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Cell Immunotherapy: Principles, Progress, and Challenges

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Abstract: Cellular immunotherapy refers to a therapeutic strategy that harnesses the patient's immune system for the purpose of recognizing and eliminating malignant cells. This article provides an overview of the fundamental principles, primary classifications, advancements in clinical implementation, obstacles encountered in practice, as well as potential directions for future development in cellular immunotherapy. Through in-depth analysis, our goal is to delve deeper into the comprehensive knowledge of cellular immunotherapy and look forward to its potential applications in the field of cancer therapy in the future, with a view to opening up new therapeutic avenues.

Keywords: Cell Immunotherapy; Cancer Treatment; CAR-T cells; TCR-T Cells; Immune Checkpoint Inhibitors.

1. Introduction

In this section, we first introduce the global burden of cancer and the limitations of traditional treatment methods. Then, we present cell immunotherapy as an emerging therapeutic approach, highlighting its potential and importance in harnessing the body's own immune system to fight cancer.

2. Cancer

As a broad term, cancer encompasses numerous malignant tumors that can develop in different organs and tissues within the human body. Currently, cancer is a major global health challenge, posing a serious threat to human health and life. With the influence of aging population, environmental pollution and lifestyle changes, the incidence of cancer is on the rise. Especially in developing countries, cancer rates are increasing more dramatically.

Among the prevalent modalities for cancer treatment are surgical procedures, radiation therapy, chemical therapy, precision-targeted therapies, immune-based therapies, and various other approaches. Surgery is a common way to treat cancer, especially for patients with early detection and resectable local lesions. The goal of surgery is to achieve radical or partial removal of tumor tissue to achieve the purpose of cancer treatment. Radiation therapy uses high-energy rays to kill cancer cells by destroying their DNA structure and preventing their growth and division. Radiation therapy is a common treatment for cancer that has spread locally or as a preventative measure after surgery. Chemotherapy involves the use of chemical drugs to stop the growth and spread of cancer cells, often given through injection or orally. It can be combined with radiation therapy or surgery to improve outcomes. Targeted therapy focuses on specific biological targets within cancer cells, allowing targeted drugs to act specifically on these cells while minimizing harm to normal cells, thereby improving treatment effectiveness. Examples include kinase inhibitors and anti-angiogenesis inhibitors. Immunotherapy uses the patient's own immune system to fight against cancer by enhancing tumor immunogenicity through molecular biology technology and cell engineering techniques. This approach supplements adequate amounts of normal immune cells and related molecules, stimulating and strengthening the body's anti-tumor immune response while increasing sensitivity towards cancerous growths. The ultimate goal is complete eradication of cancer by inducing tumor-specific and non-specific effector cells both internally and externally in order to bolster the body's ability to recognize and eliminate malignant cells effectively. Immune checkpoint inhibitors, CAR-T cell therapy, cancer vaccines, along with other strategies that augment the immune system's capacity for identifying and destroying cancerous cells are included in this category.

3. Cellular Immunotherapy

3.1. Cellular Immune System

The immune system functions as the body's fundamental line of defense, shielding it from a diverse array of threats including bacteria, viruses, and foreign substances. Additionally, it plays a crucial role in eliminating aging cells and mutated cells that may potentially develop into cancerous cells. The development of cancer depends on the interaction between cancer cells and the immune system. In healthy individuals, a strong immune system can efficiently eliminate mutated cancer cells. However, individuals with cancer often have weakened immune systems, making it challenging for them to identify and destroy cancer cells effectively. Moreover, the growth of cancer cells further suppresses the patient's immune function while also employing various mechanisms to evade recognition and destruction by immune cells.

T-cells rely on their surface receptors, specifically the T-cell receptors (TCRs), to discern peptide fragments that are presented by major histocompatibility complex (MHC) molecules. CD8+ cytotoxic T-cells are capable of identifying antigens that are displayed on MHC Class I molecules, while CD4+ helper T-cells recognize antigens that are exhibited on MHC Class II molecules. Cancer cells may exhibit abnormal proteins or protein fragments due to genetic mutations or infections. These abnormal proteins are broken down by proteasomes and transported to the endoplasmic reticulum

through TAP transporter proteins before being presented to CD8+T-cells via MHC Class I molecules.

