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Therapeutic Vaccines: Why Have They Succeeded in Some Diseases and Failed in Others?

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ABSTRACT

Background: Therapeutic vaccines generate or restore antigen-specific immunity, providing a unique clinical approach as compared to prophylactic vaccination. Although therapeutic vaccines have intermittent efficacy in different diseases, their optimistic response is reported in some infectious diseases whereas, insignificant efficacy in many chronic and immune-dysregulated malignancies. This questions the underlying biological and translational determinants and seek scientific explanations for these divergent outcomes. Therapeutic vaccines have been linked with well-characterized conserved target antigens, partially preserved immune competence, and disease settings that allow effective immune activation., which predetermines the success of therapeutic vaccines. In contrast, failure of these vaccines is often associated with antigenic variability, immune exhaustion or tolerance, prevailing immunosuppressive mechanisms, and recalcitrant disease microenvironments that impair effective immune interactions. Additional complications include vaccine platforms, poor adjuvants as well as concerns related to design of clinical trials like poor endpoints and poor patient stratification. Immunology, biomolecular profiling and vaccine engineering technologies have elucidated these challenges and identified ways of overcoming them. The translational efficacy can be improved by integrating therapeutic vaccines with immune-modulating factors, selection of targeted antigens, and the use of biomarkers to guide the clinical process. It is essential to define success and failure to guide the development of next-generation therapeutic vaccines rationally.

Keywords: Vaccines, Therapeutic; Immunotherapy; Antigens, Neoplasm; Immune Tolerance; T-Lymphocyte Exhaustion; Tumor Microenvironment; Biomarkers

Therapeutic vaccines are intended to induce, replace, or recreate antigen-specific immunity, in previously affected individuals [1]. This strategy differs from prophylactic vaccination, which is active in immunologically naïve hosts and prevents infection or the development of a disease. From pathophysiological perspective, therapeutic vaccines have to fight with the already existing pathological processes including immune tolerance, chronic inflammation, immune exhaustion, and tissue-specific immunosuppression [2]. These elements place great biological limits resulting in diverse clinical responses in terms of therapeutic vaccine efficacy. Experimental evidence has demonstrated that alterations in cellular signaling and immune-related pathways significantly influence disease progression and therapeutic responsiveness [3].

Therapeutic vaccines have been explored in numerous disease models, such as chronic viral infection, cancer, autoimmune diseases and neurodegenerative disorders [4]. Not all of these vaccines have shown a significant clinical benefit or immunogenicity in spite of an encouraging preclinical profile. This inconsistency interrogates the viability of therapeutic vaccination, demonstrating a lack of understanding about disease-specific immune dysregulation [5]. Notably, failure of therapeutic vaccines is often associated with discrepancies between vaccine design and biology of disease as opposed to inherent constraints of immunization as a therapeutic agent. Environmental and epigenetic modifications also influence disease phenotypes and therapeutic outcomes across experimental models [6,7]. To understand the reasons why therapeutic vaccines are effective in certain diseases and fail in others, this viewpoint provides a combined approach on the consideration of antigen biology, host immune status, disease pathogenesis and translational strategy [8].

Antigen Stability: Comparative analysis of reported literature indicates that there are number of persistent success factors of therapeutic vaccines across various diseases. Antigen definition and stability is one of the important factors [4]. Incidents of diseases where therapeutical vaccines have been shown to be advantageous, usually entail well-conserved, antigens that are fundamental to the survival of pathogens or the sustenance of cancers [6]. Conversely, disease with a high degree of antigenic variation or antigen evolution leads to vaccine failure since vaccination-induced immune responses can become useless due to antigen escape.

Host-Immune Competence: Another significant determinant is the host immune competence. Therapeutic vaccines have higher chance of success when they are used in an environment with intact immune effector function [5]. T-cell responsiveness and antigen presentation pathways may not be completely compromised in early-stage cancer or controlled chronic infections to allow vaccine-generated immunity [7]. In contrast, severe cases of malignancies and chronic infections are often characterized by severe immune depletion, dominance by regulatory T-cells and dysfunctional antigen-presenting cells all of which restrict the effect of vaccines [2].

Disease Microenvironment: Microenvironment of diseases is also a critical factor. Immunosuppressive tumor microenvironments or tissues with chronic inflammation enriched with inhibitory cytokines and checkpoint molecules are capable of actively inhibiting vaccine-induced immune responses [9]. Also, vaccine platform and adjuvant are significantly correlated with treatment outcome. The platforms that do not produce strong cellular immunity or long-term memory responses are less likely to create clinical benefit in therapeutic scenarios [10].

Lessons from Clinical Failures: The prime reason for the failure of therapeutic vaccination lies in the fact that similar approaches are being used to cure biologically diverse diseases [11]. Cancers and chronic infections often develop advanced immune evasion strategies, such as antigen downregulation, tolerance induction, and local immune environment remodeling [12]. Vaccination will be inconsistent in such environments to counteract immune malfunction. A combination therapy involving therapeutic vaccines and immune checkpoint inhibitors, cytokine regulation, or metabolic reprogramming may be required to have the immune responsiveness restored [13]. Moreover, the clinical trial designs such as the heterogeneity of patients, wrong endpoints, and the absence of biomarker-based stratification, led to poor consistency of efficacy signals and premature rejection of potentially effective strategies.

A Framework for Rational Design: The lack of synergistic results in therapeutic vaccine development highlights the significance of designing vaccine with disease-specific immunopathogenesis [14]. In contrast with prophylactic vaccination, therapeutic immunization does not depend on generalized immune activation but has to go around established mechanisms of immune regulation and evasion [15]. Diseases that are successfully treated with therapeutic vaccines are likely to have a number of common characteristics: stable and biologically relevant antigens, limited immune evasion and host immune systems that can generate effective effector responses [16]. Such conditions are not always universal and they have to be properly considered while developing the vaccine.

Future Directions: New biomolecular profiling and systems immunology technologies have enhanced the capability of describing disease-specific immune landscapes and identifying predictive biomarkers. The tools allow rational patient selection and optimization of the vaccine timing, dose, and formulation [17]. Neoantigen-based vaccines and other forms of personalized antigen will provide exciting solutions to overcome the antigenic heterogeneity, especially in cancer research. Moreover, new adjuvants and delivery vectors that can enhance antigen delivery and T-cell priming can be used to overcome shortcomings of previous vaccine technologies [18].

Conclusion

To sum up, therapeutic vaccines cannot be considered as a single set of intervention instead they are disease-specific immunological weapons, and their success is predetermined by a justified choice according to the pathogenesis and the condition of the host immunity [19]. The insight into the failure of therapeutic vaccines in certain diseases and their success in others provide essential guidelines for future vaccine development and highlights the requirement of mechanism-directed, biomarker-based translational approaches. Further development in therapeutic vaccination may unravel its potential in personalized therapeutics.

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