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Review

Tolerogenic dendritic cell vaccines to treat autoimmune diseases: Can the unattainable dream turn into reality?

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ABSTRACT

Autoimmune diseases affect about one in 15 individuals in developed countries and are characterized by a breakdown in immune tolerance. Current therapeutic approaches against destructive immune responses in autoimmune diseases are based on non-specific agents systemically suppressing the function of many immune effector cells. This indiscriminate immunosuppression, however, often causes serious and sometimes life-threatening side effects. Therefore, the need for more specific treatments resulting in lower toxicity and longer-term solutions is high. Because of the established role of dendritic cells (DCs) in maintaining the balance between immunity and tolerance, tolerogenic (tol)DCs might be novel therapeutic targets to prevent undesirable (auto-)immune responses. The idea behind tolDC therapy is that it is a highly targeted, antigen-specific treatment that only affects the auto-reactive inflammatory response. The therapeutic potential of tolDCs has already been proven in experimental animal models of different autoimmune disorders as well as with *in vitro* experiments using *ex vivo* generated human tolDCs, thus the challenge remains in bringing tolDC therapy to the clinic, although first clinical trials have been conducted. In this review, we will extensively discuss the use of tolDCs for induction of antigen-specific tolerance in several autoimmune disease settings, from bench to bedside, including currently applied strategies to generate tolDCs as well as technical difficulties and challenges in the field.

Contents

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1. Introduction

Autoimmune and autoinflammatory diseases affect about 1 in 15 individuals in developed countries and are in many instances a devastating health problem to the individual patient, thereby representing a heavy burden to society. They comprise a diverse collection of diseases in terms of their demographic profile and primary clinical manifestations [1–3]. Whereas in some cases autoimmunity is associated with systemic symptoms affecting multiple organs, such as systemic lupus erythematosus (SLE), most autoimmune diseases have a predilection for a specific organ, such as rheumatoid arthritis (RA), atherosclerosis, multiple sclerosis (MS), inflammatory bowel diseases (IBD), and psoriasis. Although several mechanisms are thought to be operative in the pathogenesis of autoimmune diseases, including genetic predisposition and environmental modulation, the commonality between them is that they all originate from an aberrant lymphocytic response against self-antigens, which can be primarily T or B cell-mediated or both, and requires breakdown of immune tolerance to self-antigens. However, since self-antigen driven B cell activation cannot take place without T cell help, we focus here on the studied models of breakdown of tolerance at the T cell level.

Immune tolerance is the ability of the immune system to ignore self-antigens as well as harmless constituents thereby preventing destructive responses to the body's own tissues and cells while preserving protective immunity [4]. The immune system possesses multiple complex tolerance mechanisms to keep T and B cells unresponsive to self-antigens. The early tolerance mechanisms that operate in the core immune organs, such as the thymus and the bone marrow, before the maturation and circulation of T cells and B cells, respectively, are referred to as *central tolerance* [5,6]. Additional processes used to reduce or inactivate auto-reactive immune cell lineages take place in secondary lymphoid organs and/or at sites of inflammation and are called *peripheral tolerance* [5,6].

In contrast to corticosteroid-based treatment of autoimmunity, current immune-based therapies to restore the immune tolerance and treat autoimmune diseases, such as T and B cell depletion [7,8], blocking of T cell costimulation using CTLA-4 Ig [9,10], and cytokine neutralization (anti-TNFα, anti-IL-6) [11–13] offer promising and more tailored treatment of some autoimmune diseases. Unfortunately, they do not result in a long-lasting, drug-free remission of the autoimmune disease [14]. Moreover, they act as general immunosuppressants, systemically suppressing the function of many immune effector cells and therefore often cause serious and sometimes life-threatening side effects. Thus, new – more antigen-specific and targeted – therapies resulting in lower toxicity and longer-term solutions are needed. Since dendritic cells (DCs), a specialized subset of antigen-presenting cells, appear to be essential for both central tolerance in the thymus and peripheral tolerance in the other tissues, this has provided the prospect for their use to suppress pathogenic immune responses in autoimmune diseases.

