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Analysis of the development prospects of cancer therapeutic vaccines based on the current research status of peptide vaccines

Tongyu Zhang

School of Life Science, Xiamen University, Xiamen City, Fujian Province, China

21620202200616@stu.xmu.edu.cn

Abstract. With the deepening of relevant research and the accumulation of clinical trial experience, immunotherapy based on peptide cancer therapeutic vaccines is currently considered to be one of the potential methods for treating cancer. By presenting epitope peptides of tumor antigens, peptide vaccines can activate the adaptive immune system and trigger the body's own immune response against tumor tissue, thereby achieving the effect of clearing tumors and preventing subsequent tumor formation. In addition to the common advantages of peptide vaccines such as ease of production and low cost, peptide vaccines also have great potential for designing customized therapies. At the same time, the research results of peptide vaccines also show the potential to be used in other types of immunotherapies or in combination with other therapies. However, current problems such as low immunogenicity and low general applicability still require adjustments in the design ideas and target selection of peptide vaccines. In this review, the main design ideas of peptide vaccines are discussed, and the advantages and current problems of peptide vaccines are comparatively analysed.

Keywords: Cancer Immunotherapy, Neoantigen, Peptide-Based Cancer Therapeutic Vaccine.

1. Introduction

Cancer, as one of the most common diseases with high fatality rates worldwide, poses a huge challenge to the global health and medical research fields. At present, traditional treatments such as radiotherapy and chemotherapy have been widely used in clinical practice. However, the cancer types and stages they can treat are limited, and they are often accompanied by serious side effects. Chemotherapy may cause damage to the immune system [1], which leads to a decrease in the patient's tolerance to other diseases. the cardiovascular toxic effects caused by radiotherapy also cannot be ignored [2]. In addition, traditional surgical resection is not always suitable for patients with pancreatic cancer and other types of cancer [3]. The problems inherent in these traditional therapies have prompted relevant researchers to continue to explore other effective ways to treat cancer. Immunotherapy usually refers to treatments that artificially strengthen or rebuild the immune system. It is a type of therapy that eliminates pathogens without causing an immune inflammatory response and uses the body's existing immune system to fight diseases. As the understanding of the immune system and cancer gradually deepens, clinical researchers have seen the advantages of using immunotherapy to treat cancer: reshaping the tumor microenvironment [4], forming a sustained anti-tumor immunity and gaining a higher Overall survival

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rate [5] and so on. The idea of applying immunotherapy to treat cancer is gradually becoming clearer in recent years.

Among the many existing immunotherapies, vaccines have rich clinical experience against a variety of different diseases and therefore have also been tried to be used in the clinical treatment and prevention of cancer. This article will focus on the therapeutic vaccines used to treat cancers. Cancer therapeutic vaccines have always attracted much attention due to their broad application prospects and long research tradition. Cancer therapeutic vaccines refer to presenting relevant antigens to important antigen-presenting cells (e.g., dendritic cells), inducing their maturation and the function of activating the immune system. Under this mechanism, they can cause relevant immune cells to produce effective killing of tumors in the body and tumor regression, ultimately clearing tumors and establishing lasting anti-tumor memory while avoiding adverse reactions [6]. Peptide vaccines whose main components are proteins have the advantage of being relatively simple in design and acting directly on key immune cells. They use isolated epitopes of tumor antigens to stimulate immune responses. Their advantages, such as low cost, easy production, and high stability, make them extremely effective [7]. With the in-depth research on neoantigens, peptide vaccines have shown the great potential of designing customized vaccines [8] and have become a hot spot in academic research and clinical trials. However, the strong immunosuppressive effect in the tumor microenvironment inhibits the effectiveness of immunotherapy [9] and the limited immunogenicity of vaccine proteins are the main problems to be solved. The selection of specific antigens and the design of peptides also require further research and optimization [10].

This article systematically introduces the design, use, clinical results and current problems of peptide vaccines for cancer treatment, and discusses the advantages of peptide vaccines on design ideas, application costs, difficulty of research and development by horizontally comparing other types of cancer treatment vaccines, and eventually put forward corresponding insights on the possible development directions of the main problems faced by current peptide vaccine research.

