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Therapeutic cancer vaccines: From initial findings to prospects

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ABSTRACT

With the approval of the first therapeutic cancer vaccine by US Food and Drug Administration, numerous therapeutic cancer vaccines have been under clinical trials with an inspiring antitumor immune response in cancer patients. Though there is no therapeutic cancer vaccine showing clinical efficacy in phase III trials, recent advances in personalized cancer vaccine based on neoantigens have emerged as an efficient way to induce tumor regression. In this review, we discuss the selection methods of tumor specific antigen and mainly focus on the development of therapeutic cancer vaccine strategies. Besides, we highlight the newly developed personalized cancer vaccine as a novel therapeutic approach for cancer patients. Finally, we outline the recent development of therapeutic cancer vaccine in clinical trials.

1. Introduction

Immunotherapy has become an effective way to combat cancer, which can be combined with surgery, chemotherapy and radiation therapy. As one of the most developed part of immunotherapy, therapeutic cancer vaccines achieve tremendous scientific advances, especially the development of personalized cancer vaccines [1]. Unlike the prophylactic vaccines which are used for the prevention of disease from healthy individuals like hepatitis B virus and human papilloma virus vaccines, therapeutic cancer vaccines utilize tumor antigens to stimulate the active immune of cancer patients to fight against cancer.

In the early studies of therapeutic cancer vaccine, most of researches concentrate on the advances of vaccines for patients with melanoma. In 1988, Mitchell et al. started to use allogeneic melanoma lysates together with an adjuvant, which prove to be a useful therapy with small toxicity [2]. Pioneered by Mitchell, an allogeneic melanoma cell lysate vaccine called Melacine® was produced with confirmed ability of antitumor activity in patients with metastatic melanoma [3]. With the improvements of science and technology, more lights shed on the development of dendritic cell (DC) vaccine, peptide vaccine and genetic vaccine [4–6]. Between 1995 and 2004, NCI Surgery Branch used 541 cancer vaccines treating with 440 patients who had metastatic cancer. The study mainly included peptide and viral vaccines along with adjuvants like GM-CSF or IL-12, which achieved predominant effect on those patients [7].

More lately, progression in therapeutic cancer vaccines is on the basis of increasing phase II or phase III clinical trials [8]. In 2010, the U.S. Food and Drug Administration (FDA) first approved the therapeutic cancer vaccines PROVENGE for patients with castration-resistant prostate cancer [9]. This inspired the research on other similar products like cabazitaxel [10]. However, the monotherapy of therapeutic cancer vaccines did not show obvious advantages. Therefore, combination of vaccines with other therapies such as immune checkpoint blockade, chemotherapy and adoptive cell transfer has shown more efficacy than monotherapy of vaccine [11]. Recently, mutation-associated neoantigens have been identified to activate tumor-infiltrating lymphocyte and induce tumor regressions [12,13], indicating the potential role of neoantigens in conducting vaccines to treat cancer patients. More inspiringly, personalized cancer vaccine has achieved great success in clinical trials thanks to the development of discovering tumor neoantigens [14] The timeline for the history of cancer vaccine development is shown in Fig. 1.

In this review, we discuss from the selection of tumor antigens to three main types of therapeutic cancer vaccine based on tumor antigens, including dendritic cell vaccines, peptide vaccines and genetic vaccines. And we explore the latest advances of cancer vaccines in

Abbreviations: FDA, US Food and Drug Administration; BCG, Calmette and Guerin; DC, dendritic cell; APCs, antigen-presenting cells; TSAs, tumor specific antigens; TRA, tumor rejection antigen; gp96, glycoprotein of 96 kDa; CTLs, cytotoxic T cells; SEREX, serological analysis of antigens by recombinant cDNA expression libraries; SD, stable disease; PBMCs, peripheral blood mononuclear cells; TAAs, tumor associated antigens; SLP, synthetic long peptides; PPV, personalized peptide vaccine; CRT, chemoradiation therapy; TLR, toll-like receptor; PD-1, programmed death-1; CTLA-4, cytotoxic T-lymphocyte antigen 4; TMB, tumor mutation burden; T-VEC, talimogene laherparepvec; MDSCs, Myeloid-derived suppressor cells

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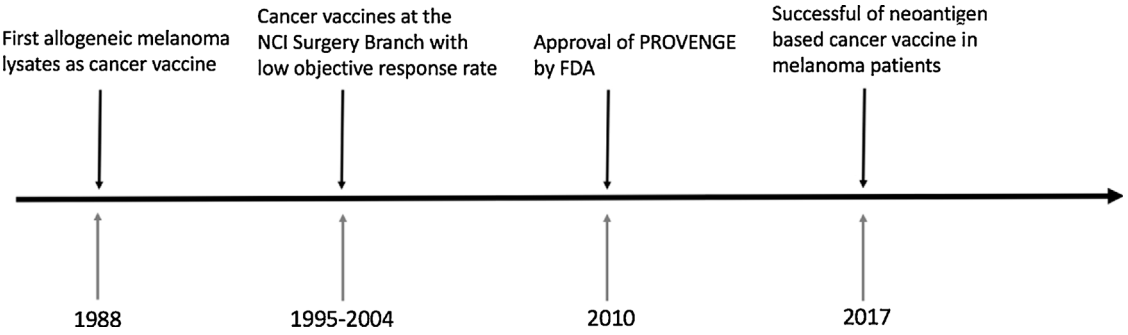

Fig. 1. Timeline for the history of cancer vaccine development.

clinical research to provide future directions for the better development of cancer vaccine.

