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Cancer Immunotherapy: Review, Advancement and Future Outlook

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Abstract. With the continuous improvement of cancer treatment, numerous approaches have achieved remarkable results and have been implemented in clinical treatment. During the few decades, surgery, radiotherapy, chemotherapy and immunotherapy for cancer therapy were created and developed. Immunotherapy for cancer has played a significant role especially. Tumor cells are adept at employing various mechanisms to evade the attack of the immune system. Therefore, cancer is currently one of the most difficult diseases to treat. After fully understanding the immune system, scientists have focused on aspects such as immune checkpoints, antibodies, and T lymphocytes, aiming to kill tumor cells and combat cancer. Immune checkpoint inhibitors, CAR-T cells, monoclonal antibodies and cancer vaccines were invented. After reviewing a large number of materials, this article summarizes the development history of cancer immunotherapy, integrates and summarizes some representative and popular cancer immunotherapy methods for introduction, and involves the obstacles in treatment and future prospects.

Keywords: Cancer immunotherapy, immune checkpoint inhibitors, CAR-T cell therapy, monoclonal antibody, cancer vaccine.

1. Introduction

In contemporary medicine, cancer is still one of the hardest problems to resolve. According to the World Health Organization (WHO), approximately 19.3 million new cancer cases and 10 million cancer deaths were registered worldwide in 2020 [1]. Although human understanding of cancer dates back to ancient Egyptian records (circa 2500 BC), transformative breakthroughs in cancer therapy emerged only with the advent of immunotherapy.

Traditional therapeutic modalities, including surgery, radiotherapy, and chemotherapy, have laid the foundation for cancer treatment but are associated with significant limitations. Radical surgical procedures often result in irreversible organ damage, while non-targeted radiotherapy and chemotherapy induce systemic toxicity and compromise immune function [2, 3]. Furthermore, metastatic disease, responsible for over 90% of cancer-related mortality, remains largely untreatable by conventional methods [4].

The immune system, characterized by its specificity and memory, has redefined cancer treatment paradigms. At the end of the twentieth century, important discoveries took place, for example, the identification of tumor antigens (TAAs), tumor-typical antigens (TSAs), and myriad mechanisms of T cell identification, which opened up potential for immunotherapy. For instance, the isolation of the melanoma-associated antigen MAGE-1 by Lloyd Old's team in 1968 provided the first evidence of tumor-specific antigen expression [5]. Subsequent milestones, including James Allison's characterization of CTLA-4 and Tasuku Honjo's delineation of the PD-1 pathway, catalyzed the development of immune checkpoint inhibitors (ICIs), revolutionizing the management of advanced malignancies [6, 7].

Through the inhibition of inhibitory pathways like PD-1/PD-L1 (PD-ligand 1) and CTLA-4, ICIs prevent tumor immune evasion. By 2023, the US Food and Drug Administration (FDA) had approved more than 50 treatment regimens based on ICI, which have achieved durable efficacy in previously incurable cancers, including metastatic melanoma and non-small cell lung cancer (NSCLC) [8]. The CheckMate-067 trial illustrated that the 5-year survival rate of patients with advanced melanoma who

received treatment with nivolumab (an anti-PD-1 antibody) combined with ipilimumab (an anti-CTLA-4 antibody) was 52%, while that of patients who received chemotherapy was 26% [9].

The concurrent progress made in immunotherapy like chimeric antigen receptor T-cell (CAR-T) therapy has broadened the scope of immunotherapy. In 2017, CD19-targeted CAR-T therapies achieved complete remission rates exceeding 80% in refractory B-cell malignancies, marking the first FDA-approved genetically engineered cell therapy [10].

Despite these advancements, challenges persist. The primary and acquired resistance to ICIs, the cytokine release syndrome (CRS) associated with CAR-T therapy, and the absence of reliable biomarkers for patient stratification all limit the clinical efficacy [11]. This review synthesizes the historical evolution of cancer immunotherapy, evaluates current clinical applications, and discusses emerging strategies to address existing barriers, including tumor microenvironment modulation, combination therapies, and novel biomarker discovery.

2. ICIs

ICIs, a cornerstone of modern cancer immunotherapy, function by counteracting immunosuppressive signals within the tumor microenvironment (TME). Unlike conventional therapies that directly enhance immune activity (e.g., cytokines or vaccines), ICIs target inhibitory pathways exploited by tumors to evade immune surveillance. Since the approval of ipilimumab in 2011 and nivolumab in 2014, ICIs have revolutionized oncology, achieving durable responses in malignancies. Mechanistically, ICIs restore T cell effector functions by blocking interactions between co-inhibitory receptors (e.g., PD-1, CTLA-4) and their ligands (e.g., PD-L1, B7-1/B7-2), thereby reprogramming the TME from immunologically "cold" to "hot".

