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Personalized Neoantigen Therapy Is an Innovative Strategy for Combating Cancer

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Abstract

Immunotherapies that use the immune system to eliminate tumor cells have shown substantial therapeutic effectiveness in several types of human malignancies. Several investigations have emphasized the importance of neoantigens in the recognition of cancer cells by innate T lymphocytes. The identification of neoantigens, which are altered proteins that are selectively produced in tumor cells and not in healthy cells, has resulted in the development of enhanced cancer vaccines. Neoantigen targeting may stimulate anti-tumor T-cell reactions to eliminate tumors while sparing healthy cells from harm. Significant progress in DNA sequencing and computational biology has enabled the identification and development of potent neoantigens for application as therapeutic cancer vaccines. Therapeutic customized vaccines that target neoantigens have demonstrated encouraging outcomes in the field of cancer therapy. Therefore, this study aims to introduce neoantigens and their use in cancer immunotherapy.

Keywords: Neoantigens, T-cell, DNA sequencing, Cancer therapy

Introduction

Detrimental stimuli, such as ultraviolet radiation, ionizing radiation, and carcinogens, can lead to various types of genetic alterations, such as single-nucleotide mutations, insertions or eliminations gene fusion, frameshift mutations, fundamental mutations, or the integration and clonal expansion of the tumor-associated virus genome within the human genome. Specifically, these genetic changes can result in somatic cell carcinogenesis (1). In recent decades, immunotherapy has shown significant promise in the management of malignancy. Cancer cells generate mutated proteins that may be identified by the body's immune system as antigens, leading to subsequent activation of cellular and humoral immune system reactions. Non-synonymous mutations may generate mutant peptides that are not identical to the original peptides (2). Human (HLA) molecules can recognize these mutated peptides and trigger T-cell responses. These mutated peptides are referred to as neoantigens. Due to the lack of influence from thymus selection or central tolerance, probably, T lymphocytes with a high avidity for leukocyte antigen neoantigens probably exist. Hence, the study topic of immunotherapy for malignant tumors, specifically targeting these non-synonymous mutant proteins, is attracting considerable attention (3).

Cancer immunotherapy encompasses a wide array

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of treatment strategies that seek to use the immune system to create specific and effective immune responses against tumors. Cancer cells possess a collection of somatic mutations that accumulate over time and occur at different rates. These mutations can trigger an immunological response and be identified by the immune system (4). Nevertheless, tumors can avoid detection by the immune system through multiple means, including interfering with the presentation of antigens, manipulating checkpoint pathways, infiltrating the tumor with cells that suppress the immunological response, and increasing the production and release of cytokines that inhibit the immune system. The study of cancer immunotherapy has revived due to an improved comprehension of the complex processes that control the inhibition of the immune system caused by tumors. Neoantigens originate from genetic abnormalities in tumor cells, such as chromosomal translocations, somatic point mutations, and insertions and deletions (indels). Most mutations occur inside introns, and some of these changes result in mistakes during splicing. The altered genes undergo transcription and translation to generate modified peptides, which are then broken down and presented by MHC molecules for identification by T-cells, leading to the activation of T-cell immune responses (5). The functional significance of cancer neoantigens may be ascribed to three factors: (1) the number of mutations in the tumor (tumor mutation burden or TMB) and the presence of neoantigens, (2) the display of neoantigens by major histocompatibility complex (MHC) molecules, and (3) the identification of cancer neoantigens by T-cells. The conventional approach for treating malignant tumors involves surgical intervention, in conjunction with either radiation or chemotherapy (6). Nevertheless, these treatment options often come with undesirable adverse reactions. In recent decades, tumor immunotherapy has shown promising results in terms of its remarkable effectiveness in treating cancer. Due to advancements in DNA sequencing and bioinformatics computations, neoantigens have emerged as attractive candidates for cancer immunotherapy because of their highly immunogenic nature. Furthermore, neoantigen-based vaccinations have shown promise in cancer treatment, mainly via enhancing T-cell responses. Additionally, neoantigens have demonstrated efficacy in immune checkpoint blockade treatment. Thus, neoantigens have the potential to function as prognostic indicators and complementary goals in cancer immunotherapy (7). The objective of this study was to offer a comprehensive summary of the current advancements in the categorization, evaluation, and medical use of neoantigens for the treatment of cancer.

