Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

The Role of Epidemic Tumor Vaccine in Cold Tumors to Hot Tumors

Yanxi Chen*

Chengdu Foreign Languages School, Chengdu, China

*Corresponding author: chenyx@ldy.edu.rs

Abstract. Compared with hot tumors, cold tumors are a more difficult problem at present. Because cold tumors lack in congenital immunity, it is difficult for ordinary immune examination inhibitors to work. Therefore, how to "ignite" cold tumors as hot tumors is the focus of the current research. At present, scholars have proposed different and corresponding methods for various causes of T cell immunodeficiency. Among them, tumor vaccines stand out from the principle of activating the immune response of T cells and NK cells, and is currently generally recognized as a new therapy and research hotspot with strong anti-cancer activity. By classifying the target sites of tumor vaccines, they can be divided into tumor-related antigen (TAAs) vaccines and new antigen (TSAs) vaccines. Both vaccines have shown significant effects in activating T cells and NK cells. In terms of the current development status of the two vaccines, more and more research teams have invested in the research of TSAs vaccines, and many teams still insist on the research of TAAs vaccines. Although these two vaccines have their own difficulties to overcome, they still have made great contributions to the development of tumor treatment research, and both have advantages and broad prospects that cannot be reached by other methods. It is believed that no more effective tumor vaccines have been put into clinical trials.

Keywords: Tumor vaccine; cold tumors; hot tumors.

1. Introduction

At present, the hot spot of scientific research still focuses on tumor treatment. Based on the current understanding of tumors, tumors can be divided into two categories: hot tumors and cold tumors. Among them, cold tumors are divided into immune rejection tumors and immune desert tumors. Due to the lack of innate immunity, it is difficult to be recognized and killed by immune cells, and the immune checkpoint inhibitor ICIs are also difficult to play a role [1]. The cause of its immune deficiency may be (1) lack of tumor-related antigens (2) deficiency of antigen-presenting cells APCs (3) deletion of T cell activation (4) damage to the transport of T cells to the tumor [2]. Therefore, how to convert cold tumors into hot tumors is also a research hotspot in tumor treatment. In response to these problems, scholars have proposed different methods, such as epigenetic induction, NK therapy, chemotherapy and radiotherapy combination therapy, etc. Among them, the tumor vaccine, which is based on the principle of activation of the immune response of T cells and NK cells, is currently considered to be an emerging therapy with strong anti-cancer activity [3]. According to the classification of target sites, tumor vaccines can be divided into tumor-related antigen (TAAs) vaccines and new antigen (TSAs) vaccines. Both of these show significant effects in the activation of T cells and NK cells [4]. Among them, TAAs vaccines have strong immunogenicity, but they need to face autoimmune problems, which may produce some side effects. TSAs vaccines have high specificity, which can avoid autoimmune problems, but the search for new antigens is a difficult point that needs to be overcome. The mutation of new antigens is high and the immunogenicity of most new antigens is low, resulting in the treatment effect of some new antigens not particularly ideal. However, the tumor vaccine is of indelible importance to tumor treatment, and it also has incomparable superiority over other methods. Therefore, the research on tumor vaccines is very important. Therefore, at present, more and more research teams have set the research direction to the search and design of TSAs vaccine antigens, but many teams still insist on the research of tumor-

related antigens. Both vaccines have achieved extraordinary results [5-7]. Some new research results show that scientists have found highly specific TAAs and relatively stable and immunogenic TSAs.

2. Cold Tumor

2.1. Characteristics of Cold Tumors

The treatment of tumors has always been on the hot list of scientific research. In addition to benign and malignant, tumors are also divided into cold and hot. Thermal tumor refers to the relatively active immune cells, the internal environment is infiltrated by a large number of T cells, and the confrontation between tumor cells and immune cells is relatively active. Thermal tumors include immune inflammatory tumors. Immunosuppressant detection for immune cells of thermal tumors can be detected through PD-1 and PD-L1 inhibitors and good results have been achieved. Cold tumors are divided into immune rejection tumors and immune desert tumors, including glioblastoma, ovarian cancer, prostate cancer, pancreatic cancer, etc. In addition, cold tumors have no immunogenicity. They lack innate immunity. Immune cells and cancer cells do not have much confrontation, so it is difficult to be recognized and killed by immune cells, and the immune checkpoint inhibitor ICIs are also difficult to play a role [1]. However, today's experimental research has found that cold tumors can be converted into hot tumors in some ways for better treatment (Figure 1).

