Review article

Neoantigen therapeutic cancer vaccines: a promising approach to personalized immunotherapy

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ABSTRACT

The tumour microenvironment diversity among patients poses a challenge for conventional therapies, leading to limited efficacy. Furthermore, conventional methods are inherently associated with a negative impact on healthy tissues. Personalized immunotherapy, focused on individual tumor characteristics, has emerged as a potential solution. Neoantigens, unique antigens arising from tumour-specific mutations, play a crucial role in personalized therapy. Identifying and utilizing neoantigens through therapeutic vaccines can induce an immune response specifically against tumour cells, offering a more targeted and less toxic for healthy tissues approach to cancer treatment. The vaccines can potentially lead to tumour regression and improved outcomes. The effectiveness of this therapy is still limited due to phenomena such as immune escape. However, ongoing scientific research, technological advancements, and emerging combination therapies offer hope for the success of neoantigen-based therapeutic cancer vaccines, ushering in a new era in personalized oncology.

Key words: cancer vaccine, personalized immunotherapy, neoantigen, immunotherapy, tumour microenvironment, immune escape

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INTRODUCTION

The issue of cancer diseases poses a significant challenge to the medical community. According to the Polish National Cancer Registry (pol. Krajowy Rejestr Nowotworów) [1], the incidence in Poland is estimated at around 170,000 cases annually, with a mortality rate of approximately 100,000 deaths per year. Traditional approaches to cancer therapy, such as surgery, chemotherapy, and radiotherapy, have been the cornerstone of oncological treatment for many years [2]. Despite the undeniable achievements of these techniques in the management of the disease, there is still an urgent need to seek new, innovative treatment methods [3].

Today's medicine offers promising prospects through the development of advanced immunotherapy methods. These methods are based on harnessing the immune system's ability to recognize and combat cancer cells [4]. Breakthroughs in immunology and genetics have led to the creation of modern immunotherapeutic technologies, such as immune checkpoint inhibitors [5, 6] and CAR-T cell therapy (chimeric antigen receptor T cells) [7, 8], which show promising results in treating certain types of cancer [9].

The introduction of innovative immunotherapies has paved the way for another potential breakthrough in cancer treatment – therapeutic cancer vaccines [10]. The aim of these vaccines is to stimulate the patient's own immune system to detect and combat cancer cells in a more targeted and effective manner [11]. Therapeutic cancer vaccines are increasingly being explored in clinical research and scientific publications, and their potential to improve cancer treatment outcomes has captured the interest of many researchers and clinicians.

In this paper, we present a literature review aimed at presenting the concept of therapeutic cancer vaccines, with a particular focus on vaccines targeting neoantigens. We provide comprehensive information on the rationale of personalized therapy, the vaccine development process, the current research findings, limitations, and new perspectives. By analysing the latest research and advancements in this field, we highlight the potential of therapeutic cancer vaccines in the context of modern oncological therapy.

TUMOUR MICROENVIRONMENT AND CHALLENGES OF CONVENTIONAL TREATMENT METHODS

A significant challenge in cancer treatment lies in the fact that each tumour in every patient is unique in terms of its microenvironment and the molecular profile it contains. The concept of the tumour microenvironment pertains to diverse (not solely tumorous) cells, vessels, extracellular matrix, and molecules present in the tumour vicinity, influencing its growth, aggressiveness, and susceptibility to treatment [12]. The heterogeneity within the microenvironment is a key reason why traditional treatment methods, such as chemotherapy or radiotherapy, don't always yield satisfactory results. Furthermore, these methods often come with indirect or direct negative impacts on healthy tissues, leading to numerous undesirable side effects [2]. Surgical approaches, on the other hand, due to their inherently invasive nature and effectiveness limited to the operated area, have restricted applicability in cases of disseminated, advanced, and haematological malignancies.

PERSONALIZED THERAPY – TARGETING SPECIFIC TUMOURS

In response to these challenges, innovative treatment methods are being sought that would be tailored to the individual characteristics of a patient's specific tumour. Personalized therapy, also known as precision or targeted therapy, aims to provide patients with optimal treatment based on their unique case [13]. This requires the examination of the tumour to detect characteristic genetic mutations and peptides that would serve as points of intervention for the applied therapy [14]. In the case of targeted immunotherapy, immune system cells are directed against the identified molecules, leading to an attack on tumour cells and ultimately achieving a therapeutic effect [15].

The potential of neoantigens in personalized therapy

Neoantigens can play a pivotal role in personalized therapy. Neoantigens are unique antigens that arise due to mutations in the DNA of cancer cells. They are characterized by their presence exclusively within the tumour microenvironment and are never found in healthy cells of the body [3, 16]. Tumours exhibit a genomic instability, making them prone to accumulating numerous mutations – this trait facilitates the emergence of many potential neoantigens within the tumour [17]. Identifying neoantigens enables the development of therapeutic cancer vaccines that stimulate the patient's immune system specifically to target cancer cells, while minimizing detrimental effects on healthy tissues devoid of neoantigens [16, 18].

NEOANTIGEN CANCER VACCINES – PERSONALIZED IMMUNOTHERAPY

Neoantigen therapeutic cancer vaccines represent a promising direction in cancer therapy. Built upon the potential of neoantigens, these vaccines are developed in a targeted manner for each individual patient, considering the unique set of neoantigens

present in their tumour [18]. The primary goal of these vaccines is to stimulate the immune system to combat cancer cells, ultimately leading to tumour growth inhibition, remission, and potential cure [11]. Therapeutic cancer vaccines are becoming a significant tool in the realm of personalized medicine, offering hope for more effective, targeted, and less toxic therapies in the battle against cancer.