In a normal physiological state, immune checkpoints maintain peripheral tolerance by restraining excessive immune activation. Tumors, however, exploit these pathways through two principal strategies.

(a) Ligand Overexpression: Tumor cells respond to inflammatory cytokines (for instance, responding to IFN-γ through the JAK/STAT signaling pathway) to upregulate the expression of PD-L1. The binding of PD-L1 to PD-1 on T cells inhibits the PI3K/AKT/mTOR pathway, thereby leading to metabolic deficiency (e.g., reduced glycolysis) and functional exhaustion.

(b) Co-opting Co-inhibitory Networks: CTLA-4 is expressed in regulatory T cells (Tregs) and activated T cells. Its binding affinity to the B7 ligand is higher than that of CD28. This not only blocks co-stimulation but also promotes Treg-mediated immunosuppression. In metastatic melanoma, CTLA-4 inhibition with ipilimumab increases intratumorally CD8+ T cell infiltration but concurrently elevates immune-related adverse events (e.g., colitis) due to systemic immune activation.

2.1. Immune Escape

Tumor cells, nevertheless, are not destroyed by the immune system so easily. Tumor cells continue to use a wide variety of strategies to avoid the immune system's attack.

Recruitment and Inducement of Immunosuppressive Cells. Immunosuppressive cells are a group of cells in the immune system that have the function of inhibiting immune responses. Tregs, myeloid-derived suppressor cells (MDSCs) and Bregs are typical immunosuppressive cells in TME.

Secretion of cytokines and chemokines. To enhance the ability of tumor cells to invade and spread, for example, TGF-β secreted by tumor cells not only helps them avoid being attacked by T cells and natural killer cells (NK cells), but it also encourages the epithelial-mesenchymal transition on tumor cells.

PD-L1 expressing. The PD-L1 expression of tumor cells and the aggregation and dofferentiation of MDSCs can be induced by the TME's hypoxia, further suppressing the functions of immune cells and helping tumor cells evade the immune surveillance of the body.

2.2. Primary types of immune checkpoint

2.2.1. PD-1/PD-L1

The surface of B cells, NK cells, and activated T cells is where PD-1 is primarily expressed. The ligands PD-L1 and PD-L2 are expressed by a variety of antigen-presenting cells and tumor cells. Once PD-1 binds to PD-L1, it can prevent cytokine secretion, cytotoxicity, and T cell proliferation, which allows tumor cells to avoid immune surveillance. By selectively preventing PD-1 and PD-L1 from binding, PD-1/PD-L1 inhibitors can reduce immunosuppression and restore T cells' capacity to destroy tumor cells.

PD-1/PD-L1 signaling has been inhibited by a multitude of anti-PD-1 and anti-PD-L1 antibodies (Abs) to date, including PD-1 inhibitors and PD-L1 inhibitors respectively, including nivolumab and pembrolizumab, for instance.

2.2.2. CTLA-4

Another effective inhibitor is CTLA-4 inhibitor. The MHC of APCs presents an antigen to the T cell receptor for recognition. Then, the CD28 of T cells binds to B7 of APC, initiating a signal cascade reaction to activate T cells. Following T-cell activation, CTLA-4s express themselves, migrate to the cell membranes, replace CD28 as B7, and inhibit T-cell activity. The balance of T-cell immunity in the body is maintained by the cooperation of CTLA-4 and CD28, particularly following infection and the development and progression of autoimmune disease. Therefore, it competitively blocks the binding of B7 to CD28, transmits inhibitory signals and inhibits T cells to be activated and proliferated. By preventing CTLA-4 from binding to B7, CTLA-4 inhibitors (like ipilimumab) enable CD28 to bind to B7 normally, increasing T cell activation and bolstering the immune response against tumors.

3. CAR-T Therapy

CAR-T therapy is one of the most concerning immunotherapies in cancer treatment, as its emergence is revolutionary. This particular T cell type has undergone genetic engineering and is prominent to the treatment of tumors.

CAR protein specifically binds to the antigens on the surface of tumor cells through its extracellular antigen-binding domain, forming an "antigen-CAR" complex. This binding activates the intracellular signaling domain of CAR protein, thereby initiating the activation signal of T cells, enabling T cells to recognize and kill tumor cells expressing the corresponding antigens, and without being restricted by MHC, overcoming the limitation of traditional T cells that require MHC presentation for antigen recognition.

Modified T cells from the patient's peripheral blood are used to produce CAR-T cells ex vivo. A variety of gene transfer methods (including viral vector methods and non-viral vector methods) have been used to introduce the CAR gene into the genome of T cells. Among them, the most common gene transfer method is to transduce T cells using replication-deficient lentiviral vectors, which integrates the CAR expression cassette into the genome of T cells. Moreover, a large number of these CAR-T cells are expanded until a sufficient dosage is achieved. After being infused into patients, these cells are able to recognize and eliminate tumor cells expressing the target antigen [11].

