HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 1, e2031699 (3 pages)
https://doi.org/10.1080/21645515.2022.2031699

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IMMUNOTHERAPY – COMMENTARY

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Future prospects for cancer immunotherapy - Strategies for ineffective cancers

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ABSTRACT

With the Nobel Prize in Physiology or Medicine in 2018, cancer immunotherapy is attracting more attention than ever before and is strongly expected to develop in the future. Immune checkpoint inhibitors were developed as drugs with a completely different mechanism from conventional chemotherapy for cancer patients, and their therapeutic effects were characterized not only by tumor shrinkage but also by long-term survival of cancer patients, which had a strong impact on cancer treatment. On the other hand, as a result of numerous clinical trials, it was found that the efficacy of immune checkpoint inhibitors alone is only about 10–30%. Currently, more than 2,500 clinical trials of combined cancer immunotherapy with immune checkpoint inhibitors are being conducted with the hope of further improving therapeutic efficacy. Another new cancer immunotherapy, Chimeric Antigen Receptor (CAR) gene transfer T-cell therapy, has been approved for B-cell hematopoietic tumors. In this article, we will outline the future prospects of cancer immunotherapy developed in this way, especially from the viewpoint of "strategies for ineffective cancer".

ARTICLE HISTORY
Received 29 December 2021
Accepted 18 January 2022

KEYWORDS
Cancer immunity cycle; combined cancer immunotherapy; immune checkpoint inhibitors

1. Introduction

With the Nobel Prize in Physiology or Medicine in 2018, cancer immunotherapy is attracting more attention than ever before and is strongly expected to develop in the future. Immune checkpoint inhibitors were developed as drugs with a completely different mechanism from conventional chemotherapy for cancer patients, and their therapeutic effects were characterized not only by tumor shrinkage but also by long-term survival of cancer patients, which had a strong impact on cancer treatment. On the other hand, as a result of numerous clinical trials, it was found that the efficacy of immune checkpoint inhibitors alone is only about 10–30%. Currently, more than 2,500 clinical trials of combined cancer immunotherapy with immune checkpoint inhibitors are being conducted with the hope of further improving therapeutic efficacy. Another new cancer immunotherapy, Chimeric Antigen Receptor (CAR) gene transfer T-cell therapy, has been approved for B-cell hematopoietic tumors.[1–3] In this article, we will outline the future prospects of cancer immunotherapy developed in this way, especially from the viewpoint of "strategies for ineffective cancer".

2. Cancer immunity cycle

Immune checkpoint inhibitors have been approved for treating several types of cancers to date, and many clinical trials have been conducted. However, of course, not all types of cancer and not all patients respond to them. For cancer types and cases that do not respond, the development of combined cancer immunotherapy, which combines multiple immunoregulatory methods and existing therapies, is expected to enhance the therapeutic effect. In order for combined cancer immunotherapy to be successful by taking advantage of the characteristics of immunotherapy, it is important to understand its mechanism. The series of immunological processes that eliminate cancer cells is called the cancer immunity cycle, and it is an important system for understanding cancer immunopathology.[4]

(1) Priming Phase

When cancer cells undergo apoptosis or necrosis, cancer antigens are released. Cancer antigens are classified into tumor-specific and tumor-associated antigens. Tumor-specific antigens include mutant and viral antigens, while tumor-associated antigens include differentiation antigens, cancer testis antigens, and overexpressed protein antigens. Most tumor-associated antigens are commonly expressed in cancer patients, but tumor-specific antigens based on mutant antigens vary from patient to patient. Released cancer antigens and dead cancer cells are phagocytosed by antigen-presenting cells, such as dendritic cells, and migrate through lymphatic vessels to lymph nodes where they are presented to T cells. Tumor antigen-specific T cells recognize the presented cancer antigen peptides via T cell receptors and activate them.

(2) Migration Phase

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Activated T cells circulate in blood vessels throughout the body and migrate toward tumor tissues induced by various chemokines. They adhere via selectins and integrins to vascular endothelial cells, which release high levels of chemokines, and invade the tumor tissue.

(3) Effector Phase

Activated T cells that infiltrate tumor tissue specifically recognize cancer antigens on tumor cells via T-cell receptors. Upon recognition of cancer cells, activated T cells release effector molecules such as perforin and granzyme to attack and kill the cancer cells. Cancer antigens are released from the dead cancer cells, and the cycle of eliminating cancer cells (cancer immunity cycle) begins to rotate.

The state in which cancer immunity is functioning effectively means that the amplification circuit of the immune response to cancer, called the "cancer immunity cycle," continues to rotate efficiently, resulting in enhanced and expanded T cell responses and increased diversity of cancer antigens recognized as targets. On the other hand, if there is a failure in any step of the cancer immune cycle or if excessive immunosuppressive mechanisms occur, this cycle stops and it becomes difficult for the cancer immune response to be effective.

3. Factors that Enhance or Suppress the Cancer Immunity Cycle and Therapeutic Methods

What factors affect the cancer immunity cycle, and what therapies are involved in the cancer immunity cycle?

