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REVIEW ARTICLE

Tolerogenic dendritic cells and rheumatoid arthritis: current status and perspectives

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Abstract Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by the influxation of synovia and synovial compartments with immune cells including dendritic cells (DCs). DCs that induce autoimmune tolerance are called tolerogenic DCs (tolDCs). As a promising immunotherapeutic strategy for RA, tolDCs have received increasing attention. In this review, we first introduce the significant role of tolDCs in autoimmune regulation and then describe the manipulation strategies to generate tolDCs; next, we summarize recent progress in the experimental application of tolDCs for RA therapy, and finally we discuss the perspectives of tolerogenic vaccination for the treatment for RA in clinic.

Keywords Rheumatoid arthritis · Dendritic cells · Tolerogenic DCs · Tregs · Autoimmune

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by the inflation of synovia and synovial compartments with dendritic cells (DCs), monocytes, T cells, B cells, neutrophils and natural killer (NK) cells [1]. RA affects multiple joints such as hands, wrists and feet and is one important cause of disability.

RA is currently treated with immunosuppressive drugs and biological agents. However, these therapeutic agents may induce a generalized immune suppression that increases the risk of infectious diseases [2]. Therefore, new therapeutic approaches should aim at the suppression of inflammation and establishment of tolerance toward arthritogenic antigens without compromising the patients' immune system [3]. Recent research has shown that a particular subset of DCs could modulate immune responses [4]. These DCs play a key role in maintaining both central and peripheral autoimmune tolerance, and the constitutive ablation of DCs destroys self-tolerance, resulting in spontaneous fatal autoimmunity [5]. The DCs that induce autoimmune tolerance are called *tolerogenic DCs* (tolDCs). As a promising immunotherapeutic strategy for RA, tolDCs have received considerable attention [6]. In this review, we first introduce the significant role of tolDCs in autoimmune regulation and then describe the strategies to generate tolDCs; next, we summarize recent progress in the experimental application of tolDCs for RA therapy, and finally we discuss the perspectives of tolerogenic vaccination for the treatment for RA in clinic.

Features of DCs associated with tolDCs: subsets and maturation stage

TolDCs are derived from DCs which exhibit tolerogenic phenotype. It has been found that the subsets and maturation stage of DCs are closely related to the generation of tolDCs. In this part, we will introduce several features of DCs that are associated with tolDCs.

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Subset of DCs and tolDCs

DCs constitute a heterogeneous population of cells characterized by the differences in tissue distribution, phenotype and function [7]. Human peripheral blood DCs can be divided into two major subsets according to the source they derive from: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) [8]. In addition to these two subsets, there is another type of DCs that is derived from monocyte and plays an important role in innate and adaptive immunity and is named monocyte-derived DCs (mo-DCs) [9]. Detailed information on these subsets of DCs and their applications in RA has been described in several reviews [10].

Mature mDCs can induce the differentiation of naïve T cells into T helper (Th) cells with increased expression of adhesion molecules and cytokine receptors as well as the production of cytokines, which can activate autoimmune responses [11]. On the contrary, immature mDCs have been commonly loaded with antigen and manipulated to generate tolDCs and suppress autoimmune responses both in vivo and in vitro [12]. TolDCs derived from mDCs have been widely used in the therapy of RA and experimental arthritis [13].

pDCs represent a naturally occurring regulatory DC subset with tolerogenic phenotype. Under certain circumstances, pDCs appear to induce the differentiation of regulatory T cells (Tregs) both in mice models and in human [14]. Thus, the use of pDCs to induce immune tolerance may offer new opportunities in autoimmunity and transplantation [15]. Recent studies have demonstrated that pDCs exhibited tolerogenic phenotype and modulated anti-inflammatory function in RA patients through IDO pathway [16].

mo-DCs are by far the most common type of cells used in clinical immunotherapeutics [17]. Data based on the use of mo-DCs have shown that mo-DCs can be manipulated with certain biological agents to generate tolDCs [18]. Moreover, tolDCs derived from mo-DCs are proposed as a promising cellular therapeutic tool for tailoring immunomodulation in the treatment for RA [19].

