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REVIEW

Tolerogenic dendritic cells as a therapy for treating lupus

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Abstract Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that is characterized by the over production of auto-antibodies against nuclear components. Thus, SLE patients have increased morbidity and, mortality compared to healthy individuals. Available therapies are not curative and are associated with unwanted adverse effects. During the last few years, important advances in immunology research have provided rheumatologists with new tools for designing novel therapies for treating autoimmunity. However, the complex nature of SLE has played a conflicting role, hindering breakthroughs in therapeutic development. Nonetheless, new advances about SLE pathogenesis could open a fruitful line of research. Dendritic cells (DCs) have been established as essential players in the mechanisms underlying SLE, making them attractive therapeutic targets for fine-tuning the immune system. In this review, we discuss the recent advances made in revealing the mechanisms of SLE pathogenesis, with a focus on the use of DCs as a target for therapy development.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder of unknown etiology that preferentially targets young women and is associated with higher morbidity, disability, and mortality compared to the general population [1]. SLE clinical presentation is diverse, ranging from mild disease to life-threatening symptoms, such as alveolar hemorrhage and neuropsychiatric manifestations (e.g., seizures and psychosis). Although the hallmark of SLE is overproduction of autoantibodies against nuclear constituents, several other components of the innate and adaptive immune responses have been implicated in the development of this disease. Paradoxically, although several mechanisms for SLE pathogenesis have intrigued immunologists for decades, specific and effective therapies have yet to be developed. FDA approval of the first drug treatment for SLE in more than 30 years, Belimumab, was granted last year. In spite of this important breakthrough, all available medications for managing lupus, including Belimumab, work via the same mode of action, namely nonspecific suppression of the immune system. For example, recent progress in using monoclonal antibodies and fusion receptors to block cytokine pathways in rheumatic diseases, such as rheumatoid arthritis and anti-neutrophil cytoplasm antibody-associated vasculitides, has encouraged lupus researchers to use these same, strategies to treat SLE. Due to the adverse effects associated with these treatments, researchers continue to pursue alternative strategies for treating lupus.

Recently, promising new data has emerged revealing the crucial role of the innate immune system, including Toll-like receptors (TLRs), dendritic cells (DCs), and type I interferons (IFNs), in SLE pathogenesis. Such findings have provided scientists and clinicians with new clues to unveiling the complex mechanisms leading to SLE, with the goal of developing novel, specific treatments aimed at restoring tolerance and suppressing the autoreactive immune system. Studies from the past decade have shown that the interaction between DCs and T lymphocytes is essential in maintaining peripheral tolerance to self-constituents. Thus, its role in many inflammatory and autoimmune diseases has been exploited to develop new therapies. DCs have the potential to modulate the effector response of autoreactive T cells by modifying cytokine profiles, thereby ameliorating immune disturbances. In addition, new technical approaches intended to fine-tune the function of immune cells are currently being developed. This review summarizes the most recent research advances in understanding SLE onset and progression, with a special focus on understanding the effects of modulating DCs, which have been revealed to be critical for SLE pathogenesis [2–5].

2. Altered DC-T interactions leading to tolerance loss and autoimmunity in SLE

DCs are the most efficient professional antigen presenting cells (APCs). Nearly ubiquitous in peripheral tissues, DCs capture antigens and direct them to lymphoid organs with the purpose of encountering and activating antigen-specific T cells. Moreover, DCs are supplied with specialized machinery that enables them to process peptide antigens and load them onto antigen presenting molecules, such as MHC-I and MHC-II [6]. DCs also present lipid antigens to T cells through CD1 molecules [7]. DCs express co-stimulatory molecules such as CD80 and CD86 which, together with MHC, provide them with the unique ability to activate naïve T cells [6,8–10]. Besides co-stimulatory molecules, DCs also express inhibitory receptors like PD-L1, which binds PD-1 to inhibit T cells [11].

DCs sense pathogen-associated molecular patterns (PAMPs) through specialized surface receptors known as pattern-recognition receptors, which include TLRs and NOD-like receptors. PAMP binding to pattern-recognition receptors promotes a phenotypic change in DCs known as maturation [12–14], which is characterized by the upregulation of surface molecules, such as signal 1 (peptide-MHC complexes) and signal 2 (co-stimulatory molecules), that enable DCs to activate naïve antigen-specific T cells (Fig. 1). A third signal, supplied by DCs already loaded with antigen, involves the release of several cytokines such as IL-12, IL-4, IFN-γ and others that define the nature of the effector response mediated by the activated T cell (Fig. 1) [5,9,10,15].

DCs maintain the balance between antigen-specific immunity and tolerance by integrating activating and inhibitory signals derived from cell surface activating/inhibitory receptor pairs (Fig. 1). A classic prototype of this dual interaction includes the Fcγ receptor family, which recognizes the Fc portion of IgG and is comprised of one inhibitory (FcRγIIB) and three different activating receptors in mice (FcγRI, III, IV) and humans (FcγRIA, IIA, IIIA) [5,10,16–19]. While activating receptors signal through immunoreceptor tyrosine-based activating motifs, inhibitory receptors function through immunoreceptor tyrosine-based inhibitory motifs [5,10,16–19]. Studies have shown that selective engagement of activating Fcγ receptors on the surface of DCs leads to enhanced DC maturation and increased priming efficiency of tumor and pathogen-induced T-cell immunity [20–22]. Accordingly, FcγRIIB knockout mice exhibit exacerbated inflammation, as evidenced by increased susceptibility to experimental autoimmune encephalomyelitis and collagen-induced arthritis (CIA) [22,23]. Furthermore, in certain genetic backgrounds, FcγRIIB deficiency causes spontaneous development of an SLE-like disease characterized by overproduction of anti-DNA