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Evaluation of the Application Value of Optogenetics Technology in the Development of Immunotherapy Methods for Tumors

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Abstract. In the field of tumor treatment, traditional methods have limitations, and tumor immunotherapy has become an important direction. As a cutting-edge discipline, optogenetics has been widely explored for application in tumor immunotherapy, such as regulating the activity of immune cells and influencing the tumor-related nervous system. However, there are still deficiencies in the application of this technology in tumor immunotherapy, such as the specific expression of photosensitive proteins and the precise delivery of light in vivo, which have not yet been resolved. This focuses the core mechanisms of optogenetic technology, elaborates in detail on its applications and research progress in regulating tumor immune cells such as T cells and macrophages, as well as improving the tumor microenvironment, and explores the prospects of its combined application with other tumor treatment technologies. The results indicate that optogenetic technology holds great potential in the development of tumor immunotherapy methods. The prospects. The results show that optogenetic technology has great potential in the development of tumor immunotherapy methods. This study provides new theoretical and practical references for tumor immunotherapy. In the future, technical challenges need to be further overcome. Subsequent research can focus on optimizing the expression of photosensitive proteins and the light delivery system, etc., to promote the application and development of optogenetic technology in tumor immunotherapy.

Keywords: Optogenetics Technology; Immunotherapy Methods; Tumor.

1. Introduction

The treatment of cancer has always been a hot topic in medical research, and traditional treatment methods, such as surgery, chemotherapy, radiotherapy, and biological therapy, have made great progress to a certain extent, but still have limitations. If it is difficult to completely remove the micrometastases after surgery, chemotherapy and radiotherapy will also have obvious toxic side effects on the nervous system, kidneys, myocardium, etc., and seriously affect the quality of life of patients. Therefore, it is urgent to develop more effective and low-toxicity cancer treatments, and tumor immunotherapy has emerged as the times require, and has gradually become an important research direction in the field of cancer treatment.

Optogenetics, a cutting-edge discipline that combines optics and genetics, is reshaping researchers' understanding and control of intracellular processes in its unique way. By utilizing light-sensitive proteins, researchers are able to precisely manipulate specific molecules within cells, enabling precise control of cellular behavior. Numerous studies have explored the application of optogenetics in tumor immunotherapy. For example, in terms of the regulation of immune cell activity, some studies have been conducted to engineer T cells through optogenetic technology, so that cells can change the flow direction of Ca2 under the control of light, reduce the inhibitory effect of some immune factors on T cells, and enhance their ability to kill tumor cells. [1] In addition, the use of optogenetics to modulate the tumor-associated nervous system has also been found to affect tumor growth and immune response.

However, the application of optogenetics in tumor immunotherapy is still in the development stage, and it faces many technical problems. How to improve the specific expression of light-sensitive proteins in tumor cells and immune cells, and how to achieve precise delivery and control of light in vivo have not been further studied.

The purpose of this article is to evaluate the application of optogenetics in tumor immunotherapy is still in the development stage, and it faces many technical problems. How to improve the specific expression of light-sensitive proteins in tumor cells and immune cells, and how to achieve precise delivery and control of light in vivo have not been further studied.

The purpose of this article is to evaluate the application value of optogenetics technology in the development of tumor immunotherapy. Through an in-depth analysis of the principle of optogenetics technology and its role in the regulation of immune cell activity, the improvement of tumor microenvironment, and the overcoming of immune escape, the application status of optogenetics technology in tumor immunotherapy is understood, and the problems and challenges faced by this technology are analyzed, so as to provide advantages for further research on tumor immunotherapy.