Maturation stage and tolDCs

Immature DCs do not express maturation markers nor produce proinflammatory cytokines. The natural function of immature DCs is to create conditions for self-tolerance either via the generation of Treg or via the induction of apoptosis or anergy of autoreactive effector cells [20]. During the past years, immature DCs have been widely used to generate tolDCs and utilized in the treatment for autoimmune diseases including RA [21]. Strikingly, while mature DCs are considered immunogenic as professional antigen-presenting cells, recent evidence suggested that tolDCs can be generated from mature DCs by genetic engineering [22], which provides additional means of generating tolDCs for RA treatment.

Interestingly, an independent subgroup of DCs has been recognized as semi-mature DCs, which express maturation markers but do not produce inflammatory cytokines, and they appear to be tolerogenic in autoimmune diseases including RA [23]. However, other reports suggest that semi-mature DCs become immunogenic when inoculated at a high dose in CIA mice [24]. Therefore, further characterization of the role of semi-mature DCs in RA pathogenesis is required.

Generation of tolDCs: strategies

Manipulations of DCs to generate tolerogenic phenotype have been extensively studied and reported. In this review, we classify the commonly used strategies into three groups: immunoregulatory drugs and biological agents, coculture with apoptotic cells, and genetic engineering. Most of the strategies have been practiced in studies aiming at RA therapy, although several of them are practiced in other autoimmune diseases.

Regulation of molecular targets on DCs

During the past years, various biological agents and pharmacological agents have been used to confer tolerogenic properties on DCs and regarded as a clinically applicable option [25]. On the basis of recent data, we will introduce the molecules that serve as targets for tolerogenic phenotype of DCs with pharmacological drugs and other agents.

RelB component of NF-κB has been shown to be critical for DCs maturation in vivo [26]. Tumor necrosis factor-α (TNF-α) is another molecular target on DCs because anti-TNF-α therapies diminish DCs maturation and their ability to produce proinflammatory cytokines and chemokines and are effective in treating patients with RA [27].

On the contrary, induction or upregulation of other molecules could be employed to generate tolDCs. PD-L1 signaling has been shown to negatively regulate T-cell response and contribute to tolerogenic phenotype of these DCs [28]. The immunoglobulin-like transcript (ILT) family consists of a group of activating and inhibitory receptors, and some of them play a role in tolerance induction [29]. The upregulation of ILT3 and ILT4 receptors on human DCs renders them tolerogenic, along with reduced expression of costimulatory molecules and induction of antigen-specific unresponsiveness in CD4+ T cells. IDO is an immunosuppressive protein expressed on DCs, and upregulation of IDO expression on DCs also makes them

tolerogenic [30]. In addition, upregulation of ICOSL, a molecule that induces anergy of T cells, could induce tolerogenic phenotype on immature DCs [31].

Uptake of apoptotic cells

Apoptotic cells induce tolerogenic properties of innate immune cells including DCs, which then recognize and phagocytose the apoptotic cells [32]. DCs produce IL-10 after ingestion of apoptotic cells and induce T-cell tolerance via immunosuppressive cytokines [32]. Immature DCs was rendered tolerogenic in vitro by pre-exposure to autologous apoptotic cells [33]. Recently, it has been found that the culture of apoptotic DCs with immature DCs in vitro results in their uptake by immature DCs, which subsequently turn into tolDCs [34]. In vivo study in mice models also demonstrated that apoptotic DCs can be taken up by viable DCs, which suppress the ability of viable DCs to undergo maturation and subsequent migration to the lymph nodes [35]. Therefore, apoptotic cells are a promising agent to induce tolDCs, which could possibly be used for therapy for RA in the future.

Genetic engineering strategy

Recently, genetic engineering was practiced as a novel strategy to induce tolDCs regardless of their maturation stages [36]. Moreover, applications aimed at treatment for RA have been practiced in experimental murine models. Both knockdown of costimulatory factors such as CD40, CD80 and CD86 and expression of immunosuppressive molecules in DCs have been exploited to generate tolDCs, which effectively suppressed the onset of collagen-induced arthritis [37].

Possible mechanisms of tolDCs function in RA therapy

Past studies have shown that tolDCs induce immunotolerance through a variety of mechanisms that have been extensively investigated, and the readers are referred to recent reviews and articles [28, 31, 38]. On the basis of literature published recently, here we highlight the potential mechanisms of tolDCs function in RA therapy.

