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Review

Design of therapeutic vaccines as a novel antibody therapy for cardiovascular diseases

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ABSTRACT

Vaccines are primarily used worldwide as a preventive medicine for infectious diseases and have recently been applied to cancer. We and others have developed therapeutic vaccines designed for cardiovascular diseases that are notably different from previous vaccines. In the case of cancer vaccines, a specific protein in cancer cells is a target antigen, and the activation of cytotoxic T cells (CTL) is required to kill and remove the antigen-presenting cancer cells. Our therapeutic vaccines work against hypertension by targeting angiotensin II (Ang II) as the antigen, which is an endogenous hormone. Therapeutic vaccines must avoid CTL activation and induce the blocking antibodies for Ang II. The goal of our therapeutic vaccine for cardiovascular diseases is to induce the specific antibody response toward the target protein without inducing T-cell or antibody-mediated inflammation through the careful selection of the target antigen, carrier protein and adjuvants. The goal of our therapeutic vaccine is similar to that of antibody therapy. Recently, multiple antibody-based drugs have been developed for cancer, immune-related diseases, and dyslipidemia, which are efficient but expensive. If the effect of a therapeutic vaccine is nearly equivalent to antibody therapy as an alternative approach, the lower medical cost and improvement in drug adherence can be advantages of therapeutic vaccines. In this review, we will describe our concept of therapeutic vaccines for cardiovascular diseases and the future directions of therapeutic vaccines as novel antibody therapies.

Contents

Introduction

Vaccines are commonly used worldwide to protect against infectious diseases and have been applied as therapy against Alzheimer's disease, cancer, and rheumatoid arthritis. Approximately

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8 years ago, I decided to start a challenging project: to develop a novel system for the therapeutic vaccine, initially for hypertension. Currently, hypertension can be well controlled by patients through lifestyle modifications and several types of medication, according to the guidelines. If the effect of a vaccine could be equal to that of medication in the future, the clinical benefit of this therapy could be an improvement in drug adherence, and the societal benefit could be a reduction in medical costs to treat lifestyle-related diseases. Recently, we and others have successfully demonstrated vaccine therapy for high blood pressure, hyperglycemia, or dyslipidemia in animal models. The goal of our study is to ultimately develop a system of novel therapeutic vaccines for human clinical trials that can also be applied to other diseases in place of antibody therapy. In this review, I will discuss the novel concept of our therapeutic vaccine and introduce recent reports of therapeutic vaccines for hypertension, hyperglycemia, and dyslipidemia.

Concept of therapeutic vaccination against a self-antigen

Vaccines are usually designed for "the invaders", such as viruses, bacteria, or cancer. However, in the case of our therapeutic vaccines, the target is usually a self-antigen. Thus, the design of our therapeutic vaccine is to induce a blocking antibody response against a self-antigen without inducing the cytotoxic immune response [1]. In our immune tolerance system, the immune reaction against self-antigens is tightly regulated by blocking the activation of self-reactive T-cells, but self-reactive B-cells are still active and can be provoked by efficient T-cell activation [2]. The primary mechanism of immune tolerance is T-cell tolerance, which involves both central and peripheral tolerance (Fig. 1). The central T-cell tolerance blocks the egress of self-reactive T-cells from the thymus, and peripheral T-cell tolerance inactivates the T-cells by induction of 'anergy', which will be explained later on. To fully activate B-cells, CD4+ T-cells are required for their differentiation into plasma and memory cells. Because of the T-cell immune tolerance, the self-reactive B-cells are reactive to antigens even though they cannot receive help from CD4+ T-cells. Thus, the key component of the vaccine for self-antigens is to borrow a foreign T-cell epitope to activate the self-reactive B-cells, leading to the induction of antibody production [3]. Based on this information, we designed a therapeutic vaccine for angiotensin II (Ang II) as our first challenge.

