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Personalized neoantigen-based therapeutic cancer vaccines

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Abstract. Tumor neoantigens are new unknown proteins or peptides encoded by somatic gene mutations, also known as tumor-specific antigens (TSAs). They are located on the surface of tumor cells and are only expressed in tumor cells. Cancer vaccines targeting neoantigens can not only effectively induce immune response, but also have the advantages of high safety and fewer side effects, so it has gradually become a research hotspot in tumor therapy. During the current clinical trials, neoantigen-based personalised tumour therapeutic vaccines have shown excellent experimental results and have also proved to be positively helpful for tumour cancer treatment. However, considering that the heterogeneity of tumours increases the uncertainty of the efficacy of disease vaccines, and the time-consuming and complicated preparation process of personalized vaccines, the research and development of personalized oncology therapeutic vaccines based on neoantigens still need different explorations and attempts.

Keywords: neoantigen, immunotherapy, cancer vaccine

1. Introduction

Cancer immunotherapy has developed rapidly in recent years, which is a cancer treatment method to control and remove tumors by inducing cellular immune response. Recently, great breakthroughs have been made in the research of tumor immunotherapy in immune checkpoint inhibitors, adoptive cell therapy and tumor vaccines [1]. Tumor vaccines introduce tumor antigens, such as lytic tumor cells, tumor-associated proteins or peptides, and genes expressing tumor antigens, into patients in different forms. Tumor antigens exert an anti-tumor effect by activating the body's immune response [2]. As a kind of tumor antigen, neoantigen has special value for the development and application of therapeutic cancer vaccines, and brings new hope for accurate treatment of cancer. Tumor neoantigens are new unknown proteins or peptides encoded by somatic gene mutations, also known as tumor-specific antigens (TSAs). They are located on the tumour cell surface and are expressed only in tumour cells. Cancer vaccines targeting neoantigens can not only effectively induce immune response, but also have the advantages of high safety and fewer side effects, so it has gradually become a research hotspot in tumor therapy. This paper summarises and analyses the research progress, challenges and prospects of personalized neoantigen-based therapeutic cancer vaccines. Therefore, this paper hopes that the analysis of neoantigen-based cancer therapeutic vaccines can provide new research ideas for subsequent cancer treatment modalities, while increasing the possibility of success.

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2. The concept and characteristics of neoantigens

2.1. The concept and characteristics of neoantigens

There are two kinds of tumor antigens. Tumor-associated antigens (TAAs) are antigens that are neither specialized for tumor cells, but are also present on standard cells, except that they are significantly increased when the cells become cancerous. And TSA is described as a tumor-specific antigen found exclusively in the cells of certain tumors and not in the standard cells, also known as neoantigens.

Neoantigens are produced by mutant from tumor cells that can be recognized by immune cells, activating an immune response. The mutation of tumor cells is different among different individuals, different tumor types or different cells of the same tumor of the same individual, and has the characteristics of evolution with tumor progression, so the neoantigen has the characteristic of personalization. Neoantigen exists within cancer cells only and is unexpressed in normal cells, so it is safe and can minimize adverse reactions and side effects, and the Neoantigens are postulated to be particularly relevant to tumour control since the quality of the T-cell pool accessible to neoantigens is independent of central T-cell tolerance [3].

2.2. Types of neoantigen-based therapeutic cancer vaccines

A variety of neoantigen-based therapeutic cancer vaccines are available, mainly including polypeptide vaccines, dendritic cell (DC) vaccines, nucleic acid vaccines and viral vector vaccines. Peptide and nucleic acid vaccines primarily target predicted neoantigens derived from somatic cell mutations, including SNVs, shifted-code INDELs, and gene fusions.DC vaccines can target either selected neoantigens by pulsing synthetic peptides or nucleic acids, or they can target the entire TSA by introducing whole-cell lysates (WCLs).

Short peptides usually refer to peptides with a length of 8 to 10 amino acids. most of them bind to MHCI (major histocompatibility complex I) directly after vaccination, resulting in weak immune response or even tolerance. The polypeptides in long peptide vaccines must be absorbed, processed, processed and presented by antigen presenting cells. Antigen presenting cells carrying long peptides activate T lymphocytes by combining T cell antigen recognition receptors and costimulatory molecules to induce a strong specific immune response [4].

