Immunology Letters 161 (2014) 216–221

Contents lists available at ScienceDirect

Immunology Letters

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

Review

Regulatory dendritic cell therapy: From rodents to clinical application

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ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 24 November 2013
Available online 4 December 2013

Keywords:
Dendritic cells
Cell therapy
Tolerance
Autoimmunity
Transplantation

ABSTRACT

Dendritic cells (DC) are highly-specialized, bone marrow-derived antigen-presenting cells that induce or regulate innate and adaptive immunity. Regulatory or "tolerogenic" DC play a crucial role in maintaining self tolerance in the healthy steady-state. These regulatory innate immune cells subvert naïve or memory T cell responses by various mechanisms. Regulatory DC (DCreg) also exhibit the ability to induce or restore T cell tolerance in many animal models of autoimmune disease or transplant rejection. There is also evidence that adoptive transfer of DCreg can regulate T cell responses in non-human primates and humans. Important insights gained from in vitro studies and animal models have led recently to the development of clinical grade human DCreg, with potential to treat autoimmune disease or enhance transplant survival while reducing patient dependency on immunosuppressive drugs. Phase I trials have been conducted in type-1 diabetes and rheumatoid arthritis, with results that emphasize the feasibility and safety of DCreg therapy. This mini-review will outline how observations made using animal models have been translated into human use, and discuss the challenges faced in further developing this form of regulatory immune cell therapy in the fields of autoimmunity and transplantation.

1. Introduction

Current therapies for autoimmune diseases and allograft rejection generally involve the indefinite use of non-specific immunosuppressive drugs, which may result in infectious complications, predisposition to certain types of cancer, and the attendant toxicities and adverse side effects of these agents. Use of these drugs also fails to induce antigen (Ag)-specific tolerance. An emerging strategy for the treatment of both autoimmunity and graft rejection is the use of regulatory immune cells [1–3], that include regulatory T cells (Treg) [4,5] and regulatory myeloid cells [6], including regulatory dendritic cells (DCreg) [7–9]. These cellular therapies have potential to promote Ag-specific tolerance.

While DCreg exist naturally in blood and both lymphoid and non-lymphoid tissues, they are rare cells, but can be generated readily in vitro from precursors in blood or bone marrow (BM) using appropriate cytokine growth factors. DCreg can be propagated in culture using biologic or pharmacologic agents, among other techniques, and promising results have been obtained using such approaches. In addition, adoptive cell transfer in animal models and humans has raised expectation that DCreg can be used to control adverse T cell-mediated immune responses in the clinic.

2. DC as regulators of immunity and tolerance

DC are a heterogeneous group of professional, antigen-presenting immune cells, that are widely distributed through lymphoid and non-lymphoid tissues [10], and that regulate immune responses, maintaining the balance between tolerance and immunity. Different subtypes of DC are distributed throughout the body and act as sentinels in peripheral tissues or in lymphoid organs, where they encounter potential Ags. When pathogen invasion occurs, tissue-resident immature DCs capture microorganisms via endocytic surveillance receptors [11], that trigger their maturation. This maturation process consists of profound phenotypic and functional modifications, that include expression of MHC-peptide complexes on the cell surface, increased expression of T cell co-stimulatory molecules (such as CD40, CD80, CD86, OX40L, or inducible costimulatory ligand [ICOSL]), together with the secretion of cytokines (including IL-1ß, IL-2, IL-6, IL-10 and IL-12) [10,11]. In vivo, this maturation process is accompanied by changes in the expression of cell traffick regulating molecules, such as up-regulation of cell surface CCR7, a chemokine receptor that enables

Abbreviations: Ag, antigen; DCreg, regulatory dendritic cells; Dex, dexamethasone; MPLA, monophosphoryl lipid A; MS, multiple sclerosis; RA, rheumatoid arthritis.

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http://dx.doi.org/10.1016/j.imlet.2013.11.016

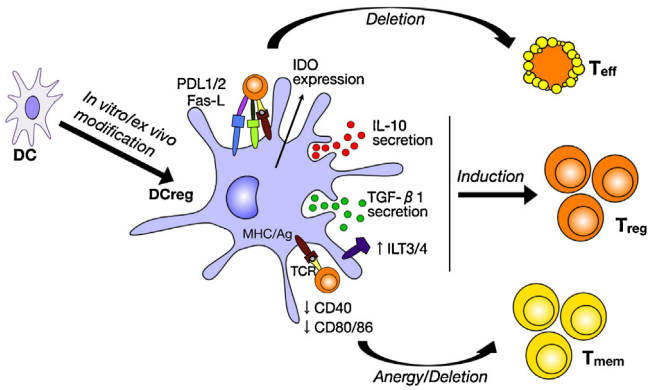

Fig. 1. Tolerogenic characteristics of DCreg. DCreg express and secrete regulatory molecules that mediate tolerogenic effects on T cells, leading to the induction of T cell deletion, T cell anergy or Treg expansion/induction.

migration of DC to lymph nodes [12]. Therein, mature DCs present Ag-derived peptides in association with MHC-II molecules to naive T helper (Th) lymphocytes, that recognize the MHC-II/peptide complex via the T cell receptor (TCR) [10,13]. After Ag recognition, and with the appropriate additional interactions mediated by co-stimulatory molecules, naive T lymphocytes become effector T cells, with different helper or cytotoxic activities. Thus, DC function as a crucial link between innate and adaptive immunity.