Introduction of neoantigens

The genesis of cancer is a multifaceted phenomenon. Genetic alterations result in changed internal signaling, leading to cellular activity changes and malignant tissue development. Ultimately, both organs and the whole body are impacted. Tumor immunology originated more than a century ago with the first discovery that antibodies might be generated in response to malignancies (8). This discovery provided evidence for the notion that cancers were considered “alien” or not native to the body. Extensive research has been conducted to discover specific targets inside tumors that might trigger an immune response against the tumor. There are two primary categories of cancer antigens. Tumor-associated antigens (TAAs), characterized by their elevated expression on cancerous cells compared to normal cells, are mostly found in tumor cells (9, 10). Cancer neoantigens, also known as tumor-specific antigens (TSAs), result from genetic modifications that cancer cells undergo throughout the development of cancer or via epigenetic processes. Tumor-specific neoantigens, which are produced by somatic mutations, may be detected by T-cells and have an impact on how patients respond to immunotherapy. Following transcription and translation, the peptide containing neoantigens undergoes processing by the antigen-processing apparatus. It is subsequently transferred onto the major histocompatibility complex (MHC) for presentation on the cell surface. In contrast to TAAs, cancer neoantigens are not influenced by central immunological tolerance. They exhibit greater immunogenicity and have a higher affinity for major histocompatibility complex class II (MHC-II), resulting in a robust tumor immune response (11). Not every somatic mutation creates neoantigens, and only a mere 10% of the non-synonymous mutations found in cancer cells can form antigenic peptides. Immunological neoantigens must possess several characteristics. Initially, the somatic mutations must modify the protein expression. Subsequently, the neoantigens may be appropriately digested and deposited onto MHC complexes, enabling them to be identified by the TCR of responsive T cells (12). Furthermore, every tumor has several distinct clonal/trunk and sub-clonal neoantigens. The presence of a large number of clonal/trunk neoantigens, but not sub-clonal neoantigens, is linked to a higher likelihood of tumor recurrence and worse survival rates in patients with early-stage NSCLC. The use of next-generation sequencing (NGS) technology and computational bioinformatics has facilitated the identification of the genetic characteristics of individual tumors, the discovery of potential neoantigens, and the analysis of immune system profiles for personalized oncology in a fast and cost-efficient manner (13).

T cells and their T cell receptors (TCRs) have a

crucial function in adaptive immune responses directed against cancer cells. During the process of tumor-mediated evasion (TME), T-cells produce a wide variety of TCR repertoires by rearranging genes in response to tumor antigens. The TCR repertory exhibits more variability in tumors compared to non-tumor tissues in different cancer (14). Due to the heterogeneity of neoantigens in the environment, each tumor in different patients has a distinct and diverse T cell repertoire, making it distinct. As the tumor advances, the quantity and variety of neoantigens also change (15). Furthermore, the process of eliminating tumors also results in the release of extra neoantigens and TAAs. The TCR repertoire becomes more diverse as tumor growth advances, due to the rise in both neoantigens and TAAs in both the tumor microenvironment (TME) and sentinel lymph nodes. Individuals exhibiting more TCR diversity demonstrate enhanced clinical responses to immune checkpoint inhibitors (ICIs) compared to patients with lesser TCR diversity in cases of lung and cervical cancer. The clonality and variety of T-cell repertoires to neoantigens differ in tumors, non-tumor tissues, and peripheral blood, and can change over the course of cancer development (16). Effective anti-tumor immune responses necessitate the proper display of tumor antigens and a tumor microenvironment (TME) that is abundant in capable immune cells. The presence of immune cells in tumors can differ both among various tumors and within the same tumor. This variation is due to different mechanisms that cause malfunction in the presentation of neoantigens, which are more prevalent in specific immune microenvironments. A comprehensive meta-analysis was conducted on more than 1000 cases treated with IPI, where exome/transcriptome data was analyzed (17). The study found that the level of clonal TMB, but not sub-clonal TMB, was the most influential factor in predicting the response to IPI treatment. The presence of immune cells differed both among various cancers and within individual tumors, with different modes of failure in presenting neoantigens being more prevalent in specific immunological microenvironments. The tumor sites that were invaded by the immune system showed ongoing immunoediting, which involved either the loss of heterozygosity in human leukocyte antigens or the hypermethylation/depletion of expressed neoantigens. Therefore, the present neoantigen vaccines are specifically engineered to focus on several clonal neoantigens to enhance the immune response to cancer in each unique patient (18).