Natural killer (NK) cells: NK cells identify cancerous cells by detecting those lacking MHC Class I molecules. Maintaining normal expression of MHC Class I molecules is crucial in suppressing NK cell activation. When attempting to evade the immune system, cancerous cells reduce their expression of MHC Class I molecules which inadvertently exposes them to surveillance by NK Cells

3.2. Cancer Cells Evading Immune Surveillance

T lymphocytes employ their T cell receptors (TCRs) on the surface to identify peptide fragments that are displayed by major histocompatibility complex (MHC) molecules. CD8+ cytotoxic T cells recognize antigens exhibited on MHC Class I molecules, whereas CD4+ helper T cells acknowledge antigens presented on MHC Class II molecules. Abnormal proteins or protein fragments may be expressed by cancerous cells as a result of genetic mutations or infections. These atypical proteins undergo degradation by the proteasome and are subsequently transported to the endoplasmic reticulum through TAP transporter proteins before being presented to CD8+T cells via MHC Class I molecules.

3.3. Cellular Immunotherapy

Cellular immunotherapy entails the extraction of immune cells from the human body, their cultivation in a laboratory to amplify their numbers and enhance their targeted killing capabilities, and subsequently reintroducing them into the body to eliminate pathogens, cancer cells, and mutated cells present in the bloodstream and tissues. This procedure disrupts immune tolerance, activates and boosts the body's immune function, serving both as a treatment method and a means of promoting overall health. T lymphocytes (T cells) play a pivotal role in the immune system, particularly in mounting an anti-cancer immune response. They constitute an essential component of the adaptive immune system with the ability to identify and eradicate infected or cancerous cells. Through cellular immunotherapy, we can augment T cell-mediated anti-cancer activity effectively combating cancer. T cells possess recognition abilities enabling them to target abnormal cells within the body including cancerous ones by identifying specific antigens on their surface such as tumor-associated antigens (TAA) along with novel antigens thereby determining their location for elimination purposes. The cytotoxic function primarily executed by CD8+T cells (cytotoxic T lymphocytes) involves direct eradication of cancerous cells. Approaches aimed at enhancing T cell anti-cancer efficacy encompass:

CAR-T Cell Therapy: This therapeutic approach employs genetic modification techniques altering T cell characteristics resulting in expression of chimeric antigen receptors (CARs), thus rendering them more precise in targeting and attacking malignant neoplastic growth.

TCR-T Cell Therapy: This therapy focuses on modifying T cell receptors (TCRs) enabling recognition of specific tumor antigens while concurrently bolstering their capacity to combat malignancies.

Immune checkpoint inhibitors are medications that hinder tumor cells from evading T cell assault by targeting immune checkpoints (such as PD-1/PD-L1), thus enabling the anticancer potential of T cells to be unleashed.

TIL Therapy: Utilizing the patient's own tumor-infiltrating lymphocytes (TILs), which have already demonstrated the ability to attack cancer cells in vivo, they are expanded in vitro and then returned to the patient to enhance their anticancer effect.

Cancer Vaccines: Designed to activate T cell immune responses against specific tumor antigens, they can be used to prevent or treat cancer.

3.4. Main Types of Cellular Immunotherapy

CAR-T Cell Therapy: In hematological malignancies, CAR-T is the absolute leader in cell therapy, with CD19 being the primary target, followed by BCMA, CD20, CD22, and CD123. In the practice of solid tumor treatment, different cell therapy strategies have been attempted, but none have achieved breakthroughs. To date, the fastest and most successful cell therapy from basic research to clinical translation is CAR-T. Since the FDA approved the first cell therapy drug in 2017, eight cell therapy products have been launched successively, as shown in Table 1. Among them, three are products from Chinese companies, namely Axicabtagene ciloleucel, Relma-cel targeting CD19 and Ciltacabtagene Autoleucel targeting B cell maturation antigen (BCMA). China is developing rapidly in this field. Since 2016, more than 300 cell therapy products have been in clinical research, and many are still in preclinical research stages. Among the three products currently listed in China, Ciltacabtagene Autoleucel, a CAR-T drug therapy targeting the BCMA target, is completely independently developed by China. Public data shows that it has significant efficacy, with an objective response rate of up to 97.9% in the treatment of relapsed/refractory multiple myeloma, including a stringent complete response rate of 82.5%, and controllable safety

