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The Application of Therapeutic Tumor Vaccines in Melanoma

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Abstract: In this review, the synergistic application strategy and technological breakthrough of new generation vaccine technology and immune checkpoint inhibitor were discussed. Combined vaccine therapy with immune checkpoint inhibitors targeting PD-1/CTLA-4 can effectively reverse T cell depletion and enhance anti-tumor immune response. For the clinical translation bottlenecks of personalized vaccines (such as patient-specific antigen synthesis and resource-intensive GMP production), the automated platforms (such as BioNTech's "RNA printer") and the universal vaccine strategies targeting conserved neoantigens (such as KRAS G12D or HPV E6/E7 virus antigens) significantly increase the scalability. The technical innovations highlighted include: 1) CRISPR-Cas9 enhances antigen presentation by editing dendritic cells (DCs) or knocks out immunosuppressive genes such as PD-L1; 2) The AI-driven platform optimizes the prediction of antigen-adjuvant combination and dosing scheme design through algorithms. These technological advances provide multi-dimensional solutions for precision immunotherapy, and promote the development of cancer vaccines in the direction of high efficiency and intelligence.

Keywords: tumor vaccine, melanoma, vaccine technology

1. Introduction

As the most malignant skin tumor, melanoma has become the leading cause of death related to skin cancer in recent years. Its annual incidence increases at a rate of 3% to 7% per year and is strongly associated with UV exposure, genetic susceptibility, and immunosuppressive status. Although early stage patients can be cured by surgical removal, about 20% of cases have metastases at diagnosis, and the 5-year survival rate for advanced melanoma is less than 30%. Although traditional therapies, such as chemotherapy and targeted drugs, can control the disease for a short time, they generally face the problem of drug resistance due to high tumor heterogeneity and rapid clonal evolution. Some clinical dilemmas have led researchers to turn to a more groundbreaking treatment strategy: tumor immunotherapy.

In recent years, the rise of immune checkpoint inhibitors has revolutionized melanoma treatment. Anti-pd-1 /CTLA-4 drugs can significantly prolong the survival of patients by relieving the inhibition of T cell function, and some patients can achieve long-term disease-free survival. However, ICIs also has limitations, with only 30 to 40 percent of patients producing a lasting response to monotherapy. At the same time, over-activation of the immune system can lead to serious adverse reactions, such as colitis and pituitaritis. These results indicate that it is difficult to

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fully overcome the immunosuppressive network of tumor microenvironment by immune checkpoint blocking alone.

Therapeutic tumor vaccines have attracted attention because of their potential to "precisely activate anti-tumor immunity." The unique biology of melanoma provides a natural advantage for vaccine development. This is because, as one of the solid tumors with the highest mutation load, DNA damage caused by ultraviolet light can produce a large number of neoantigens that provide specific targets for T cells. The immunogenicity of melanoma cells is strong, and it is easy for dendritic cells to recognize and present antigens. Vaccines can compensate for ICIs deficiencies by delivering tumor antigens or neoantigens, activating initial T cells, and inducing immune memory. However, clinical translation of vaccines still faces many challenges, such as antigenic selection bias, immunosuppressive microenvironment interference, and individual production costs. This review collates recent advances in therapeutic tumor vaccines in melanoma. This paper describes the constraints of the melanoma immune microenvironment on vaccine design, and explains the different types of vaccines, current research trends and possible future development of vaccines.

2. The immune microenvironment in melanoma

The immune microenvironment of melanoma is a dynamic and complex network that determines the balance between anti-tumor immunity and tumor progression. Ultraviolet (UV) -induced DNA damage causes melanoma to have a high mutation load and produce a large number of neoantigens, giving it a natural immunogenicity. However, tumors evade immune surveillance through complex mechanisms, forming an immunosuppressive environment that limits the effect of therapeutic interventions.The immunogenicity of melanoma stems from its unique mutational landscape. UV radiation causes mutations in oncogenes (e.g. BRAF, NRAS) and tumor suppressor genes, producing neoantigens that are recognized as foreign by the immune system. Dendritic cells (DCs) capture these antigens, migrate to the lymph nodes and activate initial CD8 + and CD4 + T cells, initiating cytotoxicity and an auxiliary immune response. Sahin et al. showed that melanoma neoantigens can trigger a strong T cell response in vitro and in vivo, validating their potential as a vaccine target [1]. However, tumors evade clearance through immunoediting. During the elimination phase, the highly immunogenic clone is destroyed, while the low immunogenic variant survives and multiplies. The key mechanism of immune escape is the downregulation of Major Histocompatibility complex Class I (MHC-I) molecules, which prevents antigen presentation to CD8 + cells. Spranger et al. found that β-catenin pathway activation is a major driver of immune rejection in melanoma: tumors that are continuously activated by this pathway secrete fewer chemokines, such as CCL4. CCL4 is critical for recruiting BATF3-dependent DCs [2]. As a result, DCs cannot infiltrate the tumor, leading to impaired T cell initiation and recruitment.

