Treg Cell And PD-1 In Cancer Immunotherapy

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Abstract. Cancer results from the abnormal life activity of some cells in the human body. These abnormal life activities are mainly reflected in uncontrolled division and proliferation and can infiltrate and destroy normal human tissues. In actuality, more than a million people die from cancer annually, and it ranks first among the main causes of death globally. Common cancers include skin cancer, lung cancer, gastric cancer, pancreatic cancer, etc. In the modern era, immunotherapy is the mainstay of treatment for some relatively common cancers, such as breast and prostate cancer. There are many ways to treat cancer in the world. In this article, the author only compares two possible ways to treat cancer: Treg cell method and PD-1 therapy. This paper tried to clarify the advantages and disadvantages of these two immunotherapies in cancer treatment by studying and comparing the two immunotherapies for cancer treatment, to help researchers find better ways to treat cancer with immunotherapy.

Keywords: Treg Cell; PD-1; Cancer; Immunotherapy.

1. Introduction

Cancer is a common disease that has been afflicting people for a long time. In all countries, the incidence rates show significant growth up until the 1970s. Only statistics from the most recent year, 2019, which had 387,820 new cancer cases diagnosed, are available for the UK. Of these cancer cases, males made up 200,386 while women made up 187,434 [1]. The traditional ways of therapy cancer include radiation therapy by employing intense radiation doses to destroy cancer cells and reduce tumors, or chemotherapy by using medications that are created chemically to treat illnesses [2]. It is a key treatment strategy for various autoimmune disorders and malignancies by hindering the production of DNA, RNA, or protein in cells impacts the development of cancer cells. However, traditional treatment methods kill the tumor cells and may also kill normal and immune cells. Furthermore, chemotherapy can lead to multidrug resistance (MDR), which refers to the cross-resistance phenomenon to several medications with various structures, functional mechanisms, and targets. Immunotherapy is now a novel therapeutic approach utilizing the immune mechanism of human body, and the diagram of immune regulation of tumor growth is shown in Figure 1. Compared with traditional ways of treatments, gene therapy has a lower rate of side effects. The mechanism of gene therapy is the repair of particular molecular deviations linked to cancer progression or development. In gene therapy, gene editing, expression, and silencing take place as soon as foreign genetic materials reach the target cells via carriers (referred to as a vector) [3]. This technology has a long history, and it was started in 1963. severe combined immunodeficiency, an inherited genetic condition, was the target of the first gene therapy clinical experiment of severe combined immunodeficiency (SCID) in 1990 [4]. Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) is the technique utilized in gene therapy. However, this method still has significant flaws, such as being off-target. The Treg cell strategy and the PD-1 method are the two primary cancer immunotherapy approaches discussed in this article.

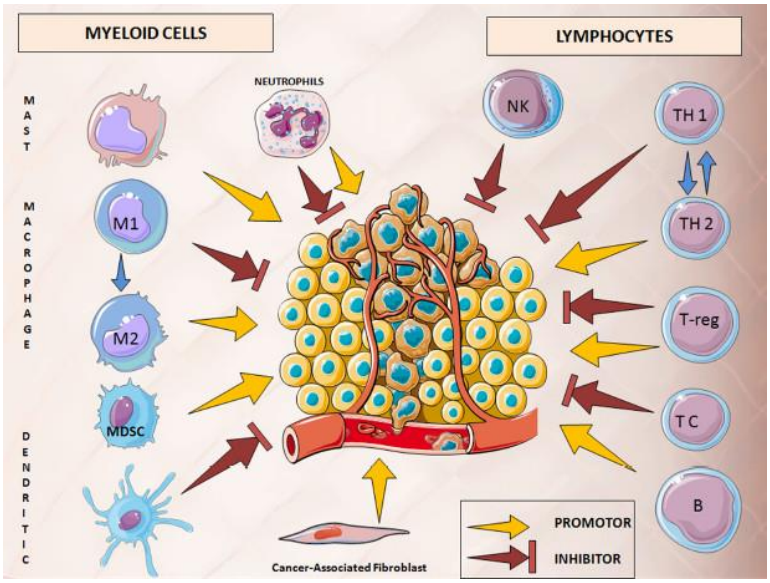


Figure 1. Immune regulation of tumor growth with myeloid and lymphoid cells [5]

