Advances in Cancer Immunotherapy: Enhancing the Immune Response and Addressing Therapeutic Challenges

Kai Song

GuangDong Overseas Chinese High School, Guangzhou, China
songkai2025@outlook.com

Abstract:

Cancer is the top cause of death around the world. In 2022, nearly 20 million people were diagnosed with cancer, and about 9.7 million died from it. In China, almost 5 million new cancer cases were reported, with over 2.5 million fatalities. Immunotherapy is a new way to treat cancer. It boosts the body's immune system to fight cancer cells. This method is less harmful to patients and more precise than older treatments like chemotherapy and radiation. There are different kinds of immunotherapy, including vaccines, treatments with substances that boost the immune system, transferring cells, and blocking proteins that stop the immune system from working. Even though immunotherapy is helpful, it can have side effects and tumors can become resistant to it. Each person's tumor is unique, which makes treatment tricky. Sometimes, tumors can change and resist the therapy. We also don't have enough markers to tailor treatments to each person's needs. This review discusses the response of immune system, and how immunotherapy can be used to treat cancer.

Keywords: Cancer; immunotherapy; challenges.

1. Introduction

Cancer is one of the main causes of death worldwide. The report shows that in 2022, there were 19.96 million new cancer cases and about 9.7 million deaths because of cancer [1]. In the year 2022, it was projected that there would be around 4.8247 million novel instances of cancer in China, while the cancer-related mortality figure was anticipated to reach 2.5742 million [2]. In fact, cancer has become a major health challenge in global. Cancer is linked to genetics, environment, and lifestyle. In recent years, people have been focusing on the complex relationship between cancer and immune system, which can recognize and kill cancer cells. However, cancer cells can find ways to avoid being detected by the immune system through many mechanisms. In the tumor environment, there are many immune cells that are related to cancer, such as T cells, B cells, Natural Killer (NK) cells, and myeloid cells. In recent years, immunotherapy, a breakthrough approach to treating cancer has become popular. Immunotherapy functions through the stimulation or enhancement of a patient's immune system, enabling it to detect and combat cancer cells. In essence, immunotherapy bolsters the body's inherent mechanisms to battle cancer. Contrasting with conventional therapies such as chemotherapy and radiation, immunotherapy is less detrimental to patients and achieves more precise targeting of malignant cells. Immunotherapy has different types like vaccines, cytokine treatments, cell transfers, and checkpoint inhibitors.

Despite the significant advantages, Immunotherapy still has side effects and tumors hiding. For example, tumors are different in each patient, making treatment hard. Some tumors may develop the ability to adapt and resist immunotherapy during the course of treatment. The lack of efficient markers limits personalized treatment. This review introduces cancer, immune response, and immunotherapy and is arming to learn new perspectives and strategies to treat cancer with immunotherapy.

2. Tumor-infiltrating Immune Cells and Their Associations With Immunotherapies

2.1 T Cell

T cells (T lymphocytes) are key players in the adaptive immune system. They have two main roles. They recognize pathogens or tumor cells using specific receptors. They either directly kill these cells or regulate the immune response to them. T cells have different subtypes, each with unique jobs and markers. Helper T cells (like Th1, Th2, Th17) help boost the immune response. Cytotoxic T cells (CTLs) kill infected or cancerous cells. Regulatory T cells (Tregs) keep the immune system balanced. Each subtype contributes uniquely to the immune system's function. T cells mature in the thymus. There, they undergo a selection process to ensure they don't react to

the body's own proteins. This helps prevent autoimmune reactions. After maturing, T cells enter the bloodstream. They use their T cell receptors (TCRs) to recognize specific antigen-MHC complexes presented by antigen-presenting cells (APCs). Activated T cells multiply and turn into effector T cells to carry out their immune functions. Like CTLs, kill target cells directly by releasing perforin and granzymes. Others, like Th cells, regulate the immune response by secreting cytokines. The basic ways to use T cells' application in immunotherapy are Adoptive Cell Therapy (ACT) and Immune Checkpoint Inhibitor Therapy.

ACT involves taking T cells from a patient's body. These T cells undergo expansion and modification outside the body. After modification, the T cells are reinfused back into the patient. This process aims to boost the immune system's response against tumors. CAR-T cell therapy is a specialized ACT that genetically engineers T cells. It equips T cells with CARs that can precisely identify antigens on tumor cells. Immune checkpoint inhibitors target PD-1 or CTLA-4 to release T cells from tumor suppression. Immune checkpoint inhibitors aim to T cells regain their antitumor capabilities. This restoration of T cell function helps fight against cancer.