Neoantigen classification

Neoantigens may be categorized into two groups: shared neoantigens and individualized neoantigens. Shared neoantigens are mutant antigens that are found in several cancer patients but do not exist in the normal genome. Neoantigens that are both shared and very immunogenic may be investigated for possible use as broad-spectrum therapeutic cancer vaccines for people with the same mutant gene. Personalized neoantigens are mutant antigens that are distinct from most neoantigens and vary totally from person to person (19). Therefore, the medicine for individualized neoantigen production must be precisely tailored to each patient, resulting in a personalized treatment (20). Neoantigens, with potent immunity, may decrease the likelihood of immune evasion by tumor cells. However, the presence of certain mutations results in distinct kinds and amounts of neoantigens among people of the same tumor, leading to evident individual heterogeneity. Consequently, the use of neoantigens in tumor immunotherapy will likely be tailored to individual patients (21). Personalized cancer vaccines may be used alone or in conjunction with other treatments to enhance the potency and longevity of the anti-tumor response, enhance survival rates and quality of life, and eventually improve the result of cancer therapy for patients. The next trend in the treatment of cancer patients will be determined by the feasibility, security, and immunogenicity of customized cancer vaccines. In the near future, it is anticipated that personalized cancer vaccinations will allow the majority of patients to get very accurate therapy (22).

Neoantigen diagnosis

While neoantigens have shown promising results in tumor treatment, the pool of neoantigens that exhibit immunogenicity is limited, making it challenging to accurately anticipate and compare their effectiveness. Thus, the neoantigen domain requires enhanced algorithms and verified techniques to precisely anticipate and identify highly immunogenic neoepitopes, ensuring their reliability. Currently, the accuracy of predicting tumor neoantigens is a pressing issue. When developing a tumor neoantigen prediction algorithm, many parameters must be taken into account. These elements include HLA type, expression analysis, mutation analysis, prediction of peptide processing, TCR binding strength, MHC affinity, PMHC stability, and the source of tumor neoantigens. Additionally, it encompasses the evaluation of T cell recognition, TCR analysis, and immune cell analysis to gauge the T cell response. To screen neoantigens and evaluate T cell responses, next-generation sequencing is commonly used. However, there are also additional approaches such as high-resolution and tandem mass spectrometry, as well as in silico methods for peptide estimation (23, 24). It is important to note that prediction algorithms based on machine learning and artificial intelligence

require ongoing training with reliable datasets. The type, quality, and quantity of the data used for training can significantly impact the accuracy of these algorithms (25). Hence, the ongoing collection of datasets, particularly the verified tumor neoantigen information, is of utmost importance in enhancing algorithm precision (26). The Tumor Neoantigen Selection Alliance (TESLA) was established via collaboration between the Park Institute for Cancer Immunotherapy (PICI) and the Cancer Research Institute (CRI). TESLA collaborates with 36 prominent biotechnology, pharmaceutical, academic, and non-profit research teams, including the National Cancer Center (NCC), PICI, Memorial Sloan-Kettering Cancer Center (MSKCC), MD Anderson Cancer Center, and over 30 other leading neoantigen research organizations. The consortium's objective is to develop algorithms and standards for worldwide neoantigen testing, collaborate to forecast more accurate targets for anticancer treatments, and promote the study and implementation of tailored tumor vaccines. Scientists at TESLA have identified algorithmic models and fundamental factors that might improve the prediction of neoantigens. Their research successfully predicted 75% of validated neoantigen targets and filtered out 98% of invalid neoantigen targets. These results were published in reputable cell publications (27, 28).

Utilization of neoantigens in clinical trials

The anticipated tumor-specific neoantigens are significant targets for therapeutic customized immunotherapies, such as a vaccination or a cellular therapy product.

