delwig A, et al. LPS activation is required for migratory activity and antigen presentation by tolerogenic dendritic cells. J Leukoc Biol 2009;85(2):243–50.
[107] Holmdahl R, Andersson ME, Goldschmidt TJ, Jansson L, Karlsson M, Malmstrom V, et al. Collagen induced arthritis as an experimental model for rheumatoid arthritis. Immunogenetics, pathogenesis and autoimmunity. APMIS 1989; 97(7):575–84.
[108] van Duivenvoorde LM, Han WGH, Bakker AM, Louis-Plence P, Charbonnier L-M, Apparailly F, et al. Immunomodulatory dendritic cells inhibit Th1 responses and arthritis via different mechanisms. J Immunol 2007;179(3):1506–15.
[109] Orange DE, Blachere NE, Fak J, Parveen S, Frank MO, Herre M, et al. Dendritic cells loaded with FK506 kill T cells in an antigen-specific manner and prevent autoimmunity in vivo. Elife 2013;2:e00105.
[110] Stoop JN, Harry RA, von Delwig A, Isaacs JD, Robinson JH, Hilkens CMU. Therapeutic effect of tolerogenic dendritic cells in established collagen-induced arthritis is associated with a reduction in Th17 responses. Arthritis Rheum 2010;62(12):3656–65.
[111] Garate D, Rojas-Colonelli N, Pena C, Salazar L, Abello P, Pesce B, et al. Blocking of p38 and transforming growth factor beta receptor pathways impairs the ability of tolerogenic dendritic cells to suppress murine arthritis. Arthritis Rheum 2013; 65(1):120–9.
[112] Yang J, Yang Y, Ren Y, Xie R, Zou H, Fan H. A mouse model of adoptive immunotherapeutic targeting of autoimmune arthritis using allo-tolerogenic dendritic cells. PLoS One 2013;8(10):e77729.
[113] Ren Y, Yang Y, Yang J, Xie R, Fan H. Tolerogenic dendritic cells modified by tacrolimus suppress CD4(+) T-cell proliferation and inhibit collagen-induced arthritis in mice. Int Immunopharmacol 2014;21(1):247–54.
[114] Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. J Immunol 2004;172(5):2731–8.
[115] Hensvold AH, Magnusson PK, Joshua V, Hansson M, Israelsson L, Ferreira R, et al. Environmental and genetic factors in the development of anticitrullinated protein antibodies (ACPAs) and ACPA-positive rheumatoid arthritis: an epidemiological investigation in twins. Ann Rheum Dis 2015;74(2):375–80.
[116] Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. J Exp Med 2001;193(2):233–8.

[117] Giannoukakis N, Phillips B, Finegold D, Harnaha J, Trucco M. Phase I (Safety) study of autologous tolerogenic dendritic cells in type 1 diabetic patients. Diabetes Care 2011;34(9):2026–32.
[118] Di Caro V, Phillips B, Engman C, Harnaha J, Trucco M, Giannoukakis N. Retinoic acid-producing, ex-vivo-generated human tolerogenic dendritic cells induce the proliferation of immunosuppressive B lymphocytes. Clin Exp Immunol 2013; 174(2):302–17.
[119] Di Caro V, Phillips B, Engman C, Harnaha J, Trucco M, Giannoukakis N. Involvement of suppressive B-lymphocytes in the mechanism of tolerogenic dendritic cell reversal of type 1 diabetes in NOD mice. PLoS One 2014;9(1):e83575.
[120] Thomas R, Street S. Safety and preliminary evidence of efficacy in a phase I clinical trial of autologous tolerising dendritic cells exposed to citrullinated peptides (Rheumavax) in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70(Suppl. 3):169.
[121] Ferreira GB, Kleijwegt FS, Waelkens E, Lage K, Nikolic T, Hansen DA, et al. Differential protein pathways in 1,25-dihydroxyvitamin d(3) and dexamethasone modulated tolerogenic human dendritic cells. J Proteome Res 2012;11(2):941–71.
