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Progress in autoimmune disease and vaccine

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Abstract. Autoimmune diseases (ADs) are caused by an overactive immune system, which frequently results in irreversible damage to organs and physiological systems. Despite the extensive research conducted on Autoimmune Diseases (ADs) over numerous years, the etiology and contributory factors remain only partially elucidated. Presently, the therapeutic drugs encompasses glucocorticoids (GCs), Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). However, these agents exert a modicum of efficacy against the malady, and are prone to elicit severe adverse reactions as well as drug resistance. Therefore, the development of vaccines targeting the pathogenesis of ADs may bring great progress to the treatment of ADs. This article delineates the concepts underpinning vaccine development leveraging human immune tolerance, encompassing the induction of tolerance, the targeting of pathogenic T cells, and the engagement of regulatory pathways. Concurrently, the paper expounds upon certain vaccine technologies that have emerged in the study of specific autoimmune diseases, including type 1 diabetes, rheumatoid arthritis, and multiple sclerosis.

Keywords: ADs, vaccine, immune tolerance.

1. Introduction

Immune system, consisting of immune cells, immune organs and immunoactive substances, plays a vital role in defending against attack of pathogens. Misidentification and accidentally attacking your body, however, result in autoimmune disease, while inducement of which is unknown and complicated[1].

Witebsky hypothesis is the most widely used diagnostic criteria for ADs[2]. According to the hypothesis, organ-specific and systemic are two classes of ADs. Organ-specific ADs refer to those pathological damage and dysfunction of tissues and organs are limited to a certain organ targeted by antibodies or sensitized lymphocytes. typical organ-specific ADs include Hashimoto thyroiditis, type 1 diabetes and multiple sclerosis; Extensive deposition of antigen-antibody complexes in the blood or other parts of your body may cause systemic ADs. Some common human systemic disorders, like systemic Lupus Erythematosus and rheumatoid arthritis, always leads to systemic multi-organ damage eventually.

Can happen in various system, including connective tissue neuromuscular system, endocrine system, respiratory system etc. Once the disease high concentration of autoantibody and activation of sensitized lymphocytes will arise local inflammation, and most of ADs will recur and persist chronically. The pathogenesis of ADs is unclear. However, multiple hypotheses have been proposed. In addition to

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immunological research, objective evidence from family and epidemiology has let study at the genetic level on a hot spot.

ADs affect about 1 in 10 people, and the burden of disease continues to increase at variable rates over time[3]. In recent years, there has been a noted escalation in the incidence of ADs. This increase is particularly pronounced among individuals aged 40-50 years. Furthermore, a reserch who has compared incidence rates of 9 different ADs(Table 1) illustrates that there is a notable gender disparity, with further evidence supports that women are significantly more affected by ADs than men [4-5].

Table 1. Crude incidence rates per sex for each autoimmune disease[6]

Autoimmune diseaases	IR (95%CI) per 100,000 PYs	
	Female	Male
ADEM	6.14 (6.00-6.29)	4.31 (4.19-4.44)
Bell's palsy	23.82 (23.54-24.11)	23.86 (23.57-24.15)
GBS	1.74 (1.66-1.82)	2.39 (2.30-2.48)
ITP (broad definition)	20.47 (20.20-20.73)	23.11 (22.83-23.40)
ITP (narrow definition)	3.95 (3.84-4.07)	3.69 (3.57-3.80)
Kawasaki desease	0.52 (0.47-0.56)	0.81 (0.76-0.87)
Narcolepsy	1.12 (1.06-1.19)	1.04 (0.98-1.10)
Optic neueitis	4.42 (4.29 4.54)	2.39 (2.29-2.48)
SLE	8.47 (8.30-8.65)	2.05 (1.97-2.14)
Transverse myelitis	1.10 (1.03-1.17)	0.83(0.77-0.89)

A large number of epidemiological studies of ADs have been conducted revolving around the description of disease distribution and the exploration of environmental risk factors, and results have shown that morbidity of ADs is not only closely related to gender and race, but also depends on living schedule and diet [7]. Molecular epidemiological studies have confirmed the genetic correlation of ADs at the genetic level [8]. With the development of epigenetics, environmental and genetic influences on ADs are often considered simultaneously [9].

Immunosuppressive drugs play an important role in the treatment of ADs [10]. The traditional medications extensively employed in clinical practiced are glucocorticoid(GC), Nonsteroidal anti-inflammatory drugs (NSAIDs), and conventional synthetic disease-modifying anti-rheumatic drugs(csDMARDs).