Name	Target spot	Research development enterprise	and initial approved indications	First market countries	Initial market dates
Kymriah	CD19	Novartis	Acute B-cell lymphoblastic leukemia	USA	2017
yecarta	CD19	Kite/Gilead	B-cell lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma	USA	2017
tecartus	CD19	Kite/Gilead	T-cell lymphoblastic lymphoma	USA	2020
breyanzi	CD19	Newgen/BMS	B-cell lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, follicular lymphoma	USA	2021
abecma	BCMA	Bluebird/BMS	Multiple myeloma	USA	2021
Acalabrutinib	CD19	Fosun Kite	Adult relapsed/refractory large B-cell lymphoma	China	2021
Rucaparib	CD19	WuXi AppTec	Diffuse large B-cell lymphoma	China	2021
Sitravatinib	BCMA	Legend Biotech / Johnson & Johnson	Relapsed/refractory, refractory multiple myeloma	USA	2022

Figure 1. Eight globally marketed cancer cell immunotherapy products

- TCR-T Cell Therapy: TCR-T cells recognize tumor-specific antigens presented by major histocompatibility complex (MHC) molecules through their TCRs on the cell surface. These antigens can be neoantigens produced by tumor cells due to genetic mutations, viral infections, or other mechanisms, or they can be protein fragments abnormally expressed by tumor cells. The TCRs of TCR-T cells bind to antigen peptide fragments on MHC molecules, activating the T cells and subsequently killing tumor cells or activating other immune cells through cytokine secretion to participate in the antitumor response. Compared to CAR-T cell therapy, TCR-T cell therapy has advantages in recognizing neoantigens within tumors and those produced by mutations, especially showing potential in the treatment of solid tumors. However, its application is limited by MHC matching and potential off-target effects.

Inhibitors of immune checkpoints: Immune checkpoints are regulatory mechanisms that play a vital role in maintaining the balance of the immune system. Consequently, drugs known as immune checkpoint inhibitors can alleviate the suppression caused by tumors on the immune system. By blocking interactions between PD-1/PD-L1 and CTLA-4/B7, PD-1 inhibitors (such as pembrolizumab and nivolumab) and CTLA-4 inhibitors (such as ipilimumab) disrupt inhibitory signals, enabling T cells to regain their functionality and enhance their ability to identify and attack tumor cells. These inhibitors have demonstrated significant clinical efficacy in treating various cancers like melanoma, non-small cell lung cancer, renal cell carcinoma, among others. However, it is important to note that they may also lead to immune-related side effects such as autoimmune diseases; hence careful monitoring and management are necessary during their usage.

Tumor infiltrating Lymphocyte therapy and cancer vaccines: TIL therapy and cancer vaccines are two different types of immunotherapy, both of which aim to harness the patient's own immune system to fight cancer. TIL therapy requires the extraction of tumor infiltrating lymphocytes (TILs) from the patient's tumor tissue. These cells are naturally present in the tumor microenvironment and have the ability to recognize and attack cancer cells. In the lab, these TILs are augmented to increase their numbers and then reinjected into the patient to strengthen the immune system's attack on the tumor. TIL therapy has shown some success in treating certain types of solid tumors, particularly advanced melanoma. For example, lifileucel, a TI-based approach, has been approved by the U.S. Food and Drug Administration for some types of advanced melanoma. In addition, TIL therapy is also undergoing clinical trials in other types of cancer, such as lung and pancreatic cancer, showing potential for treatment.

Cancer vaccines work by introducing specific tumor antigens or related molecules to activate T cells and B cells in the patient's immune system, triggering an immune response against tumor cells. These antigens can be proteins expressed on the surface of tumor cells, neoantigens produced by tumor cell mutations, or tumor-related molecules presented in other ways. Clinical research on cancer vaccines is more extensive, covering various types of cancer and different vaccine strategies. Some vaccines are undergoing early-phase clinical trials to assess their safety and immunogenicity. Other vaccines, such as mRNA-based cancer vaccines, are exploring combination therapy with other treatments, such as immune checkpoint inhibitors, to improve therapeutic effects.

Overall, TIL therapy and cancer vaccines are promising immunotherapy strategies that are continuously being developed and refined to provide more effective and personalized treatment options for cancer patients. With further clinical research, the effectiveness and safety of these treatment approaches will be further validated and optimized.

γδT Cell Therapy: γδT cells are a type of unconventional T cell that recognizes non-peptidic antigens through T cell receptors composed of γ and δ chains. They play crucial roles in early immune responses and mucosal immunity. In cancer treatment, γδT cells can directly kill tumor cells or enhance antitumor effects by secreting cytokines and modulating immune responses. Although γδT cell therapy has shown potential therapeutic effects on certain types of cancers in some clinical trials, its exact position and effectiveness in cancer treatment still need further research and validation.

