MEDS Chinese Medicine (2021)
ISSN 2616-1753 Volume 3 Issue 2
DOI: 10.23977/medcm.2021.030207
Clausius Scientific Press, Canada

Research Progress of Tumor Cell Vaccine

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Keywords: Tumor cell vaccine, Progress, Clinical effect, Tumor immune escape, Adverse reactions

Abstract: With the rapid development of biotechnology in recent years, the research of tumor vaccine has made gratifying progress. In recent years, the research of tumor cell vaccine has been paid more and more attention. In 1893, Coley used the bacterial extract of Dandu patients to stimulate tumor specific immune response and treat malignant tumor. Subsequently, Corynebacterium and BCG were widely used as Immunoenhancers in clinical. In the 1950s, people began to study autogenous tumor vaccine. Therefore, active immunotherapy (tumor vaccine) is the fourth effective tumor treatment method after surgery, radiotherapy and chemotherapy. As active and specific immunotherapy, tumor vaccine plays an increasingly important role in clinical treatment. This paper reviews the introduction, research history, mechanism, challenges and prospects of tumor cell vaccine.

1. Introduction

Malignant tumor is one of the major diseases threatening human health and life. Its incidence rate is increasing year by year. It is a long-term and arduous task to treat malignant tumor effectively. At present, the conventional treatment of cancer surgery, radiotherapy, chemotherapy and other means can not achieve satisfactory therapeutic effect, and are accompanied by obvious toxic and side effects. Therefore, it is an urgent need to find a treatment method that can effectively control tumor growth and metastasis with less side effects. Tumor biotherapy, represented by immunotherapy, has emerged as the fourth mode of tumor therapy. In recent years, with the research progress of cell biology, molecular biology and tumor immunology, the in-depth study of tumor immune mechanism and the discovery of tumor associated antigens, active immunotherapy of tumor has attracted much attention, among which tumor cell vaccine has become one of the hot spots of tumor prevention and treatment. This article reviews the current status and challenges of whole cell tumor vaccines.

2. Introduction of Tumor Cell Vaccine

Among the tumor therapeutic vaccines, the first research is tumor cell vaccine. As early as the early 20th century, people began to use tumor cells or their cleavage products as immunogen to explore the therapeutic effect of tumor bearing body, but because of the weak immunogenicity of tumor cells, the remission rate is very low. With the development of tumor immunology and

molecular biology, gene engineering technology has been introduced into the research of tumor cell vaccine. People use retrovirus, adenovirus and other vectors to introduce foreign genes into tumor cells to improve their immunogenicity. The main exogenous genes were MHC gene, B7 gene, cytokine gene, adhesion molecule gene, etc. There are many cytokines used, such as il.2, IL-3, IL4, IL-5, IL-6, IL-7, TNF- α(TNF- α), Interferon- γ(IFN- γ), Granulocyte. Monocyte colony stimulating factor (GM CSF) and so on[1].

From the perspective of the source of tumor cells, allogeneic tumor cell lines are the most studied and applied. Although the autologous tumor cell vaccine has the advantages of the best matching with the human leukocyte antigen (HLA) of patients and the same expressed antigen, it is often unable to get enough tumor cells to immunize patients. Although allogeneic tumor cell lines can induce strong anti HLA immune response in patients, they are abundant in source and easy to obtain enough number of cells, so they are widely used. At present, many tumor cell lines have been used in I clinic. Vaishampayan et al. Used two allogeneic melanoma cell lines, cell lysate as vaccine, supplemented with immune adjuvant, monophosphate a (MPL) - lecithin. The results showed that in 39 patients, the total response rate was 10.2%, 64% of the patients' stable period was more than 16 weeks, the median time before disease progression was 8 months (6-13 months), and the remission period was significantly prolonged. The side effects were mild, including injection site pain, granuloma formation (related to immune adjuvant) and fever[2].

Compared with other tumor therapeutic vaccines, tumor cell vaccines have the strongest immunogenicity, mainly because tumor cells not only express multiple immunogenic epitopes, but also express multiple epitopes which can be presented by different HLA molecules. Many tumor cells even express a variety of different tumor associated antigen (TAA) or tumor specific antigen (TSA)[3]. The deficiency of tumor cell vaccine lies in its poor specificity. The autologous tumor cell vaccine is not easy to break through the immune tolerance, while the allogeneic tumor cell vaccine is easy to be eliminated by the body.