2. Analysis of the Core Mechanism of OptogeneticsTechnology

At the heart of optogenetics is the use of light-sensitive proteins. These photosensitive proteins are usually derived from microorganisms such as algae, bacteria, etc. Take, for example, Channelrhodopsin-2 (ChR2), which is a light-driven ion channel composed of retinaldehyde and proteins. When exposed to blue light at a specific wavelength, the conformational alteration of retinaldehyde causes channels to open up to allow cations, mainly Na, to flow inward. This change in ion flux can alter the membrane potential of the cell, triggering a series of intracellular signal transduction events. In neurons, this property of ChR2 is widely used to control the activity of neurons. In tumor immune cells, the introduction of the ChR2 gene artificially initiates specific signaling pathways through blue light irradiation, thereby modulating immune cell functions, such as activating the killing activity of T cells [1]. In addition to ChR2, there are a variety of other photosensitizing proteins, such as those that are sensitive to red light, which play their own unique roles in different optogenetic application scenarios, and together form the basis for optogenetics technology to precisely regulate cell function.

3. Current Status and Dilemma of Tumor Immunotherapy

Tumor immunotherapy refers to exogenous intervention in the body's immune system, restarting and maintaining the "tumor-immunity" cycle, restoring and improving the body's anti-tumor immune response, and strengthening the recognition and killing ability of tumor cells, so as to achieve the therapeutic effect of controlling or even specifically removing tumors. Immune checkpoint inhibitors are an important means of tumor immunotherapy. Although immune checkpoint inhibitors have prolonged survival in some patients in the treatment of a variety of tumors, including melanoma and non-small cell lung cancer [2], the overall response rate is not ideal, with only about 20% to 40% of patients benefiting from this [3]. Due to the heterogeneity of tumor cells, the expression levels and patterns of immune checkpoint molecules on the surface of tumor cells vary greatly among different patients, and tumor cells in some patients may evade T cell attack with the help of other immune escape mechanisms [4]. In addition, immune checkpoint inhibitor therapy may also trigger immune-related adverse reactions (irAEs), involving multiple organ systems such as the skin, endocrine, and digestive systems, which can affect patients' treatment compliance and quality of life in severe cases [5].

Adoptive cell therapy also plays an important role in tumor immunotherapy. Chimeric antigen receptor T cell (CAR-T) therapy has been shown to be effective in the treatment of hematologic cancers such as leukemia and lymphoma. Chimeric antigen receptors that recognize tumor-associated antigens are introduced into T cells through genetic engineering, enabling them to specifically recognize and kill tumor cells.In the Novartis-sponsored ELIANA trial at 25 centers in 11 countries around the world, 75 patients with acute lymphoblastic leukemia younger than 25 years of age received CTL-019 infusions. Eighty-one percent of patients achieved complete remission and complete recovery of blood counts after 3 months of follow-up, and recurrence-free survival in these patients was 80% after 6 months of treatment and 59% at 12 months. Event-free survival and overall

survival were 73% and 90% at 6 months and 50% and 76% overall survival at 12 months in all 75 patients, respectively [6]. However, CAR-T therapy is far less effective in the treatment of solid tumors than in hematologic tumors. The tumor microenvironment of solid tumors is complex, with high heterogeneity of tumor-associated antigens, difficulty in target antigen selection, and difficulty in effective infiltration of CAR-T cells into tumor tissues. At the same time, CAR-T therapy may also cause serious adverse reactions such as cytokine release syndrome (CRS) and neurotoxicity, which threaten the life and health of patients. Tumor-infiltrating lymphocyte (TIL) therapy is also an adoptive cell therapy, in which lymphocytes are isolated from tumor tissues, expanded in vitro and then infused back into the patient's body, which has a certain effect in some tumors such as melanoma, but faces problems such as difficulty in obtaining cells, low expansion efficiency, and inhibition by the tumor microenvironment.

As an active immunotherapy modality, cancer vaccines are divided into preventive vaccines and therapeutic vaccines. Preventive vaccines, such as the human papillomavirus (HPV) vaccine, effectively reduce the risk of cervical cancer and other cancers by preventing related viral infections. Therapeutic vaccines are designed to stimulate the body's immune response to pre-existing tumors, and many therapeutic cancer vaccines are currently in clinical trials, but the overall effect has not yet reached expectations. The weak immunogenicity of tumor cells, the complexity of tumor antigens, and the immunosuppressive effects of the tumor microenvironment have hindered the widespread application of therapeutic vaccines.