Reduction in Th17

Th17 is a new and unique subset of T cells that plays a critical role in host defense against certain extracellular pathogens and also contributes to the pathogenesis of various autoimmune diseases including RA [39–43]. Notably, Th17 produces inflammatory cytokines such as IL-17 and is a subset of osteoclastogenic Th cells, which was demonstrated to induce tissue destruction in RA [44–46].

IL-23 is essential for the expansion of Th17 cells, and IL-23 receptor is expressed on DCs [47]. Moreover, DCs that are tolerogenic demonstrated reduction in IL-23, which gives rise to lower number of Th17 [48]. Recently, studies have shown that tolDCs led to the reduction in Th17 responses in experimental RA models, which is a potential mechanism by which tolDCs help treat RA [49].

Anergy and apoptosis in effector T cells

As an autoimmune disease, RA is partially characterized by the excessive activation and infiltration of T cells toward synovium and synovial compartments [1]. DCs induce naive T cells to differentiate into T helper cells in process of RA, which results in inflammation and bone destruction [2]. Therefore, suppression of mature DC-induced T-cell differentiation and activation is a crucial pathway for the therapy for RA with tolDCs. It has been reported that tolDCs could lead to incomplete signaling to T cells through inhibition of IL-12 production and generation of TGF-β, which induce alloantigen-specific T-cell hyporesponsiveness, anergy or apoptosis in vitro and suppress immune reactivity [50]. During the past years, studies have shown that tolDCs suppress effector T-cell response via upregulation of molecules including IDO, FasL, PD-L1 and CTLA-4 Ig that are associated with immunoregulation and apoptosis and downregulation of self-peptide-MHC complex in couple with limited costimulatory molecules (especially CD86) [51]. These mechanisms have been recapitulated in experimental model of RA and arthritis and provide support for therapy of RA with tolDCs [13].

TolDCs suppress the activation of memory T cells

RA is characterized by the accumulation of CD4(+) T cells in the inflamed synovium, and most of them are CD4+ memory T cells. Recent evidence suggests that steady-state immature DCs, which constitutively present an endogenously expressed antigen, can inactivate fully differentiated memory CD8+ T cells in vivo through deletion and inactivation [52]. Moreover, studies have shown that tolDCs that are generated with different immunosuppressive agents and cytokines can induce antigen-specific anergy and regulatory properties in CD4+ memory T cells [48, 53]. Recently, it is reported that tolDCs can regulate CD4+ memory T-cell differentiation. Xu X et al. found that coculture of tolDCs with CD4+ T cells results in the secretion of Th2 cytokines (IL-4, IL-5, IL-10 and IL-13) and negative immune regulation by memory T cells [54]. Taken together, these studies suggest that inhibition of the activation of memory T cells is another possible mechanism for tolDCs function in RA treatment.