3.5. Progress in Clinical Applications

CAR T cell therapy, or chimeric antigen receptor T cell (CAR-T) therapy, leverages the power of genetic engineering to transform a patient's T cells, enabling them to precisely identify and target specific tumor antigens. While this therapy has demonstrated remarkable response rates and prolonged therapeutic benefits in the treatment of hematological malignancies like acute lymphoblastic leukemia (ALL) and certain non-Hodgkin's lymphoma subtypes, its efficacy in solid tumors remains limited. Additionally, CAR-T therapy may be accompanied by significant side effects, including cytokine release syndrome (CRS) and neurotoxicity, which are important considerations in its administration.

CIK cell therapy: CIK (cytokine induced Killer cells) is a mixture of immune cells expanded in vitro with a wide range of antitumor activities. CIK cell therapy has been tested in clinical trials for solid tumors such as non-small cell lung cancer (NSCLC). The results showed that CIK cell combined chemotherapy had better disease control rates and improved survival than chemotherapy alone.

Dendritic cell vaccine therapy: Dendritic cells (DCS) are powerful antigen-presenting cells that activate T cell immune responses against tumors. Dendritic cell vaccine therapy involves loading tumor antigens onto dendritic cells, which are then re-injected into the patient to activate a specific anti-tumor immune response. Although dendritic cell vaccine therapy has shown some effectiveness in some clinical trials, its effectiveness compared to existing treatments still needs to be further confirmed.

Immune checkpoint inhibitors: Immune checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors activate the antitumor activity of T cells by reducing the suppression of the immune system by tumors. These inhibitors have shown significant therapeutic efficacy and improved survival in a variety of cancers, such as melanoma, lung cancer, and kidney cancer. However, not all patients respond to these therapies, and they may be associated with immune-related side effects.

γδT Cell Therapy: γδT cells are a special subset of T cells that can recognize non-peptide antigens. γδT cell therapy has shown potential therapeutic effects for certain cancer types in some clinical trials, but more research is needed to determine its exact role in cancer treatment.

Overall, cell immunotherapy has made progress in improving the survival and quality of life of some cancer patients, but it still faces challenges such as low response rates, side effect management, and effectiveness in solid tumors.

Future research needs to further optimize treatment methods, improve therapeutic effects, and provide more personalized treatment options for patients.

3.6. Challenges Facing Cell Immunotherapy

Drug resistance is a significant factor leading to poor therapeutic outcomes, a problem that exists in chemotherapy, radiotherapy, and targeted drug therapy for tumors, and is also unavoidable in immunotherapy. Intrinsic factors of patients, such as their genome, epigenome, and autoimmune system, contribute to and determine their response to therapeutic drugs. Additionally, as treatment drugs are exposed and accumulate during therapy, the tumor and immune microenvironment of the patient will also evolve accordingly, which may also affect the drug's effectiveness. Although cell immunotherapy, especially CAR-T therapy, has shown great potential in the field of cancer treatment, it still faces challenges such as high cost, safety issues, and durability of therapeutic effects. To reduce costs, researchers are exploring automated production and economies of scale, while introducing "safety switches" and optimizing CAR-T cell design to improve the safety and durability of treatment. These technological advancements are gradually pushing cell immunotherapy towards more economical, safer, and more effective directions.

The advent of immune checkpoint inhibitors and their success in the treatment of cancer made tumor immunotherapy number one on Science magazine's top 10 scientific breakthroughs in 2013. Even so, however, their clinical effectiveness is limited. For example, anti-PD-1 /PD-L1 antibodies in the treatment of esophageal cancer, prostate cancer, pancreatic cancer, ovarian cancer and other tumors, the overall clinical response rate is less than 30%. Only in colorectal cancer patients with high microsatellite instability did the response rate exceed 50%, but this type of colorectal cancer is relatively rare.

4. Future Development Directions

Firstly, the future development direction of cellular immunotherapy can be combination therapy. When monotherapy has limited therapeutic effects, combination therapy has become a trend, especially for complex immune regulation. As a complex disease, tumor therapy usually involves the combined use of multiple drugs, aiming to maximize therapeutic effects, reduce toxic and side effects, and delay the occurrence of drug resistance. In the clinical application of tumor immunotherapy, different combination therapy protocols are also being tried. Currently, there are over 5000 ongoing clinical trials globally on the combined use of PD-1/PD-L1 inhibitors, covering almost all malignancies.