2. Targeting antigen selection

In vivo, tumor antigens (TA) are processed by cells, decomposed into polypeptides and assembled into HLA (human leukocyte antigen) molecules as products of MHC (major histocompatibility complex), expressed on the surface of dendritic cells (DCs), and participate in the activation process of T cells. CD8+ T cells recognize the presented HLA-peptide complex substance and produce an immune response. Since the design idea of peptide vaccines is to stimulate relevant immune cells to respond to the tumor antigens provided by the vaccine to target tumor tissues where the same antigens exist in the body, identifying and selecting which antigens to present naturally becomes a key step in designing. The choice mainly revolves around two types of TA: tumor-associated antigen (TAA) and tumor-specific antigen (TSA).

2.1. TAA

Tumor-associated antigens refer to antigens expressed in both tumors and normal tissues. Considering the targeting required for immunotherapy, the priority issue that needs to be considered when selecting TAA as the antigen provided by the vaccine is the distinction between tumor tissue and normal tissue. Usually, the first requirement during screening is that the expression level of the selected TAA should be significantly different from that of normal tissues (generally manifested as a much higher expression level on tumor cells than that of ordinary cells). In addition, the selected antigen should preferably pass Participating in tumor formation or otherwise directly related to tumor cell survival [7]. Finally, the selected antigen should have immunogenicity equivalent to that of the foreign antigen to be recognized by T cells [11]. On the basis of meeting the above requirements, further specific screening can be conducted based on the type of cancer being treated and its unique TAA.

Currently, some TAAs have been screened and used in clinical attempts to treat cancer, including but not limited to the application of human epidermal growth factor receptor 2 (HER2) in the treatment of breast cancer [12]. It is worth noting that when the research on TAA is applied in cancer immunotherapy,

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it is often not limited to vaccines and shows more potential to be tapped in CAR-T therapy (Chimeric Antigen Receptor T-Cell Immunotherapy) and monoclonal antigen therapy.

Using TAA as an antigen is in line with the design idea of using shared tumor antigens to design widely applicable cancer therapeutic vaccines. Currently, those who use TAA to design other immunotherapies are also interested in its universal application, that is because TAA they are widely and identically present in different patients and can be used to treat multiple patients with the same treatment method.

The primary problem faced when choosing TAA as the antigen provided by the vaccine is that the presented antigen is ineffective due to the body's own tolerance to TAA. Since immune tolerance only acts on the dominant epitope of TAA, some studies have tried to enhance the therapeutic effect by targeting the cryptic epitope of TAA. However, the cryptic epitope needs to be enhanced in advance to obtain sufficient immunogenicity to induce an immune response. [13]. In addition, other studies have attempted to enhance the effect of related immunotherapy by manipulating the antigen presentation pathway [14].

2.2. TSA

Compared with TAA, the main difference of TSA is that it is only expressed in tumor cells. These antigens, which are not present in normal tissues, have attracted increasing attention with the development of immunotherapy and proteomics in the past decade. The characteristics of TSA determine that it has stronger targeting and non-immune tolerance when used as a vaccine antigen: the core of using TSA for immunotherapy design is to accelerate the immune system to recognize that the non-self TSA provided by the vaccine and form specific immunity to achieve the purpose of killing tumors. TSA can be divided into mutated antigens and non-mutated antigens.

2.2.1. Cancer-testis antigen (CTA). Currently, non-mutated antigens used in cancer vaccines include endogenous retrofactor-derived tumor-specific antigens, CTA, etc. As a type of TSA, CTA is only expressed in some germ cells and tumor tissues. Compared with TAA, which relies on expression level to distinguish tumor tissues from normal tissues, CTA shows greater advantages in specificity. Moreover, CTA is commonly shared among different patients, which is considered to be an important idea for designing widely applicable cancer therapeutic vaccines. In addition, CTA is considered to be involved in tumor immune evasion and tumor formation [15], which makes it have an important impact on tumor survival. It also means that choosing CTA as a vaccine antigen can directly take into account the advantages of treatment and prevention of subsequent tumor formation. However, the types of tumors expressing CTA are limited, and the role of CTA in cancers suitable for treatment with this therapy, including ovarian cancer, melanoma, etc., is not yet fully understood [16,17], as is its timeliness in the treatment of advanced tumors unknown.