It is currently acknowledged that DC are important not only in the generation of T cell-mediated immune responses, but also in the induction and maintenance of central and peripheral tolerance. Under steady-state conditions, DC may present self-Ags (from captured apoptotic bodies) and silence autoreactive T cells [14]. These naturally-occurring DCreg also maintain tolerance in peripheral tissues to commensal microorganisms, Ags derived from food and the airways, etc, within the steady-state environment. DCreg are characterized by low expression of co-stimulatory molecules (mainly CD40, CD80, CD86), and usually by reduced production of pro-inflammatory IL-12 and increased secretion of anti-inflammatory IL-10 [15], together with reduced ability to induce T cell proliferation. While these properties can help explain their ability to induce regulatory T cells (Treg) rather than T effector cells, several other mechanisms may play a role in tolerance induction by DCreg [16]. The molecular mechanisms involved in the tolerogenic function of DCreg in the periphery (Fig. 1) include induction of anergy, promotion of Treg differentiation and induction of T cell death (deletion).

3. Strategies for generating DCreg

As DC are involved in the regulation of both tolerance and immunity, they could have many clinical applications for treatment of immune-based diseases. Indeed, the potential of DCs for clinical application has been under extensive investigation for some time [17–19]. Many strategies have been described for the generation of potent regulatory/tolerogenic DC in mouse or human systems. These DC are most frequently generated in vitro from murine BM precursors [20] or human blood monocytes [21]. Although a wide variety of conditions have been reported to support DC generation, the growth factor most commonly used to generate conventional murine or human DC is granulocyte-macrophage colony-stimulating factor (GM-CSF), combined with IL-4 [22]. DCreg features can be induced in vitro by exposure of DC to pharmacological agents, anti-inflammatory biologicals, or following their genetic modification [2,23].

Diverse biomolecules that are encountered physiologically under tolerogenic conditions in vivo, can induce DCreg differentiation in vitro. For instance, incubation of DC with IL-10 confers an ability to induce Tregs [24] that have suppressive capacity in models of organ allograft rejection, allergy, and graft-versus-host disease (GVHD) [23]. Signaling through the IL-10 receptor maintains DC in their immature state, even in the presence of maturation signals [25]. Transforming growth factor-β (TGF-β), a cytokine produced by Treg and other cells, allows DC to attenuate the neuropathology associated with experimental allergic encephalomyelitis (EAE) [26], a model of multiple sclerosis (MS). When treated in vitro with pro-inflammatory stimuli and the active metabolite of vitamin D: 1α,25-dihydroxyvitamin D3 (vitD3), human DC express indoleamine dioxygenase (IDO), CCL2, IL-10, TGF-β, tumor necrosis factor (TNF) receptor apoptosis-inducing ligand (TRAIL), and the inhibitory receptors CD300LF and CYP24A1, that have been implicated in immune tolerance [27]. Also, hepatocyte growth factor induces a tolerogenic phenotype (low IL-12; high IL-10) in human monocyte-derived DC [28] that induce Treg. Several other factors, such as estrogen, vasoactive intestinal peptide (VIP), binding immunoglobulin protein (BiP), thymic stromal lymphopoietin (TSLP), GM-CSF, prostaglandin (PG) E2, and TNFα, may also promote Treg-inducing ability of DCreg [29,30].

Pharmacological agents have been employed very successfully to manipulate DC function, both in vitro and in many disease models [31,32]. These include: anti-inflammatory agents (such as acetylsalicylic acid), histamine, adenosine receptor agonists, and immunosuppressive drugs such as corticosteroids, cyclosporine A, rapamycin, deoxyspergualin, tacrolimus (FK506), mycophenolate mofetil (MMF), and BAY-117085 [33]. Treatment with prednisolone or dexamethasone (Dex) leads to DCreg differentiation with the ability to instruct Treg [34,35], and negatively modulate the nuclear factor (NF)κB pathway, inflammatory cytokines, chemokines, and Ag-presenting molecules [36]. Inhibition of the mechanistic target of rapamycin (mTOR) by rapamycin promotes DCreg that stimulate Treg expansion in vivo and in vitro [37–39]. BAY-117085 is an irreversible NF-κB inhibitor, and DC treated with this agent induce Treg and suppress established experimental autoimmune arthritis [33].

Several genetic manipulations have been used to modulate the maturation of DC to induce DCreg [2]. Towards this end, selected genes can be transferred to DCs through viral or non-viral delivery systems (including liposomes and electroporation) [40], or knocked-down by selective gene silencing using e.g. anti-sense oligodeoxynucleotides (ODNs) and small interfering RNAs (siRNA) [41]. Using these techniques, DCreg have been generated by either inducing the expression of different immunomodulatory molecules (such as IL-4, IL-10, TGF-β, cytotoxic T lymphocyte Ag (CTLA)-4, or programmed death ligand (PDL)-1, among others) or, in contrast, by inhibiting specific molecules involved in DC activation (i.e. IL-12p35, CD40, or CD86) (reviewed in [2,9]). These genetically-induced DCreg have been shown, in some instances, to induce T cell hyporesponsiveness and to prolong allograft survival in mice [42], to induce Treg differentiation [43], and to suppress autoimmune diabetes or delayed-type hypersensitivity in mice [44].

While different methods to generate DCreg have shown very promising results in murine models of transplantation and autoimmune disease, there are some discrepancies in the effectiveness of these approaches between mice and humans. For this reason, careful studies that compare different DCreg-generating strategies are essential. For instance, the study performed by Naranjo-Gómez et al. [45] compared the use of different agents to generate human DCreg for prospective clinical use, and demonstrated significant differences in DCreg features, highlighting the importance of appropriate agent selection. On the other hand, a recent study by Boks et al. [46] that also compared different agents for generating clinical grade DCreg, concluded that IL-10-treated DC possessed the most potent tolerogenic phenotype, with promise for clinical use.