In the priming phase, anticancer drug therapy and radiotherapy are considered effective in releasing many cancer antigens from cancer cells. Some therapies kill cancer cells in a way that can easily elicit an immune response, and this type of cell death is called immunogenic cell death (ICD).[5,6] Although several mechanisms have been reported, including exposure of calreticulin molecules to the surface of cell membranes, it has not yet been proven which therapy is particularly superior.[7] It has also been reported that cancer cells with many genetic mutations often have highly immunogenic mutant antigens, which strongly induce activated T cells.[8–10] Antigen-presenting cells, especially dendritic cells, play an important role in the recognition and activation of cancer antigens by T cells. TLR and CD40 molecules are important for the activation of dendritic cells, and many clinical trials using these molecules have been conducted. In addition, clinical trials of dendritic cell vaccines that mature dendritic cells outside the body and return them to the body are being conducted, and Sipuleucel-T (Provenge®) was approved for prostate cancer.[11] In addition, T-cell activation requires co-stimulatory molecules, and clinical trials using anti-CD137(4–1BB) and anti-OX40 antibodies as therapeutic agents have been conducted and their efficacy has been verified.

In the Migration phase, production of endothelin and VEGF from the tumor microenvironment, inactivation of chemokines, and suppression of the expression of adhesion factors (ICAM, VCAM, etc.) inhibit the migration of activated T cells. In addition, inhibition of integrin-mediated adherence of T cells to vascular endothelium and inhibition of access by extracellular matrix decrease tumor tissue infiltration of activated T cells. T cells activated by dendritic cells are also unable to reach the tumor site without induction, resulting in wandering in blood vessels. It is well known that patients with cancer who have a tertiary lymphoid structure (TLS) in their tumor tissue have a good prognosis, and a recent report has shown that there are many high endothelial venules (HEV) in TLS. However, recent reports have shown that mature dendritic cells are important for HEV construction.[12–14] It was also reported that HEVs were induced by anti-VEGF and anti-PD-L1 antibodies.[15] These results suggest the usefulness of anti-VEGF antibodies and immune checkpoint inhibitors in the migration and infiltration of activated T cells.

In the effector phase, immune escape against activated T cells in the tumor microenvironment is important. In the environment where the cancer immune response is functioning, IFN-γ, IL-12, and TNFα are dominant in the Th1 environment. In this environment, M1 macrophages, which are inclined to eliminate foreign substances, and Th1-type CD4-positive T and NK cells, which enhance cellular immunity, function. Activated T cells are functionally and numerically superior to regulatory T cells. However, when the cancer immune response ceases to function locally in the tumor, immunosuppressive factors such as IL-6, IL-10, TGFβ, and IDO from exosomes released from cancer cells and surrounding connective tissues become dominant. These factors further induce the formation of cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and bone marrow-derived immunosuppressive cells (MDSCs), leading to an increasingly immunosuppressive state and the establishment of a suppressive tumor microenvironment. The loss/mutation of MHC molecules and cancer antigens in cancer cells is another immune escape mechanism to escape the attack from activated T cells. When cytokines such as IFN-γ produced by activated T cells induce upregulation of immune checkpoint molecules in cancer cells and tumor-infiltrating immune cells, the activated T cells become PD-1-mediated unresponsive, i.e., exhausted, T cells and cease to function. In this way, cancer cells successfully use their own immune evasion ability and immunosuppressive mechanisms to avoid attacks from immune cells. The administration of immune checkpoint inhibitors can restore the cancer immunity cycle to a normal cycle by restoring the ability of exhausted CD8-positive T cells to recognize and kill cancer antigens on cancer cells.

The state of suppression in the cancer immunity cycle is thought to vary from patient to patient, and a system for accurately assessing this state is being developed. In the future, it will be important to evaluate the suppressive state at each step of the cancer immunity cycle in each patient and to provide therapies that simultaneously release single or multiple suppressive factors accordingly. Thus, identification of biomarkers that can assess the immune status of individual patients and the development of efficient combined cancer immunotherapy based on these biomarkers are important strategies for ineffective cancers.

4. Conclusion

With the advent of cancer immunotherapy, the future direction of cancer treatment is expected to be an era in which priority is given to therapies aimed at curing cancer, rather than selecting therapies that are expected to prolong patients' lives as in the past. Cancer immunotherapy up to now has focused on how to efficiently

induce and enhance the immune response to cancer. Considering the cancer immunity cycle, it is theoretically difficult to achieve success with this alone. In addition, the usefulness of immune checkpoint inhibitors, the mainstay of cancer immunotherapy that has led to its current success, has only partially covered the cancer immunity cycle. In the future, it is important to consider how to overcome the problems in each phase and to consider combination therapy so that they can function efficiently. Since the mechanism of action of cancer immunotherapy is completely different from that of conventional cancer drugs, it is necessary to consider treatment methods based on a good understanding of its characteristics. In particular, combination therapy with immune checkpoint inhibitors has great potential for future development, and its use with a good understanding of the characteristics of each drug will provide not only additive but also synergistic effects. The history of conquering cancer by cancer immunotherapy has begun, and long-term and unyielding efforts will be required to achieve a cure for cancer, so it is important to continue to develop basic research and clinical development.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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