Melanoma TME is rich in immunosuppressive cells and soluble factors that inhibit anti-tumor immunity. For example, Tregs constitutively express CTLA-4 and secrete immunosuppressive cytokines IL-10 and TGF-β, which directly inhibit effector T cell function. In melanoma, Treg infiltration is associated with poor prognosis and resistance to immune checkpoint inhibitors. MDSCs inhibit T cell activity through argininase-1 and ROS, while promoting angiogenesis and metastasis. M2-type TAMs secrete vascular endothelial growth factor VEGF and matrix metalloproteinases MMPs to promote tumor angiogenesis and extracellular matrix remodeling. Metabolic competition further exacerbates immune suppression. Melanoma cells have high glycolytic activity, resulting in lactic acid buildup in TME. Hanggi and Ruffell showed that lactate inhibits T cell receptor signaling and promotes PD-L1 expression in tumor cells. In addition, adenosine produced by CD73 and CD39 enzyme activity binds to A2A receptors on T cells, inducing an exhaustive phenotype characterized by high expression of PD-1 and TIM-3 [3].

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3. Categories of therapeutic tumor vaccines

Melanoma therapeutic vaccines are designed to activate tumor-specific T cells by delivering antigens in an immunogenic form. These vaccines are classified according to antigen type, delivery platform and cell composition, each with unique mechanisms and clinical significance.

3.1. Polypeptide vaccines

Polypeptide vaccines target tumor-associated antigens (TAAs) common to melanoma patients, such as gp100, MART-1, or tyrosinase. These vaccines typically consist of 8-10 amino acids that bind to the MHC-I molecule on the APCs. Despite their low cost, polypeptide vaccines require adjuvants to enhance immunogenicity. For example, a Phase III trial combining gp100 peptides with high doses of IL-2 produced an objective response rate of only 10% [4]. Modern strategies employ long peptide vaccines containing CD4 + and CD8 + T cell epitopes to induce a wider immune response.

3.2. Nucleic acid vaccines

mRNA vaccines encode tumor antigens, or neoantigens, delivered via lipid nanoparticles (LNPs) to protect them from degradation and target dendritic cells (DCs). For example, BioNTech's FixVac platform uses mrnas encoding shared melanoma antigens, such as NY-ESO-1, combined with PD-1 blocking. In a pivotal trial, a personalized mRNA neoantigen vaccine combined with pabolizumab induced a durable response in 44% of patients with advanced melanoma [5]. Innovative designs, such as comb structure mRNA, integrate double-stranded RNA (dsRNA) adjuvants that enhance CD8 + cell activation by stimulating the TLR3 and RIG-I pathways [6]. DNA vaccines are stable and easy to produce, but face delivery efficiency challenges. Electroporation devices or viral vectors (such as adenoviruses) are used to enhance cellular uptake.

3.3. Cell vaccines

In dendritic cell (DC) vaccines, autologous DCs are loaded with tumor lysates, peptides, or mRNA in vitro and transfused back to activate T cells. The PROVENGE model approved for prostate cancer (Sipuleucel-T) inspired the melanoma DC vaccine. However, clinical efficacy depends on optimizing DC maturation and migration. FLT3 ligand combination can amplify DC precursors and improve antigen presentation [7]. Tumor cell vaccines Irradiated tumor cells engineered to express immune-stimulating molecules such as GM-CSF can be used as an antigen source. Due to the complexity of preparation, such vaccines are rarely used.

3.4. Nanoparticle vaccines

Nanocarriers co-deliver antigens and adjuvants to lymph nodes to enhance DCs uptake and cross-presentation. Sasaki et al. developed LNPs targeting the DC-specific receptor Clec9A to enhance antigen-specific T cell responses in mouse melanoma models [8]. Hybrid designs that combine mRNA with TLR agonists are being investigated to synergize innate and adaptive immunity.

3.5. Viral vector vaccines

Viral vectors (such as adenovirus and poxvirus) deliver antigen genes to APCs. Oncolytic herpes virus T-VEC expresses GM-CSF, lyses tumor cells to release antigens and stimulates DCs recruitment. Although T-VEC has been approved for melanoma, it has limited efficacy as a single agent and needs to be used in combination with ICIs [9].

