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Viral infections: Evasion of the Immune System by Cancerous Cells

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Abstract

Prophylactic vaccination against infectious diseases is one of the most successful public health measures of our lifetime. More recently, therapeutic vaccination against established diseases such as cancer has proven to be more challenging. In the host, cancer cells evade immunologic regulation by multiple means, including altering the antigens expressed on their cell surface or recruiting inflammatory cells that repress immune surveillance. Nevertheless, recent clinical data suggest that two classes of antigens show efficacy for the development of anticancer vaccines: tumor-associated antigens and neoantigens. In addition, many different vaccines derived from antigens based on cellular, peptide/protein, and genomic components are in development to establish their efficacy in cancer therapy. Some vaccines have shown promising results, which may lead to favorable outcomes when combined with standard therapeutic approaches. This review provides an overview of the innate and adaptive immune systems, their interactions with cancer cells, and the development of various different vaccines for use in anticancer therapeutics.

Keywords: Cancer; Cancer vaccines; Antigens; Immunotherapy

Introduction

Prior to the development of smallpox vaccination by Edward Jenner in the eighteenth century, immunization and protection methods against infectious diseases provided unpredictable results for patients. Since its discovery, many scientific pioneers have fine-tuned the techniques necessary for vaccine development, which paved the way for modern vaccination protocols. The protective nature of vaccines has resulted in the prevention of infections and the eradication of many different diseases. For example, some diseases that are now preventable through immunization include tetanus, diphtheria, tuberculosis, influenza, measles, mumps, rubella, hepatitis, and varicella-zoster, among others. Interestingly, immunization against some viral infections, such as the human papillomavirus or hepatitis, can also prevent the development of cervical and liver cancer, respectively, by preventing infection with cancer-causing viruses [1]. In more recent years, studies have evaluated whether vaccines can also be used in cancer therapy. With the success of vaccines in containing infections utilizing the host's immune system, research is now focused on developing methods to harness this technology for cancer prevention and elimination. However, progress has been slow due to the lack of validated biomarkers that predict vaccine efficacy, challenges relating to vaccine stability and delivery, and the costs associated with the production of personalized patient-specific vaccines. As vaccines move from disease prevention to therapy, cancer vaccines are becoming an integral part of therapeutic strategies for tertiary and primary cancer prevention [2].

The current standard of care for cancer treatment consists of various options, including surgery, chemotherapy, radiotherapy, hormonal therapy, molecularly targeted therapy, and immunotherapy, which provide variable results due to several factors. Immunotherapy focuses on harnessing the host immune system, both humoral and cellular, to attack malignant cells. The immune system is a complex network of cells and proteins that provide innate (general) and adaptive (specific) defense mechanisms for the body [3]. Innate immunity includes anatomical barriers and physiological barriers, endocytic and phagocytic barriers, and inflammatory barriers. The phagocytic macrophages of the innate immune system generally provide the first line of defense against many different microorganisms and are essential for controlling common bacterial infections. In addition to cellular immunity, the innate immune system also consists of proteins of the complement system, which can form pores directly in the bacterial cell surface, thereby killing the pathogen. Notably, the innate immune response makes a crucial contribution to the activation of the adaptive immune system. Adaptive immunity functions to differentiate self-antigens from non-self-antigens, eliminate the pathogen or the infected cells, and produce immunologic memory in case there is a future infection with the same pathogen [4].

Cancer Immunotherapy

Cancerous cells can reside in the host body undetected through a variety of different regulatory processes, as described above. Immunotherapy is a new form of cancer therapy focused on harnessing the host immune system to attack specific types of cancer cells. Immunotherapy exists in both passive and active forms, such as adoptive cellular immunotherapy, natural killer cell therapy, chimeric antigen receptor T (CAR T) cell therapy, and the use of ICIs. Adoptive T cell therapy allows for in vitro growth of patient-derived tumor antigen-specific T cells that are then reintroduced back into the patient [5]. Since Tregs are suppressive in the tumor microenvironment, lymphodepletion approaches are performed prior to re-infusing the T cell product back into the patient. Adoptive cell therapy relies on the immune system to recognize tumor cells by modifying tumor-infiltrating lymphocytes, T cell receptors, or introducing chimeric antigen receptors. When combined with cancer vaccines, adoptive cell therapy was shown to provide synergetic effects in solid skin tumors [6]. On the other hand, natural killer (NK) cell therapy focuses on the cells' innate ability to recognize and eliminate cancerous cells without prior sensitization. In metastatic solid tumors, clinical trials have demonstrated that activation of NK cells provides better immunotherapy outcomes when compared with T cells. Immune checkpoint proteins, such as CTLA-4 and PD-1, prevent T