Secondly, the metabolic regulation of immune cells by the three major nutrients mediated by SLCs and some potential strategies for targeting SLCs on immune cells to enhance tumor immunotherapy.

Thirdly, the biological function of soluble T cell immunoglobulin and mucin domain 3 (sTIM3) and its important role in tumor immunotherapy. The level of sTIM3 in the plasma of patients with various diseases is abnormal, especially in cancer patients. Future research can explore the potential of sTIM3 as an immunotherapy target.

Fourthly, macrophages are key members of the immune system with powerful phagocytic and digestive functions. Utilizing chimeric antigen receptor (CAR) technology, macrophages undergo genetic modifications that empower them with the ability to uniquely identify and recognize antigens expressed on the exterior of tumor cells, combining the natural immune function of macrophages with the high specificity of CAR to enhance their targeting and killing abilities against tumors, achieving effective immunotherapy. Macrophages with CARs (CAR-Ms) can stimulate tumor phagocytic function transduction and induce CAR-Ms to exhibit an M1-type phenotype by recombining CARs of human macrophages, secreting proinflammatory cytokines to repolarize M2 macrophages in the TME and promote immune responses of T cells.

5. Conclusion

Cell-based immunotherapy harnesses the body's inherent immune capabilities to identify and combat cancerous cells, offering a novel therapeutic approach. It holds significant importance and immense potential in the field of cancer treatment. By activating and enhancing the patient's own immune cells, cell immunotherapy can not only extend the survival period of cancer patients but also significantly improve their quality of life.

Firstly, cell immunotherapy targets specific tumor antigens to precisely attack cancer cells, minimizing damage to normal cells. Compared to traditional radiotherapy and chemotherapy, this method has fewer side effects, reducing the physical burden on patients and improving their quality of life. Secondly, cell immunotherapy can activate immune memory within the patient's body, enabling the immune system to continuously monitor and eliminate cancer cells, potentially leading to long-term disease control or even cure. For patients with advanced cancer, this represents greater hope and a better prognosis. Additionally, as scientific research continues to advance, methods of cell immunotherapy are constantly being optimized and innovated. For instance, CAR-T cell therapy has achieved remarkable therapeutic effects in certain types of hematologic malignancies, while strategies for cell immunotherapy against solid tumors are also being actively explored and developed.

In summary, cell immunotherapy provides a novel treatment option for cancer patients, extending their survival period and improving their quality of life, bringing revolutionary changes to cancer treatment. With continuous progress in future research, cell immunotherapy is expected to play a crucial role in the treatment of various types of cancer, offering patients greater hope.

References

[1] Maude, S.L., et al., Chimeric antigen receptor T cells for sustained remissions in leukemia. New England Journal of Medicine, 2014. 371(16): p. 1507-1517.

[2] Porter, D.L., et al., Chimeric antigen receptor T cells persisting and mediating sustained remissions in multiple myeloma. New England Journal of Medicine, 2015. 373(3): p. 2548-2549.

[3] Schuster, S.J., et al., Chimeric Antigen Receptor T Cells in Refractory B-Cell Non-Hodgkin's Lymphoma. New England Journal of Medicine, 2017. 377(26): p. 2545-2554.

[4] Davila, M.L., et al., Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Science Translational Medicine, 2014. 6(224): p. 224ra25.

[5] Grada, Z. and S.L. Maude, CD19-targeted T cells for the treatment of B cell malignancies. Immunology, 2016. 147(3): p. 369-379.

[6] Ruella, M., et al., Dual CD19 and CD123 targeting prevents antigen-loss relapses after CD19-directed immunotherapies. J Clin Invest, 2016. 126(10): p. 3814-3826.

[7] Shah, N.N., et al., Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nat Med, 2020. 26(10): p. 1569-1575.

[8] Choi, B.D., et al., CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity. Nat Biotechnol, 2019. 37(9): p. 1049-1058.

[9] Liao, Q.B., et al., Engineering T cells with hypoxia-inducible chimeric antigen receptor (HiCAR) for selective tumor killing. Biomark Res, 2020. 8(1): p. 56.

[10] Fraietta, J.A., et al., Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. Nature, 2018. 558(7709): p. 307-312.