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4. Current trends of tumor vaccine research

Recent advances in melanoma vaccine research have focused on personalized approaches, innovative delivery systems, and synergistic combination therapies to overcome the limitations of traditional vaccines. Personalized vaccines use patient-specific mutations to generate customized immune responses. Sahin et al. pioneered the use of RNA vaccines to encode up to 20 neoantigens per patient [2]. In the Phase I trial, 60% of vaccinated patients showed an antigen-specific T cell response, with some achieving complete remission. Modern platforms such as Moderna's mRNA-4157 combine next-generation sequencing (NGS) and machine learning to predict high-affinity neoantigens. In Phase II trials, the objective response rate of mRNA-4157 combined with pembrolizumab was 44%, compared with 18% for monotherapy [5]. In situ vaccination converts tumors into immunogenic centers by local delivery of an immunostimulant. Hammerich et al. demonstrated that intratumoral injection of SD-101 (TLR9 agonist) combined with PD-1 blockade induced systemic anti-tumor immunity in advanced melanoma, with regression of non-injected lesions [10]. Similarly, oncolytic virus T-VEC lysates tumor cells to release antigen and GM-CSF, recruit DCs and enhance T cell infiltration. A Phase II trial showed that T-VEC combined with pabolizumab doubled progression-free survival compared with monotherapy [9].

Personalized vaccines hold great promise, and their high cost and complexity have driven the search for universal vaccines that target shared antigens. For example, MAGE family antigens. MAGE-A3 and NY-ESO-1 are expressed in 20-50% of melanomas, but not in healthy tissues (except testicles). The DNA vaccine encoding MAGE-A3 induced a CD8 + T cell response in early trials, but had limited clinical efficacy. Radiotherapy induces immunogenic cell death (ICD) and releases damage-related molecular patterns (DAMPs) such as ATP and HMGB1. These DAMPs activate DCs and enhance antigen presentation. A Phase I trial in combination with radiotherapy and DC vaccine showed increased T cell infiltration in radiotherapy lesions [11]. Chemotherapy drugs such as cyclophosphamide can clear Tregs, creating a favorable environment for vaccine-induced immunity. New generation delivery technologies include microneedle patches and biomaterial scaffolds. Microneedle patches are resident DCs that target the skin through intradermal delivery of vaccines. Hammerich et al. developed a microneedle patch loaded with TLR7/8 agonists and tumor antigens to achieve potent T cell activation in a preclinical model. Biomaterial scaffolds that can sustainably release antigens and adjuvants can maintain long-term immune activation [10]. For example, a PLGA scaffold co-delivers mRNA and STING agonist to induce durable anti-tumor immunity in mouse melanoma.

5. Challenges and future directions

Despite significant progress, therapeutic melanoma vaccines still face significant hurdles in clinical translation. Addressing these challenges requires multidisciplinary innovation and strategic collaboration. First, accurate prediction of neoantigens remains a bottleneck. Existing algorithms preferentially select mutations based on MHC binding affinity, but often omit low affinity epitopes or fail to consider HLA diversity. Lang et al. proposed to integrate exon sequencing, transcriptomics, and MHC ligand to improve prediction accuracy [7]. Functional verification using T cell receptor (TCR) sequencing or in vitro T cell activation experiments is critical to confirm immunogenicity. Second, the metabolic and cellular barriers of TME limit vaccine efficacy. Promising strategies include inhibition of lactate transporters (MCT-1/4) or adenosine receptors (A2A antagonists) to ease T cell inhibition for metabolic regulation; Setting targeted immune checkpoints, the vaccine combined with PD-1/CTLA-4 inhibitors reversed T cell depletion. At the same time, personalized vaccines have a large resource consumption, requiring patient-specific antigen synthesis and GMP production. Automated platforms such as BioNTech's "RNA printer"

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aim to simplify production. Universal vaccines that target conserved neoantigens (such as KRAS G12D) or viral antigens (such as HPV E6/E7) offer scalable alternatives. There is now a new generation of technologies such as CRISPR engineered vaccines and AI-driven vaccine design. CRISPR-Cas9 can edit DCs to enhance antigen presentation or delete immunosuppressive genes (such as PD-L1). AI can learn the model to predict the best antigen-adjuvant combination and optimize the dosing regimen.

6. Conclusion

Therapeutic tumor vaccines represent a transformative approach to melanoma treatment, bridging the gap between targeted therapy and immunotherapy. By taking advantage of the high mutational load and immunogenicity of melanoma, personalized neoantigen vaccines show great potential to induce tumor-specific immunity, especially when combined with immune checkpoint inhibitors. Innovations in mRNA technology, nanoparticle delivery, and in situ vaccine strategies are reshaping the cancer immunotherapy landscape. However, challenges such as immunosuppressive TME, inaccurate antigen prediction, and production complexity still require continued innovation. Future success will depend on integrating multiple omics data, advancing AI-driven design, and fostering collaboration between academia and industry. As these efforts converge, therapeutic vaccines may shift from complementary therapies to cornerstone treatments, offering hope for long-term remission or even a cure for advanced melanoma.

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