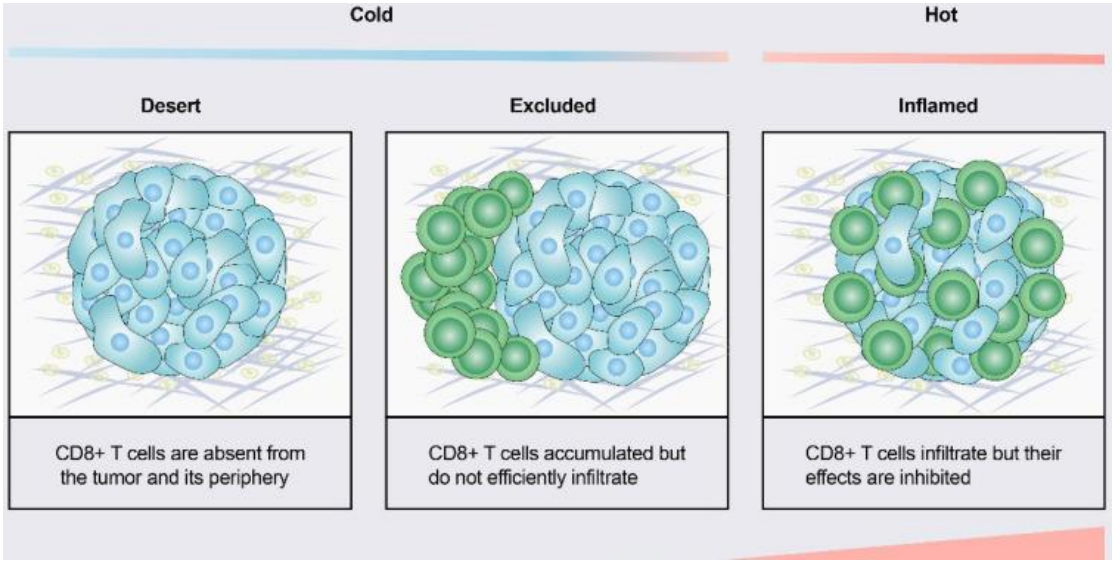

Fig. 1 The difference between cold tumors and hot tumors [1].

In the process of tumor immune activation, the deletion of T cells in cold tumors leads to its congenital immunodeficiency, which is a difficult point that needs to be overcome. The reasons for its immunodeficiency may be as follows: (1) Lack of tumor-related antigens (2) APCs defect in antigen-presenting cells (3) Loss of T cell activation (4) Damaged transportation of T cells to the tumor [2]. Therefore, the hot spot of the current research focuses on how to ignite cold tumors into hot tumors for these pathways, so as to improve the therapeutic effect of ICI [8, 9].

2.2. Different Treatment Ideas for Cold Tumors

At present, the popular directions are as follows: (1) Use drugs that can induce epigenetics, such as DNA methyltransferase inhibitor DNMTi, to enhance the expression of tumor antigens [10](2) Use NK therapy, such as in vitro activated natural killer cells, to improve tumor antigen deficiency or antigen presentation mechanism [11]. (3) For The activation and deletion of T cells can be restarted or synergistic with a small number of activated T cells [12] by radiotherapy, chemotherapy [13], PRR or CD40 agonists [14,15], oncolytic viruses [16], tumor vaccines and other methods (4) If T cells are transported to the tumor, TGF-β receptor antagonists and PD- 1 Antibody combined use, so as to jointly induce T cells to recruit tumors [17], and antiangiogenic drugs can also be used to increase the

infiltration of T cells in tumor cells. (5) Develop specific immune cytokines that combine tumor antigen antibody fragments with modified cytokines to specifically activate the immune system in the tumor and reduce Side effects of the whole body [18].