4. Application of Optogenetics Technology in the Regulation of Tumor Immune Cells

Optogenetics has opened up a new way for the precise regulation of tumor immune cells. When the light-sensitive protein gene is introduced into immune cells, the function of immune cells can be precisely controlled through specific light signals.

In terms of T cell regulation, researchers have used optogenetics to engineer T cells. For example, a gene encoding Channelrhodopsin-2 (ChR2), a blue light-sensitive cation channel protein, is introduced into T cells. Upon exposure to blue light, ChR2 channels open and cation influx depolarizes T cells, which in turn activates T cell signaling pathways. In vitro experiments have shown that the killing activity of this photo-controlled T cell on tumor cells is significantly enhanced, and its killing efficiency on tumor cells is several times higher than that of unengineered T cells under specific blue light irradiation conditions. At the same time, optogenetics can also regulate the proliferation and differentiation of T cells. By precisely controlling the duration and intensity of light, it is possible to regulate the differentiation of T cells into different subpopulations, such as promoting the differentiation of Th1 cells and enhancing the cellular immune response.Researchers at Texas A&M University in the United States have developed an optogenetic tool called LiSmore (Light - Inducible Smoc - Like Repeats). LiSmore-expressing dendritic cells (LiSmore-DCs) can specifically activate the STING signaling pathway under the action of blue light, promote the maturation and antigen presentation of DC cells, and then activate the tumor killing effect of $CD8^+$T cells.

In the experiment, the researchers transfused LiSmore-expressing dendritic cells into tumor-bearing mice and irradiated them with blue LEDs. The results showed that blue light could specifically activate LiSmore-DCs transduced into the body, promote their antigen-presenting effects, and effectively inhibit the growth of B16-OVA tumors. In addition, LiSmore-DC can also be combined with PD-L1 monoclonal antibody to synergistically inhibit monoclonal antibody failed tumors, and blue-light-activated LiSmore-DC has the effect of killing distal tumors, which can effectively inhibit melanoma growth on the non-photolit side and prolong the survival of mice [7]. This provides a new way of thinking to solve the problem that it is difficult to precisely control the activity and function of T cells in traditional T cell therapy.

Macrophages have complex functions in the tumor microenvironment, and their polarization status has a significant impact on the development of tumors. M1 macrophages have antitumor activity and secrete pro-inflammatory cytokines to kill tumor cells; M2 macrophages have pro-tumor effects.

Optogenetics can be used to precisely regulate the polarization state of macrophages. Researchers introduced the photosensitive protein gene into macrophages, and changed the signaling pathway within macrophages through specific wavelength light irradiation, so as to achieve the regulation of their polarization state. For example, macrophages introduced into specific light-sensitive proteins are polarized towards the M1 type, and their ability to secrete pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) is enhanced, and the phagocytic and killing activity of tumor cells is significantly enhanced. In the tumor microenvironment, light-controlled macrophages can reshape the immune microenvironment, recruit more immune cells, and enhance the anti-tumor immune response [8]. The study of light-controlled macrophages implanted in tumor-bearing mice found that the proportion of M1 macrophages in tumor tissues increased and tumor growth was significantly inhibited under light stimulation, which further confirmed the effectiveness and application potential of optogenetics technology in macrophage regulation.

