Review

Role of dendritic cells in the initiation, progress and modulation of systemic autoimmune diseases

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ABSTRACT

Dendritic cells (DCs) play a key role in the activation of the immune response against pathogens, as well as in the modulation of peripheral tolerance to self-antigens (Ags). Furthermore, an imbalance in the activating/inhibitory receptors expressed on the surface of DCs has been linked to increased susceptibility to develop autoimmune diseases underscoring their immunogenicity potential. It has been described that modulation of activating or inhibitory molecules expressed by DCs, such as CD86, TLRs, PDL-1 and FcγRs, can define the immunogenic phenotype. On the other hand, T cell tolerance can be achieved by tolerogenic DCs, which have the capacity of blocking undesired autoimmune responses in several experimental models, mainly by inducing T cell anergy, expansion of regulatory T cells and limiting B cell responses. Due to the lack of specific therapies to treat autoimmune disorders and the tolerogenic capacity of DCs shown in experimental autoimmune disease models, autologous tolDCs are a potential therapeutic strategy for fine-tuning the immune system and reestablishing tolerance in human autoimmune diseases. New advances in the role of DCs in systemic lupus erythematosus (SLE) pathogenesis and the identification of pathogenic self-Ags may favor the development of novel tolDC based therapies with a major clinical impact. In this review, we discuss recent data relative to the role of DCs in systemic autoimmune pathogenesis and their use as a therapy to restore tolerance.

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1. Introduction

The major function of the immune system is to detect and eliminate pathogens and detrimental Ags to protect the integrity of the host [1]. Recognition of self-Ags plays a crucial role in shaping the repertoire of T and B cell receptors (TCR and BCR), preventing the occurrence of harmful autoreactive cells and generating tolerance mechanisms that reduce the susceptibility to autoimmune diseases [2]. However, in susceptible hosts immune tolerance may fail, leading to autoimmunity. Although the etiology for autoimmunity remains unknown, environmental factors and genetic determinants are the most important contributors [3].

Dendritic cells (DCs) play a crucial role in both initiation of immune responses and induction of T cell tolerance, mostly by fine tuning the signaling of activating and inhibitory receptors [4]. The relevance of the inhibitory receptors expressed by DCs has been highlighted by the observation that PDL-1 blocking modulates T cell activation during experimental autoimmune encephalomyelitis [5,6]. However, the mechanisms responsible for peripheral T cell anergy mediated by DCs are not well understood.

Autoimmunity may involve any tissue or cell types of the body and the severity and duration of the disease vary widely [7]. Patients suffering from autoimmune diseases may have more than one concurrent disorder. Depending on involved tissues, autoimmune diseases are classified as organ-specific or systemic. The complexity of autoimmune diseases and the side effects associated with unspecific immunosuppression approaches have dampened the development of new and more Ag-specific therapies, particularly in systemic autoimmune diseases. One of the most injurious autoimmune diseases is systemic lupus erythematosus (SLE). SLE is a chronic disease that preferentially affects women and is clinically characterized by an extensive range of heterogeneous symptoms that may affect the blood vessels, kidneys, the peripheral and central nervous systems, skin and mucosa.

It has been widely demonstrated that both innate and adaptive immune cells contribute to SLE pathogenesis [8–10]. Antigen presenting cells (APCs) such as DCs and monocytes from SLE patients have been shown to present phenotypic and functional abnormalities. It has been postulated that self-reactive T cells specific for nuclear self-Ags may arise from an impaired clearance of apoptotic fragments by monocytes [11]. Moreover, we and others have shown that DCs from SLE patients display increased expression of the co-stimulatory molecules CD40 and CD86, as well as a higher ratio of activating to inhibitory Fc gamma receptors (FcγRs) as compared to DCs from healthy controls [9]. These observations suggest that DC maturation may be involved in an inefficient peripheral tolerance in these patients [9].