2.2 B Cell

B cells, also known as B lymphocytes, are another important part of the adaptive immune system. They are mainly responsible for humoral immune responses. B cells use their B-cell receptors (BCRs) on their surface to recognize antigens. When activated, B cells turn into plasma cells. Plasma cells produce and release specific antibodies. These antibodies can stop pathogens or make them easier for other cells to absorb. In addition, antibodies can kill infected or cancerous cells through a process called antibody-dependent cell-mediated cytotoxicity (ADCC).

The stimulation of B cells is dependent on receiving two crucial signals. Primarily, this initiation occurs when the B-cell receptor (BCR) engages with a specific antigen. The second signal comes from T cells, specifically the interaction between CD40 and its ligand. When B cells receive both signals, they start to multiply and change. This process creates two types of cells: memory B cells and plasma cells. Memory B cells remember antigens and can respond faster if they encounter the same antigen again. Plasma cells produce a lot of antibodies to fight against pathogens. For example, cancer vaccines work by activating B cells. When B cells are activated, they produce antibodies against tumor-specific antigens. In addition to amplifying the body's humoral immune reaction to cancer, B cells fulfill the role of antigen-presenting cells (APCs). In their capacity as APCs, B cells introduce tumor antigens to T cells, thereby reinforcing the T cells' immune reaction to combat tumor cells.

2.3 NK Cell

NK cells are a crucial part of the innate immune system, known for their rapid response in eliminating virus-infected or cancerous cells. They have the ability to quickly respond to threats. They kill cells that are infected with viruses or have become cancer. NK cells use receptors to identify their targets. These receptors include activating receptors like NKG2D and CD16. They also have inhibitory receptors like KIRs that can stop them from attacking.

The balance of these receptors decides whether an NK cell will attack or not. NK cells are able to recognize cells that have lost or changed their MHC I molecule expression. When activated, NK cells release toxic granules called cytotoxic granules. These granules contain perforin and granzymes, which cause the target named undergo apoptosis (programmed cell death). In addition to releasing toxic granules, NK cells can also kill target cells through a process called antibody-dependent cell-mediated cytotoxicity (ADCC). In ADCC, NK cells work together with antibodies to target and destroy infected or cancerous cells.

NK cells are used in immunotherapy in two main ways: adoptive cell therapy and NK cell activation therapy. Adoptive cell therapy is a procedure where natural killer (NK) cells are proliferated ex vivo, prior to their reintroduction into the patient, thereby augmenting the immune system's tumor-fighting capabilities. In contrast, NK cell activation therapy stimulates these cells through the administration of cytokines, such as interleukin-2 (IL-2), or the use of monoclonal antibodies, to enhance their activity against cancerous growths. This activation increases their ability to kill tumor cells.

2.4 Myeloid Cells

Myeloid cells, comprising macrophages, dendritic cells, and neutrophils, are crucial for the innate and adaptive immune responses. They detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) via pattern recognition receptors (PRRs), thereby contributing significantly to immune defense mechanisms. Myeloid cells recognize pathogens and damage. They clear pathogens and dead cells by phagocytosis. They also make cytokines and chemokines to control the immune system. Dendritic cells are special APCs. They activate T cells by showing antigens. Macrophages eat pathogens and make cytokines to help immune control.

Myeloid cells have many potential uses in cancer immunotherapy. For example, dendritic cell vaccines are used.

They carry tumor antigens to activate T cells against tumors. Another approach is modifying myeloid cells into CAR-macrophages. This enhances their ability to target and kill tumors. Immunomodulators like GM-CSF are also important. They boost the growth and activity of myeloid cells in the tumor microenvironment. This helps them function better in fighting cancer.

3. Immunotherapy in Cancer Treatment

Immunotherapy functions through the enhancement of a patient's immune system, enabling it to identify and combat cancer cells. In contrast to conventional chemotherapy and radiation treatments, this approach seeks to preserve and leverage the body's inherent defense systems for a more precise cancer attack. It encompasses various strategies such as vaccination against cancer, the use of cytokines to boost immune responses, the transfer of immune cells to augment anti-tumor activity, and the use of inhibitors to block immune checkpoints that tumors exploit to evade detection.