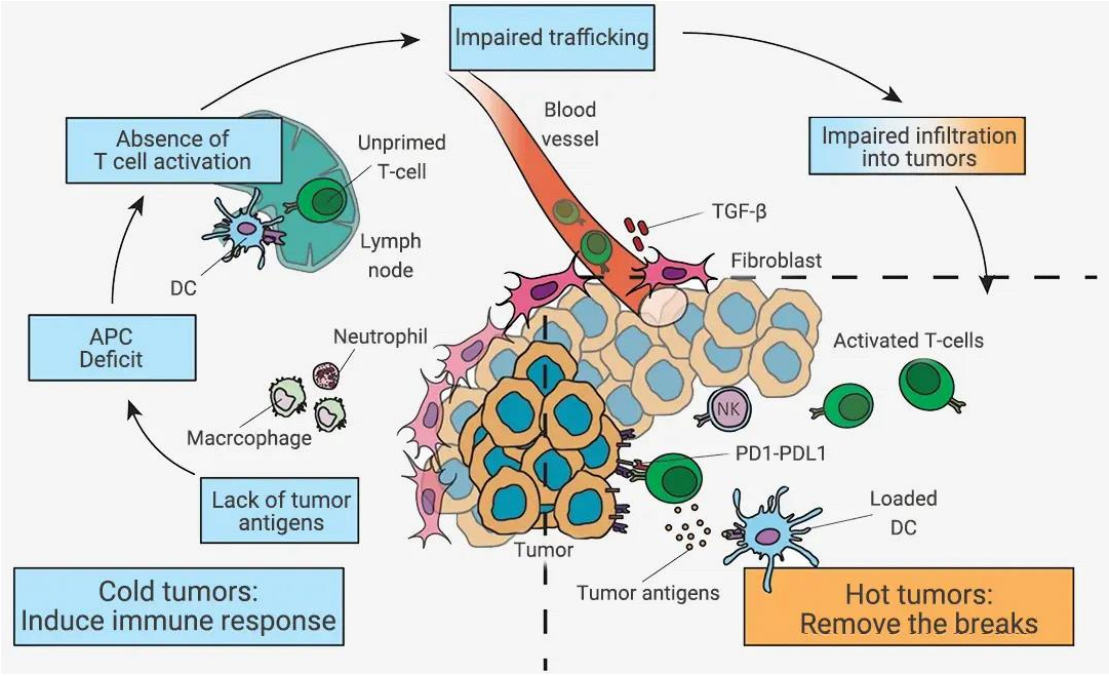

Fig. 2 Cold tumors turn into hot tumors [2].

Among the above methods, tumor vaccine is a new therapy that is considered to have strong anti-cancer activity (Figure 2). It mainly realizes the conversion of cold tumors to hot tumors by activating the immune response of T cells and NK cells [4]. Tumor vaccine can expand the number of specific T cells and increase the transportation of T cells to the tumor area [19].

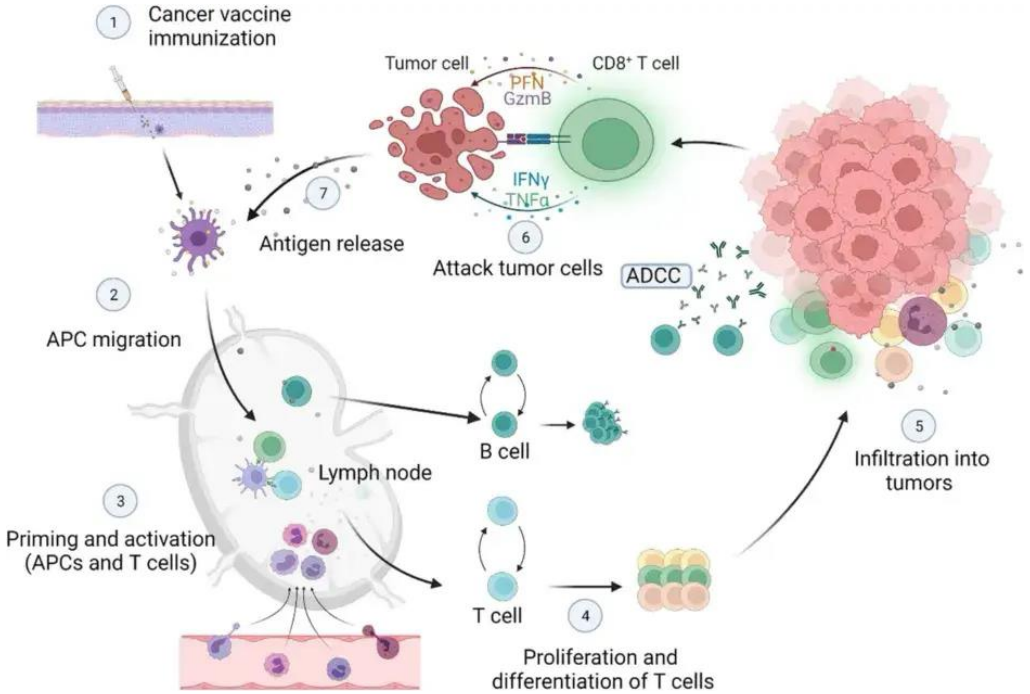

Fig. 3 Tumor immune cycle induced by tumor vaccines [20].