2. Screening for tumor antigens

The cancer immunotherapy is based on tumor antigens and tumor specific T lymphocytes which can recognize tumor antigens presented by antigen-presenting cells (APCs). Therefore, it's important to identify tumor antigens for the development of optimal cancer vaccines. Tumor antigens can be classified into tumor shared antigens and tumor specific antigens (TSAs). Shared antigens mainly include tissue differentiation antigens, viral antigens and tumor germline antigens [15]. TSA is personalized antigens or neoantigens that are the product of somatic nonsynonymous mutations and more specific to tumor cells compared to shared antigens [16]. With the improvement of technology, more and more tumor antigens are found.

One of the major early achievements in screening tumor antigens is the identification of tumor rejection antigen (TRA), which are confirmed in tumor graft rejection tests [17,18]. The TRAs are specific for tumor cells of the host versus normal cells, inspiring scientists to identify for cancer immunotherapy. Early method of identifying TRA are biochemical methods. Ullrich et al. purified a TRA by using biochemical fractionations from a methylcholanthrene-induced sarcoma, Meth A [19]. This antigen is identified to be a heat shock protein. Meanwhile, Srivastava et al. used chemically induced sarcoma CMS5 fractions isolating a glycoprotein of 96 kDa (gp96), which can also be isolated from Meth A with specific immunogenicity. However, these proteins have the same cDNAs, so there is no basis for the specificity of these antigens [20]. Therefore, a direct genetic approach is needed for interpreting the cellular genome of tumor antigens. Boon identified a gene encoding antigen MZ2-E by the approach that transfection of cDNA of cells expressing the relevant antigen, after which transfectants are identified by specific anti-tumor cytotoxic T cells (CTLs) [21]. With a similar approach, Rosenberg isolated a gene that encoded a melanocyte lineage-specific protein [22]. The studies of Boon and Rosenberg are seen as the landmark of antigen-specific cancer immunotherapies. Tandem mass spectrometry is used to identify peptide epitopes presented by HLA molecules [23]. However, it requires a custom-tailored equipment and adequate present peptides.

Due to the difficulties of prior availability of cancer cell restricted T cells that are able to recognize tumor antigens, in vitro sensitization techniques are developed that are used to develop T lymphocytes against candidate antigens. The T cells present reactivity of recognizing intact cancer cells, implying the candidate proteins like gp 100 are considered to be tumor antigens [24]. The other approach called serological analysis of antigens by recombinant cDNA expression libraries (SEREX) is also developed [25,26]. This method has been used to identify tumor antigens, such as NY-ESO-1, NY-CO-37 [27,28].

The identified tumor antigens are mainly involved in shared antigens with limited cancer vaccine efficacy. However, TSAs are more important than TAAs in cancer immunotherapy because TSAs are more unique in different types of cancer than tumor shared antigens and are possible targets for personized cancer vaccine. The early strategy for TSAs is HSP, as briefly mentioned above. HSP is an intracellular molecular chaperones that can display polypeptide-binding activity. Together with its ability to internalize into antigen-presenting cells and deliver antigens to them, HSP can serve as an extraordinary ability of personized cancer vaccine [29]. The early clinical experience of HSP in cancer immunotherapy utilized gp96-peptide complexes isolated from patients' tumor as a personized vaccine that contained a TSA repertoire of each patient, which proved to be feasible in melanoma patients [30]. With the development of cancer genome sequencing techniques, more attentions are paid to TSAs with somatic mutations [31,32]. By comparing tumor and normal DNAs using whole exome sequencing, somatic mutations are identified. Then, using the exome sequencing data and the transcriptome data from tumor RNA sequencing, predicted neoantigens and possible affinities to HLA molecules are acquired by computer algorithms [33]. The predicted TSAs are first identified and validated in melanoma and sarcoma in a relative short time compared with the traditional T-cell cloning method [34,35]. More recently, a mutant in ERBB2 interacting protein identified as a cancer neoantigen by whole-exomic sequencing has showed a therapeutic effect on personalized adoptive cell therapy [36]. The techniques enable to discover potential patient–specific therapeutic neoantigens [37]. These neoantigens now can be used as personalized cancer vaccines and prove to have clinical benefits in melanoma patients [1,38]. Besides, the proteomic approach becomes an emerging method to identify potential tumor antigens. The serological proteome analysis has been used to identify tumor antigens like triosephosphate isomerase in lung cancer, breast cancer, colorectal cancer and prostate cancer [39–42]. Another proteomic approach called mass spectrometry is emerged as a useful tool for the discovery of neoantigens. This method uses immunopeptidomics analysis directly identifying presented neoantigens, which is more precise than the prediction technologies [43]. Antigens and techniques discussed in this chapter are summarized in Table 1.

The tumor antigens must prove to be immunogenicity before being developed to identify cancer vaccine. Therefore, the T cell assays are used to validate the immunogenicity of identified tumor antigens. In short, tumor antigens or cancer vaccines are released from tumor cancer cells or injected into the human body. Then the tumor antigens or vaccine antigens are successfully captured by DCs. After successfully activating DCs, DCs move to the lymph node and present or tumor antigens or vaccine antigens to T cells, where the T cells are activated and differentiated into effector T cells and memory T cells. Then, effector T cells and effector memory T cells go through the blood vessel to tumor microenvironment. In this place, reactivated T cells conducted the tumor antigen specific immune responses that lead to death of cancer cells. The immune mechanisms underlying tumor immunity that successfully induce anti-tumor T cell responses in human body are shown in Fig. 2.