DCs are the main orchestrators of the immune symphony. They constitute a heterogeneous family of professional antigen-presenting cells that play a central role in the (dys)regulation of immune responses [15–17]. As sentinel members of the *innate immune system*, they patrol the body to capture antigens, including self-antigens, invading pathogens and certain malignant cells. These antigen-loaded DCs migrate to the secondary lymphoid organs and the internalized antigen is processed and presented to other immune cells. Depending on the context in which the antigen is captured, DCs induce tolerance or immunity. Indeed, DCs respond to antigens and molecules containing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by the generation of protective cytokines [15]. In doing so, they trigger effective immunity against invading pathogens and altered self-antigens by stimulation of naive T cells, effector T cells and memory T cells, as well as B cells [15,18,19].

Extensive evidence from numerous studies has directly or indirectly demonstrated the role of DCs in autoimmune disease development. For example, constitutive ablation of conventional (c)DCs, plasmacytoid (p) DCs and Langerhans cells breaks self-tolerance and leads to spontaneous fatal autoimmunity under steady-state conditions [20]. Given the critical role of DCs in the negative selection of auto-reactive T cells and positive selection of regulatory T cells (Tregs) [21], this is most likely mediated by a failure to induce T cell tolerance in the thymus and the subsequent release of auto-reactive T cells into the periphery. However, transient (short-term) depletion of DCs in mice abrogates T cell priming to antigens [22] and inhibits the development of autoimmune diseases, even after disease onset [23]. This suggests that either the presence of DCs in the young animal is sufficient to promote long-term immune tolerance or that spontaneous priming and expansion of auto-reactive T cells in the periphery can only occur when DCs are depleted for a prolonged period of time [20]. Moreover, upon constitutive ablation of cDCs only, mice remain healthy without any signs of autoimmunity [24], indicating that pDCs and Langerhans cells may have a more prominent role in the maintenance of immune tolerance. Indeed, both pDCs and Langerhans cells have been shown to exert potent tolerogenic functions to prevent or dampen activation of alloreactive [25–27] or allergen-specific [28] T cells as well as to mediate oral tolerance [29].

The abundant presence of DCs at sites of autoimmune inflammation, such as synovial fluid and tissue of RA patients [30], salivary glands of Sjögren's syndrome patients [31], atherosclerotic plaques [32] and cerebrospinal fluid (CSF) of MS patients [33], further supports their involvement in autoimmune mechanisms. Also in serum of patients with various autoimmune diseases, high numbers of inflammatory DCs were detected [34–36] and a positive association was shown between high levels of circulating DCs secreting pro-inflammatory cytokines and severity of MS [37].

In this review, we discuss the dual role of DCs in the pathogenesis of autoimmunity and subsequently provide prospect for their use as tolerance-inducing cell-based treatment strategy for a number of autoimmune diseases. For this, we concentrate on RA, atherosclerosis, MS and IBD. An overview of different currently applied strategies is given Q4 to generate stable tolerogenic DCs (tolDCs) as well as technical difficulties and challenges that remain in the field.

2. DCs in autoimmunity: a double-edged sword

Continuous research efforts have contributed substantially to current knowledge regarding the DC-mediated tolerance mechanisms. Nevertheless, uncovering the underlying pathways as well as identification of new ones in peripheral tissues remain a big challenge for immunologists [38]. Thymic DCs, together with medullar thymic epithelial cells (mTECs), play a critical role in maintaining *central tolerance* whereby T cells recognizing self-antigens with high affinity are eliminated through apoptosis (*i.e.* negative selection) during their development in the thymus [39,40]. However, since many self-reactive T cells may have low or intermediate affinity for the self-antigen, not every potential auto-reactive lymphocyte is deleted in the thymus. Furthermore, not all self-antigens are expressed in the thymus. Hence, T cells recognizing proteins that are only found at other sites in the body or only at certain times during development must be initiated in the periphery [6]. DC-mediated *peripheral tolerance* mechanisms are more diverse. Tolerance-inducing DCs can mediate apoptosis or deletion of mature auto-reactive T cells in the peripheral lymphoid organs [41]; or, DCs can induce unresponsiveness of T cells, a process that is called anergy [42]. Indeed whereas cooperative action of a TCR signal, a costimulatory signal mediated by CD28 ligation and secreted cytokines interacting with TCRs in a paracrine fashion is mandatory for T cell activation [43], it was believed that antigen recognition in the absence of a costimulatory signal induces long-term hyporesponsiveness of the T cells characterized by an active repression of TCR signaling [6]. However, to date a variety of costimulatory pathways have been identified and are currently classified based on their impact on primed T cells [44]. Indeed, pathways delivering activatory signals to T cells are termed

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