According to the target site of the tumor vaccine, it can be divided into tumor-related antigen (TAAs) vaccine and new antigen (TSAs) vaccine. TAAs is a self-antigen that is prioritized or abnormally expressed in tumor cells, but it may also be expressed to a certain extent in normal cells (Figure 3). TSAs is composed of antigens expressed by carcinogenic viruses and new antigens encoded by cancer

mutations. If they are not expressed or rarely expressed in normal cells, they are really tumor-specific antigens [21].

3. Tumor Vaccine

3.1. The cutting-edge Development of TAAs Vaccine

Recently, Kai W.Wucherpfenning, a famous oncologist at Harvard University, has developed a new TAAs vaccine at the Dana-Farber Cancer Institute in the United States. This vaccine can enhance the presentation process by inhibiting the degradation of the key protein MICA/B protein during antigen presentation (Figure 4). The most important thing is that this vaccine can enhance the immune response of NK cells and T cells, coordinate the joint attack of NK cells and CD4+T cells on tumors, and reduce the immune escape of tumors, thus realizing the conversion of cold tumors to hot tumors and greatly enhance the anti-tumor effect [4].

This vaccine is designed for the highly conservative a3 domain in MICA/B, which is the site of protein dissolution and shedding, and is designed to induce tumor immunity of T cells and NKI cells. MICB-vax induces high-titer antibodies, which strongly mark B16F10 (MICB) tumor cells but do not control B16F10 tumor cells. The vaccine also induces the response of CD4+T cells and CD8+T cells to MICB [4].

In order to study the mechanism of action of vaccines, the controlled trial conducted in the melanoma mouse model was conducted to characterize tumor-invasive immune cells through flow cytometry (FACS) and scRNA-seq. Multiple effector lymphocyte groups of MICB-vax immune mice were strongly enriched. Compared with mice receiving Ctrl-vax (control group), CD4+T cells were enriched by 17.9 times and NK cells were enriched by 38.9 times. In addition, in MICB-vax immune mice, CD4+ and CD8+T cells showed enhanced functions. scRNA-seq analysis showed that the immune infiltration of all control groups was mainly medullary cells, while the CD45+ immune cells in the experimental group that received MICB-vax+ potentomycin were mostly T cells and NK cells. These experimental data show that MICB-vax induces a variety of effect T cells and NK cell groups to be effectively recruited into highly activated tumors, thus promoting the conversion of cold tumors to hot tumors [4].

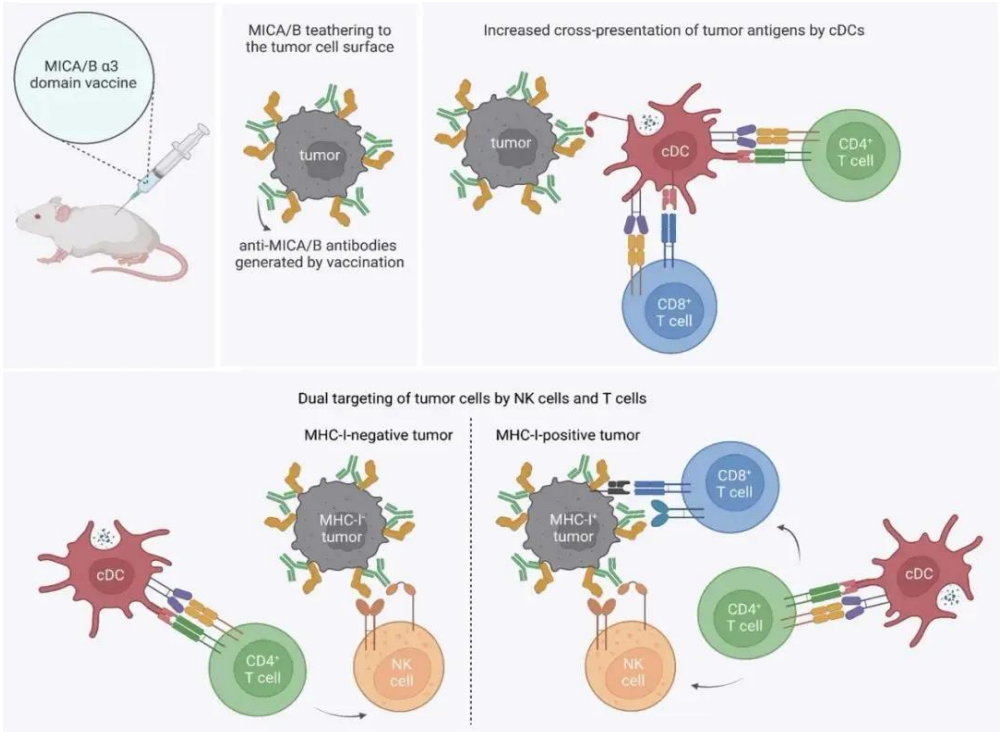

Fig. 4 Mechanism of action of MICA/B-vax-induced antibodies [22].

