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Developments and applications of therapeutic tumor vaccines

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Abstract. The incidence and mortality rates of malignant tumors have rapidly increased. Cancer has become the leading cause of death worldwide. Traditional treatment methods such as surgery, chemotherapy, and radiation have limited effectiveness, with poor prognosis, drug resistance, and low specificity. As a result, cancer immunotherapy has emerged as a promising approach in biotechnology. The development and application of tumor vaccines in tumor immunotherapy have garnered significant attention. These vaccines employ TAA or TSA to activate the body's specific immune response against tumor cells. This review provides an overview of the tumor microenvironment, tumor immunotherapy, and various types of therapeutic cancer vaccines, including peptide, cell, DC, nucleic acid (DNA and mRNA), and neoantigen vaccines. In conclusion, this review summarizes the current progress and future prospects of tumor vaccines.

Keywords: Tumor, Tumor vaccine, Immunotherapy

1. Introduction

With the development of society, the change of environment and people's lifestyle, the incidence and mortality of malignant tumors have increased rapidly, and cancer has become the first cause of death of human beings. A tumor emerges as a novel entity resulting from the localized proliferation of tissue cells within the body, triggered by a range of tumorigenic influences. The proliferation of cancer cell is un-inhibited. In the past few decades, the usual treatment was surgical operation, chemotherapy and radiation. However, the poor prognosis of surgery, drug resistance of chemotherapy and low specificity of radiotherapy all make the treatment of cancer difficult. With the development of biotechnology, cancer immunotherapy was developed to treat tumor. In terms of cancer immunotherapy, the tumor-associated antigen (TAA) and tumor specific antigen (TSA) play critical roles.

In tumor immunotherapy, the development and application of tumor vaccines are also attracting the attention of researchers. Tumor vaccine is a kind of immune intervention strategy that uses TAA or TSA to activate the body's specific immune response to kill tumor cells. According to the purpose of cancer vaccines, they are divided into two categories: preventive vaccines and therapeutic vaccines. Preventive cancer vaccines are primarily designed to target tumor-inducing pathogens, such as the HPV vaccine to prevent cervical cancer. Therapeutic cancer vaccines are mainly designed for TAA and TSA.

This review mainly provides an overview of the tumor microenvironment and tumor immunotherapy, and introduces the types and applications of therapeutic cancer vaccines. At the end of this review, a summary is made and the future of tumor vaccines is prospected.

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2. Tumor immunity

2.1. Tumor Microenvironment

Tumor microenvironment (TME) encompasses the surroundings where cancer cells thrive. This includes elements such as blood vessels, fibroblasts, immune cells, bone marrow-derived inflammatory cells, lymphocytes, signal transduction and extracellular matrix (ECM) [1]. Cancer cells are usually embedded in dense ECM composed of collagen and proteoglycans to form their microenvironment by producing various cytokines, chemokines and other factors. A series of studies have revealed the key role of tumor microenvironment in regulating tumor progression. Korneev et al. [2] have identified that tumors closely and continuously interact with the surrounding microenvironment and organs through the lymphatic or circulatory system. Consequently, tumor cells can impact the microenvironment by emitting extracellular signals, such as paracrine signals, leading to the induction of peripheral immune tolerance and the promotion of tumor angiogenesis. In addition, abnormally high expressions of tumor matrix remodeling genes such as matrix metalloproteinase (MMPs) and collagen are poor prognostic factors in patients with breast cancer [3]. In conclusion, tumor cells and the tumor microenvironment mutually complement one another. During the tumorigenesis and progression process, the tumor microenvironment and tumor cells collaborate to modulate tumor immune tolerance, consequently impacting the clinical outcomes of immunotherapy.

2.2. Tumor Immunotherapy

Immunotherapy pertains to the therapeutic approach aimed at modulating the body's immune function artificially, either to boost or suppress it, in alignment with the body's hypoactive or hyperactive immune status, with the intention of addressing various diseases. Conventional treatments, such as chemotherapy and radiotherapy, act on the tumor itself. Because the environment in which tumors live is rich and complex, sometimes the desired effect cannot be achieved if only directly acting on the tumor itself without inhibiting the tumor microenvironment. Therefore, immunotherapy has been found which is a kind of therapy aimed at the tumor microenvironment. This has the potential to counteract the immunosuppressive condition within the tumor microenvironment, alleviating immune suppression and reinstating the immune system's capacity to mount attacks [4].

