Immune Checkpoint Inhibitors: An Innovative Direction in Cancer Immunotherapy

Xinrun Xie

Guangdong Country Garden School, Foshan, Guangdong, China

13823020197@139.com

Abstract. Immune checkpoint inhibitors (ICIs) are a type of immunotherapy. They work by blocking certain inhibitory pathways in the body, like PD-1/PD-L1 and CTLA-4, which helps reactivate the immune system's T cells to find and attack cancer cells. Current studies primarily focus on key targets, including PD-1, PD-L1, and CTLA-4. These treatments are used for various cancers, including melanoma, non-small-cell lung cancer, kidney cancer, and Hodgkin lymphoma, and researchers are also testing them on other types like triple-negative breast cancer and brain tumors. There have been significant advances: several ICIs, such as pembrolizumab, nivolumab, and ipilimumab, have been approved for use, becoming standard treatments for many advanced cancers and helping patients live longer, even achieving long-term remission in some cases. However, there are problems: some tumors resist ICIs from the start or develop resistance later, making the treatments less effective. Additionally, ICIs can cause immune-related side effects because they overactivate the immune system, which can affect the skin, digestive system, or hormone-producing glands, with rare but serious issues, such as heart inflammation. Future research will aim to find ways to overcome resistance and manage these side effects better, so ICIs can be safer and more effective.

Keywords: Immune Checkpoint Inhibitors; Cancer Immunotherapy; PD - 1/PD - L1; CTLA-4; Immune-related Side Effects.

1. Introduction

Cancer continues to be one of the most lethal diseases globally. Despite advances in treatment strategies, many cancer patients still face poor outcomes from traditional therapies like chemotherapy and radiation. Traditional cancer treatment methods mainly include surgery, chemotherapy, and radiotherapy. Surgery aims to treat cancer by removing tumor tissues, which is suitable for patients with solid tumors that have not metastasized extensively. However, it is ineffective for tiny metastatic lesions or hematological tumors. There may also be a risk of recurrence after surgery, and it may cause trauma to the patient's body, affecting their quality of life. Chemotherapy utilizes cytotoxic drugs to target and kill cancer cells. While these drugs target cancer cells, they also harm normal cells that divide rapidly, such as those in hair follicles and the digestive tract mucosa, resulting in severe side effects, including hair loss, nausea, vomiting, and decreased immunity. Radiotherapy destroys the DNA of cancer cells through high-energy rays to inhibit their proliferation. It can also damage healthy tissues around the tumor, causing problems such as local inflammation and fibrosis. Moreover, its therapeutic effect is often limited for cancers metastasizing to distant sites. In addition, traditional treatment methods are difficult to eliminate all cancer cells, and many patients will experience recurrence or drug resistance after treatment, posing significant challenges to subsequent treatment.

Cancer immunotherapy has emerged as a promising new treatment approach in recent years. One of the most notable advancements in this field has been the development of **immune checkpoint inhibitors**, a class of drugs that has revolutionized cancer treatment. The immune system protects the body against foreign pathogens and abnormal cells, including those that cause cancer. T cells, a type of immune cell, play a critical role in detecting and attacking tumor cells. However, cancer cells have developed sophisticated strategies to evade immune surveillance [1], one of which is the activation of immune checkpoint pathways. These pathways act as "brakes" on the immune system, preventing it from attacking cancer cells. Immune checkpoint inhibitors release these brakes, allowing the immune system to recognize and destroy cancer cells more effectively [2].

The immune system has evolved primarily to defend the host from foreign invaders, such as harmful microorganisms, viruses, and pathogens, all of which have the potential to cause damage to the body. The immune system relies on T, B, natural killer, and other immune cells to identify and eliminate these threats [3]. At the same time, the immune system must also maintain tolerance to the body's cells and tissues, preventing attacks on self-antigens. This balance is achieved through mechanisms such as deleting auto-reactive T and B cells during their development in the thymus and bone marrow, a process known as central tolerance.

2. Biological Mechanism of the Immune Checkpoints

2.1 Function of the Immune Checkpoints

Immune checkpoints are crucial regulators in the immune system, and PD-1/PD-L1 and CTLA-4 represent two classic inhibitory pathways that act as “brakes” to fine-tune immune activation.