2. Treg cells

Reversing the inhibitory effect of local Treg in the tumor can produce a therapeutic effect on advanced tumors. Treg cells inhibit T cells against tumors, and removing them can enhance the body's anti-tumor immune function. They cannot only inhibit the functions of T cells through intercellular contact but also secrete cytokines to inhibit their normal work. Clearing Treg cells to treat various diseases such as lung, breast, liver, ovarian, gastric, and lymphoma. The treatment strategies utilizing Treg cells can be classified as non-specific and specific clearance, which can be found in the IL-2-diphtheria toxin fusion protein. This experimental method was proposed by Foss for the first time, but the effect is not good, because the tumor is the immune escape the tumor [6]. A variety of genes lead to the fact that even if Treg plays a leading role, a single elimination can only temporarily reduce the number of Treg, and it is easy to eliminate normal immune cells together. Another approach is to control the Treg number and function. Based on this principle, the first way is to inhibit cell differentiation by regulating the function-related molecules of Treg cells such as Foxp3, and the second way is to avoid the chemotaxis and aggregation of Treg cells by editing the genes of Treg cells [5,7]. The last is to improve the ability of T cells to suppress Treg to improve their immune function.

3. PD-1

Studies on vaccination have also drawn attention to the link between the expressions of PD-1 as well as the detection of hyperresponsive particular T-cells. Mice with epithelial tumors expressing HPV-associated E-7 protein were immunized with E-7 protein, which stimulated the proliferation of PD-1C-specific CD8C T-cells and thus partially decreased tumor growth.

On their cell surfaces, activated T-cells, NK-cells, B-cells, macrophages, and various DC subsets all express PD-1. The T-cell receptor (TCR) activates PD-1 expression in T-cells [8–10]. This transient expression is diminished without TCR signaling. However, it can be kept with persistent epitope targeting following chronic activation including cancer and chronic viral infections. TCR signaling and CD28 co-stimulation are inhibited by PD-1 ligation with its ligands, PD-L1 and PD-L2.

Researchers hypothesized that PD-1 expression was coupled with the expressions of other receptors with inhibition functions, that is Tim-3, LAG-3, or TIGIT, altering T cell function and allowing tumor escape, both of which were associated with tumor microbiomes. Tumor cells and immune infiltration cells in the surrounding area express the ligand PD-L1. Constitutive PD-1

expression limits autoimmune disorders by serving as an immunological adaptation to long-lasting stimuli. This immune adaptation causes a physiological restriction on the immune response. As a result, tumor cells manipulate this system to promote peripheral tolerance, which is why PD-1 is a sign of malfunctioning T lymphocytes.

The PD-1/PD-L1 signaling system, which initially serves many roles, is involved in the dynamic process of inducing an immunosuppressive milieu, which results in cancer immune evasion [7]. The employment of PD-1 or PD-L1-specific antibodies to target this pathway in a rising number of solid tumors has steadily altered patient care and resulted in clinical outcomes in many advanced human cancers previously unheard of. In light of the tight regulation of its statement on tumor-specific T-cells, PD-1 is a crucial biomarker to identify high-affinity specific T lymphocytes for immunotherapeutic applications. In addition, customized T-cell genome editing targeting immune checkpoint inhibitors appears to be a promising means of reducing autoimmune adverse impacts related to anti-PD-1 systemic therapeutics while retaining the possibility of combination therapy [1].

Torres et al. published the first study using CRISPR/Cas9 technology to develop cancer models in 2014 [11]. In this study, Cas9 cut DNA at specified locations on chromosomes with the help of a specific sgRNA, causing inversion and translocation of the cut chromosomes, which precisely mimicked the development of various human cancers like acute myeloid leukemia and Ewing's sarcoma. The tumor suppressor genes p53 and pten were successfully double-mutated by using CRISPR/Cas9 genome editing technology, and an animal model of liver cancer was created. An effective mouse model of lung cancer was created using organ-targeted AAV vectors of different subtypes as a CRISPR/Cas9 delivery system to induce precise expression of Cas9 ribozyme in the liver, brain, lung, and other organs. The combined use of CRISPR/Cas9 technology and AAV vector will become more crucial in the customized treatment of cancer.

