

Development of cell-based vaccines in cancer treatment

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Abstract. Cancer, as a serious global disease, becomes a severe threat to human life. Due to the problems of environmental pollution and life habits, many people die each year from various kinds of cancer, which also includes many young and middle-aged people. Nowadays, cancer has become one of the most concerned public health problems in the world, and the efforts and attempts to actively explore new treatments for cancer have never stopped. The creation of therapeutic cancer vaccines has solid biological and preclinical rationales, however, it has been difficult to translate this treatment approach into the clinical therapies. Immunotherapy has gained widespread attention as an emerging tool for cancer treatment. Among them, cell-based vaccines have achieved ideal outcomes in multiple tumor killings. This review introduces vaccines based on induced pluripotent stem cells (iPSC) and dendritic cells (DC), summarizes the related research progress of cell vaccines in cancer treatment and discusses the limitations of cell-based vaccines.

Keywords: Cell-based Vaccines, DC, iPSC, Cancer Treatment.

1. Introduction

Cancer cells refer to malignant cells with abnormal proliferation, loss of growth control, and biological characteristics such as invasive and metastatic properties. Different cancer cells arise from different causes and are all multifactorial, multistep, and complex processes. They are mainly divided into internal and external factors, which refer to genetic factors, immunological factors, etc., while external factors are related to life habits, environmental pollution, etc. Current clinical diagnostic methods for cancer are mainly medical imaging tests and biopsy by puncture or section.

Cancer, a disease with a high incidence rate, has plagued the global people for many years. It has been reported that enormous people develop cancer. Per year, 18.8 million new cancer cases were diagnosed in 2018 alone according to the WHO Global Cancer Observatory (GLOBOCAN) [1]. Moreover, cancer has a high mortality rate. Cancer claimed the lives of three out of every ten people who passed away too young from noncommunicable diseases [2]. Cancer is characterized by multiple occurrences, it can develop in a wide variety of tissues and cell types. Once the cancer cells spread throughout the body, the survival time of patients become very limited. Referring to the WHO's epidemiological trend of the five major causes of death from 2016 to 2060, malignant tumors will become the leading cause of death worldwide after 2030 [1].

There are numerous cancer treatments available nowadays. Surgical resection, radiotherapy, and chemotherapy, as the traditional treatment methods, are still widely used in clinical, at the same time, immunotherapy has also received extensive attention. For example, CAR-T therapy has achieved the desired cancer cell elimination effect in some clinical trials, especially in leukemia. Despite the outstanding advantages of CAR-T therapy, many clinical trials have demonstrated its limitations in the treatment of solid tumors and challenge in the treatment of systemic immune syndrome. In terms of immune stimulation, as a new vaccine treatment method, cancer cell vaccines, such as the induced pluripotent stem cells (iPSC) vaccine and dendritic cells (DC) vaccine, have made significant progress in research and achieved good efficacy. Researchers have also carried out a large number of experiments and clinical explorations on the treatment of cancer cell vaccines for many different types of tumors.

2. IPSC

2.1. Principle

IPSCs are a type of somatic cell generated by combining with various exogenous transcription factors to undergo reprogramming process [3]. It is characterized by self-renewal and pluripotency, and has received extensive attention in medicine.

The unlimited reproductive capacity of cancer cells is one of the important reasons for the loss of control. Similar with the cancer cells, iPSC also has the characteristics of unlimited reproduction and self-renewal. The root cause of this multiple similar phenotypes is the increased expression levels of oncogenes in these two types of cells [4].

Since a large number of tumors associated antigens have been discovered, certain features expressed during embryonic development can also be recovered in adults with cancer. Upwards of 100 human tumor-related and tumor-specific antigens, which are protein signals that the immune response may identify, as well as several cancer-related genes are among the genetic and transcriptome properties shared by human iPSC and tumor tissues [5]. The large number of overlapping gene expression profiles of cancer cells and iPSC confirmed the feasibility of using iPSC-based vaccines to generate extensive tumor immunity against multiple cancer types, indicating that the vaccine can equip the immune response with several specific antigens and activate the immune recognition system in patients [6]. In addition, in terms of epigenetics, some studies have shown that iPSC shows many abnormal epigenetic changes inclined to tumor formation characteristics during reprogramming [7]. Many similarities make the treatment of cancer vaccine with multi-inducible stem cells an ideal breakthrough point for eliminating tumors.