Cancer vaccines

Personalized vaccinations may be created using several methods, such as synthetic long peptide (SLP), DNA, RNA, and DC, as well as viral and bacterial components (29). The findings obtained from many clinical studies including neoantigen vaccinations in individuals diagnosed with melanoma or glioblastoma are quite promising. Carreno et al. first discovered that the DC vaccination enhanced existing neoantigen-specific immunity and triggered previously unnoticed neoantigen-induced T-cell responses in three patients with advanced melanoma. HLA-A*02:01 molecules digest and express neoantigens. In 2017, two consecutive clinical trials were reported that validated the efficacy of tailored neoantigen vaccines for the treatment of melanoma patients (30). Ott et al. administered a vaccine to six patients, targeting specific tumor neoantigens that were expected to be present. The clinical trial identifier for this study is NCT01970358. Out of the six patients, four did not have their tumors come back during the next 25 months after receiving the immunization. The other two patients who had tumor recurrence were able to achieve full tumor remission after undergoing anti-PD-1 treatment (31).

An additional study revealed that eight individuals at high risk had long-lasting T-cell responses produced by neoantigens. It is promising that over four years after receiving vaccinations, all individuals are still alive, and six of them do not have any ongoing illness. Sahin et al. developed the first personalized RNA mutanome vaccines for 13 patients diagnosed with stage melanoma (NCT02035956). During the follow-up period, eight patients did not have any recurrence of tumors. Out of the five patients with metastatic illness, two had objective answers, and one had a full response when treated with a combination of an RNA vaccine and a PD-1 inhibitor (32). The promising findings suggest that the tailored neoantigen vaccination strategy is viable for immunologically "cold" cancers characterized by a low tumor mutation load. A recent vaccination research conducted in Washington, D.C. for ovarian cancer demonstrated encouraging clinical results, with no significant negative effects. Vaccination enhanced the activation of T cells in response to neoantigens, hence inducing a wide-ranging immune response against tumors (33, 34). Consistent with prior research, the EpiGVAX vaccination, which is based on neoantigens, enhanced the body's ability to fight against tumors in colorectal cancer. Ott et al. recently carried out a clinical study (NCT02897765) where they coupled a tailored neoantigen-based vaccination called NEO-PV-01 with nivolumab in patients suffering from advanced melanoma, non-small cell lung cancer, and urothelial carcinoma. Neoantigen-specific T cells were identified in all immunized individuals, and no significant adverse effects were reported. The method described here stimulates the proliferation of T lymphocytes, which may effectively suppress tumor development and eliminate tumor cells, resulting in potential advantages for therapeutic applications (35).

Assisted cell therapy

Adoptive cell therapy is another neoantigen-targeted therapeutic strategy. Patients get ex vivo expansion of natural or engineered T cells injected into them to boost T cell responses and eliminate cancer cells. Adoptive T cell treatments involve the adoptive transfer of TILs, T cells genetically modified to produce a chimeric antigen receptor (CAR) or a T cell receptor (TCR), and other immune cells such as natural killer cells (36). Neoepitopes produced by somatic mutations were recognized by personal TILs in gastrointestinal malignancies. Adoptive transfer of T lymphocytes targeted against oncogenic mutations has been shown in many trials to be able to induce tumor regression in metastatic breast,

colorectal, cervical, and cholangiocarcinoma (37). Neoantigen-reactive CD4+ TILs administered by Rosenberg et al. in 2014 to a patient with metastatic cholangiocarcinoma (NCT01174121) completely regressed the tumor. The discovery provided proof that epithelial carcinoma regression may be mediated by CD4+ T lymphocytes against neoantigens. Then, in TILs from a patient with metastatic colorectal cancer, CD8+ T cells were identified that could selectively target mutant KRAS G12D (NCT01174121) (38). There was objective remission of all lung metastases after infusion of the HLA-C*08:02–restricted TILs. One lesion that worsened nine months later was found to have lost chromosome 6, which encodes the HLA-C*08:02 MHC class I protein (38). Moreover, in cervical carcinoma linked to the virus, therapeutic TILs against mutant neoantigens produced immunodominant antitumor T cell responses rather than against antigens of the human papillomavirus (HPV), leading to total tumor regression. Metastatic breast cancer patients were also observed to benefit from adoptive treatment (NCT01174121). The individual had long-lasting tumor reduction over 22 months after receiving TILs against four neoantigens (SLC3A2, KIAA0368, CADPS2, and CTSB). These studies all provided evidence in favour of the essential function of adoptive transfer of neoantigen-based TILs in immune therapy (39, 40).