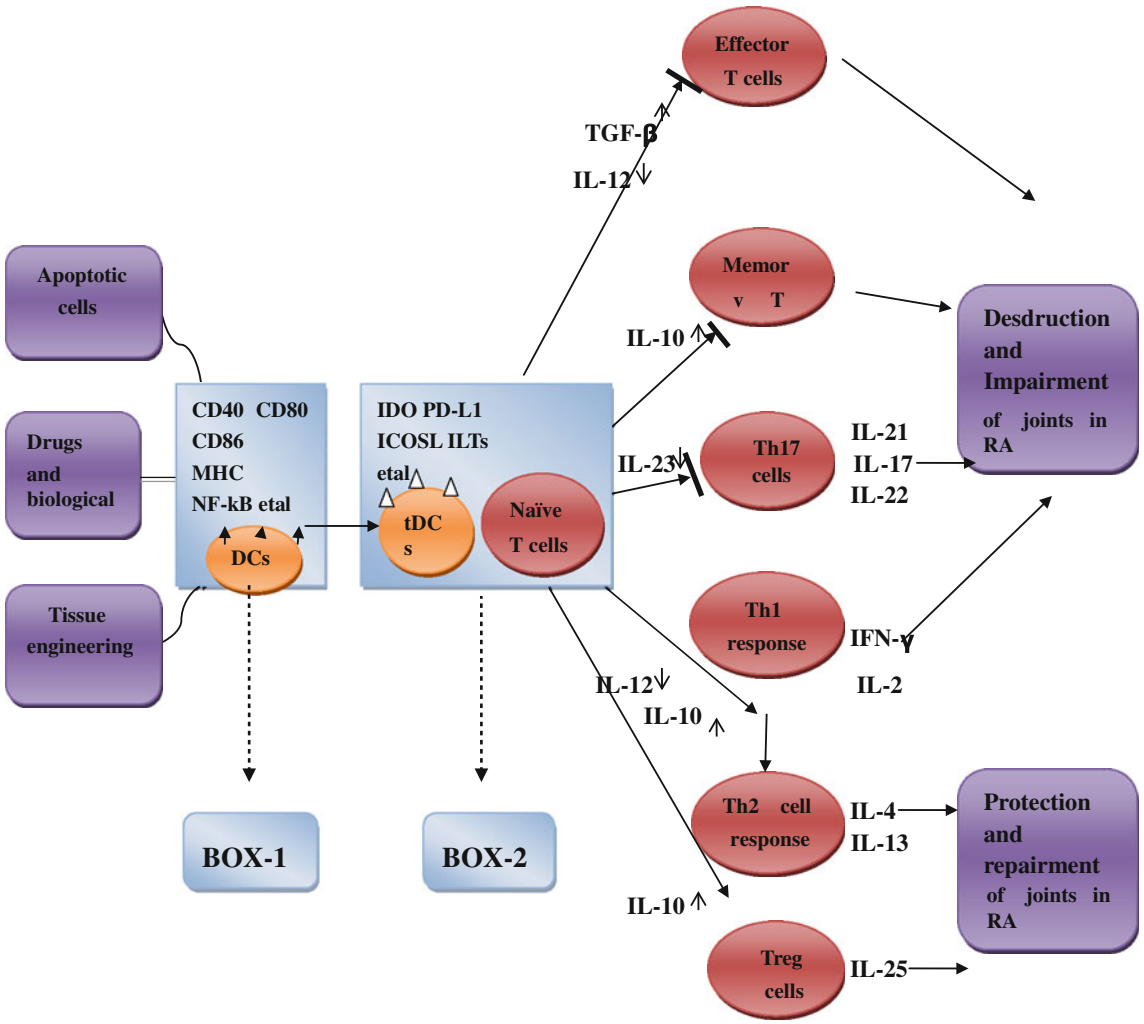

Fig. 1 Manipulation strategies to generate tolDCs and potential mechanisms underlying tolDC-induced autoimmune tolerance. Various cytokines (such as ILs, TNF and TGF-β), and immunoregulatory molecules (such as IDO, PD-L1, ICOSL and ILTs) participate in all this process during which tolDCs induce special differentiation of naïve T cells, which cause tolerance of autoimmunity and protect and improve RA. *IL* interleukin, *MHC* major histocompatibility complex, *TGF-β* transforming growth factor-β, *Th* helper T cells, *PD-L1* programmed death 1 ligand, *DC* dendritic cell, *lIDO* indoleamine 2,3-dioxygenase, *RA* rheumatoid arthritis; *NF-kβ* nuclear factor-kappa B; *Treg* regulatory T cell; *ILT* immunoglobulin-like transcript, *ICOSL* inducible costimulator ligand. ⟶▌ Prevention/inhibition; ↑ upregulation; ↓ downregulation. *BOX-1* (1) Genetic engineering as a novel tool for the generation of tolDCs by suppressing expression of costimulatory molecules (CD40, CD80 and CD86) and promoting expression of immunosuppressive proteins (e.g. IDO). (2) Uptake of ACs leads to ligation of individual receptors on human DCs that recognize apoptotic cells (such as CR3 and CR4), during which process DCs get tolerogenic phenotype to inhibit IL-12 production, generate transforming growth factor β (TGF-β) and produce IL-10. (3) Drugs and biological agents that target inhibition of costimulatory molecules such as MHC, CD40, CD80 and CD86, and upregulation of immunosuppressive molecules including IDO, PD-L1, ILTs and ICOSL can induce tolerogenic phenotype of DCs. *BOX-2* (1) Naive T cells can differentiate into Th17, which produces inflammatory cytokines and results in tissue destruction in RA. TolDCs lead to the reduction in IL-23, which is essential for the expansion of Th17 cells. (2) Effector T cells comprise main part of autoimmune reactions in RA. TolDCs could inhibit IL-12 production, generate TGF-β and induce hyporesponsiveness, anergy or apoptosis of effector T cells. (3) CD4+ memory T cells accumulate in RA synovium and take part in T-cell inflammatory response. TolDCs can produce cytokines (e.g. IL-10), which induce antigen-specific anergy in CD4+ memory T cells. (4) RA is characterized by a marked shift toward the Th1 phenotype, which is proinflammatory, with overproduction of IFN. TolDCs lead to a switch from Th1 to Th2 response with more Th2 cytokines (e.g. IL-4, IL-13) and result in autoimmune tolerance. (5) Tregs have been proved to attenuate RA via secretion of cytokines such as IL-25. TolDCs can express IDO and produce TGF-β and IL-10, which facilitate Foxp3+ Tregs

