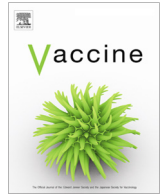


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## Review

## Recent advances in the development of vaccines for chronic inflammatory autoimmune diseases

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## ABSTRACT

Chronic inflammatory autoimmune diseases leading to target tissue destruction and disability are not only causing increase in patients' suffering but also contribute to huge economic burden for the society. General increase in life expectancy and high prevalence of these diseases both in elderly and younger population emphasize the importance of developing safe and effective vaccines. In this review, at first the possible mechanisms and risk factors associated with chronic inflammatory autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE) and type 1 diabetes (T1D) are discussed. Current advances in the development of vaccines for such autoimmune diseases, particularly those based on DNA, altered peptide ligands and peptide loaded MHC II complexes are discussed in detail. Finally, strategies for improving the efficacy of potential vaccines are explored.

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## 1. Introduction

The major chronic inflammatory autoimmune diseases (CIDs) like rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE) and type 1 diabetes (T1D) are usually affecting multiple organ systems both specifically as well as systemically. Increase in the prevalence of such CIDs has been well documented [1]. However, current therapeutic options available are mostly targeting the effector functions but not aim to cure the disease because the causative factors for these CIDs are not yet well defined. Moreover, identification and targeting of pathogenic pathways during the autoimmune phase of the disease before the onset of clinical manifestations are optimal to prevent these debilitating diseases. Until now, vaccination is one of the most effective strategies available to fight against infectious diseases. However, attempts at developing effective vaccines for CIDs are limited. This is mainly because the ideal goal for treating CIDs should aim to interfere with the harmful autoreactive immune responses while at the same time should neither alter the normal immune responses that are necessary for combating infectious agents nor induce any generalized immune suppression. So understanding of the basic immunological processes involved in these diseases is essential for an effective vaccine development. Most interestingly, many of these CIDs share certain pleiotropic genes [2] and hence it is plausible that common disease pathways could affect many of these CIDs. If potential vaccine candidates modulating the common disease pathways (for example MHC-based vaccines, cytokine inhibitors etc.) are identified that would be a highly promising approach for the future.

In spite of extensive efforts to develop preventive and therapeutic treatments for CIDs, no effective curative methods have been developed because of the disease complexity and treatments' side effects. Thus, exploring the etiological mechanisms and development of new effective vaccines become essential. Studies on the prevention and treatment of CIDs have been focused on the identification of antigens from pathogens or autoantigens responsible for triggering autoimmune reactions [3]. Thus, autoantigen identification is essential for developing CID vaccines.

## 2. Possible mechanisms and risk factors for CIDs

### 2.1. Environmental and genetic risk factors

Although the etiology of the CIDs is still being investigated, some possible environmental risk factors have already been identified (Fig. 1). For example, hormones and ultraviolet light are considered as environmental risk factors for SLE [4,5]. As to RA, smoking, hormones and bacterial infections are considered as possible environmental risk factors. Human leukocyte antigen (HLA) gene was the first described genetic risk factor associated with both SLE and RA [6,7]. In humans, T1D risk is strongly associated with combinations of the HLA-DR4/DQ8 and DR3/DQ2 haplotypes and 90% of T1D patients harbor DQ8 or DQ2 alleles [8]. Other non-HLA genes have also been identified to play a relevant role in CID susceptibility. For example, PTPN22 C1858T (R620W) single-nucleotide polymorphism is associated with RA, SLE and T1D [9,10]. However, there is no significant correlation reported with MS [11]. CTLA-4, also a negative regulator of T-cell activation, is

associated with many of these CIDs [12] with certain specific populations. It is also of interest to note that interactions between genetic and environmental factors contribute more to disease phenotypes than the individual factors. For example, in RA, smoking and shared epitopes together were identified as high risk factors for developing seropositive RA [13]. Results from recent studies suggest that inflammation in the lungs [14] and gut microbes [15] might also contribute to RA development.

### 2.2. Sex difference in CIDs

Accumulating evidence supports sex-based differences in susceptibility to CIDs [16,17]. The average age of MS onset is earlier in females than in males and the percentage of SLE patients is much higher in females. Enhanced expression of sphingosine-1-phosphate receptor 2 [18] and ZAS3, a regulator of inflammatory pathways [19], were connected to female susceptibility to central nervous system (CNS) and lupus autoimmunity respectively. Low androgen levels, as well as reduced androgen/estrogen ratios, have been identified in both male and female RA patients, suggesting that sex hormones play a critical role in RA [20]. Although the effects of sex hormones on susceptibility to autoimmune disease provide some insights into the sex bias observed in autoimmunity, other sex-dependent factors are yet to be well defined. In general, females develop higher antibody immune responses to vaccines than males and against some vaccines females respond with higher cell mediated immune responses as well. But, females also develop frequent and severe adverse reactions to vaccines. Hence more attention should be given to understand the heterogeneity in the unintended reactions to vaccines based on sex differences [21].

### 2.3. T cells

Based on their cytokine profile, T cell are classified into different subsets: interferon-gamma (IFN- $\gamma$ ) and tumor necrosis factor alpha (TNF- $\alpha$ ) producing Th1 cells; IL-4, IL-5 and IL-13 secreting Th2 cells; IL-17 producing Th17 cells, regulatory Th cells ( $T_{regs}$ ), IL-9 producing Th9 cells and IL-22 producing Th22 cells. Many of the CIDs are considered to be T cell-mediated, which leads to destruction of specific tissue or organs. For example, T1D is a T cell-mediated autoimmune disease that leads to  $\beta$ -cell destruction. In animal models, it has been well documented that both CD4+ and CD8+ T cells are necessary for the progression of diabetes [22]. Any approach that may skew the T cell compartment from pathogenic Th1, Th17 subsets to protective Th2 and  $T_{reg}$  phenotypes provides protection against development of CIDs [23,24]. For the development of Th2 and  $T_{regs}$ , a strong IL-2 signaling is required [25,26] but  $T_{regs}$  need TGF- $\beta$  for survival, Foxp3 expression and suppressor function [27]. On the other hand, TGF- $\beta$  inhibits GATA3 and Gfi-1 expression leading to suppression of Th2 cell differentiation [28]. Innate cytokines like IL-25, IL-33 and thymic stromal lymphopoietin are important in developing Th2 immune responses [29]. However, some plasticity exists between differentiation of different Th cell populations [30].

During vaccination, an adjuvant is commonly used along with the vaccine and toll-like receptors (TLRs) in myeloid dendritic cells essentially act as adjuvant receptors and sustain the molecular basis of adjuvant activity [31]. Activation of TLRs regulates co-

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