GC are steroid hormones secreted by the adrenal cortex, pervasive throughout all bodily tissues and organs. They possess the capacity to exert influence on nearly every organ and tissue, thereby contributing to the upkeep and modulation of human physiological homeostasis. Moreover, at supraphysiological dosages, these hormones elicit additional pharmacological responses beyond metabolism, including anti-inflammatory, immunosuppressive, anti-allergic, and anti-shock therapeutic properties [11]. Prolonged utilization of GC may elicit deleterious impacts on a multitude of cells across various organ systems, including the circulatory, digestive, musculoskeletal, neuropsychiatric, metabolic and endocrine systems [12-15]. Concurrent use of steroids potentially entails a hazard of disease progression and exacerbation. Consequently, the prescription of GC is typically limited to brief durations and minimal dosages in the majority of clinical interventions(Table 2).

Table 2. Immunosuppressive drugs used to treat autoimmune disease[16]

Agent	Mechanism of Action	Use (s)	Major Adverse Effect/ Toxcities
Methotrexate Leflunomide	• Inhibits lymphocyte folate metabolism • Inhibitor of lymphocyte pyrimidine synthesis	• Inflammatory bowel disease • Rheumatoid arthritis • Rheumatoid arthritis	• Nausea, diarrhea • Alopecia • Hepatotoxicity • Hepatotoxicity • Renal impairment

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Table 2. (continued).

Etanercept, Infliximab, Adalimumab	• TNF-a inhibitor	• Rheumatoid arthritis • Psoriasis • Inflammatory bowel disease	• Teratogenic • Gl disturbances • Alopecia • Infection • Myelosuppression • Heart failure • Demyelinating disease • Hypersensitivity
Glucocorticoids	• Inhibit inflammatory gene transcription • Induce lipocortins	• Rheumatoid arthritis • Inflammatory bowel disease • Inflammation	• Hyperglycemia • Osteoporosis • Hypercortisolism • Growth impairment • Impaired wound healing

NSAIDs are frequently utilized in the management of joint autoimmune disorders. These medications exert a multifaceted therapeutic action, including antipyretic, analgesic, anti-inflammatory, and anti-rheumatic properties, by inhibiting the enzymatic activity of cyclooxygenase during the metabolism of arachidonic acid, thereby diminishing the biosynthesis and deposition of prostaglandins within the body. Commonly prescribed NSAIDs include ibuprofen, indomethacin, meloxicam, among others. The adverse effects of NSAIDs encompass a range of central nervous system disturbances, cardiovascular risks, gastrointestinal manifestations, hematologic alterations, hepatic and renal dysfunctions, bronchial asthma exacerbations, and cutaneous drug reactions [17]. Nonetheless, it is important to note that NSAIDs do not provide a curative solution for the underlying diseases and may not entirely inhibit the activity or slow the progression of the conditions.

csDMARDs can inhibit the activity of immune cells and reducing the production of inflammatory mediators, thereby alleviating the inflammatory response in joints and other tissues. Commonly used csDMARDs include methotrexate, leflunomide, sulfasalazine, etc. Methotrexate, as an anchor drug for RA, is usually used as the first-line treatment for RA [18-19]. However, long-term utilization of DMARDs is susceptible to develop drug resistance [20].

With the advancement of biomedicine, significant strides have been taken in the investigation of monoclonal antibody(mAb) therapies for the treatment of ADs. mAb reefers to proteins produced by B cells and capable of specifically targeting antigens, have garnered widespread application in the treatment of a myriad of diseases, including cancer and ADS. Monoclonal antibodies (mAbs) are capable of specifically targeting disease-related targets, while producing minimal toxicities and adverse effects on the body. These characteristics enable them to exert therapeutic effects effectively, positioning them as the optimal choice for the treatment of ADS at the current stage.

Due to the constraints of conventional treatment modalities for ADs, vaccines have garnered attention for their numerous benefits, including the activation of the immune system, maintenance of immune efficacy, and enhancement of therapeutic outcomes. Consequently, the development of vaccines targeting ADs has emerged as a significant trend in future treatment strategies.

2. Vaccine for ADs

Conventional vaccines are comprised of attenuated or inactivated components of a particular microorganism (antigen), capable of initiating an immune response within the body. For ADs, in the contrary, vaccine development has focused on reversing the immune system's response to antigens.

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2.1. Immune tolerance

The core idea of an autoimmune vaccine is recovering immune tolerance, which consists of the thymus and central tolerance and peripheral tolerance(Figure 1).