PD-1 expression indicates T-cell activation, although it suppresses T-cell responses in response to ligand attachment. Strong infiltration of activated PD-1C T-cells, which can be recovered following PD-1 inhibition, is related to good clinical outcomes in head and neck malignancies that are HPV-positive. The same outcomes in solid tumors not brought on by a virus were also described. TILs from melanoma patients with tumor-reactive CD8C T-cells were identified by PD-1 expression in melanoma. Furthermore, the neoantigen-specific T-cells that were solely present in this PD-1-positive fraction probably expressed high-affinity TCRs. Despite PD-1 being presented, these T-cells could still eradicate autologous tumor cells. To counteract T-cells activation and regulate the immunological response, PD-1 expression is inversely proportional to TCR signaling strength. Also, the TCRb gene repertoire showed that most of the PD-1C T-cell fraction was oligoclonal. This shows that these PD-1C T lymphocyte clonotypes grew because of antigens in the tumor. The presence of PD-1 on circulating T-cells suggests that anti-tumor T-cell responses are equivalent to TILs.

This shows a relationship between PD-1 expression and high functional affinity in human CD8C T-cell clones that share the antigens found in melanoma, melanoma A, 34, 35, and MELOE-136. Melanoma-specific T-cell clones did not show obvious effects on PD-1 existence after T-cell activation. The Pdcd1 promoter's ongoing methylation was the cause of the loss of PD-1 expression. Despite being resistant to PD-L1-negative signaling, these PD-1neg T-cell clones' antitumor effectiveness without PD-L1-negative signaling was lower to that of their PD-1pos counterparts. It is conceivable that PD-1-positive T-cell clones are more functionally affine to ACT fertility than PD-1-negative counterparts, indicating that they are more concerned with ACT fertility. These T-cells' PD-1 inhibition or gene silencing, along with the selective growth of clonotypes with high functional affinities, may enhance their in vivo anticancer effectiveness. Certain c-T cells had a restored Vb repertoire distinct from that obtained under control conditions. These findings support a recent work that used NTAmers to look at the kinetic mechanism through which TCR binds to the peptide major histocompatibility molecule (pMHC). In fact, this study demonstrates a significant relationship between the rate of TCR pMHC shutdown and CD8C T-cell potency, which is related to the activation of the co-stimulatory/coin inhibitory receptor in activated CD8C T cells, where PD-1 is present.

In this instance, the anti-tumor actions of PD-1 blockers and vaccinations work together. 33 Another recent study found that specific CD8 T-cell responses to immunization with modified peptide ligands with optimal CMH or TCR affinity were potent yet ineffectual, and that activated specific T-cells consistently expressed PD-1 (and other inhibitory receptors). As a result, combination therapy that targetRTPD-1 can increase the anti-tumor effectiveness of such vaccinations. PD-1 is a crucial marker for identifying high-affinity specific T lymphocytes for immunotherapeutic applications as a result of the tight control of its expression on tumor-specific T-cells. The use of specialized T-cell genome editing to target immune checkpoint inhibitors looks promise for decreasing the autoimmune adverse effects of anti-PD-1 systemic treatment, leaving the door open for combination therapy.

4. Conclusion

It has been found that Treg cells and PD-1 have different advantages in immunotherapy for cancer due to their different mechanisms of action. Treg cells play a crucial function in tumor cell immune evasion, and it is believed that the immune escape effect of tumors can be weakened by inhibiting the related functions of Treg cells at the tumor site. It can then allow the killer T-cells of the human body to gather in the tumor to use the human body's immune system to clear the tumor. For PD-1 therapy, the use of PD-1 antibody can alleviate or even relieve the inhibition of tumor cells on T-cell activation, to achieve the goal of treating cancer. Although cancer is still a physical and health problem that people worldwide have to face, it is also expected that with the joint efforts of medical workers worldwide, there will be more effective methods to treat cancer.

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