Challenges

Although there have been recent improvements, there are still several obstacles to overcome in implementing tailored neoantigen-based vaccines or adoptive cell transfer. An urgent problem that requires attention is the costly and labor-intensive manufacturing process (39). While the expense of genome sequencing has dropped, the identification of neoantigens and adherence to good manufacturing procedures still incur significant costs. The whole duration from obtaining the patient's sample to administering the vaccination was around 3 to 5 months. It is crucial to expedite the manufacturing turnaround time, particularly for patients suffering from metastatic illness. Standardizing these cell-based investigations is challenging and requires a substantial quantity of cells. Therefore, it may be necessary to use high-throughput and unbiased computational algorithms to choose neoantigens (41). Another potential challenge might arise in the prediction and confirmation of neoantigens. Although there are now computational algorithms and laboratory validation methods (such as tetramers or multimers, ELISpot) being utilized to select neoantigens, more efforts are required to better optimize these processes. Strategies include enhancing the ability to forecast MHC-peptide binding and creating extensive datasets and novel algorithms. Furthermore, tumor heterogeneity is prevalent and may arise from multiple causes, such as 1) natural mutations occurring during tumor development, 2) modulation of tumor microenvironments or loss of neoantigens, and 3) the presence of numerous lesions or a single tumor originating from diverse subclones. Tumor heterogeneity may diminish the precision of antigen clone prediction in heterogeneous tumor masses. Hence, it is essential to meticulously examine advantageous mutations (42). Moreover, the successful implementation of individualized immunotherapy that specifically targets several clonal neoantigens may face the challenge of tumor heterogeneity. Another obstacle is the task of establishing precise immune biomarkers that can accurately forecast antitumor immunity and potential survival advantages. While immune-related response criteria (irRC) aim to assess the impact of immunotherapy in clinical settings, they may not comprehensively capture all aspects of clinical responses. In addition, the T-cell responses generated by neoantigen-based therapy may not immediately result in long-lasting clinical responses. Therefore, it is feasible to detect immune response indicators in a methodical manner (43).

Concluding remarks and outlook

New research suggests that tumor neoantigens are crucial for the effectiveness of cancer immunotherapies and the body's immune response against tumors. Precision medicine, namely tailored or public neoantigen vaccination, signifies state-of-the-art progress and potential for cancer therapy. Neoantigens, which originate from diverse and fluctuating origins, have been scientifically shown to be unique to tumors and extremely capable of triggering an immune response. Furthermore, they can create long-lasting immunological memory that protects against cancer. Neoantigen-focused cancer treatments have advanced significantly in recent years, including the discovery, forecasting, and evaluation of neoantigens, as well as therapeutic alternatives. Neoantigen vaccines have shown significant safety and effectiveness in several forms of cancer via clinical studies, and numerous current investigations are further exploring their potential. Neoantigen vaccines, which use mRNA as a delivery method and target public neoantigens, are a novel and promising technique. These vaccines have shown enhanced clinical characteristics and drugability, making them very attractive for the advancement of precision cancer immunotherapy. Nevertheless, there are still obstacles to overcome in the development of neoantigen vaccines, since some elements need further optimization to get more favorable clinical outcomes. Neoantigen-targeted treatments are projected to become more feasible,

affordable, and successful due to many factors. These include a decrease in production turnaround time, a reduction in manufacturing cost, enhanced detection of immunogenic neoantigens, advancements in computational methods, and the identification of more effective treatment biomarkers. Neoantigen-based treatments can transform cancers that lack an immune response into tumors that elicit a strong immune response. Thus, it is justified to investigate the combination of different immunotherapies, such as checkpoint blockade therapies or traditional treatments like chemoradiotherapies, kinase inhibitors, anti-angiogenesis therapies, and others. Therefore, it is reasonable to believe that personalized medicines based on neoantigens might soon be extensively used in the treatment of different types of cancer.

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Authors' Contribution

Parisa Sanaati and Neagar Pour Naghshband were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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