[122] Gomez-Martin D, Diaz-Zamudio M, Galindo-Campos M, Alcocer-Varela J. Early growth response transcription factors and the modulation of immune response: implications towards autoimmunity. Autoimmun Rev 2010;9(6):454–8.
[123] Hammer GE, Ma A. Molecular control of steady-state dendritic cell maturation and immune homeostasis. Annu Rev Immunol 2013;31:743–91.
[124] Tong X, Yin L, Washington R, Rosenberg DW, Giardina C. The p50-p50 NF-kappaB complex as a stimulus-specific repressor of gene activation. Mol Cell Biochem 2004;265(1–2):171–83.
[125] Cao S, Zhang X, Edwards JP, Mosser DM. NF-kappaB1 (p50) homodimers differentially regulate pro- and anti-inflammatory cytokines in macrophages. J Biol Chem 2006;281(36):26041–50.
[126] Dissanayake D, Hall H, Berg-Brown N, Elford AR, Hamilton SR, Murakami K, et al. Nuclear factor-kappaB1 controls the functional maturation of dendritic cells and prevents the activation of autoreactive T cells. Nat Med 2011;17(12):1663–7.
[127] Larghi P, Porta C, Riboldi E, Totaro MG, Carraro L, Orabona C, et al. The p50 subunit of NF-kappaB orchestrates dendritic cell lifespan and activation of adaptive immunity. PLoS One 2012;7(9):e45279.
[128] Bhattacharyya S, Zhao Y, Kay TW, Muglia LJ. Glucocorticoids target suppressor of cytokine signaling 1 (SOCS1) and type 1 interferons to regulate toll-like receptor-induced STAT1 activation. Proc Natl Acad Sci U S A 2011;108(23):9554–9.
[129] Hanada T, Yoshida H, Kato S, Tanaka K, Masutani K, Tsukada J, et al. Suppressor of cytokine signaling-1 is essential for suppressing dendritic cell activation and systemic autoimmunity. Immunity 2003;19(3):437–50.
[130] Hanada T, Tanaka K, Matsumura Y, Yamauchi M, Nishinakamura H, Aburatani H, et al. Induction of hyper Th1 cell-type immune responses by dendritic cells lacking the suppressor of cytokine signaling-1 gene. J Immunol 2005;174(7):4325–32.
[131] Park SJ, Nakagawa T, Kitamura H, Atsumi T, Kamon H, Sawa S, et al. IL-6 regulates in vivo dendritic cell differentiation through STAT3 activation. J Immunol 2004; 173(6):3844–54.
[132] Melillo JA, Song L, Bhagat G, Blazquez AB, Plumlee CR, Lee C, et al. Dendritic cell (DC)-specific targeting reveals Stat3 as a negative regulator of DC function. J Immunol 2010;184(5):2638–45.
[133] Kowalczyk A, D'Souza CA, Zhang L. Cell-extrinsic CTLA4-mediated regulation of dendritic cell maturation depends on STAT3. Eur J Immunol 2014;44(4):1143–55.
[134] Matsumura Y, Kobayashi T, Ichiyama K, Yoshida R, Hashimoto M, Takimoto T, et al. Selective expansion of foxp3-positive regulatory T cells and immunosuppression by suppressors of cytokine signaling 3-deficient dendritic cells. J Immunol 2007; 179(4):2170–9.
[135] Li Y, Chu N, Rostami A, Zhang GX. Dendritic cells transduced with SOCS-3 exhibit a tolerogenic/DC2 phenotype that directs type 2 Th cell differentiation in vitro and in vivo. J Immunol 2006;177(3):1679–88.
[136] Gosset P, Charbonnier AS, Delerive P, Fontaine J, Staels B, Pestel J, et al. Peroxisome proliferator-activated receptor gamma activators affect the maturation of human monocyte-derived dendritic cells. Eur J Immunol 2001;31(10):2857–65.