For the PD-1/PD-L1 pathway, PD-1is a receptor mainly expressed on activated T cells. PD-L1 (Programmed Death-Ligand 1) and its ligand can be highly expressed on various cells, including cancer cells and cells within the tumor microenvironment. When PD-L1 on target cells binds to PD-1 on T cells, it triggers intracellular signaling events. As described in the literature [4], this binding recruits the Src homology region 2 domain-containing phosphatase-2 (SHP2). SHP2 then dephosphorylates key signaling molecules associated with the T-cell receptor (TCR), such as CD3 and ZAP70 signalosomes. This process attenuates downstream TCR signaling, ultimately suppressing T-cell activation, proliferation, and cytokine secretion, effectively putting a “brake” on the T-cell-mediated immune response [4].

Regarding the CTLA-4 pathway, CTLA-4 is expressed on activated CD4+ and CD8+ T cells. It shares structural homology with CD28, a co-stimulatory receptor on T cells, and competes with CD28 for binding to the same ligand, CD80 (B7-1) and CD86 (B7-2), which are present on antigen-presenting cells (APCs). As indicated in relevant literature [5], by outcompeting CD28 for these ligands, CTLA-4 delivers inhibitory signals to T cells. This blocks the co-stimulatory signals necessary for full T-cell activation, thereby reducing T-cell proliferation and the production of pro-inflammatory cytokines, serving as another critical “brake” to prevent excessive immune activation [4,5].

2.2 T Cells and the Blocked Links in the Activation Process

T cells play a central role in adaptive immunity, and their activation relies on a “dual-signal” system, which can be interrupted by immune checkpoints at specific steps. First, for T-cell activation to occur, antigen-presenting cells can capture and process the antigens, then present them to the T-cell receptor via major histocompatibility complex molecules. This is the first signal. The second signal comes from co-stimulatory molecules, the CD80/CD86 on APCs bind to CD28 on T cells, providing essential co-stimulatory signals that fully activate T cells to target and eliminate pathogen-infected or abnormal cells.

Immune checkpoints interfere with this activation process. In the case of the PD-1/PD-L1 pathway, as T cells express PD-1, the binding of PD-1 to PD-L1, which is expressed on APCs or other cells, can disrupt the downstream signaling of the TCR-CD3 complex. As I mentioned earlier, SHP2-mediated signaling molecules (CD3, ZAP70) attenuate the intensity of TCR signaling, making it challenging for T cells to receive sufficient activation signals, even when the initial signal (TCR-MHC interaction) is present [4].

For the CTLA-4 pathway, since CTLA-4 competes with CD28 for binding to CD80/CD86, it directly blocks the second signal (co-stimulatory signal) required for T-cell activation. Without adequate co-stimulation, T cells cannot be fully activated, and their proliferation and effector functions (such as cytokine production and cytotoxic activity) are significantly inhibited, even if the TCR has recognized the antigen presented by MHC.

2.3 Cancer Cells Immune Evasion

Cancer cells can hijack immune checkpoints to evade recognition and elimination by the immune system, with PD-1/PD-L1 being a well-documented mechanism of escape.

A pivotal study in this field first demonstrated that cancer cells can highly express PD-L1 to evade T-cell attack. For example, research has shown that in non-small cell lung cancer and other malignancies, the tumor cells often regulate PD-L1 expression. By doing so, they can bind to PD-1 on infiltrating T cells in the tumor microenvironment, triggering the inhibitory signaling described earlier. This leads to the dysfunction or exhaustion of T cells, allowing cancer cells to avoid immune surveillance. Another aspect of immune evasion involves the interaction between cancer cells and the tumor microenvironment. Cancer cells may also induce surrounding stromal cells, such as macrophages and dendritic cells. To express PD-L1, creating a more immunosuppressive microenvironment. This collective up-regulation of PD-L1 further reinforces the "brake" on T cells, enabling cancer cells to proliferate and survive.

3. The Role of Immune Checkpoint Inhibitor Drugs in Solid Tumor Therapy

In the treatment of solid tumors, immune checkpoint inhibitor (ICI) drugs have emerged as transformative agents, reshaping therapeutic approaches for lung and breast cancer.

For lung cancer, a leading cause of global cancer-related mortality, ICIs have made substantial inroads. Non-small cell lung cancer (NSCLC), accounting for around 85% of lung cancer cases, has seen notable advancements. Drugs targeting checkpoints such as PD - 1/PD - L1 have redefined treatment. As noted in "Small-molecule inhibitors, immune checkpoint inhibitors, and more: FDA-approved novel therapeutic drugs for solid tumors from 1991 to 2021", in NSCLC treatment, these ICIs can reactivate the immune system to combat cancer cells. Clinical data from relevant trials show improved objective response rates in some patients [5]. For example, certain studies highlight prolonged progression-free survival, granting patients more time with stable disease.