2.2. Clinical application

2.2.1. Breast cancer

In the study of breast cancer, researchers found that iPSC-based vaccine can be used to carry out preventive immunity to mice, from local helper T cells and cytotoxic T cells to systemic increase over time, which can produce effective immune response to a variety of cancer types. Researchers gave 10 breast cancer mice CpG (an immune adjuvant) + iPSC vaccine, and 7 mice showed tumor shrinkage after one week. Four weeks after tumor inoculation, five mice were killed and their immune spectra were analyzed. The other five mice carried out a one-year long-term survival study. Two of them survived for one year and had similar antibodies targeting iPSCs and breast cancer in the initial experiment, and were able to completely reject the reintroduced cancer cells.

In order to test whether the immunity generated by the vaccine was stimulated by the shared epitope between iPSC and cancer cells, the researchers conducted a two-way immune test. They respectively tested the cancer immunity of T cells recognized jointly and specifically by CpG + iPSC and the iPSC immunity of lymphocytes experienced tumor stimulation, both of which achieved the expected results. The test results proved the collective epitope both iPSCs and cancer cells.

Through these experiments suggested, it can prove that CpG + iPSC sensitized T cells were able to reject breast cancer cells, and sensitized lymphocytes could reduce the size of teratomas or completely prevent the formation of tumors [6].

2.2.2. Pancreatic cancer

Some researchers tested the effect of iPSC vaccine on pancreatic cancer. They subcutaneously injected mice with pancreatic ductal adenocarcinoma and the groupings were as follow: (1) control group: phosphate buffered saline, (2) CpG alone, (3) iPSCs alone, (4) CpG + iPSCs once a week during four weeks, with 7-8 mice in each subgroup. 75% of the infected animals in the C+I subgroup outright ignored the cancer cells. On 49th day after tumor inoculation, the average tumor volume of the C+I-immunized mice was significantly lower than that of the other three groups of mice, and there were no mice within those studies developed tumors from iPSCs. The outcomes proved usefulness and anti-tumor effect of tumor vaccination based on iPSCs in pancreatic cancer, which can prevent

tumor formation, induce anti-tumor effect, memory T cell response and B cell response, and reduce immunosuppression [8].

More and more researches have shown that iPSC vaccines provide a large number of tumor antigens to the immune system, and it is feasible to use iPSC-based vaccines to generate a wide range of tumor immunity for a variety of cancer types. Compared with the current immunotherapy strategy, iPSC vaccine can activate the immune system to target the identified cancer, and can produce effects within a few weeks after treatment, without treatment related side effects. These beneficial characteristics make iPSC vaccine a potential choice for personalized adjuvant immunotherapy in the short-term following the traditional primary treatment of cancer [6].

However, it is worth noting that before the iPSC treatment is transferred to the clinical environment, it is necessary to pay attention to its carcinogenesis and autoimmunity, which poses additional restrictions and challenges to the effective execution and security in the iPSC based cancer vaccine. In addition, iPSC reprogramming and status maintenance still have limitations. In conclusion, although the current iPSC vaccine seems to exceed the risk somewhat, it still needs to explore the long-term impact of iPSC-based tumor vaccine on patients after receiving treatment in a large number of clinical settings [5].

3. DC

3.1. Introduction

Dendritic cells (DC), as the most effective antigen presenting cells, have an ideal effect in activating the primary immune response [9]. It can regulate the innate and adaptive immune responses of patients through activating and resistance. These characteristics make them playing a central role in regulating the immune response and have been widely used in the clinical application of cancer [10]. Many researchers are committed to the exploration of DC cancer therapeutic vaccine, and many relevant reports have appeared as early as 1999 [11].