CAR endows T cells with the ability to directly recognize tumor antigens without relying on the antigen presentation of the MHC [10], thereby overcoming the mechanism by which tumor cells evade T cell recognition by down-regulating MHC molecules.

When CAR binds to tumor antigens, it activates the signal transduction pathways within CAR-T cells. This will lead to the upregulation of co-stimulatory molecules on the surface of T cells and simultaneously activate a series of downstream signaling molecules. This initiates the activation program of T cells, causing them to enter the proliferation and differentiation stages. After activation, CAR-T cells will proliferate massively in the body, forming a large number of effector cells with

specific killing capabilities, including cytotoxic T lymphocytes (CTL), helper T lymphocytes (Th), etc. They can specifically recognize and kill tumor cells expressing the corresponding antigens.

CAR-T cells mainly kill tumor cells through two ways. On the one hand, after the effector-type CAR-T cells are closely bound to tumor cells, they will release cytotoxic substances, for instance, perforin and granzyme. These substances will cause the cell membranes of tumor cells to be perforated, leading to the leakage of substances inside the cells and ultimately causing the apoptosis of tumor cells. On the other hand, additionally, CAR-T cells have the ability to release cytokines like tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) to stimulate the body's immune system and attract additional immune cells like NK cells and macrophages to work together to eliminate tumor cells.

At present, significant achievements have been made in the treatment of hematological malignancies such as leukemia and lymphoma, enabling some patients to achieve long-term remission or even cure. For instance, in the case of B-cell acute lymphoblastic leukemia (ALL), the remission rate of CAR-T cell therapy is relatively high. However, CAR-T cell therapy is not a panacea. It still has certain obstacles to overcome in the treatment of solid tumors.

CAR-T cell therapy also has some side effects and toxicities. These toxicities still pose life threatening risks to patients.

Cytokine release syndrome (CRS). This is one of the most common and serious side effects of CAR-T cell therapy. When CAR-T cells attack tumor cells, they release a large number of cytokines, such as IL-6, TNF-α, etc., triggering a systemic inflammatory response. Patients may experience symptoms such as high fever, chills, headache, muscle pain, hypotension, shortness of breath, etc. In severe cases, it can lead to multi-organ dysfunction and even endanger life.

Toxicity of the blood system. It can cause anemia, thrombocytopenia and neutropenia, etc. This might be due to the non-specific effect of CAR-T cells on hematopoietic stem cells in the bone marrow, or it could be that inflammatory factors have inhibited hematopoietic function.

4. Other popular therapies

In addition to the therapies discussed above, therapies such as seagull monoclonal antibody and cancer vaccine are used in cancer treatment.

4.1. Monoclonal Antibody

Monoclonal antibodies are highly uniform and highly specific antibodies. They are produced by a cell population that is formed through the cloning of a single B lymphocyte, and they act solely on a specific antigenic determinant. Among the more than 30 targets and diseases for which monoclonal antibody therapies have been approved, cancer is the most prevalent. Once reliant on small molecules, antibodies have become the new cornerstone of the research and development and production of drugs [12]. Today they are used to treat a variety of diseases, including anti-idiotype vaccines, cancer, autoimmune diseases, allergic diseases, and transplantation [13].

Monoclonal antibodies are obtained by hybridoma technique and animal cell culture technology [14]. The most common method for obtaining mAbs is the traditional hybridoma technique, which involves combining immortalized cancer cell lines with spleen cells from immunized (using the target antigen) immune cells (such as B cells) from animals (e.g., rats, mice, or rabbits) [15]. Choose suitable animals, typically mice, and immunize them with particular antigens to stimulate the production of B lymphocytes that are specific to the antigens by the animals' immune systems. Extract spleen cells and myeloma cells containing B lymphocytes from the immunized animals and fuse them under the action of fusion agents such as polyethylene glycol (PEG) to form hybridoma cells. After culturing the hybridoma cells, positive hybridoma cells are screened to produce the desired specific antibodies with specific methods. The positive hybridoma cells screened out are subjected to clonal culture to obtain clones of individual cells, ensuring that the antibodies produced have high homogeneity. The mAbs can be produced in large quantities through in vivo culture (inoculating cells into animals to

form ascites and obtaining antibodies from ascites) or in vitro culture (massively culturing cells in bioreactors using cell culture techniques and collecting the culture medium to obtain antibodies).