The thymus not only nurtures the development of T lymphocytes, but also actively participates in the mechanism of immune tolerance, guiding T lymphocytes to form tolerance to their own tissues. It is now generally accepted that immature thymocytes in the thymus develop a healthy and mature TCR repertoire through an affinity selection mechanism. With moderation of the affinity of TCR and MHC-peptide complex, the TCR thymocytes will be selected by positive selection and further mature. If the affinity is too low, the TCR thymocytes will be neglected and die without selection. While if affinity is too high, negative selection will be elicted, and such autoreactive immature thymocytes will undergo clonal deletion or clonal anergy. Thus, autoimmune tolerance is formed [21].

The mechanism of peripheral immune tolerance mainly depends on clonal inactivation, clonal deletion and regulatory T cells (Treg). However, the imbalance of antibody secretion pathway(misactivation of B cells), TLRs signaling pathway(the lack of helper T cells leads to the generation of costimulatory signals and activation of a large number of autoimmune T cells) and complement pathway(The absence of complement components may cause lymphocytes to be activated and secrete a variety of lymphokines to regulate the immune response) can result in the disruption of peripheral immune tolerance among lymphocytes. [22].

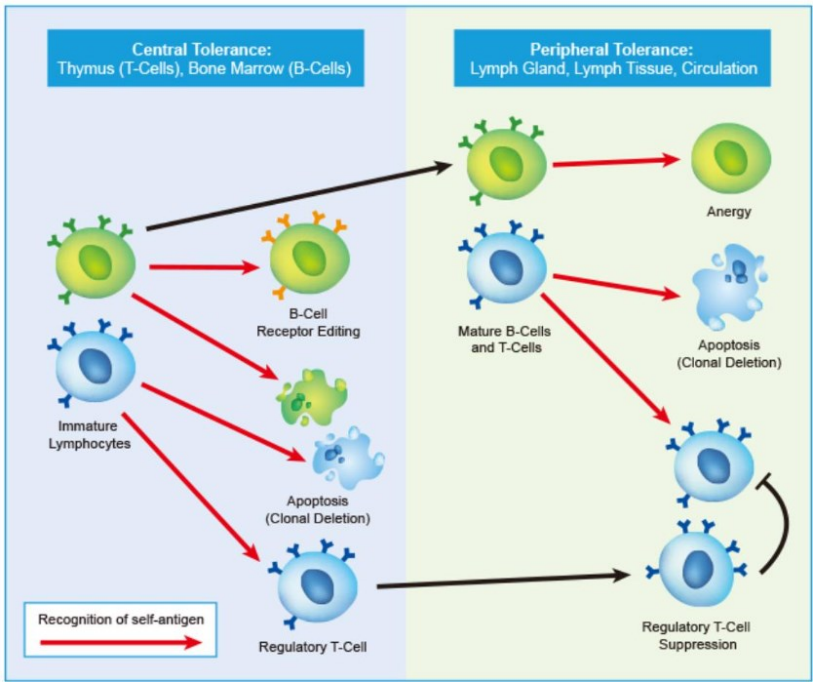

Figure 1. Mechenisim of immune tolerance[23]

2.2. Type of vaccine for immune tolerance

2.2.1. Inducing Tolerance

The use of a wide range of immunosuppressive drugs is the most common clinical treatment for ADs. The current approved treatments, including tumor necrosis factor-α inhibitors and interleukin-1 antagonists, necessitate ongoing administration and are only effective following the onset of immune dysfunction; however, they fail to prevent or elicit immune tolerance.

At the same time, scientists are concerned about whether they can restore immune tolerance by modifying autoimmune antigens, thus allowing for the dissociation of the antigen on endocytosis and its presentation in the immunoregulatory environment [24].

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2.2.2. Targeting Pathogenic T Cells

Therapies that selectively target highly active pathogenic T cells involved in the regulation of tissue-reactive immunity are available with a well-soluble CD2 costimulatory receptor LFA-3 (alefacept), an anti-CD3 monoclonal antibody (teplizumab), and antithymocyte globulin with a low dose[25-26]. It has been well documented that these biologics can induce apoptosis and functional inactivation of highly activated effector cells, leaving naive T cells and dendrites intact and even promoting the expansion of regulatory pathways.

2.2.3. Targeting Regulatory Pathways

Defects or regulatory impairments within crucial immune cells, including tolerogenic FoxP3-positive Treg cells, have been identified. These findings imply that an increase in the number of Treg cells, an enhancement of their function, or a combination of both, may serve as potential strategies to prevent the development of autoimmunity[27]. Through vivo manipulation or adoptive therapy, Treg therapy exploits two distinct factors to enhance immune tolerance: bystander suppression and infectious tolerance. These mechanisms enable Tregs to broadly suppress immune responses in the local environment and create a tolerogenic environment so that to suppress unexpected immune cells, thereby averting autoimmune responses and maintaining transplantation tolerance[28].