In the existing studies, it has been confirmed that DC based vaccines are safe for cancer patients. Only in a small number of patients, mild to moderate side effects were caused, including fever, erythema, flu like symptoms, rash or fatigue. In addition, several clinical studies have reported promising clinical responses to vaccination, including partial and complete elimination of stable disease or tumor, significantly longer survival time in patients treated with DC based vaccines have also been observed [12].

3.2. Clinical application

3.2.1. Leukemia

The maintenance of acute myeloid leukemia (AML) after treatment is not ideal. According to statistics, the 5-year overall survival rate (OS) of patients with AML is only 25%. One of the main reasons for this is that patients do not fully recover after traditional chemotherapy reaches the standard of complete remission (CR), but most of them will relapse, which is usually caused by a small amount of residual and uncleared leukemia cells.

Some researchers tested the clinical application of DC vaccine in adjuvant therapy to reduce the risk of recurrence and improve the survival rate after chemotherapy. In this test, 30 AML patients in remission stage after receiving comprehensive chemotherapy were vaccinated with DC vaccine without any chemotherapy. Immune tests results showed that 13 of the 30 patients showed significant anti leukemia effect, equivalent to 43% of the clinical response rate [13]. The five years overall survival rate of individuals who have immune response to DC vaccination was 53.8%, while that of patients without immune response was 25.0%. At the same time, in terms of recurrence rate, the 5-year relapse free survival rate of immune responders is 50%, which is also far higher than 7.7% of non immune responders [14].

3.2.2. Ovarian cancer

Ovarian cancer (OC) is the most lethal gynecologic malignant tumor all over developed countries, besides, for women suffering cancer diagnoses, it is the sixth most leading cause of mortality in the globe. The vast majority of OC patients were diagnosed only in phase III (51%) or IV (29%), resulting in an overall 5-year survival rate of only 30%. At present, there are several therapies for OC, including tumor resection, chemotherapy and targeted therapy. Although there has been some progress in various new treatments, about 80-85% of patients with advanced stage still relapse [15]. Some researchers explored the clinical efficacy of DC vaccine in ovarian cancer. They randomly divided 71 patients into two groups: chemotherapy (32 patients) and DC vaccine+chemotherapy (39 patients). The experimental results showed that although the DC vaccine+chemotherapy group did not improve the progression free survival period, the total survival period was indeed extended by 13.4 months, with a significant effect [16].

The efficacy of DC vaccines in cancer therapy is obscure, and more than 200 clinical trials in DC vaccine efficacy testing have shown that DCs are safe vaccines, highly immunogenic, and capable of periodically activating the occurrence of antitumor immune responses, enabling advanced cancer patients to exhibit long-lasting, objective tumor regression phenomena and clinical responses. Currently, a new direction of research on DC vaccines lies in determining the DC subsets and optimal antigen, loading strategy, dose, route of Administration for optimal clinical efficacy [17].

4. Conclusions

Both iPSC vaccines and DC vaccines have attracted much attention from researchers since they can activate a patient's autoimmune system in terms of targeting cancer. After years of development, many clinical tests of DC vaccines, including tests in melanoma, breast, lung, pancreatic cancer have demonstrated the efficacy of DC vaccines in cancer treatment despite some limitations still need to be advanced. Nowadays, many research directions focus on the exploration of combination therapy with DC vaccines and other immunotherapies, and the enhancement of immune efficacy with DC cell activation. Compared with the large number of results of DC vaccine, the iPSC vaccine is a very new vaccine treatment technology, which lacks the support of the results of a large number of clinical trials, needs more further studies in the future by researchers. In addition, there have been many skeptical and scrutinized concerns about the safety of iPSC vaccines, e.g., the exogenous gene of the reprogramming process has oncogenes, genetic instability, etc. This requires further development of iPSC technology and increased general acceptance. Overall, the ability of both iPSC vaccines and DC vaccines to prolong the survival of patients with immune responses, is obvious and celebrated as shown in the current findings, but their limitations and safety are directions for further exploration.

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