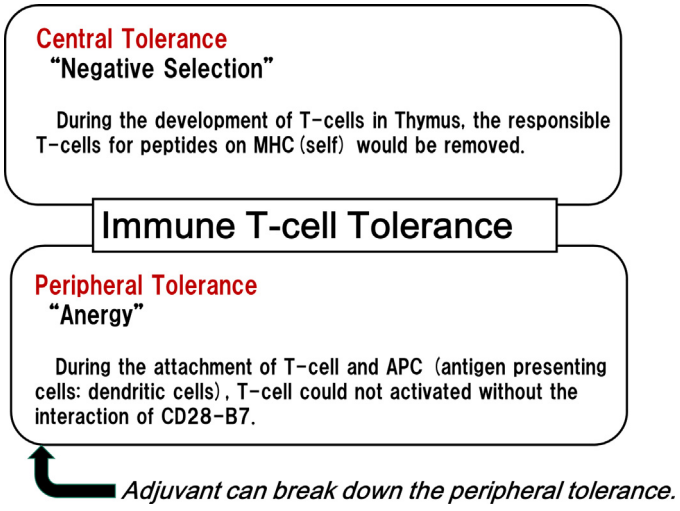

Fig. 1. T-cell immune tolerance. The mechanism of T-cell tolerance involves both central and peripheral tolerance. The central T-cell tolerance blocks the egress of self-reactive T-cells from the thymus, and peripheral T-cell tolerance inactivates the T-cells by induction of 'anergy'.

Design of Ang II peptide vaccines

The design of our therapeutic vaccine therapy is shown in Fig. 2. We utilized keyhole-limpet hemocyanin (KLH) [4,5] as a carrier protein, including the foreign T-cell epitopes, and immunized mice or rats with Ang II-KLH conjugate and adjuvants to circumvent T-cell tolerance. In the immunization phase, antigen-presenting cells (APCs) phagocytose Ang II-KLH and present a T-cell epitope of Ang II-KLH to T cells through the major histocompatibility complex (MHC), and T-cells recognize the antigen through the T-cell epitope and become activated (i.e. they differentiate to effector T cells) (step 1). As I mentioned above, T-cell anergy arises with the recognition of the MHC when the T-cell does not receive co-stimulation by CD28-B7 interactions from APCs. Importantly, co-treatment with adjuvants effectively induces the CD28-B7 interaction.

Thus, the combination of Ang II-KLH and adjuvants successfully induces the proliferation and differentiation of T-cells against Ang II-KLH. B-cells that are specific to Ang II phagocytose and present the epitope of Ang II-KLH to T-cells through the MHC. Then, B-cells differentiate to plasmacytes and produce antibodies with the help of activated T-cells (effector T-cells) (step 2).

Indeed, we confirmed that the vaccine with Ang II-KLH and adjuvants efficiently induced an anti-Ang II antibody titer and induced T-cell activation [3]. For T-cell epitopes, a T-cell proliferation assay and an enzyme-linked immunosorbent spot (ELISPOT) assay were conducted to confirm the study design. The results showed that Ang II-KLH and KLH induced T-cell activation, but Ang II alone did not, which may suggest that only KLH contains a T-cell epitope. Because this finding suggests that eight amino acids of Ang II could activate B-cells but not T-cells, our therapeutic vaccine requires the foreign T-cell epitope. Additionally, for pharmacological evaluation, continuous Ang II infusion was conducted. Interestingly, immunized mice did not show an increase in the anti-Ang II antibody titer even after Ang II infusion. These results suggest that the co-treatment of Ang-KLH and adjuvants produces an antibody against Ang II that is assisted by helper T-cell activation, and this vaccine system does not induce an autoimmune response because T-cells recognize the foreign T-cell epitope of KLH, which is completely "non-self".

Historical background of therapeutic vaccines for hypertension

The use of vaccines to target self-antigens has been reported for cancer [6], rheumatoid arthritis [7], Alzheimer's disease [8,9], hypertension [10–15], and dyslipidemia [16]. Because safe and effective drug therapies have already been established for several of these conditions, the adverse effects of vaccines should be carefully considered. The Alzheimer's disease clinical trial was halted because the participants developed aseptic meningoencephalitis due to an autoimmune response [7].

Vaccines for hypertension in animal models, targeting the renin-angiotensin system, have been reported for more than 50 years. An angiotensin I vaccine (PMD3117) reduced blood pressure in rat and mouse models, but it was not effective in the reduction of blood pressure in a human clinical trial [10,11]. An Ang II vaccine (AngQb-Cyt006) was also reported to be effective in producing anti-Ang II antibodies in both rodents [12] and humans [13]. However, further clinical studies of the Ang II vaccine failed to reproduce the reduction in blood pressure. Therefore, the development of an Ang II vaccine for clinical applications has been halted. Therapeutic vaccines for renin and angiotensin type 1 receptors have been reported, and these vaccines were effective in a hypertensive rat model [14,15].

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