MECHANISM OF ACTION OF NEOANTIGEN THERAPEUTIC CANCER VACCINES

After administration of the vaccine, neoantigens are captured by antigen-presenting cells (APCs), primarily dendritic cells [19]. There is also a type of vaccine involving the administration of previously prepared dendritic cells capable of presenting neoantigens [20, 21]. Dendritic cells are pivotal components of the immune system with the ability to present antigens to T lymphocytes [19]. Antigen presentation occurs using major histocompatibility complex (MHC) molecules present on the surface of dendritic cells [18, 22]. In the case of neoantigen vaccines, dendritic cells present a selected set of tumour neoantigens on their surface [20].

Presented neoantigens are recognized by T lymphocytes – CD8+ cytotoxic T lymphocytes and CD4+ helper T lymphocytes [3]. CD8+ T lymphocytes activated by neoantigens undergo replication and become capable of directly inducing death in cancer cells [23] that carry the same neoantigens. CD4+ T lymphocytes enhance the immune response by secreting cytokines and supporting the activation of other immune cells [24].

Results from clinical trials assessing the efficacy of therapeutic cancer vaccines suggest that the induced immune response to neoantigens can contribute to restraining tumour growth and preventing recurrences [11]. The contemporary approach to cancer therapy, based on treatment personalization and utilizing individual neoantigens, has the potential to usher in a new era in oncology, leading to the development of more effective and personalized anti-cancer strategies.

THERAPEUTIC CANCER VACCINE PRODUCTION PROCESS

DNA sequencing – the process begins by collecting samples of both healthy tissue (such as peripheral blood mononuclear cells) and tumour tissue from the patient. DNA sequencing is then conducted on both samples. By comparing the sequencing data from the tumour and healthy tissue, unique mutations specific to the tumour, absent in healthy tissues, are identified [25, 26]. Only mutations present in exons, the coding sequences, are significant in later stages, as neoantigens can only be encoded on them. Whole exon sequencing (WES) is a frequently utilized method allowing the examination of all coding sequences [27].

Neoantigen selection – the sequencing data is analysed, and mutations that are predicted to strongly stimulate T cell responses are considered potential candidates for vaccine production [25]. Advanced computational technologies (such as deep learning, machine learning, or mass spectrometry) are used for this purpose, enabling predictions of immunogenicity, neoantigen binding strength to MHC molecules, quantitative neoantigen expression in the tumour, and the clonality of a given mutation, among others [16]. The final selection considers mutations most likely to induce a robust immune response [26].

Individualized vaccine production – the selected neoantigens are designed and manufactured into vaccine forms tailored to each patient. Possible forms include DNA [28, 29], mRNA [30, 31], peptides [2, 32], or the aforementioned dendritic cells [20, 21]. This stage is particularly challenging, as manufacturing molecular polymers is a complex and lengthy process, demanding advanced chemical and biological techniques [33, 34].

In summary, the production process of therapeutic cancer vaccines involves a meticulous analysis of the patient's tumour DNA sequence, the selection of the most appropriate neoantigens, and the customization of the therapy form to optimally stimulate the immune system against the tumour. This advanced approach to cancer treatment, targeting the unique characteristics of each patient, opens new perspectives in the management of this challenging disease.

EFFECTIVENESS OF THERAPEUTIC CANCER VACCINES

In individual studies exploring the application of therapeutic cancer vaccines in monotherapy, these preparations have induced immune responses reliant on CD4+ and CD8+ lymphocytes, and in certain cases, led to prolonged progression-free survival [11, 35–38]. Additionally, the method has been associated with a low frequency of adverse events [11]. The results from three randomized multicentre trials investigating the use of vaccines as adjuvant therapy after resection of colorectal cancer indicated significant efficacy in less advanced tumour stages [39]. However, another summary suggests that monotherapy with cancer vaccines does not exhibit higher efficacy compared to other forms of therapy [40].

Cancer cells develop diverse mechanisms to evade detection and destruction by the patient's immune system. This phenomenon, known as immune escape or immune evasion, is one of the fundamental challenges in the effective application of immunotherapy [41]. For this reason, significant hopes lie in combination therapies, where the effect of neoantigen vaccines is potentiated by concurrent use of other therapies, such as immune checkpoint inhibitors, which further stimulate the immune system [42]. Existing research has indicated the superiority of combination therapies over the use of vaccines in monotherapy [16, 38, 43, 44].

LIMITATIONS AND CHALLENGES OF THERAPEUTIC CANCER VACCINES

Despite promising results there are significant challenges and limitations in the development and application of neoantigen vaccines. The identification and selection of appropriate neoantigens and methods of their production require further research to optimize the efficacy of these preparations in stimulating immune cell responses. Proper selection of optimal therapies is also crucial in the context of combination therapies [45, 46].

The immunosuppressive tumour microenvironment can hinder the effectiveness of the immune response to the vaccine [47]. Therefore, strategies that modify the tumour microenvironment to enhance the effectiveness of neoantigen vaccines represent an important avenue for future research [40].

Despite these challenges, personalized neoantigen vaccines hold the promise of a new era in cancer therapy, where patients receive treatment based on the unique profile of their disease. Continued research and technological advancements in this field will contribute to a better understanding of immune mechanisms and further refine and expand the application of this promising approach in combating various types of cancer.

CONCLUSION

In the future, continued technological advancements, better understanding of immune mechanisms, and the identification of suitable neoantigens will be crucial for further optimizing and expanding the application of neoantigen-targeted cancer vaccines. Combining these vaccines with other therapies could open new perspectives in cancer treatment, offering hope for improved therapeutic outcomes and enhanced quality of life for patients dealing with various types of cancer [47]. Fascinating challenges and discoveries still await us in this field, and innovative approaches drawing from the evolving knowledge of neoantigens and cancer vaccines could hold the key to significant advancements in the battle against cancer.

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