3.2. Cutting-edge Development of TSAs Vaccine

In May 2023, the Vinod P. Balachandran research team of the Sloan-Caitlin Cancer Center in the United States published a research paper in Nature. The study developed an individualized mRNA vaccine scheme - autogene cevumeran (BNT122), an mRNA vaccine made of patients' own 20 new tumor antigens, combined with PD-L1 and four chemotherapy drugs to treat patients with pancreatic duct adenocarcinoma [23].

The team adopted a new individualized treatment plan in the first phase of clinical trial, the core of which is a new antigen vaccine made of mRNA-liposome nanoparticles: (1) Atezolizumab, an anti-PD-L1 drug, was given in the 6th week (2) Individualized new Antigen vaccine (3) uses a four-drug chemotherapy regimen in week 21. The clinical results of the first phase showed its excellent therapeutic effect: there was no recurrence within 18 months, and vaccine-induced new antigen-specific T cells (responders) were detected in the patient's body, which activated the immune response of T cells and promoted the conversion of cold tumors to hot tumors [23].

Next, in order to detect the antigenic immunogenicity of its vaccine, the research team used ELISpot to detect the immune response of T cells. 8 out of 16 vaccinators produced T-cell responses. Half of these responses are for more than one new antigen. Before vaccination, T cells did not respond to these new antigens, and after vaccination, it was detected that 100 to 3,000 cells in less than one million peripheral blood mononuclear cells (PBMCs) responded. Therefore, in most PDAC patients, it is their own new antigen that induces new specific T cells, and within two years after surgery, a large number of long-term specific CD8+T cells are found in the patient's body. It promotes the conversion of cold tumors to hot tumors [23].

In addition, some other new antigen vaccines have also been put into use and have shown good results. For example, GEN-009 is a personalized new antigen vaccine, which has been tested in 8 solid tumor patients with a high risk of recurrence. At present, it has been found that at least one antigen in all patients has peripheral blood CD4+T cells and CD8+ reactions. 99% of peptides stimulate the immune response of T cells and promote the conversion of cold tumors to hot tumors. RO7198457 is a personalized new antigen vaccine encoding up to 20 new antigens. In the Ib study, a joint trial of atezolizumab was conducted on 132 patients with advanced solid tumors. The results showed that 77% of patients detected the response of circulating T cells to new antigens with a median of 2.6 in vitro. Vaccine-specific CD8+T cells of more than 5% were detected in peripheral blood, which induced the specific immune response of T cells and promoted the conversion of cold tumors to hot tumors [24].

4. Conclusion

Both TAAs vaccine and TSAs vaccine have very significant effects in the process of converting cold tumors to hot tumors, which are of great significance to the development of tumor treatment, but there are also some defects respectively. For TAAs vaccines, because most of these antigens are also expressed in normal cells, immunotherapy targeting this type of antigen usually faces autoimmune problems, that is, the immune system cannot judge whether it is normal cells or cancer cells simply by the amount of expression, so it will inevitably kill normal cells. The side effects of. We expect to find more specific antigens as targets, or modify tumor antigen vaccines through gene editing and other means to avoid its killing side effects on normal cells. For TSAs vaccines, the selection and transformation of new antigens are the key to technological breakthroughs. As we can see, most TSAs vaccines are made of a variety of antigens, or even dozens of antigens, or can be combined with other methods for combined treatment to achieve relatively good results. It can be seen that most new antigen sites have extremely low immunogenicity, and antigen sites with immunogenicity also have different performance and effects in different patients, which leads to the extreme instability of TSAs vaccine. Therefore, I think we should expect to find more stable, immunogenic and wider range of TSAs, or find some signaling pathways to respond to the immune response of TSAs that can have a cascaded amplification effect. At present, combined treatment is also a good choice, with certain superiority, applicability and good prospects.

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