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Challenges and Limitations of Personalized Cancer Immunotherapies

Nemat Khansari*
Tehran University of Medical Sciences, School of Medicine, Department of Immunology, Tehran, Iran

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***Corresponding author:** Nemat Khansari, Tehran University of Medical Sciences, School of Medicine, Department of Immunology, Tehran, Iran

OPINION

The development of personalized cancer immunotherapies represents a significant advancement in cancer treatment, aiming to tailor treatments based on the unique genetic makeup of individual tumors. Tumor-specific antigens (TSAs) are not expressed in normal cells. TSAs are suitable choices for cancer immunotherapy and cancer vaccines. Tumor cells harbor mutations in genes controlling cell growth and other genes. Mutation in genes that prevent the repairs of deoxyribonucleic acids (DNA) errors in cell division so, so-called mismatch repairs, have the potential to express neoantigens on the surface of the tumor cells and be used for personalized cancer immunotherapy [1]. Based on our experiences and available data, neoantigen-based vaccines represent a potential new class of cancer immunotherapy [2].

However, despite their promise, several challenges and limitations hinder their widespread implementation and effectiveness. These challenges can be categorized into neoantigen identification, immunogenicity, manufacturing complexities, and the biological environment of tumors. One of the primary challenges in developing personalized cancer vaccines is the identification of suitable neoantigens. Neoantigens are unique tumor-specific antigens that arise from mutations in the tumor DNA. Identifying these neoantigens is complex, as it requires comprehensive genomic sequencing of the tumor and the identification of mutations that can elicit a robust immune response. Studies have shown that the variability in tumor mutation burden among patients can significantly affect the availability of neoantigens, thereby limiting the potential for effective vaccine development [3,4].

Furthermore, the high degree of tumor heterogeneity complicates the identification of immunogenic neoantigens, as different tumor cells may express different mutations, necessitating a highly personalized approach to vaccine design [5,6]. Immunogenicity is another critical factor that influences the efficacy of personalized cancer vaccines. Even when neoantigens are successfully identified, their ability to provoke a strong immune response can be limited. Factors such as immunosuppressive tumor microenvironments, which can inhibit T-cell activation and proliferation, pose significant barriers to achieving adequate immunogenicity [7,8]. Additionally, the immune system's tolerance mechanisms can lead to a failure to recognize neoantigens as foreign, further diminishing the potential for a robust immune response [9,10]. This phenomenon is particularly evident in tumors with low mutation burdens, where the

lack of distinct neoantigens may result in insufficient immune activation [11]. Manufacturing personalized cancer vaccines presents its own set of challenges. Creating these vaccines is resource-intensive and requires sophisticated technologies for sequencing, neoantigen prediction, and vaccine formulation. Rapid and scalable manufacturing processes are crucial, especially in clinical settings where timely intervention can significantly impact patient outcomes [12,13].

Moreover, the variability in the physicochemical properties of neoantigens can complicate the standardization of vaccine production, leading to inconsistencies in vaccine efficacy [13]. This variability necessitates the development of robust platforms that can accommodate the diverse nature of neoantigens while ensuring consistent quality and effectiveness [14,15]. The biological environment of tumors also plays a pivotal role in the success of personalized cancer vaccines. Tumors often create immunosuppressive microenvironments that inhibit immune cell activity, reducing vaccine effectiveness [16,17]. For instance, regulatory T cells and myeloid-derived suppressor cells within the tumor microenvironment can significantly dampen the immune response elicited by vaccines [18].

Additionally, the systemic immune response can be influenced by factors such as the patient's overall health, prior treatments, and co-morbidities, which can further complicate the efficacy of personalized vaccines [19]. Despite these challenges, ongoing research and technological advancements are paving the way for improvements in personalized cancer vaccines. Innovations in genomic sequencing technologies and computational methods for neoantigen prediction enhance the ability to identify immunogenic targets more accurately [20]. Furthermore, combining combination therapies, such as immune checkpoint inhibitors, with personalized vaccines is promising in overcoming some limitations associated with immunogenicity and tumor microenvironment suppression [21,22]. These combinatorial approaches aim to create a more favorable immune landscape for the effective action of personalized vaccines, thereby improving patient outcomes [23,24].

In conclusion, while personalized cancer vaccines promise to revolutionize cancer treatment, several significant challenges and limitations must be addressed. The complexities of neoantigen identification, immunogenicity, manufacturing processes, and the tumor microenvironment present substantial hurdles that researchers and clinicians must navigate. Continued technological advancements and innovative therapeutic strategies are essential for overcoming these barriers and realizing the full potential of personalized cancer vaccines in clinical practice.

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