In breast cancer, ICIs are also carving out a role. While traditional cytotoxic drugs and hormonal therapies remain pivotal, ICIs offer new possibilities, especially in specific subtypes. For hormone receptor (HR) - positive breast cancers, which constitute a large share of cases, the exploration of combining ICIs with other treatments is underway. As referenced in the same source, early research suggests that ICIs can enhance the immune system's capacity to target cancer cells in select scenarios, potentially improving treatment efficacy [5].

4. Potential Challenges

Cancer immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), has significantly transformed the treatment of cancer. But there are significant challenges that stop them from working better for more people, like drug resistance, side effects, and only helping some patients.

Resistance to ICIs happens because cancer cells find ways to escape the immune attack. Initially, ICIs work by activating the immune system to fight tumors. However, cancer cells may hide over time by altering the way they present antigens that the immune system recognizes. Alternatively, they may initiate new immunosuppressive pathways, such as activating other checkpoint molecules, including TIM-3 or LAG-3. Take melanoma as an example. The tumors might lose MHC molecules, so T cells can't find and attack them anymore. This immune evasion diminishes the initial beneficial effect of ICIs, as the immune system struggles to target the altered cancer cells [6] effectively.

ICIs activate the immune system, but this can lead to excessive activity, causing immune-related side effects. These include pneumonitis, a lung inflammation that causes coughing and shortness of breath, and colitis, where the intestines become irritated, leading to diarrhea and stomach pain. Once ramped up, the immune system may accidentally attack healthy tissues, such as the lungs or gut, because they share some similar antigens with tumors. Doctors often use immunosuppressive drugs, such as corticosteroids, to manage these side effects. However, these can reduce the effectiveness of ICIs and impact patients' daily lives.

ICIs are most effective for patients with specific biomarkers. P-L1 positivity is a big one. Tumors with high PD-L1 have more “targets” for ICIs to block, so T-cells get activated better. In non-small cell lung cancer, patients with PD-L1-positive tumors respond better to PD-1/PD-L1 inhibitors; additionally, factors such as tumor mutational burden and microsatellite instability also play a role. Tumors with high TMB or MSI-H have more neoantigens, allowing the immune system to recognize them more easily. Therefore, patients without these markers typically don't derive significant benefit, which means ICIs can only help a limited number of people.

5. Future Research Directions of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have revolutionized cancer treatment over the past decade, but their effectiveness is still limited in many cases. To unlock their full potential, three research directions deserve more attention.

5.1 Combined Therapies

Mixing immune checkpoint inhibitors with other treatments has become a hot topic, as it often boosts anti-tumor effects. At the 2024 European Society of Medical Oncology (ESMO) Congress, researchers presented a study on non-small-cell lung cancer (NSCLC) patients, showing that when nivolumab, relatlimab, and platinum-based doublet chemotherapy were used together, the objective response rate reached 51.3%, significantly higher than the 43.7% achieved with nivolumab plus chemotherapy alone. Besides chemotherapy, radiotherapy also works in conjunction with these inhibitors by helping to release tumor antigens, thereby strengthening the immune response. Combining them with newer immunotherapies, such as CAR-T cell therapy or tumor vaccines, might break the "immune-suppressive wall" surrounding the tumor.

5.2 Exploration of New Targets

Most inhibitors focus on PD-1/PD-L1 and CTLA-4, but these aren’t the only immune checkpoints. Molecules such as LAG-3, TIM-3, and TIGIT are now being closely studied. A 2024 review in Cancer Biology & Medicine by researchers from Guangdong Pharmaceutical University highlighted that these new targets could help address the issue of resistance to current PD-1/CTLA-4 inhibitors. For example, monoclonal antibodies targeting LAG-3 are already in early development, and they might work better for patients who don’t respond to existing drugs.

6. Conclusion

Immune checkpoint inhibitors have significantly changed cancer treatment. Studies from the 2024 ESMO Congress, along with tools like the SCORPIO model, demonstrate their effectiveness. However, challenges remain: finding the optimal mix in combined therapies, maximizing the benefits of new targets such as LAG—3, and improving personalized predictions. As research progresses, soon, immune checkpoint inhibitors will become more precise and safer ways to fight cancer. They’ll reshape how we treat cancer and bring new hope to patients worldwide.

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