Dendritic cells are antigen presenting cells in the body, which can recognize antigens, phagocytize and process antigens, and finally activate T cell-mediated anti-tumor immune response. Most DC vaccine products are isolated or cultured from blood, amplified *in vitro* and loaded with antigen [5]. Several DC vaccines have been validated through a number of clinical application and research.

Nucleic acid vaccines include DNA vaccine and mRNA vaccine. DNA vaccine has the advantages of low cost, convenient production and stable preparation, but DNA vaccine also has the potential risk of foreign gene integration into the host cell genome, resulting in mutation [6]. With the wide application of novel coronavirus mRNA vaccines around the world, the related technologies of mRNA vaccines are becoming more and more mature. MRNA vaccine has the advantages of high expression efficiency *in vivo*, short survival time, no infection of host, no insertion mutation and high safety.

Viral vector vaccines are vaccines that use modified viruses as carriers to introduce tumor-specific antigens into the human body, thereby stimulating the immune system to produce an immune response against cancer cells [7]. Many different types of viruses are used as vectors, including adenoviruses, poxviruses, herpesviruses, and alphaviruses [8]. Viral vector vaccines are relatively mature, highly safe, and can induce strong immune responses without the use of adjuvants. One limitation of viral vector vaccines is that the body's antiviral immune response after the initial immunization will lead to a reduction in the immune efficiency of repeated vaccinations [9]. There are studies showing that utilizing different vaccine delivery platforms and using combination therapies can trigger stronger immune responses [10,11].

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2.3. Screening and prediction of neoantigens

The tumor cell mutations are different in different patients, the neoantigens are also different, so it is necessary to screen and predict neoantigens. Studies thus far indicate that only a small number of neoantigens can induce T cell immune response, so accurate screening and prediction of neoantigens is crucial for clinical success [5].

Virtual peptidomes were created from NGS data and potential neoantigens were identified in silico. The current screening and prediction of personalized neoantigens includes the following four steps: Firstly, sequencing whole genome and exome of DNA from normal cells and tumor tissues to identify the mutation sites in tumor tissues. Secondly, determining the patient's HLA (human leukocyte antigen) genotypes. Next, neoantigen filtering and prioritization based on HLA binding affinity, finally, experimental validation of immunogenic neoantigens using T cell-based assays [12].

3. Research progress of neoantigen-based therapeutic cancer vaccines

By September 2023, a total of 124 clinical trials related to neoantigen vaccines have been registered on the international clinical trial registration platform, National Library of Medicine. With the increasing maturity of neoantigen screening and prediction technology, a variety of neoantigen-based cancer vaccines have entered the clinical trial stage. Among the personalized neoantigen-based therapeutic cancer vaccine clinical trials that have been carried out, more than 40 types of solid tumors have been involved, including melanoma, glioma, lung cancer, bladder cancer, pancreatic cancer, liver cancer, ovarian cancer, and so on [13].

Table 1. Vaccine therapies for clinical trials using neoantigens [13]