With the development of genomics, bioinformatics and other technologies, rapid recognition of tumor antigens and screening of appropriate tumor antigens are the key to tumor vaccine design. According to their tissue distribution, expression level and central tolerance state, the main tumor antigens studied at the present stage are mainly divided into two categories: tumor-associated antigens (TAA) and tumor specific antigens (TSA) [5]. TAA is an antigen present on both tumor cells and normal cells. This includes embryonic proteins, glycoprotein antigens, squamous cell antigens, among others, frequently employed in clinical tumor diagnostics. TSA is a neoantigen that is only expressed on the surface of certain tumor cells but not on normal cells, so it is also called unique tumor antigen, an abnormal antigen that can be recognized by immune cells. At present, more and more tumor antigens have been identified, such as oncogene products HER-2/neu, non-mutated proteins expressed only in cancer cells and testis (MAGE, BAGE family), etc [6]. Some antigens have high immunogenicity, which can induce the body to produce corresponding antibodies and cytotoxic T cell (CTL) response, and induce the body to reject the tumor.

Anti-tumor immunity is mainly mediated by $CD8^+$CTL, and the full activation of CTL needs at least two signals [7]. The first signal is provided by major histocompatibility complexes (MHC), antigenic peptides and T cell receptors on the surface of antigen presenting cells (APC). The second signal involves a co-stimulatory signal provided by the co-stimulatory molecules such as the B7 molecule. Tumor cells evade immune recognition by reducing the expression of tumor antigen, reducing the expression of MHC and co-stimulatory molecules on the cell surface through antigen modulation, and produce inhibitory cytokines to inhibit the function of the immune system and induce immune cell apoptosis. Therefore, the development of tumor vaccine should be considered from the two aspects of

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how to improve the immunogenicity of tumor cells and how to enhance the ability of immune cells to recognize tumor cells.

3. Therapeutic tumor vaccines

3.1. Peptide Vaccine

Peptide vaccine uses TSA epitopes as vaccine antigen components to identify, select and construct candidate antigenic epitopes or polypeptide vaccine antigens. The peptide vaccine synthesized by using the peptide sequence of tumor antigen epitopes can mimic the tumor antigen determinant recognized by T cells. Without APC presentation, it can directly bind to MHC molecules, activate T lymphocytes and induce strong specific anti-tumor cellular immunity. At present, the main research and development direction of peptide vaccines is to develop polyvalent vaccines. For example, seviprotimut-L, a polyvalent melanoma vaccine developed by Polynoma, contains multiple melanoma antigens such as MAGE-A3, MelanA, and gp100. Clinical trials have shown that the vaccine can induce humoral and T cell immune responses at the same time, improving patients' progression-free survival (PFS) [8].

The stability, immunogenicity, and targeting of peptide vaccines can be improved by designing appropriate delivery systems to assist in vaccine delivery. In the past decades, a series of nanoparticles with different sizes have been used as vaccine carriers to stabilize and deliver adjuvants and antigens, thus forming a suitable vaccine adjuvant delivery system (VADS), including liposomes, inorganic or metal nanoparticles (iNP), virus-like particle (VLP), emulsion, immunostimulating complex (ISCOM), polymer nanoparticle and self-assembled peptide nanoparticle (SAPN) [9]. The nanoparticles themselves or after surface modification can enhance the targeting of the polypeptide vaccine and help the vaccine enter the targeted cells, and some nanoparticles can also trigger the immune response by themselves [10]. Studies have shown that a variety of metal ions have prominent regulatory roles in activating innate immune stimulation and overcoming acquired immune tolerance [11]. Nano-adjuvant delivery system based on metal nanoparticles can improve the targeted accumulation of metal ions in tumor tissues or lymphatic organs, so as to effectively induce immunogenic death of tumor cells or directly activate antigen-presenting cells to initiate anti-tumor specific immune response [12].

There are many advantages of peptide vaccine: the molecular weight of antigen peptides in vaccine is small, easy to synthesize; the polypeptide has good stability, the preservation condition is not high, and can be stored for a long time. And the low cost of producing peptide vaccine is conducive to the large-scale production of peptide vaccine. However, peptide vaccine has the disadvantage of poor immunogenicity. This problem can be enhanced or even regulated by screening carriers with appropriate size, shape and composition to enhance and even regulate the intensity of immune response caused by peptide vaccines.