2.2.2. Neoantigen. In addition to non-mutated antigens, TSA also contains neoantigens. Neoantigens refer to antigens produced due to mutations that occur in the tumor genome, that is, mutated antigens, which account for a considerable part of TSA. The key reason for being classified is that these cells are not expressed by epithelial cells in the thymic medulla, which means the body has not developed immune tolerance to neoantigens. Neoantigens can be targeted to enhance anti-tumor immunity after being recognized by the immune system. The source of neoantigens is random mutations, which is not only its greatest advantage, but also a key factor limiting its application. Compared with searching for shared expression antigens between different patients, which is difficult to ensure immunogenicity, selecting new antigens generated by mutations in the patient's tumor tissue can better ensure targeting and reduce the possibility of autoimmunity. Neoantigens have been used in several clinical trials and are emerging as central to the design of therapies in immunotherapies including, but not limited to, peptide cancer therapeutic vaccines. In clinical trials using neoantigens in combination with immunosuppressants, combination therapies have shown strong anti-tumor effect [18]. The recent application of multi-modal combination therapy of neoantigen vaccines, chemotherapy and anti-PD-L1 (anti-Programmed cell

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death 1 ligand 1) immunotherapy has also been proven to be safe and effective in the face of high-fatality pancreatic ductal adenocarcinoma [19].

Since neoantigens are unique antigens that are not shared among patients, the establishment of individual-based customized therapies is an inevitable direction for the application of neoantigens, therefore, their identification and targeting must be solved before they can be put into use. The design of personalized methods for neoantigens must be based on the development and application of genomics and bioinformatics, which poses challenges to its recent application in terms of efficiency and cost. Common problems currently existing with all types of TSA include the inconsistency between "inducing an immune response against TSA" and "producing anti-tumor activity", that is, the immune response induced is often difficult to achieve the purpose of clearing tumors [20]. As well as the difficulty in directly determining whether the selected antigen is necessary for tumor cell survival, these factors still restrict the application of TSA vaccines.

3. Clinical application

Currently, peptide cancer therapeutic vaccines have been used alone or in combination with other drugs in some clinical trials. The application directions of peptide cancer therapeutic vaccines are mainly divided into design ideas based on shared antigens (shared target molecules) and based on personalized immunotherapy.

The core of research based on shared antigens is various types of TAA, covering a wide range of cancer types: breast cancer vaccines designed using breast cancer-related TAA have been proven to be safe and effective [21]; recent research has strengthened the therapeutic ability on breast cancer by combining nanotechnology [22]; the application of peptide vaccines using TAA in colorectal cancer has been studied for more than a decade and is considered a promising treatment method [23]; for liver cancer, recent discoveries have been based on TAA design Vaccines combined with immune checkpoint inhibitors may be effective in its treatment [24]. Some other studies are trying to design vaccines based on the changes in tumor tissue after other therapies. For example, some studies have shown that after chemotherapy treatment, the danger signal molecules released by tumor cells may become qualified antigens for peptide vaccines [25]. In addition, for rare cancers that currently lack universal treatments, some researchers have tried to use peptide vaccines to design standard treatments based on the idea of shared target molecules among multiple cancers, and have discovered possible treatment strategies [26].

