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Review

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

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ABSTRACT

To date, the available options to treat autoimmune diseases such as rheumatoid arthritis (RA) include traditional corticoids to 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.

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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]. Q4

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