Switch of Th1/Th2 balance to Th2 cells selectively

RA is characterized by a marked shift toward the Th1 phenotype, which is described as proinflammatory, with overproduction of IFN and inadequate production of Th2 cytokines such as IL-4 and IL-13 [55]. The immune deviation (skewing of T cells toward the Th2 type) and the role of Th2 cytokines in immune tolerance have been discussed

[56]). Th2 cells induce processes involved in cartilage repair, including collagen synthesis [57]. Studies have shown that therapies aimed at switch of Th1/Th2 balance attenuated RA and CIA. Accumulating evidence has shown that prophylactic treatment with tolDCs is associated with a reduced collagen II-specific IgG2a/IgG1 ratio, indicating a switch from a Th1- toward a Th2-driven collagen II-specific immune response, which inhibits CIA in experimental arthritis models [3, 58].

Effect of tolDCs on regulatory T cells (Treg)

It has been well established that Foxp3+ Treg cells could lead to the suppression of autoimmune response. Interestingly, recent data showed that induction of Treg cells facilitates the restoration of immune tolerance in RA [59]. The potential role of Treg cells in RA was reviewed very recently [60].

Tregs can be induced by repeated stimulation with allogeneic immature human or mouse mDCs. In addition, pDCs express tolerogenic phenotype and induce Treg cell through the expression of IDO [61–64]. In vivo study further showed that selective ablation of DCs led to the loss of FoxP3-expressing Treg and the development of proinflammatory autoreactive T effectors, resulting in excessive autoimmunity [65]. Recent studies have shown that tolDCs can attenuate RA and experimental arthritis through induction of Tregs [66], which represents another promising mechanism for treatment for RA with tolDCs.

Treatment for RA with tolDCs: current situation and perspectives

Current situation of tolDCs for RA

Up to now, the therapeutic application of tolDCs is practiced mostly in animal models of RA. The development of animal models in which DCs are selectively depleted will help characterize the specific role of these cells in the pathogenesis of RA. Studies have shown that repetitive injection of immature DCs or DCs, which were modulated with TNF, IL-10, dexamethasone or LF 15-0195, could induce tolerance to autoimmunity and result in the amelioration of inflammation and destruction in experimental RA models. Furthermore, DCs transduced with Fas ligand or IL-4 could prevent CIA and inhibit arthritic symptoms in mice with established disease [3, 67, 68]. In addition, tolDCs modified by other drugs or cytokines have been used successfully to prevent the onset of CIA and alleviate established arthritis in the antigen-induced arthritis model [69].

TolDCs induced via drugs or other agents have also been evaluated for therapeutic effects in RA patients. Anti-TNF therapy has been proven to be effective in treating patients with RA clinically, which ameliorates clinical symptoms partially through induction of tolDCs in vivo. Moreover, analysis of the immunophenotypes of circulating DCs in RA patients before and after treatment with infliximab demonstrated that tolerogenic phenotype of DCs is closely correlated with clinical outcome of RA [70].

Perspectives

The utilization of tolDCs as a promising cellular vaccine for tumor, infection and some autoimmune diseases has been well described in the literature [71–75]. Fortunately, the application of tolDCs as potential vaccine for the clinical treatment for RA is getting more attention [22, 76, 77].

TolDCs for immunotherapy must be safe, standardized and controlled [78, 79]. Recently, it was reported that tolDCs generated in one study exhibited high-level expression of a certain receptor TLR-2, which is an appropriate quantity control marker [19] for safety purposes. This is encouraging for the therapeutic use of tolDC vaccines in RA clinically. In conclusion, we can see that although there are still challenges for its clinical use, tolDC-based vaccination has a promising future to treat RA safely, conveniently and effectively (Fig. 1).

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