3. Available vaccine therapies

3.1. Human insulin dependent diabetes mellitus (IDDM, type 1 diabetes)

IDDM happens when pancreatic beta cells were attacked by the immune system, with destruction and fails of function, resulting in an absolute deficiency of insulin. Current treatments for IDDM in clinic have side effect, resistance or addiction to some extent, while vaccine for IDDM, aiming to inhibiting autoimmune in advance, may potentially provide a safer therapeutic alternative for managing IDDM [29-30].

Single-peptide IDDM vaccine has been studied for a period. Extensive evidence has corroborated that the likelihood of triggering ADs is minimal when autoantigen peptides are administered individually in appropriate quantities [31]. It have been proved that a large variety of peptides, including insulin and GAD655, which is naturally secreted in the human body, or DiaPep277, A 24-amino acid peptide derived from HSP607,and have made great progress in inhibiting IDDM[32-33].

Based on the studies above, adjuvant-stimulated IDDM vaccine are anticipated to elicit more effective preventive outcomes by augmenting the immune response to the antigens they deliver without eliciting a potent immune reaction. I Some adjuvants with proven safety and efficacy, like incomplete Freund's Adjuvant (IFA) and aluminum adjuvant, are expected to cooperate with traditional single-peptide IDDM vaccine [34-35].

3.2. Rheumatoid Arthritis (RA)

Clinically, therapeutics for rheumatoid arthritis primarily encompass NSAIDs, glucocorticoids, DMARDs(including conventional DMARDs, bDMARDs, and tsDMARDs) and other medications. While these treatments can alleviate the symptoms of RA effectively, their side effects are not negligible. There is an urgent requirement for more efficacious and safe drugs for the treatment of RA.

Basing on antigen specific immunotherapy, teams of Zhan and Hu have cooperated and successfully design the citrullinated collagen type II polypeptide (citAg) vaccine. By targeting pathogenic T cells or B cells without damaging systemic immunity, citAg successfully inhibits the recall response of antigen-specific T cells in collagen-induced arthritis (CIA) mice, corrects the imbalance of V (D) J rearrangement of B cells, restores the normal immune repertoire, and thus plays a therapeutic role in experimental arthritis [36].

The clonal diversity and abundance of the TCR repertoire in rheumatoid arthritis (RA) render it a promising biomarker [37]. In Lewis CIA rats, the TCR Vβ5.2 and TCR Vβ8.2 are identified as the principal pathogenic T cell clonotypes. A recombinant DNA vaccine targeting these TCR Vβ5.2 and

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TCR Vβ8.2 has demonstrated efficacy in effectively inhibiting the corresponding T cells, which has been corroborated to exert a favorable impact on the management of RA [38-39].

3.3. Multiple sclerosis (MS)

MS is a prevalent demyelinating disorder of the central nervous system, arising from the immune system's assault on the myelin sheath—the insulating covering around nerve cells. This condition is typified by its multifocal lesions, periods of remission, and relapses. It can lead to disorders in visual acuity, balance, muscle coordination, and other fundamental bodily functions. The resultant cognitive decline and physical disabilities can be significantly debilitating [40].

Peripheral Tolerance is a regulatory mechanism within the body that prevents the immune system from launching an attack against every damaged cell or foreign substance it encounters. A research team at the University of Chicago has engineered a novel "reverse vaccine," referred to as N-acetylgalactosamine (pGal), this compound emulates the peripheral immune tolerance mechanism by conjugating to myelin protein to induce antigen-specific tolerance. As a result, the treatment was able to restore normal nerve function and reverse the symptoms of the disease in animal models [41].

4. Conclusion

Since the first discovery of ADs, the treatment of ADs is still a global problem. The main reason is that the pathogenesis of ADs is complex and the exact cause has not been found. With the development of biomedical science and relative subjects, more and more therapeutic approaches, such as cell therapy, cytokine therapy and gene therapy, have been gradually developed and applied to the study of ADs.

More and more patients are learning about and embracing the transformative and innovative therapies of the 21st century, while Cell and gene therapy is a new field of cancer treatment and the most promising development direction of life medicine. With the promising development situation of cell and gene therapy, related therapeutic regimens and drugs have been approved worldwide.

Meanwhile, with a better understanding of the human immune system, scientists have tried to prevent or cure ADs by vaccine. It is expected that future vaccines against ADs will completely conquer the "immortal cancer" of ADs and provide new solutions for other immune diseases.

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