[137] Nencioni A, Grunebach F, Zobywlaski A, Denzlinger C, Brugger W, Brossart P. Dendritic cell immunogenicity is regulated by peroxisome proliferator-activated receptor gamma. J Immunol 2002;169(3):1228–35.
[138] Housley WJ, O'Conor CA, Nichols F, Puddington L, Lingenheld EG, Zhu L, et al. PPARgamma regulates retinoic acid-mediated DC induction of Tregs. J Leukoc Biol 2009;86(2):293–301.
[139] Cohen N, Mouly E, Hamdi H, Maillot MC, Pallardy M, Godot V, et al. GILZ expression in human dendritic cells redirects their maturation and prevents antigen-specific T lymphocyte response. Blood 2006;107(5):2037–44.
[140] Ayroldi E, Riccardi C. Glucocorticoid-induced leucine zipper (GILZ): a new important mediator of glucocorticoid action. FASEB J 2009;23(11):3649–58.
[141] Hamdi H, Godot V, Maillot MC, Prejean MV, Cohen N, Krzysiek R, et al. Induction of antigen-specific regulatory T lymphocytes by human dendritic cells expressing the glucocorticoid-induced leucine zipper. Blood 2007;110(1):211–9.
[142] Benkhoucha M, Molnarfi N, Dunand-Sauthier I, Merkler D, Schneiter G, Bruscoli S, et al. Hepatocyte growth factor limits autoimmune neuroinflammation via glucocorticoid-induced leucine zipper expression in dendritic cells. J Immunol 2014;193(6):2743–52.
[143] Nguyen NT, Kimura A, Nakahama T, Chinen I, Masuda K, Nohara K, et al. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. Proc Natl Acad Sci U S A 2010;107(46):19961–6.
[144] Chan YH, Chiang MF, Tsai YC, Su ST, Chen MH, Hou MS, et al. Absence of the transcriptional repressor Blimp-1 in hematopoietic lineages reveals its role in dendritic cell homeostatic development and function. J Immunol 2009;183(11):7039–46.
[145] Kim SJ, Zou YR, Goldstein J, Reizis B, Diamond B. Tolerogenic function of Blimp-1 in dendritic cells. J Exp Med 2011;208(11):2193–9.
[146] Cella M, Dohring C, Samaridis J, Dessing M, Brockhaus M, Lanzavecchia A, et al. A novel inhibitory receptor (ILT3) expressed on monocytes, macrophages, and dendritic cells involved in antigen processing. J Exp Med 1997; 185(10):1743–51.
[147] Colonna M, Samaridis J, Cella M, Angman L, Allen RL, O'Callaghan CA, et al. Human myelomonocytic cells express an inhibitory receptor for classical and nonclassical MHC class I molecules. J Immunol 1998;160(7):3096–100.
[148] Brenk M, Scheler M, Koch S, Neumann J, Takikawa O, Hacker G, et al. Tryptophan deprivation induces inhibitory receptors ILT3 and ILT4 on dendritic cells favoring the induction of human CD4 + CD25 + Foxp3 + T regulatory cells. J Immunol 2009;183(1):145–54.
[149] Ge G, Tian P, Liu H, Zheng J, Fan X, Ding C, et al. Induction of CD4 + CD25 + Foxp3 + T regulatory cells by dendritic cells derived from ILT3 lentivirus-transduced human CD34 + cells. Transpl Immunol 2012;26(1):19–26.
[150] Gianchecchi E, Delfino DV, Fierabracci A. Recent insights into the role of the PD-1/PD-L1 pathway in immunological tolerance and autoimmunity. Autoimmun Rev 2013;12(11):1091–100.