5. Research Progress on the Role of Optogenetics on Tumor Microenvironment

5.1. Validation of Optogenetics in Animal Tumor Models

Among a variety of animal tumor models, optogenetics technology has shown unique advantages. For example, after constructing a tumor-bearing mouse model, light-controlled immune cells (such as light-controlled T cells, light-controlled macrophages, or light-controlled NK cells) are injected into mice. Significant changes in tumor growth can be observed by irradiating the tumor site of the mouse with an external specific light source. In some studies, tumor-bearing mice given regular light growth rates were significantly lower than those in the unexposed group or control mice treated with normal immune cells alone. Moreover, by adjusting parameters such as the timing, intensity, and frequency of light, the effect of optogenetic therapy can be further optimized. For example, intermittent light exposure may be more beneficial than continuous light exposure to maintain the activity and function of immune cells while reducing potential damage to normal tissues. In addition, advanced imaging techniques such as two-photon microscopy can be used to observe the dynamic changes of light-controlled immune cells in the tumor microenvironment in real time, including the migration pathways of cells, interactions with tumor cells, and the effects on other cellular components in the tumor microenvironment, providing intuitive data support for in-depth understanding of the mechanism of optogenetics in the tumor microenvironment [9].

5.2. The Technical Problems and Coping Strategies Faced by the Current Application

Although optogenetics technology has shown great potential in tumor immunotherapy, there are still some technical difficulties. First, the specific expression of light-sensitive proteins in tumor cells and immune cells needs to be improved. In some cases, photosensitive proteins may also be expressed in cells other than the target cells, resulting in unwanted changes in cell function. To address this issue, researchers are exploring the use of tissue-specific promoters that allow photosensitive proteins to be expressed only in tumor cells or specific immune cells. For example, for tumor cells, a gene promoter that is highly expressed in tumor tissues and low in normal tissues can be used to drive the expression of light-sensitive protein genes. Secondly, the precise delivery and control of light in the body is a major challenge. Due to the absorption and scattering of light in biological tissues, the propagation distance and intensity of light in the body are limited, and it is difficult to act accurately on tumor sites. To overcome this problem, it is essential to develop new optical delivery systems. For example, by using nanomaterials as light carriers, the surface properties of nanomaterials can be specifically enriched around tumor tissues to improve the effective intensity of light at tumor sites. At the same time, combined with imaging technology, such as fluorescence imaging, magnetic resonance imaging, etc., the distribution and transmission of light in the body can be monitored in real time, so as to accurately adjust the lighting parameters. In addition, the potential toxicity of long-term light exposure to normal tissues also needs to be studied in depth to minimize the adverse effects on normal tissues by optimizing the wavelength, intensity, and duration of light [10].

6. Conclusion

In this study, the application potential of optogenetics in the field of tumor immunotherapy was comprehensively analyzed. After in-depth analysis of the core mechanism of optogenetics, we will focus on exploring its practice in the field of immune cell regulation. By introducing photosensitive protein genes into T cells and macrophages, the light-controlled regulation of the key functions of these cells was successfully realized, which significantly improved the killing efficiency of immune cells on tumor cells, reshaped the immune pattern in the tumor microenvironment, and demonstrated the unique advantages of optogenetics technology in stimulating the body's anti-tumor immune response. At the same time, the exploration of the combined application of optogenetics technology with other tumor treatment methods also provides a new idea for multi-modal synergistic anti-cancer.

The results of this study are of great significance. Optogenetics technology has broken the bottleneck of imprecise control of immune cells in traditional immunotherapy, and opened up a new path to improve the accuracy and safety of treatment. This not only helps to overcome the problems of low response rate and large side effects of traditional immunotherapy, but also provides solid theoretical and practical support for the innovation and development of subsequent tumor immunotherapy strategies, in terms of precise cell regulation and combined treatment plan design. However, there is a lack of in-depth research on the long-term stability and functional sustainability of immune cells, and it is difficult to determine whether optogenetic-engineered immune cells can maintain high-efficiency anti-tumor activity in the complex physiological environment of the human body for a long time.

Further research should focus on the innovation of photosensitive protein delivery systems, and the development of more targeted vectors to achieve accurate and efficient expression of photosensitive proteins in tumor-associated immune cells. In addition, large-scale and long-term preclinical and clinical trials need to be carried out to systematically evaluate the long-term safety and efficacy of optogenetic tumor immunotherapy regimens, so as to promote the technology from the laboratory to the clinic and bring new therapeutic hope to cancer patients.

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