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The importance of CTLA-4 and PD-1 pathways in the cancer treatment

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Abstract

For 30 years, chemotherapy method has been used in end-stage cancer treatments, the biggest obstacles are that this method has too many side effects and limited number of therapeutics for treatment. With the increasing information about the immune system, the interest in immune cells and immune response has increased. Although the immune response from cancer patients is kept under control, the immune system is not effective, because the cancer cells have developed more than one resistance mechanism (such as the inhibition of regional immunity). However, cancer cells can escape from many obstacles that prevent the immune response, including immune checkpoints. Taking advantage of this information, the idea developed that T cell activation checkpoints could be more effective for cancer treatment. The first of these checkpoints, the cytotoxin T lymphocyte-associated protein-4 known as CTLA-4, and the second important pathway PD-1 (programmed cell death pathway-1) are the most effective. In addition, it is known by researchers that immune checkpoints are more effective in fighting cancer than the most known treatment techniques. In this review proceeding we will be focusing on these two pathways for the cancer treatment.

Introduction

One of the biggest problems in the immune system is the disorder in the immune tolerance. Immune tolerance is able to distinguish the body's own cells from antigens. But cancer cells can escape immune tolerance. The main reason for this is that cancer cells are composed of self-cells and immune cells cannot recognize such cells. Therefore, the immune system is being investigated more in cancer treatments. It is very important that the standard methods in cancer treatment become ineffective and the development of treatments that prevent the recurrence of cancer for cancer patients [1]. Treatment strategies aiming to benefit from the body's immune system are being developed in cancer treatments. It is known that immune checkpoints, one of these methods, are more effective than the most known treatment techniques [2].

Results

The immune checkpoint-based treatment methods have become increasingly widespread today and positive progress has been achieved in many cancer types. One of these treatment methods can enable immune cells to distinguish cancerous cells from normal cells by blocking immune checkpoints with monoclonal antibodies. In other words, they are signals that regulate and inhibit immune responses. Some of the immune checkpoints are as follows, there are many such as TIM-3, CTLA-4, LAG-3, and PD-1, but the most important and most studied immune checkpoints are CTLA-4, PD-1 [3]. These two receptors regulate T cell expression negatively. The working mechanism of the receptors is to prevent tissue damage and autoimmune diseases by preventing excessive immune response. By advancing in the opposite direction of the working mechanisms of these inhibitors, the

researchers increased the importance of immune cells in cancer treatment by preventing the proliferation of cancerous cells and enabling them to be differentiated [4].

The first immune checkpoint clinical studies were conducted on the CTLA-4 receptor. The CTLA-4 inhibitor is in the immunoglobulin superfamily member, is expressed on T cells, and is the protein that controls immune responses. It binds to a protein known as B7, inhibiting the functioning of T cells, preventing the destruction of many cells, including cancer cells [5]. Anticancer drugs have been developed that inhibit the CTLA-4 receptor in order to increase the efficiency in the destruction of cancer cells. In this way, T cells work more effectively to destroy cancer cells. One of the biggest disadvantages of CTLA-4 blockade has been observed in many studies that it is not very effective when only this blockade is used in the treatment, and its effectiveness is increased when the combination is used [5]. The first immune checkpoint inhibitor, ipilimumab, got approval from the FDA in 2011, making advances in the treatment of the late-stage melanoma cancer [6].

PD-1 receptor, T cells and natural killer cells (NK), B lymphocytes, monocytes, dendritic cells act on immune system cells, and cytokine release limits immunological activity. PD-1, PD-1L and PD-2L show its effectiveness by interacting with these two ligands found on cancer cells and antigen presenting cells. Tumors containing these ligands bind to PD-1, inhibiting the immune response and evading the immune system [7]. In 2015, nivolumab and pembrolizumab got approved by the FDA so that they can be used against non-small cell lung cancer (NSCLC) [8]. It is known that PD-1 inhibitors are more effective than other methods in advanced melanoma and many cancer types (bladder cancer, digestive system cancers, pancreatic cancer, brain tumors).

Discussion

The purpose of using the immune system in cancer treatment methods is to create a more effective anticancer response by strengthening the immune system. While methods in cancer treatment directly target cancer cells, immunotherapy methods aim to improve the cancer microenvironment by utilizing the immune system. Today, studies on immune checkpoints have become more popular. Immune checkpoints have important roles in controlling autoimmune diseases, that is, immune tolerance, but they cause cancer cells to escape by suppressing the immune system [9, 10]. For this reason, it is very important to focus on this area in cancer treatment. In the treatments studied on CTLA-4 and PD-1, their efficacies alone are low, but the combination of their targeting with the most known treatment techniques such as radiotherapy and chemotherapy, and the combination of the two receptors with each other increased their efficacy more [10]. Therefore, more attention should be paid to studies on the combination of these receptors with traditional methods and with each other.

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