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Vaccination for Autoimmune and Other Chronic Inflammatory Disorders

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INTRODUCTION

At the dawn of the new millennium, chronic noncommunicable disorders are the major cause of morbidity and mortality among populations living in industrialized and transitional countries. The rising tide of autoimmune and allergic diseases is overshadowed even by diseases associated with subtle low-grade inflammation including obesity, insulin resistance and type 2 diabetes (T2D), atherosclerosis and cardiovascular disease, and, arguably, Alzheimer's disease and cancer. These disorders demand novel preventative and therapeutic approaches, one of which is vaccination. Classically, after Jenner, vaccination has been a means of inducing an immune response resulting in resistance to infectious disease. This ''positive'' vaccination is targeted against exogenous, nonself antigens. Vaccination for therapeutic purposes can also be targeted to endogenous self-antigens, to achieve gain or loss of function depending on the type of induced immune response. Like many drugs, antibodies to receptors or other molecules can have agonist or antagonist properties and thereby modify cell function. This is illustrated by autoantibodies in experiments of nature, for example, by agonist autoantibodies to the thyrotropin receptor that cause hyperthyroidism in Graves' disease or by antagonist autoantibodies to the acetylcholine receptor that cause muscle weakness in myasthenia gravis. Just as experimental immunologists employ antibodies passively in vitro and in animal models to block mediators of pathology, so also can vaccination be used to induce antibodies that modify cell function in vivo. Some understanding of physiology and disease mechanisms and a glance at the index of a medical textbook would suggest a range of applications for ''autovaccination,'' from suppression of inflammation to prevention of conception. The author is not aware of autovaccination being used to deliberately up-regulate ''self'' function but there is no theoretical reason why the immune system could not be manipulated to do so.

Likewise, the cellular arm of the adaptive immune system can be manipulated to modify the function of the immune and other systems. T cells that recognize self-antigen peptides presented by antigen-presenting cells in tissues or draining lymph nodes can modify other cells and the local environment, for example, induce cell death, suppress antigen-presenting cell or pathogenic T-cell function, or reduce inflammation and vascular permeability. This is illustrated by $CD8^+$ cytotoxic T-lymphocyte (CTL) immunity against tumors on the one hand and by Tregs that protect against autoimmune disease on the other.

Vaccination strategies to prevent or ameliorate autoimmune disease could: (*i*) avert causative environmental agents, (*ii*) delete or inactivate pathogenic T cells, (*iii*) induce protective/regulatory T cells or therapeutic antibodies, or (*iv*) promote a therapeutic effect downstream of autoimmune pathology [an example might be to enhance insulin sensitivity in autoimmune or type 1 diabetes (T1D)]. Vaccination with an autoantigen to induce, paradoxically, disease-specific immune tolerance/protection can be termed ''negative vaccination.'' It is based on the concept that autoantigen-specific immune tolerance mechanisms are physiological and can be boosted or restored to prevent pathological autoimmunity (1). For autoimmune disease, autoantigen-specific vaccination is the therapeutic Holy Grail. It is efficacious in rodent models but has yet to be effectively translated to humans. The likely reasons for this are discussed later. In theory, vaccination with autoantigen should be relatively safe and inherently more acceptable for prevention of autoimmune disease in asymptomatic individuals than treatment with conventional, nonspecific immunosuppressive agents. However, allergic reactions and acceleration rather than retardation of underlying disease are possible outcomes that require attention. In particular, vaccination with autoantigen is a double-edged sword that can also induce CTLs, as exemplified by attempts to induce antitumor immunity. In the context of autoimmune disease, the desired outcome, immune tolerance/protective immunity, depends on a range of factors. These include the ''load'' of activated, pathogenic effector cells to overcome, route of delivery (e.g., mucosal vs. systemic), nature of the autoantigen (e.g., the presence of CTL epitopes), dose of autoantigen, and context of autoantigen recognition (e.g., the nature of the antigen-presenting cell, cytokine milieu). Protective immunity has been achieved in rodent models by administering autoantigen protein, peptide, or DNA via ''tolerogenic'' routes, cell types, modes, or forms (Table 1), to delete or anergize pathogenic lymphocytes and/or induce regulatory T cells (Tregs) (2). Some Tregs secrete the immunosuppressive cytokines IL-10 or TGF-β that suppress the ability of antigen-presenting cells to elicit effector T-cell responses to any antigen, a phenomenon called ''bystander suppression.'' Thus, although autoimmune disease is frequently associated with immunity to more than one autoantigen, bystander suppression by Tregs stimulated by one antigen