3.2. Cell Vaccine

The principle of tumor cell vaccine is to treat the own or allogeneic tumor cells by physical, chemical or biological methods. On the basis of retaining its original immunogenicity, tumor cell vaccine is obtained by changing or eliminating its tumorigenicity, and then injected into the body for active immunity [13]. However, the autoimmunogenicity of most tumor cells is low, and tumor cell vaccine alone cannot effectively activate the anti-tumor immune response. Therefore, it is necessary to genetically modify tumor cells and add or increase the secretion of cytokines that induce immune response, such as GM-CSF, cytokines interleukin-2 (IL-2), etc. [14,15]. This is done in order to enhance the immunogenicity of the vaccine. At present, the most researched is the cell vaccine expressing GM-CSF. For example, the tumor cell vaccine GVAX expressing GM-CSF can significantly promote the antigen presentation, activation and survival of DC, and has shown good efficacy in various mouse tumor models [16]. In tumor immunotherapy, new combination therapies can produce greater anti-tumor effects or fewer side effects than monotherapies. GVAX is mainly used in combination with other drugs to improve efficacy, such as in combination with anti-PD-1 [17].

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The potential problem with tumor cell vaccine is that it is difficult to culture some tumor cells in vitro for a long time. At the same time, whether there is a risk of carcinogenesis of oncogenes and tumor viruses carried by tumor cells, and whether vaccine may produce immune tolerance to their own tumor antigens should also be considered.

3.3. DC Vaccine

Dendritic cell (DC) classified as an antigen-presenting cell (APC), holds a significant function in initiating immune response and maintaining immune tolerance, and acts as a bridge between innate immunity and adaptive immunity. DC has the ability to activate Naive T cells, CD4+T and B cells [18]. It is an effective antigen presenting cell that can help the immune system recognize tumor cells. Its function is to recognize, process and present exogenous antigens to T cells. Therefore, it can decompose tumor cells into peptides and present peptide antigens to T cells, so that immune cells can easily recognize and attack tumor cells.

Early DC vaccine used antigens in the form of proteins or long peptides plus adjuvants that promote DC maturation [19]. However, the targeting of traditional DC vaccine is poor. In order to enhance its targeting, it is necessary to find and use vectors with high affinity for DC or to find new adjuvants about DC. The principle of targeting DC vaccine is that by coupling or fusing antibodies from DC surface receptors with antigens that need to be delivered, the vaccine itself can be taken, processed and presented by DC more efficiently. These targeted receptors include DEC205, Clec9A, Clec12A, CD11c, CD40, CD11b, etc. [20].

In addition, the in vitro induction of DC loaded antigen after the transfusion of DC vaccine in the prevention and treatment of infectious diseases and malignant tumors has also attracted much attention. In April 2010, the FDA approved the world's first DC vaccine "Sipuleucel-T" for clinical use in the treatment of metastatic prostate cancer [21]. Sipuleucel-T is used to collect blood from patients, enrich DC precursor cells by leukocyte removal, incubate with prostate acid phosphatase (PAP) for 36~44h in the presence of GM-CSF, and transfuse DC back to patients after loading antigen. Although the overall efficacy of the vaccine did not achieve the purpose of curing the disease, it is of great significance for the development of DC vaccine.

As the only antigen presenting cell that can activate initial T cells, DC plays an important role in the immune process of the body. However, at present, the understanding of DC function, disease mechanism and target is limited. If DC vaccine wants to make a breakthrough, these basic theories need to be discussed more deeply and in detail. In addition, due to the rarity of DC in the human body and immune rejection among different individuals, the preparation of DC vaccine requires personalized and exclusive customization, which brings many problems to the popularity of DC vaccine, such as high price, difficult industrialization and so on. In summary, DC vaccine is a new type of vaccine that has attracted much attention in recent years. It can prevent and treat diseases from the perspective of antigen presentation, and has great potential for development.

3.4. Nucleic Acid Vaccine

Nucleic acid vaccines are divided into DNA vaccines and mRNA vaccines, both of which are composed of vectors and genes encoding tumor antigens [22].

