Toward a precision medicine approach for autoimmunity

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Autoimmune diseases are characterized by the immune-mediated attack on seemingly healthy tissue. This attack is caused by a misdirected immune response to self-antigen. A key element of most autoimmune disorders is the recognition by T lymphocytes of specific antigenic peptides loaded onto major histocompatibility complex molecules and known as epitopes. There is firm consensus in the field that inducing immunological tolerance to disease-relevant epitopes would be the ideal approach to treating autoimmunity. In PNAS, Postigo-Fernandez et al. (1) describe their systematic approach to testing this strategy in a mouse model for autoimmune (type 1) diabetes with a DNA vaccination platform they recently developed.

Inducing immune tolerance

The immune system comprises an adaptive arm that includes T and B lymphocytes capable of reacting to specific antigens. Lymphocyte activation can be induced by immunization with either whole pathogens (live or dead), with proteins, or with short peptides. This activation forms the basis of protective vaccination that has been in use for more than two centuries (2). However, the encounter with antigen does not always result in immune activation. Since the 1950s, immunologists have known that lymphocytes can also be inactivated in response to specific antigens under the right circumstances. This was first described by Felton (3) as "immunologic paralysis" to denote the lack of reactivity to a particular antigen. In the early descriptions of what was later called "immunologic unresponsiveness" and is now known as immune tolerance, researchers noted that the antigen dosing was critical in determining the fate of immune cells (4).

Immune tolerance was initially thought to derive from the intrinsic inability of relevant lymphocytes to respond to antigen following tolerance induction. Experiments in the 1970s showed that immune tolerance can instead involve an active, dominant mechanism of immune suppression. A key observation came from McCullagh (5), who tolerized rats to sheep erythrocytes and found that immune responsiveness could not be restored by simply transplanting lymphocytes from a nontolerized animal into a tolerant one. Instead, responsiveness could only be reestablished by first ablating endogenous immune cells in the tolerant animal using irradiation before transplanting lymphocytes from a nontreated animal. We now know that this active suppression stems primarily from regulatory T cells, which can be induced or expanded in response to immunization. These two attributes of immune tolerance, the absence of a response and its active suppression by a regulatory population, are the foundations for the precision medicine strategy pursued by Postigo-Fernandez et al. (1) to halt autoimmune diabetes.

DNA vaccination for tolerance induction

A particular feature of the work described by the group in PNAS is the use of DNA vaccination. The first demonstrations of tolerance induction made use of whole proteins, cells, or pathogens. Later, peptides were shown to be similarly effective and to provide a high degree of specificity. Recent and ongoing clinical trials have made use of whole proteins or peptides to induce specific antigen tolerance in autoimmunity (6, 7). The induction of immune tolerance has proven very effective in many animal models but has yet to show long-term efficacy in modifying human disease.

The first report of DNA vaccination 30 y ago showed that administering nucleic acids encoding relevant proteins could be used instead of protein immunization to protect against influenza (8). Within a few years of this seminal work, researchers started using DNA vaccination to induce immune tolerance to self-antigen. One early report demonstrated the potential of this approach in the experimental autoimmune encephalomyelitis (EAE) model for multiple sclerosis. Tolerance induction to myelin basic protein by DNA immunization was shown to prevent EAE triggered by the same antigen in nontolerized animals (9). Studies in other diseases followed, including in two models for autoimmune diabetes where insulin DNA immunization offered significant protection against diabetes (10, 11).

Over the past two decades, the use of DNA immunization to induce tolerance to disease-relevant proteins or epitopes has gained traction and has even been tested in early clinical trials (12–14). The key advantages of a DNA vaccination strategy are that this method is relatively inexpensive, safe, and highly modular, allowing—in principle—the rapid production of individualized therapeutic products. These are features highlighted in the work by Postigo-Fernandez et al. (1), who developed an "endotope" platform to deliver multiple epitopes either as cleaved intracellular epitopes or as a secreted polypeptide from a single plasmid. This contrasts to earlier work by others who employed a mixture of plasmids to target multiple disease-relevant epitopes (15).

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Optimizing multi-epitope tolerance induction

The induction of immune tolerance using multiple epitopes, delivered as peptides or as a DNA vaccine, has shown efficacy in animal models. Meaningful therapeutic effects have yet to be achieved in humans, but initial results from clinical trials in multiple sclerosis employing a mixture of peptides to tolerize patients are encouraging (7). In the hope of optimizing the approach, Postigo-Fernandez et al. (1) proceeded to systematically test how the route of administration, frequency of dosing, and treatment duration would affect the outcome of a tolerizing DNA vaccine in a model for type 1 diabetes. In their work reported in PNAS, the group show that antigen produced from a single vaccination was still detectable up to 14 d later. However, despite the longevity of a single dose, disease protection necessitated more frequent, weekly dosing. In their system, intradermal vaccination with a secreted polypeptide was most effective as opposed to intramuscular injection and to a plasmid encoding intracellular peptides. Further, they showed that preventive treatment even close to the time of disease onset was partially effective. Finally, their data suggest that the endotope platform generates or expands antigen-specific regulatory T cells. Overall, the study by Postigo-Fernandez et al. (1) is a rigorous demonstration that DNA vaccination can be effective but that it has to be fine-tuned. Significantly, the data suggest that the effective time window for a preventive vaccination in type 1 diabetes could be close to diagnosis because a treatment of short duration proved effective at this stage but not when administered to a larger group of mice long before disease onset, when a longer treatment duration was required to achieve some efficacy.

A particularly enticing feature of their platform is the modular nature of endotope plasmids that can be constructed to encode and deliver multiple relevant peptides for tolerance induction. Significantly, because these peptides are generated within host cells, they can be modified posttranslationally in a manner resembling endogenous autoantigens (16). Ultimately, the most critical aspect of any immune-tolerizing regimen is the nature of the antigens that are used. While preclinical disease models are often very well characterized, autoimmune disease in humans is heterogenous and can entail different antigens in different patients with the same disease. A successful DNA vaccination for type 1 diabetes will not only require a suitable platform and a carefully optimized vaccination schedule but also, the right choice of antigens. In this respect, a modular construct such as the one developed by Postigo-Fernandez et al. (1) may lend itself to tailoring DNA vaccines to an individual's immunological profile. The dominant T cell reactivities could be quantified in patients (for treatment) or persons at risk (for prevention) before manufacturing a personalized vaccine. While many more hurdles will have to be overcome to reach this stage, the research presented in PNAS takes us a step closer to a precision medicine approach to autoimmunity.

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