Although much progress has been made in autoimmunity research, specific and effective therapies for systemic inflammatory disorders have not yet been developed. Nevertheless, some progress has been made in the development of therapy of different autoimmune disorders with the use of biological agents that mainly prevent signaling of pro-inflammatory cytokines [12]. However, current medications for treating SLE have not been significantly effective because they induce systemic immunosuppression that can lead to a wide spectrum of adverse effects [13]. Recently, it has been proved that the use of a biological agent that blocks the B-lymphocyte stimulator (BLyS) (Belimumab) in SLE patients ameliorates clinical symptoms [14].

Due to their capacity to modulate autoreactive responses by inducing T cell anergy and regulatory T helper (Th) polarization profiles, the use of DCs for immunotherapy has become an attractive possibility for autoimmune disease treatment, where reestablishing immune tolerance is essential [15]. Currently, most work is focused on developing "tolerogenic" DCs (tolDCs) with the capacity of blocking undesired specific autoimmune responses [16,17]. In fact, several approaches based on pharmacological and genetic modifications of DCs that intend to enhance their tolerogenic capacity are currently in progress [17,18]. Herein, we discuss current knowledge relative to the understanding of DCs in systemic autoimmune pathogenesis, focusing on the role of activating and inhibitory receptors expressed on DCs which interact with T cells. In addition, we discuss recent data on tolDCs in autoimmunity and new technical approaches related to carry out tolDC immunotherapy with a special focus on systemic autoimmunity, such as SLE.

2. Contribution of endogenous TLR ligands to autoimmune diseases

DCs sense pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) through membrane and cytosolic receptors known as pattern-recognition receptors (PRRs), such as Toll like receptors (TLRs) and NOD-like receptors [19]. Pro-inflammatory stimuli, such as PAMPs and DAMPs promote functional, morphological and phenotypic changes in immature DCs that lead to maturation and increase their immunogenicity. Mature DCs show strong co-stimulatory and T cell activating capacity, with high MHC-II and CD80/CD86 expression [20–22]. In addition, mature DCs can produce large amounts of pro-inflammatory cytokines such as IL-12, IL-23, IL-6 and others that will define the T helper (Th) profile and subsequently the nature of the effector immune response triggered by a particular antigen [23–26].

During the past decades, evidence has accumulated for associations between PRR polymorphisms and pro-inflammatory cytokine production with the pathogenesis mechanisms underlying immune-mediated diseases in humans [27,28]. For instance, Crohn's disease patients usually show polymorphisms in the NOD2 receptor, which may lead to an imbalance in IL-1β, TNF-α and GM-CSF production that results in mucosal inflammation [28,29].

Several TLRs (TLR1, TLR2, TLR3, TLR4, TLR7, TLR8 and TLR9) also recognize endogenous molecules such as DAMPs as HMGB1, HSP60-70, surfactant protein A, fibronectin, fibrinogen, lactoferrin, serum amyloid A, hyaluronic acid fragments, heparan sulfate, mRNA, ssRNA and immunocomplexes (ICs) containing chromatin [30–32]. Recognition of these endogenous molecules by TLRs can contribute to tissue damage due to inflammation. For example, it is well known that circulating ICs containing self nucleic acids can promote immune-inflammatory activation and tissue injury in SLE. Interestingly, HMGB1 present in circulating DNA-containing ICs was crucial for anti-dsDNA development in SLE by a mechanism likely to be driven by a TLR2/MyD88/microRNA-155 dependent pathway [31]. Also, the effective activation of rheumatoid factor-specific B cells is mediated by IgG2a-chromatin ICs and requires engagement of the BCR and TLR9, highlighting an important role for receptors of the innate and adaptive immune responses in the development of systemic autoimmunity [32]. Furthermore, some extracellular DAMPs, such as self-DNA, need to be transported into PRR containing endosomes in plasmacytoid DCs (pDCs) in order to trigger autoimmunity. The association of the antimicrobial peptide LL-37, a cathelicidin polypeptide, with self-DNA targets this DAMPs to intracellular compartments to be recognized by TLR9 leading to cellular activation and IFN-α production [33–35]. During psoriasis, a common immune mediated disease, LL-37 can be overexpressed and turns quiescent self-DNA into a potent IFN-α inducer by changing DNA structures and targeting this DAMP to early endocytic compartments, where it is recognized by TLR9 in pDCs [35] (Fig. 1).