3.1 Oncolytic Virus Therapies

Oncolytic viruses are a new type of cancer treatment. They use the natural abilities of some viruses or are genetically modified. These viruses selectively replicate inside tumor cells. This causes the tumor cells to break down and die. Concurrently, it facilitates the enhancement or potentiation of the immune system's reaction to combat cancer. The basic principle of oncolytic virus therapy is that oncolytic viruses can specifically recognize and bind to receptors on tumor cells. By entering the tumor cells, they replicate inside, causing the cells to die. During this process, the breakdown of tumor cells releases tumor antigens. Some genetically modified oncolytic viruses are able to express immune-stimulatory molecules, like granulocyte-macrophage colony-stimulating factor (GM-CSF). These molecules further enhance the immune response against tumors. This activates the immune system, trigger a specific immune reaction against the tumor. There are many types of oncolytic virus therapies available [3]. Among them, Talimogene Laherparepvec (T-VEC) is the first oncolytic virus treatment approved by the FDA in the US [3].

T-VEC is a modified version of the herpes simplex virus-1 (HSV1) used to treat recurrent melanoma. Administered through intratumoral injection, T-VEC selectively replicates inside tumor cells and induces an anti-tumor immune response [3]. In a study that was both prospective and randomized, T-VEC successfully met its main goal, which was to increase the Durable Response Rate (DRR). Additionally, the study showed significant enhancements in the Objective Response Rate (ORR), as well as in the duration of Progression-Free Survival (PFS) and Overall Survival (OS) [3]. Based on these results, T-VEC received full approval from the FDA in 2015 and has also been approved in Europe, Australia, and Israel [3].

3.2 Cancer Vaccines

Cancer vaccines are immunotherapies used to treat or prevent cancer. They work by activating or boosting the body's immune system to recognize and attack cancer cells. Cancer vaccines use antigens from tumor cells to stimulate the immune system. There are two types: shared antigen vaccines for common cancers and personalized vaccines for unique tumors. Personalized vaccines can use mRNA technology to select antigens based on a person's tumor genes. Cancer vaccines can also be divided into two groups: Ex vivo vaccines: Tumor samples are used to train dendritic cells in a lab. These cells take up tumor antigens, get activated, and are then injected back into the patient. In situ vaccines: Activate the immune response directly in the patient[4]. Cancer cells are killed by radiation or viruses, releasing antigens[4]. Drugs are given to activate dendritic cells, which take up these antigens and trigger an immune response [4].

HPV vaccine is a highly representative example of cancer vaccines. It utilizes the L1 capsid protein of HPV as its primary antigen. This L1 protein has the ability to self-assemble into Virus-Like Particles (VLPs) [5]. VLPs, as antigens, are recognized by the immune system. Recognition of VLPs activates Antigen-Presenting Cells (APCs) such as dendritic cells[5]. Activated APCs then stimulate specific B cells and T cells. Activated B cells differentiate into plasma cells[5]. Plasma cells produce neutralizing antibodies against the HPV L1 protein[5]. These neutralizing antibodies provide passive immunity against HPV infection. In clinical trials, HPV vaccines have demonstrated excellent safety profiles. Most adverse reactions to HPV vaccines are mild and temporary. Individuals vaccinated with HPV vaccines are able to generate high titers of HPV-specific antibodies. This indicates that HPV vaccines possess potent immunogenicity. The protective effect of HPV vaccines can persist for many years. HPV vaccines may offer long-term or even lifelong protection against HPV infections.

3.3 Cytokine Therapy

Cytokine therapy is a type of biological immunotherapy that harnesses cytokines to modulate and enhance the body's immune system. Cytokines are small, protein molecules that play crucial roles in the body. In immune cell activation, cytokines like IL-2 (Interleukin-2) and IFN-γ (Interferon-gamma) can activate T cells, Natural

Killer (NK) cells, and other immune cells. Cytokines also enhance the function of antigen-presenting cells such as dendritic cells, improving their ability to present tumor antigens. The tumor microenvironment is often characterized by immune suppression, which leads to weaker tumor killing effects. Cytokine therapy is a treatment approach that targets the tumor microenvironment, which is often suppressive to immune responses. It operates by decreasing the quantity of cells that inhibit immune function and by enhancing the effectiveness of those that promote it. Moreover, cytokines, particularly chemokines, have the ability to guide immune cells to travel towards the tumor sites. This migration is crucial as it concentrates immune cells at the tumor location, which strengthens the immune system's attack against cancer.