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cells from destroying cancer cells, as described above. The PD1-Vaxx vaccine produces polyclonal antibodies that inhibit PD-1 in breast and pancreatic cancer cells, resulting in a significant decrease in tumor growth in mice. As a consequence, Imugene Ltd. has received FDA approval for clinical testing [7].

Adoptive T cell transfer, ICIs, and bispecific antibodies are the most prevalent types of immunotherapies. Although ICI-based immunotherapy has shown remarkable progress in cancer treatment, many cancers relapse over time. However, due to this relapse, research is now focused on developing combinatorial therapies, including ICIs and cancer vaccines. Cancer vaccines, as compared with ICIs, have the advantage of utilizing the entirety of the host immune system, instead of just an individualized component, for cancer cell targeting. As demonstrated in preclinical models, when both are combined, treatment success is greatly improved. This makes cancer vaccines an area of interest to pursue further [8].

Evasion of the immune system by cancerous cells

For the adaptive immune system to mount an efficient anticancer response, a series of events must be initiated and allowed to proceed, known as the Cancer-Immunity Cycle. The first step involves the production of cancer-specific antigens, known as neoantigens, that are released and captured by dendritic cells (DCs) for processing. To induce an anticancer response, the presentation of these antigens must be accompanied by signals that specify tumor immunity versus tolerance. In the presence of the proper costimulatory molecules, engagement of the T cell receptor with MHC: antigen complexes on DC cells results in priming and activation of effector T cell responses. Finally, the activated T cells migrate and infiltrate the tumor [9], which presents the processed neoantigens in complex with MHC class I on the cell surface, resulting in cancer cell killing. Dying cancer cells release further tumor-associated antigens, thereby potentiating the process.

Each step of the Cancer-Immunity Cycle is coordinated by many different factors, including molecules that are either stimulatory or inhibitory. Stimulatory factors promote immunity, whereas inhibitory molecules keep the process in check to prevent autoimmunity. Unfortunately, cancer cells can evade the immune response in several different ways. For example, tumor antigens may not be detected, DCs and T cells may develop tolerance to the antigen, treating it as self rather than foreign, or T cells may not properly home to the tumor site. Additionally, T cells can be prevented from infiltrating the tumor upon arrival, or factors present within the tumor microenvironment may suppress the effector T cell function [10].

Conclusions

Vaccinations have long protected humans from the devastating effects of infectious diseases and cancer. However, aspects of the innate and adaptive immune system are routinely utilized by cancer cells to evade immunologic responses in the host. The challenge is now to use vaccines as first-line cancer therapeutics. New vaccinations are being developed to target preexisting cancerous cells using the same techniques employed in cancer prevention. By targeting those mechanisms, cancer vaccines may also prevent cancer progression. Establishing and prioritizing immunogenic neoantigens will be critical to providing an optimal response during vaccine development. In addition, multiple different types of cancer vaccines can be employed to determine maximal effectiveness depending on the type of cancer. While research has shown promising results for cancer vaccines, additional studies have shown that the combination of cancer vaccines with previous standard therapies may provide the best results for cancer eradication.

There are still many challenges to overcome for vaccine-based anticancer therapeutics. Notably, the ability of T cells to respond to antigenic challenges is affected by numerous factors, including age, diet, gut microbiome, and the tumor microenvironment. Potential areas of study for the future of cancer vaccines include tumors that are not responsive to immunotherapy. Another issue is that a patient may express heterogeneity of tumor cells leading to inadequate treatment if the vaccine focuses on only one particular neoantigen. This limitation could be mitigated by creating a vaccine targeting multiple neoantigens specific to the patient. However, producing an individualized, patient-specific vaccine is very expensive due to analysis and production costs. While still limited in some aspects, the continued advancement in cancer vaccination will provide better treatment outcomes for patients in the future.

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