[151] Pedersen AW, Holmstrom K, Jensen SS, Fuchs D, Rasmussen S, Kvistborg P, et al. Phenotypic and functional markers for 1alpha,25-dihydroxyvitamin D(3)-modified regulatory dendritic cells. Clin Exp Immunol 2009;157(1):48–59.
[152] Manicassamy S, Ravindran R, Deng J, Oluoch H, Denning TL, Kasturi SP, et al. Toll-like receptor 2-dependent induction of vitamin A-metabolizing enzymes in dendritic cells promotes T regulatory responses and inhibits autoimmunity. Nat Med 2009;15(4):401–9.
[153] Bonifaz L, Bonnyay D, Mahnke K, Rivera M, Nussenzweig MC, Steinman RM. Efficient targeting of protein antigen to the dendritic cell receptor DEC-205 in the steady state leads to antigen presentation on major histocompatibility complex class I products and peripheral CD8 + T cell tolerance. J Exp Med 2002;196(12): 1627–38.
[154] Ring S, Maas M, Nettelbeck DM, Enk AH, Mahnke K. Targeting of autoantigens to DEC205(+) dendritic cells in vivo suppresses experimental allergic encephalomyelitis in mice. J Immunol 2013;191(6):2938–47.
[155] Fujikado N, Saijo S, Yonezawa T, Shimamori K, Ishii A, Sugai S, et al. Dcir deficiency causes development of autoimmune diseases in mice due to excess expansion of dendritic cells. Nat Med 2008;14(2):176–80.
[156] Zhou Y, Kawasaki H, Hsu SC, Lee RT, Yao X, Plunkett B, et al. Oral tolerance to food-induced systemic anaphylaxis mediated by the C-type lectin SIGNR1. Nat Med 2010;16(10):1128–33.
[157] Samsom JN, van Berkel LA, van Helvoort JM, Unger WW, Jansen W, Thepen T, et al. Fc gamma RIIB regulates nasal and oral tolerance: a role for dendritic cells. J Immunol 2005;174(9):5279–87.
[158] Desai DD, Harbers SO, Flores M, Colonna L, Downie MP, Bergtold A, et al. Fc gamma receptor IIB on dendritic cells enforces peripheral tolerance by inhibiting effector T cell responses. J Immunol 2007;178(10):6217–26.
[159] Boruchov AM, Heller G, Veri MC, Bonvini E, Ravetch JV, Young JW. Activating and inhibitory IgG Fc receptors on human DCs mediate opposing functions. J Clin Invest 2005;115(10):2914–23.
[160] Rothlin CV, Ghosh S, Zuniga EI, Oldstone MB, Lemke G. TAM receptors are pleiotropic inhibitors of the innate immune response. Cell 2007;131(6):1124–36.
[161] Lu Q, Lemke G. Homeostatic regulation of the immune system by receptor tyrosine kinases of the Tyro 3 family. Science 2001;293(5528):306–11.
[162] Hammer GE, Turer EE, Taylor KE, Fang CJ, Advincula R, Oshima S, et al. Expression of A20 by dendritic cells preserves immune homeostasis and prevents colitis and spondyloarthritis. Nat Immunol 2011;12(12):1184–93.
[163] Kool M, van Loo G, Waelput W, De Prijck S, Muskens F, Sze M, et al. The ubiquitin-editing protein A20 prevents dendritic cell activation, recognition of apoptotic cells, and systemic autoimmunity. Immunity 2011;35(1):82–96.
[164] Musone SL, Taylor KE, Nititham J, Chu C, Poon A, Liao W, et al. Sequencing of TNFAIP3 and association of variants with multiple autoimmune diseases. Genes Immun 2011;12(3):176–82.
[165] Chauveau C, Remy S, Royer PJ, Hill M, Tanguy-Royer S, Hubert FX, et al. Heme oxygenase-1 expression inhibits dendritic cell maturation and proinflammatory function but conserves IL-10 expression. Blood 2005;106(5):1694–702.