NKTR-214 is a medicine for cancer treatment. It's an engineered IL-2. Clinical trials are testing its effectiveness. This medicine works by binding to immune cells. It makes the cells more active against tumors. NKTR-214 is also tested with nivolumab. Nivolumab is an immune booster. The PIVOT-02 trial is a Phase I study. It looks at the safety and effects of NKTR-214 and nivolumab together. The trial found the combination is safe and active against tumors [6]. Thirty-eight patients were treated. More than half saw their tumors get smaller. Seven patients had no cancer left [7]. These results are promising [7].

3.4 Adoptive Cell Transfer

Adoptive cell transfer is a treatment. It starts by taking immune cells from the body. Then, these cells are grown and changed in a lab. After that, the changed cells are put back into the patient. They can directly kill tumors or help the body's immune system fight cancer. There are many types of cells used in ACT, like NK cells, LAK cells, DCs, CIKs, CTLs, TILs, and special T cells like CAR-T and TCR-T. ACT has advantages over other cancer treatments. It can recognize tumors very well and help the body fight cancer. Prior to the reintroduction of the cells, medical professionals may modify the patient's physiological environment to facilitate the cells' efficacy in battling cancer [8].

CAR-T cell therapy is a well-known example of ACT. CAR T cells are genetically modified versions of T cells that harness the power of the immune system to target and eliminate infected or cancerous cells CAR stands for a combination of different receptors[9]. It enables CAR T cells to recognize cancer proteins on the surface of cancer cells [9]. The design of CAR incorporates three crucial domains: the binding domain, the signaling domain, and the transmembrane domain [10]. The binding domain aims to bind and recognize the target antigen. Traditional T-cell receptors are limited in that they can only recognize antigens presented on MHC molecules, not directly on the surface of cancer cells, significantly restricting their range of applications. To overcome this, scientists innovatively introduced specific antibody fragments derived from B cells, which have the ability to bind to a wide range of proteins. The signaling domain sees the ingenious fusion of the signaling transduction domain of the CD3ζ chain with signaling elements from co-stimulatory molecules like CD28 at the end of CAR. This design ensures that CAR T cells receive sufficient activation signals after recognizing cancer cells. The transmembrane domain provides flexibility to the binding domain when binding to antigens, thereby increasing the chances of successful binding.

Axi-Cel is a type of this therapy that homes in on CD19, a protein often seen on large B-cell lymphoma. The ZUMA-1 trial showed good results with Axi-Cel. It helped 82% of patients with their tumor shrinkage and 54% had a complete disappearance of cancer [11]. Thanks to these results, Axi-Cel was approved by the FDA in 2017 [11]. It's now a treatment for adults with recurring or hard-to-treat large B-cell lymphoma [11]. This approval is a big step for CAR T-cell therapy in blood cancer treatment and opens up possibilities for treating solid tumors too.

3.5 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a groundbreaking class of drugs used to treat cancer. They work by blocking inhibitory receptors or their ligands on immune cells, lifting the brakes on the immune system. This enhancement facilitates the improved recognition and destruction of cancer cells by T cells. Typically, immune modulators, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) with its ligand (PD-L1), are engaged to keep T-cell reactions in check. Such regulation is vital for curbing overly aggressive immune reactions and for the prevention of autoimmune conditions. When T cells are activated, these checkpoints send signals to limit their proliferation and activity. However, tumor cells can use these checkpoints to suppress T-cell activity, evading immune surveillance. Immune checkpoint inhibitors specifically target and block these molecules, disrupting the tumor's inhibitory effect on T cells. With the checkpoints blocked, T cells regain their ability to recognize and attack tumor cells, boosting the immune response against cancer. Pembrolizumab is a PD-1 blocker used for cancer treatment. It was studied in a trial named KEYNOTE-001 for advanced melanoma [12]. The study found 25% of patients had their tumors shrink. The effects were long-lasting [12]. This gives a new option for treating late-stage melanoma.

4. Conclusion

As a major global killer, the interplay between cancer and the immune system is crucial in medical research. Immunotherapy, a revolutionary approach in cancer treatment, activates or enhances the patient's immune system to recognize and attack cancer cells. The article explores the complex link between cancer and immunity, and introduces new immunotherapy strategies for cancer treatment. The review comprehensively introduces multiple types of immunotherapy, such as cancer vaccines, cytokine therapy, adoptive cell transfer, and immune checkpoint inhibitors. Although immunotherapy has achieved remarkable success in treating some cancers, challenges remain in enhancing efficacy, reducing side effects, and overcoming tumor immune evasion.

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