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Opinion Article

Neoantigen Vaccines and Therapeutic Cancer Vaccines: A Personalized Approach to Cancer Immunotherapy

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DESCRIPTION

Cancer immunotherapy has gained significant attention in recent years as a potential approach to treating malignancies that have historically been difficult to target using traditional methods. Among these immunotherapeutic strategies, neoantigen vaccines and therapeutic cancer vaccines have emerged as two innovative and personalized tools designed to utilize the immune system to fight cancer. Both strategies aim to trigger immune responses specifically against tumor cells while sparing normal tissue, offering an avenue for highly selective and durable cancer treatments.

Understanding neoantigens

Neoantigens are tumor-specific antigens that arise from mutations in cancer cells. Unlike normal self-proteins, neoantigens are generated *de novo* as a result of genetic alterations unique to cancer cells. These mutations can lead to the production of new protein sequences that are recognized as foreign by the immune system, making them ideal targets for immunotherapy. Neoantigens differ from other Tumor-Associated Antigens (TAAs) in that they are not expressed by normal cells, thereby minimizing the risk of autoimmunity when used as a target in cancer vaccines.

Neoantigen vaccines are a form of personalized cancer therapy designed to stimulate the immune system specifically against these mutation-derived antigens. The basic premise of neoantigen vaccines is to identify patient-specific mutations through tumor sequencing and then design a vaccine to induce a strong immune response against the neoantigen-containing tumor cells.

The process of creating a neoantigen vaccine begins with whole-exome or RNA sequencing of the patient's tumor and matched normal tissue to identify non-synonymous mutations. Bioinformatic algorithms predict which of these mutations are likely to give rise to peptides that can be presented on the surface of cancer cells by Major Histocompatibility Complex (MHC) molecules. These peptides are potential neoantigens.

Once a set of candidate neoantigens is identified, synthetic peptides, DNA, or RNA encoding these neoantigens can be used to create a vaccine. In some instances, viral vectors or dendritic cells loaded with neoantigens may be used to deliver the vaccine. The vaccine is then administered to the patient with the goal of stimulating a robust T-cell-mediated immune response that specifically targets the tumor.

Mechanism of action

Neoantigen vaccines work by inducing a targeted immune response. Following vaccination, Dendritic Cells (DCs) present the neoantigens to T-cells, specifically cytotoxic $CD8^+$ T-cells. Once these T-cells recognize the neoantigen-MHC complex on the surface of tumor cells, they are activated and proliferate, leading to the killing of the cancer cells. This process is highly specific, as the immune system is essentially trained to attack only cells displaying these neoantigen peptides.

Several clinical trials have demonstrated the potential of neoantigen vaccines in various cancer types, including melanoma, Non-Small Cell Lung Cancer (NSCLC), and glioblastoma. For instance, in melanoma, neoantigen vaccines have been shown to elicit robust $CD8^+$ and $CD4^+$ T-cell responses against targeted neoantigens, leading to tumor regression in some patients.

Moreover, neoantigen vaccines are often combined with immune checkpoint inhibitors such as anti-PD-1 or anti-CTLA-4 antibodies to enhance therapeutic efficacy. Checkpoint inhibitors release the brakes on the immune system, allowing T-cells to attack cancer cells more effectively. When combined with neoantigen vaccines, which act as a personalized guide for the immune system, the anti-tumor effect can be significantly enhanced.

However, there are challenges to the broader application of neoantigen vaccines. These include the high cost and time associated with identifying patient-specific neoantigens, manufacturing the vaccine, and the variable immunogenicity of different neoantigens.

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Therapeutic cancer vaccines

Therapeutic cancer vaccines, unlike prophylactic vaccines, are designed to treat existing cancers rather than prevent them. These vaccines aim to stimulate the patient's immune system to recognize and attack cancer cells, either by targeting tumor-associated antigens or by more generalized mechanisms. While neoantigen vaccines focus on mutation-derived antigens specific to individual tumors, therapeutic cancer vaccines often target TAAs. TAAs are proteins that may be overexpressed or aberrantly expressed by cancer cells compred to normal tissue. Examples of well-known TAAs include HER2 in breast cancer, PSA in prostate cancer, and MUC1 in multiple cancers.

In therapeutic cancer vaccines, TAAs are used to induce an immune response against cancer cells that express these antigens. Although TAAs are not as uniquely specific to tumors as neoantigens, they are widely shared among patients with similar cancer types, allowing for the development of more broadly applicable vaccines.