The discovery of serum autoantibodies in numerous diseases during the 1960s supported the theory of autoimmune diseases, which was first proposed by Sir Frank McFarlane Burnet. Human leukocyte antigen (HLA) associations recorded in the 1970s suggested the role of T-cells once the peptide-presenting function of HLA was recognized, and this suggested a role for B-lymphocytes [12]. Trastuzumab (Herceptin®), a humanized human epidermal growth factor receptor 2 (HER2) mAb, was the first to be used in modern mAb therapy for solid tumors. Patients respond favorably to trastuzumab, the first monoclonal anti-cancer antibody that successfully treats solid tumors. It was precisely this rigorous science that gave rise to this pioneering monoclonal antibody, and at the same time ushered in a new era of personalized/biomarker-driven drug discovery and treatment in oncology [12].

4.2. Cancer Vaccine

Cancer vaccine is also one of the most popular and hotly debated approaches to cancer treatment recently. Immunotherapeutic ways, for example, CAR-T, ICIs, and DC-based cancer vaccines, have radically transformed the way cancer is treated. For example, immunotherapies based on checkpoint inhibitors, which can activate T cells, have improved clinical outcomes; however, their tumor targeting ability is insufficient. The clinical application of CAR-T therapy is restricted because it fails to bring clinical benefits for solid tumors and has risks of cytokine release syndrome and neurotoxicity, despite its specific tumor targeting ability [16]. As a result, cancer vaccine therapy has garnered a lot of interest lately.

In 1988, the initial iteration of the cancer vaccine was developed. Through the use of allogeneic melanoma lysate, Mitchell et al. were able to successfully stimulate an immune response of resisting the damage of melanoma in a large amount of patients [17]. A ground-breaking study on tumor antigens was published in Science in 1991 by Ludwig's Brussels-based researchers, van der Bruggen et al. They were the first to report that cytotoxic T cells could specifically recognize a tumor antigen expressed by human melanoma (MAGE Ag) [18].

Vaccines against cancer will use a variety of strategies to boost immunity and produce potent anti-tumor reactions. The effectiveness of cancer vaccines is largely dependent on the tumor antigens that T lymphocytes recognize. The two main types of peptides selected for the creation of cancer vaccines are TSAs and TAAs. Antigen-presenting cells capture, internalize, process, and present these peptides to cell-mediated immunity [18]. In one approach, Tumor antigens or immune-stimulating chemicals are used to mature and activate DCs. The DCs are given back to the patient after being loaded with tumor-specific antigens that are obtained from tumor cells or genetic material. After migrating to lymphoid organs, these DCs engage with immune cells like T, B, and NK cells. The DCs activate CD4+ helper T cells and CD8+ cytotoxic T lymphocytes (CTLs) by presenting them with the tumor antigens [19]. Using whole-cell preparations made from cancer cells is another tactic. Tumor cells are extracted from the patients and inactivated or genetically modified, and then administered to the patients. Different cells, for instance, NK cells, macrophages, and DCs, recognize the whole cells, which immediately sets off a non-specific inflammatory response [19]. Cancer vaccines based on induced pluripotent stem cells (iPSCs) are a promising strategy. The tumor microenvironment specific antigens, such as TSAs or immunosuppressive molecules, are expressed by these iPSC-derived cells. When these cells are given to the patient, immune cells recognize them and a strong immune response is triggered [19].

However, there are still some intrinsic barriers on cancer vaccine treatment, including tumor heterogeneity, individual differences and development difficulty, etc.

(a) Tumor heterogeneity: Tumor cells exhibit high heterogeneity. Cancer vaccines are difficult to target all tumor cell antigens, which may lead to some tumor cells evading the immune attack induced by the vaccines.

(b) Individual differences: There are variations in immune system functions and tumor characteristics among different patients, and their responses to vaccines also differ. Some patients may fail to generate effective immune responses.

(c) Development difficulty: The development of cancer vaccines requires the identification of tumor-associated antigens, and also needs to take into account the immunogenicity and safety of the antigens. The process is complex and costly.

5. Conclusion

A vital component of cancer treatment, cancer immunotherapy is a promising avenue for future research. Immunotherapy for cancer is more efficient than traditional radiotherapy and chemotherapy, and has relatively fewer side effects. With the continuous development of immunological technologies, cancer immunotherapy has demonstrated a broad application prospect in the fields of cancer treatment and prevention. At present, nonetheless, the comprehension of immunotherapy is merely superficial. There are still lots of obstacles and challenges. CAR-T cell therapy presents no obvious therapeutic effect on solid tumors and is costly to treat, for instance, and long-term use of monoclonal antibody therapy may lead to the drug resistances in tumor cells, and some monoclonal antibodies may still have some immunogenicity. Maximizing the reduction of side effects, and using different immunotherapy approaches to treat different tumors to expand the scope of application, etc., might be the development direction of cancer immunotherapy in the future.

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