Conditions	Intervention/Drug	Formulation	Administration	Sponsor/Collaborators
Melanoma, Non Small Cell Lung Cancer, Bladder Urothelial Cancer	Drug: EVAX-01-CAF09b	Up to 15 peptides with CAF09b as adjuvant.	Intraperitoneal and intramuscular injections	Herlev Hospital
Solid Tumor, Adult	Biological: ASV® AGEN2017 + QS-21 StimulonÂ® adjuvant	ASV® AGEN2017 with QS-21 Stimulon® adjuvant	Subcutaneous injection	Agenus Inc.
Advanced Cancer	Drug: personalized vaccine|Drug: Pembrolizumab	Personalized vaccine	Intravenous infusion	Ezra Cohen|University of California, San Diego
Advanced Malignant Solid Tumor	Biological: iNeo-Vac-P01	iNeo-Vac-P01 (5 – 20 peptides) vaccine with GM-CSF adjuvant	Subcutaneous injections at the dose of 100 μg per peptide	Sir Run Run Shaw Hospital|Hangzhou Neoantigen Therapeutics Co., Ltd.
Locally Advanced or Metastatic Solid Tumours	Biological: VB10.NEO Drug: Bempegaldesleukin	VB10.NEO in with bempegaldesleukin (NKTR-214)	Intravenous injection	Nykode Therapeutics ASA|Nektar Therapeutics|Vaccibody AS
Urothelial/Bladder Cancer	Drug: Atezolizumab, Poly ICLC |Biological: PGV001	Up to 10 peptides, one teatanus helper peptide mixed with poly-ICLC.	Intravenous infusion	Matthew Galsky|Genentech, Inc.|Icahn School of Medicine at Mount Sinai
Melanoma	Biological: Poly-ICLC, Peptides	Peptides with poly-ICLC	Subcutaneous injection	Dana-Farber Cancer Institute
Glioblastoma	Biological: NeoVax, Nivolumab, Ipilimumab	Up to 20 peptides with poly-ICLC	Subcutaneous injection	Washington University School of Medicine|Bristol-Myers Squibb

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4. Challenges and prospects

Challenges also exist in the discovery and implementation of personalised cancer therapeutic vaccines based on neoantigens. The first is heterogeneity. Spatial heterogeneity is mainly reflected in different tumor types, the same tumor in different patients and different parts of the same tumor.Time heterogeneity means that the composition of cancer cells may change at different stages of the development of the same tumor [14]. Heterogeneity makes it almost impossible for existing immunotherapy methods to cover the targets of all tumor cells in tumors. And the samples used for tumor neoantigen screening and prediction are only a small fraction of tumors, which means increased uncertainty about the efficacy of neoantigen cancer vaccines.

The second is tumor microenvironment. An essential factor in the investigation of tumour immunotherapy is the tumour microenvironment. Tumor cells, immune cells, interstitial cells and other factors form a complex immunosuppressive microenvironment, which plays an immunosuppressive role in the key links of immune response [15]. This creates a good growth environment for the development of tumor cells and immune escape. And tumor cells can down-regulate the expression level of antigens or MHC molecules, thus reducing immunogenicity [16]. Because of the complex immunosuppressive mechanism, combined therapy is the key to overcome this problem.

The third is the time-consuming and complex process of preparing individualized neoantigen vaccines. Neoantigen tumor vaccines are highly personalized, and their preparation process, from tumor specimen collection, sequencing, bioinformatics analysis to vaccine preparation, usually takes several months, and Many patients with advanced cancer may have passed away before the vaccine was prepared and vaccinated.

The personalized neoantigen-based therapeutic cancer vaccines have shown good efficacy in many preclinical and clinical studies. The strategy of neoantigen cancer vaccine combineds with other immunotherapy may be more effective in the treatment of tumors. For example, Heather L. Kinkead et al. proved that in Panc02-bearing mice, triple therapy with PancVAX (a neoantigen-targeted vaccine), anti–PD-1, and agonist OX40 elicits a potent antitumor immune response and durable tumor clearance [16]. Data from several other clinical studies have also demonstrated that neoantigenic tumor vaccines, in combination with therapies such as immune checkpoint inhibitors, can slow and control tumor progression and produce greater clinical efficacy than a single treatment modality.

Although there are still many challenges, with the deepening and accumulation of researches, it is believed that the research and development of personalized neoantigen-based therapeutic cancer vaccines will develop rapidly in the near future.

5. Conclusion

This paper summarises and analyses the research progress, challenges and prospects of personalised neoantigen-based therapeutic cancer vaccines just by means of a literature review. With the development of personalised neoantigen-based therapeutic cancer vaccines and the increase in clinical trials, personalised neoantigen-based therapeutic cancer vaccines have shown promising efficacy in many preclinical and clinical studies. This could also demonstrate that the strategy of neoantigen-based cancer vaccines in combination with other immunotherapies may be more effective in treating tumours. However, although neoantigen-based immunotherapies have shown relatively positive results in clinical studies, there is still a need for continued breakthroughs in the future, taking into account the evolution of the cancer cells themselves, as well as the need to overcome the disadvantages of their heterogeneity, complexity and high consumption.

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