3. Research History of Tumor Cell Vaccine

The research of tumor vaccine has been more than 100 years old. As early as the early 20th century, some scholars proposed the idea of using active immune response to treat tumor. People realize that the important factor of tumor immunity is the existence of tumor specific antigen and the effective response of the body to tumor specific antigen. Therefore, it has begun to use tumor immune response to treat tumor[4]. In the 1960s, some scholars used tumor cells as vaccine to induce immune response to treat tumor, and achieved certain clinical effect. Since then, with the further research of tumor immune mechanism, the rapid development of molecular biology technology and the cross penetration of related disciplines, a variety of tumor cell vaccines have appeared, including the whole cell vaccine of tumor, modified tumor cell vaccine, cytokine-transfer-based tumor cell vaccine, etc. A large number of studies have been carried out on these tumor cell vaccines, mainly to animals to observe whether these cell vaccines can induce effective protective anti-tumor immune response in the body. Some of them are used as an important auxiliary means for tumor treatment in clinical trials, together with tumor surgery, chemotherapy and radiotherapy. M-vax vaccine, produced by avax in 2001, is a vaccine for the treatment of malignant melanoma, which is marketed in Australia from melanoma cells in patients. The vaccine can activate the immune system to attack cancer cells effectively by inputting the vaccine several times. The nine-year follow-up survey of dozens of advanced melanoma patients using the vaccine showed that 80% of the patients did not recur and the overall survival rate was 85%[5]. The newly approved tumor vaccines include brain cancer vaccine, cervical cancer vaccine and renal cancer vaccine. More than 20 tumor cell vaccines are undergoing phase III clinical

research on various tumor indications worldwide, and the products approved for marketing will also increase.

4. Mechanism of Tumor Cell Vaccine

Many years of studies have found that most whole cell vaccines need T cell activation to work. However, the mechanism of T cell response induced by whole cell tumor vaccine is still controversial. There are two possible mechanisms: one is the direct and endogenous MHC peptide complexes presented by tumor interact with T cells; The other is that tumor antigen is absorbed and presented to the immune system by dendritic cells, which is called “cross priming”. These two mechanisms have been confirmed by studies[6]. According to the background of tumor, some can be explained by these two mechanisms. For “cross priming”, the matching degree between MHC and APC is much higher than that between host and tumor. Antigen presenting cells capture and present antigen to CD8 + T cells through dendritic cells. In addition, cross presentation of tumor antigen will not start when tumor enters T cell region of secondary lymphoid organs to trigger anti-tumor immune response. It has been reported earlier that CD4 + T cells are also needed in some effective anti-tumor models. They used tumor cells expressing homogeneic MHC Ⅱ to directly initiate CD4 + T cell response, which in turn could induce anti-tumor immune response. Later studies also found that the above-mentioned anti-tumor effect disappeared after the deletion of dendritic cells, and MHC molecules also completely metastasized between the dead tumor cells and dendritic cells[7]. This phenomenon is consistent with the conclusion that immune response is directed against tumor MHC, and is also distinguished from the direct initiation process of immune response. However, the initiation mechanism of immune response of natural T cells to tumor whole cell vaccine remains to be studied. The above reports suggest that there may be more direct or indirect mechanisms.

5. Challenge and Prospect of Tumor Cell Vaccine

Although we have some new understanding and understanding of tumor immunotherapy in recent years, in addition to some autogenous T-cell therapy (especially effective for melanoma treatment), the clinical treatment effect of tumor cell vaccine is not satisfactory. It is undeniable that the research on tumor cell vaccine is still in the exploratory stage. Because of the different subjects or animals used by researchers, vaccine types and immune schemes, the results of the test are also very differently, especially the clinical application time of tumor cell vaccine and the combined use of radiotherapy and chemotherapy, All of these have affected the clinical application of tumor cell vaccine. Therefore, the development of a set of clinical guidelines related to the use of tumor vaccine may help to promote the clinical play of tumor cell vaccine in clinical play its due value. Some scientists have suggested that the following three areas should be improved: to find biological markers that can evaluate the immune response of the vaccine; The adjuvant is selected correctly; The combination of vaccine and chemotherapy and radiotherapy. However, some scientists believe that the whole cell vaccine is very promising in tumor immunotherapy, and it is also an important method to eliminate the bottleneck of tumor vaccine development. Because tumor whole cell is a good source of tumor related antigen, it can stimulate CTL cells and CD^{4+} helper T cells activation, and can effectively induce anti-tumor immune response. Therefore, we should learn more lessons from the past failures, focus on more methodological innovations, and believe that the whole cell vaccine will have a better future in the field of tumor treatment.

Acknowledgement

This work was supported by the Jiangsu Provincial Training Program for Innovation and

Entrepreneurship for Undergraduates(202010324021Z)

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