[166] Blancou P, Tardif V, Simon T, Remy S, Carreno L, Kalergis A, et al. Immunoregulatory properties of heme oxygenase-1. Methods Mol Biol 2011;677:247–68.
[167] Remy S, Blancou P, Tesson L, Tardif V, Brion R, Royer PJ, et al. Carbon monoxide inhibits TLR-induced dendritic cell immunogenicity. J Immunol 2009;182(4): 1877–84.
[168] Simon T, Pogu S, Tardif V, Rigaud K, Remy S, Piaggio E, et al. Carbon monoxide-treated dendritic cells decrease beta1-integrin induction on CD8(+) T cells and protect from type 1 diabetes. Eur J Immunol 2013;43(1):209–18.
[169] Puig-Kroger A, Relloso M, Fernandez-Capetillo O, Zubiaga A, Silva A, Bernabeu C, et al. Extracellular signal-regulated protein kinase signaling pathway negatively regulates the phenotypic and functional maturation of monocyte-derived human dendritic cells. Blood 2001;98(7):2175–82.
[170] Arce F, Breckpot K, Stephenson H, Karwacz K, Ehrenstein MR, Collins M, et al. Selective ERK activation differentiates mouse and human tolerogenic dendritic cells, expands antigen-specific regulatory T cells, and suppresses experimental inflammatory arthritis. Arthritis Rheum 2011;63(1):84–95.
[171] Ramachandran IR, Song W, Lapteva N, Seethammagari M, Slawin KM, Spencer DM, et al. The phosphatase SRC homology region 2 domain-containing phosphatase-1 is an intrinsic central regulator of dendritic cell function. J Immunol 2011;186(7): 3934–45.
[172] Kaneko T, Saito Y, Kotani T, Okazawa H, Iwamura H, Sato-Hashimoto M, et al. Dendritic cell-specific ablation of the protein tyrosine phosphatase Shp1 promotes Th1 cell differentiation and induces autoimmunity. J Immunol 2012;188(11):5397–407.

[173] Lamagna C, Scapini P, van Ziffle JA, DeFranco AL, Lowell CA. Hyperactivated MyD88 signaling in dendritic cells, through specific deletion of Lyn kinase, causes severe autoimmunity and inflammation. Proc Natl Acad Sci U S A 2013;110(35): E3311–20.
[174] Mascanfroni ID, Yeste A, Vieira SM, Burns EJ, Patel B, Sloma I, et al. IL-27 acts on DCs to suppress the T cell response and autoimmunity by inducing expression of the immunoregulatory molecule CD39. Nat Immunol 2013;14(10):1054–63.
[175] Manicassamy S, Reizis B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, et al. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. Science 2010;329(5993):849–53.
[176] Oderup C, LaJevic M, Butcher EC. Canonical and noncanonical Wnt proteins program dendritic cell responses for tolerance. J Immunol 2013;190(12):6126–34.
[177] Valencia J, Hernandez-Lopez C, Martinez VG, Hidalgo L, Zapata AG, Vicente A, et al. Wnt5a skews dendritic cell differentiation to an unconventional phenotype with tolerogenic features. J Immunol 2011;187(8):4129–39.
[178] Jinushi M, Nakazaki Y, Dougan M, Carrasco DR, Mihm M, Dranoff G. MFG-E8-mediated uptake of apoptotic cells by APCs links the pro- and antiinflammatory activities of GM-CSF. J Clin Invest 2007;117(7):1902–13.
[179] Baghdadi M, Chiba S, Yamashina T, Yoshiyama H, Jinushi M. MFG-E8 regulates the immunogenic potential of dendritic cells primed with necrotic cell-mediated inflammatory signals. PLoS One 2012;7(6):e39607.
[180] Castellano G, Woltman AM, Nauta AJ, Roos A, Trouw LA, Seelen MA, et al. Maturation of dendritic cells abrogates C1q production in vivo and in vitro. Blood 2004; 103(10):3813–20.