4. Comparison of peptide vaccines with other cancer therapeutic vaccines

In addition to peptide vaccines, cancer vaccines currently used for treatment also include virus vaccines, dendritic cell vaccines, nucleic acid vaccines. Virus vaccines using viruses as vectors, dendritic cell vaccines that accelerate the antigen presentation process by culturing dendritic cells in vitro and injecting them, and nucleic acid vaccines that directly or indirectly inject nucleic acid molecules encoding antigens. From the perspective of design ideas and core mechanisms, the core advantage of peptide vaccines is that they directly act on key steps of the immune response in a simple and effective way, avoiding the technical difficulties associated with excessively long in vitro culture procedures or excessive in vivo steps in which many uncontrollable factors brought by it. From the perspective of relevant necessary biotechnology, the booming development of proteomics in recent years has promoted the improvement and improvement of important aspects of peptide vaccine design such as antigen screening, separation and purification, and even in vitro design and synthesis. From the perspective of cost, if a broad-spectrum cancer therapeutic vaccine can be designed which can be widely used in a variety of cancers, the development and production costs of peptide vaccines will also have considerable advantages. In addition, peptide vaccines have the advantage of being easy to store and transport, supporting their potential for application in a wider geographical range.

5. Conclusion

In this article, various types of peptide vaccines for cancer treatment are analysed and compared. The TAA vaccine, which mainly attempts to focus on antigens shared between different cancers and patients,

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has a relatively long history of research and has accumulated rich clinical experience. It is considered to have the potential to develop applicable treatments for multiple cancers and research ideas that may provide standard treatments for rare cancers, but its current specificity is unsatisfactory. Current research mainly focuses on improving its specificity and ensuring the induction of effective immune responses by improving delivery methods and other means. For TSA vaccines that value specificity and are based on customized design, their main advantages and limitations both come from the high specificity of the antigen. On the one hand, it ensures the targeting of immunotherapy. On the other hand, before its application, it is required to obtain specific antigens for each cancer type and even each patient. This requires a combination of relevant disciplines and technologies to screen, identify and predict potentially available mutations for available antigens. The complexity of this work and the immaturity of the current technical process make this type of vaccine difficult to conduct clinical trials and difficult to promote on a large scale.

This article believes that the current key issue for cancer therapeutic vaccines is the choice and trade-off of design ideas. Vaccines with the potential to be universally applicable to multiple cancer types can be put into practice by designing combination therapies or by applying their core principles on more mature technologies while ensuring the effectiveness of research. Current research has shown the commonalities and cross-application effectiveness of different approaches to immunotherapy. Combined application with other mature therapies has been proven to retain its "general use" advantage while overcoming its "weak effect" disadvantage to a certain extent, that is: cancer therapeutic vaccines should not be the only solution and the search for universally applicable immunotherapy should not be limited to the scope of “vaccines”.

In contrast, design ideas that focus on specificity and mutation identification seem to inevitably lead to customized immunotherapy. Therefore, the screening, identification and mutation site prediction of relevant antigens require a standardized process to ensure its clinical treatment efficiency. In addition, customized immunotherapy, including but not limited to cancer vaccines, is currently generally considered to lack cost-effectiveness. Under this design concept, whether the original advantages of easy-to-production and relatively low price of peptide vaccines can continue to be maintained still needs to be verified. If these advantages that make peptide vaccines more competitive than other cancer therapeutic vaccines cannot be maintained during the customization process, the selected value of peptide vaccines will naturally continue to be lost. On the other hand, the potential implication of customized vaccines is that their design and production are later than the diagnosis of cancer, and the testing, design, production and other steps all require a lot of time. Clinical questions such as how long it takes after the injection to take effect and whether the patient will still have an intact immune system and sufficient physical situations to receive immunotherapy are also cannot be ignored.

The problems existing in these cancer therapeutic vaccines affect the current situation of this treatment method by separating it from using other treatment methods together, and fundamentally affect the application ability of immunotherapy. The advanced design ideas of cancer therapeutic vaccines have huge potential, which makes researchers more willing to seek solutions than change their ideas when faced with these problems. Treatment methods always need to give priority to clinical needs. The hope brought by the idea and the problems brought by the demand will be the main driving force for the continued progress and development of cancer therapeutic vaccines: We need effective treatments for cancer, but we also need affordable, fast-acting treatments.

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