3.4.1. DNA Vaccine. DNA vaccine uses small circular DNA molecules of plasmids carrying genetic information of pathogens to induce specific immune responses. After vaccination with DNA vaccine, the plasmid enters the human cell, passes through the cytoplasm, passes through the nuclear membrane, and enters the nucleus; the corresponding enzyme in the nucleus converts the exogenous gene carried by the plasmid into mRNA, and then mRNA enters the cytoplasm, translates and synthesizes into proteins, and the immune system recognizes exogenous proteins and initiates immune response [23]. DNA vaccine shows a good prospect of clinical application in the preliminary study of prostate cancer and other tumors. MVI-118 (pTVG-AR) is a DNA-based vaccine. The results of a phase I trial showed that

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pTVG-AR treatment is safe and immunogenic in patients with metastatic castration-sensitive prostate cancer and can delay castration resistance [24].

DNA vaccine has the advantages of low cost, easy to make, large-scale production and stable in vivo and in vitro. The disadvantage of DNA vaccine is that foreign genes into the host nucleus may be integrated into the genome after vaccination, thus changing the genetic information of some cells, resulting in gene mutation and bringing disease risk to patients [25]. In addition, plasmid DNA immunization may induce the production of antibodies against plasmid itself, thus reducing the immune effect.

3.4.2. mRNA Vaccine. The mRNA vaccine is to introduce the mRNA encoding the antigenic protein into the body, and then translate it to produce the antigenic protein, thereby activating the immune response. The mRNA vaccine needs to go through several steps: first, the mRNA vaccine needs to be encapsulated by a suitable carrier and delivered to the patient; second, the mRNA vaccine protected by liposomes is endocytosed into the cell; finally, the mRNA is released in the cytoplasm and use various organelles and various related enzymes in the cytoplasm to translate and express tumor antigen proteins to trigger the body's immune response [26].

mRNA vaccine has the advantages of simultaneous expression of multiple antigens, high in vivo expression efficiency, short survival time, no host infection, non-integrated expression, no insertion mutation, etc., so it has good safety. In addition, mRNA vaccines have the advantages of high production efficiency, low cost, and easy to scale preparation [27,28]. Therefore, mRNA tumor vaccines show a very good development prospect. So far, no mRNA tumor vaccine has been approved for market in the world, but the competition in this field is extremely fierce, and many companies at home and abroad have laid out in this field. With the rapid increase in research and development investment and continuous technological breakthroughs, mRNA tumor vaccines will open a new era of tumor immunotherapy.

3.5. Neoantigen Vaccine

Neoantigen is a non-self protein with individual specificity, which is produced by non-synonymous mutations in the genome of tumor cells [29]. Compared with TAA, tumor neoantigen has obvious advantages in activating the immune system - it is only specifically expressed in tumor cells but not in normal cells, and it can be prepared as a vaccine to induce stronger tumor-specific T cell immunity reaction. The principle of neoantigen vaccine is to find the epitope produced by tumor mutation, synthesize it in vitro, and then introduce it into the body to activate the specific anti-tumor immune response [30]. In addition, the tumor-specific immune response induced by neoantigen vaccine will persist, generate long-term immune memory, and inhibit tumor recurrence and metastasis after treatment [31]. DCs based neoantigen vaccines have been explored in several clinical studies. Carreno et al. [32] demonstrated a significant increase in the breadth and diversity of neoantigen specific T cells induced by neoantigen DCs vaccine in patients with stage III melanoma. At present, neoantigen vaccine has become a hot direction in tumor immunotherapy.

4. Conclusions

Tumor immunotherapy is another method to treat tumor after radiotherapy, chemotherapy and surgical treatment, and it has been recognized as the most promising tumor treatment method. And tumor vaccine shows great potential in tumor immunotherapy. The research and development of tumor vaccine has experienced decades. Although there are some products on the market, the overall progress is still slow, and there are still many problems to be solved urgently. The core issues of developing anti-tumor vaccine mainly include how to overcome the immune evasion of tumor, induce targeted cellular immunity, enhance the immunogenicity of vaccine and improve the safety of anti-tumor vaccine. With the continuous breakthrough of immunology and precision medicine technology, and the cross-integration of immunology and biotechnology, materials science, pharmacy, chemistry, etc., new antigen vaccines and mRNA vaccines have gradually moved from theoretical research to clinical

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practice, and have shown good therapeutic potential, and more and more enterprises have poured into the field of tumor vaccines.

To sum up, despite the twists and turns in the development of tumor therapeutic vaccines, there are still many challenges, and there remains considerable distance to cover prior to achieving widespread clinical implementation. However, it is believed that with the breakthrough of key science and technology and the increasing investment in research and development, the development of tumor therapeutic vaccine will finally usher in the dawn and bring hope to the majority of tumor patients.

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