[181] Teh BK, Yeo JG, Chern LM, Lu J. C1q regulation of dendritic cell development from monocytes with distinct cytokine production and T cell stimulation. Mol Immunol 2011;48(9–10):1128–38.
[182] Hosszu KK, Valentino A, Vinayagasundaram U, Vinayagasundaram R, Joyce MG, Ji Y, et al. DC-SIGN, C1q, and gC1qR form a trimolecular receptor complex on the surface of monocyte-derived immature dendritic cells. Blood 2012;120(6):1228–36.
[183] Driessler F, Venstrom K, Sabat R, Asadullah K, Schottelius AJ. Molecular mechanisms of interleukin-10-mediated inhibition of NF-kappaB activity: a role for p50. Clin Exp Immunol 2004;135(1):64–73.
[184] Nefedova Y, Cheng P, Gilkes D, Blaskovich M, Beg AA, Sebti SM, et al. Activation of dendritic cells via inhibition of Jak2/STAT3 signaling. J Immunol 2005;175(7): 4338–46.
[185] Vogel CF, Wu D, Goth SR, Baek J, Lollies A, Domhardt R, et al. Aryl hydrocarbon receptor signaling regulates NF-kappaB RelB activation during dendritic-cell differentiation. Immunol Cell Biol 2013;91(9):568–75.
[186] Gerbal-Chaloin S, Iankova I, Maurel P, Daujat-Chavanieu M. Nuclear receptors in the cross-talk of drug metabolism and inflammation. Drug Metab Rev 2013; 45(1):122–44.
[187] Scapini P, Pereira S, Zhang H, Lowell CA. Multiple roles of Lyn kinase in myeloid cell signaling and function. Immunol Rev 2009;228(1):23–40.
[188] Chamorro S, Garcia-Vallejo JJ, Unger WW, Fernandes RJ, Bruijns SC, Laban S, et al. TLR triggering on tolerogenic dendritic cells results in TLR2 up-regulation and a reduced proinflammatory immune program. J Immunol 2009;183(5):2984–94.
[189] Shrimpton RE, Butler M, Morel AS, Eren E, Hue SS, Ritter MA. CD205 (DEC-205): a recognition receptor for apoptotic and necrotic self. Mol Immunol 2009;46(6): 1229–39.
[190] Klechevsky E, Flamar AL, Cao Y, Blanck JP, Liu M, O'Bar A, et al. Cross-priming CD8 + T cells by targeting antigens to human dendritic cells through DCIR. Blood 2010; 116(10):1685–97.
[191] Meyer-Wentrup F, Cambi A, Joosten B, Looman MW, de Vries IJ, Figdor CG, et al. DCIR is endocytosed into human dendritic cells and inhibits TLR8-mediated cytokine production. J Leukoc Biol 2009;85(3):518–25.
[192] Gringhuis SI, den Dunnen J, Litjens M, van Het Hof B, van Kooyk Y, Geijtenbeek TB. C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. Immunity 2007;26(5):605–16.
[193] Zhou M, Peng JR, Zhang HG, Wang HX, Zhong ZH, Pan XY, et al. Identification of two naturally presented MAGE antigenic peptides from a patient with hepatocellular carcinoma by mass spectrometry. Immunol Lett 2005;99(1):113–21.
[194] Caparros E, Munoz P, Sierra-Filardi E, Serrano-Gomez D, Puig-Kroger A, Rodriguez-Fernandez JL, et al. DC-SIGN ligation on dendritic cells results in ERK and PI3K activation and modulates cytokine production. Blood 2006;107(10):3950–8.
[195] Bergenfelz C, Janols H, Wullt M, Jirstrom K, Bredberg A, Leandersson K. Wnt5a inhibits human monocyte-derived myeloid dendritic cell generation. Scand J Immunol 2013;78(2):194–204.