ORIGINAL RESEARCH PAPER

Microbiology

KEY WORDS: "chimeric antigen receptor T-cell", carcinoembryonic antigen (CEA), vitamin E-binding plasma protein, Cancer immunotherapy (CI), CD4+ helper T lymphocytes, CD8+ cytotoxic T lymphocytes, Antigen-presenting cells (APCs) , New Antibody therapy

IS IMMUNOTHERAPY A GAME-BREAKING MOVE IN CANCER TREATMENT?

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ABSTRACT

Immunotherapy has been a landmark discovery in cancer therapeutics. "It has changed the way to treat many advanced cancers. Immunotherapy helps in killing the cancer cells and boosting the immune system. Cancer immunotherapy in India is advancing with a focus on innovation, affordability, and accessibility, including the development of indigenous therapies and research into targeted treatments. Cancer immunotherapy is an innovative treatment for tumors today. These drugs are designed to stimulate the body's anti-tumour immune response and thereby cause tumour destruction. Immunotherapy was a revolutionary approach to combat cancer by leveraging the body's immune defences. CAR-T therapy, short for "chimeric antigen receptor T-cell", is a cutting-edge treatment that reprogrammes a patient's immune cells to fight their cancer. This innovative approach involves taking T-cells, a type of white blood cell that plays a crucial role in the immune system, from a patient and modifying them in a laboratory to better recognise and attack cancer cells. Antibody therapy holds exciting prospects in oncology owing to the level of precision an antibody can provide in binding to its target. Strategies are expected to provide solutions to many of these challenges. The explosion of more effective antibody-based therapeutics receiving regulatory approval will probably continue to follow the trend shown in the past two and a half decades.

INTRODUCTION

Cancer is a heterogeneous and multifactorial disease in which a series of genomic/molecular alterations cause the uncontrolled growth and proliferation of the cells, causing a rapid increase in tissue mass in the affected parts of the body. (1)

Cancer cells grow using the body's oxygen and supplements, depriving other cells of regular supplements and growth factors. (2)

Some of the biomarkers that are currently being used to detect cancer include human epididymis protein 4 (HE4), carcinoembryonic anti (CEA), legumain, mesothelin, osteopontin, and vitamin E-binding plasma protein. (3)

A plethora of anti-cancer drugs and natural medicinal compounds have been devised over the years, which can suppress tumor growth through diverse mechanisms. Some of the drugs/compounds work on crucial cellular enzymes, while others may alter cell metabolism. (4)

They have also shown the potential to interfere with some critical cellular processes, e.g., programmed cell death/apoptosis, drug resistance, DNA damage, DNA replication, or immune reactions. These drugs have distinct modes of action and selectivity for multiple cancer types. (5)

The idea of chemotherapy (utilizing toxic compounds and drugs to destroy cancerous cells) came into existence after the reports of mustard gas killing lymphatic tissues and bone marrow. The effects were later validated in mice using an effective derivative of the gas (nitrogen mustard) that showed effective regression of lymphoma tissues (6)

The first patient receiving this nitrogen mustard was years 15-year old lymphosarcoma patient whose cancer softened and cleared initially. Unfortunately, later he died after relapsing, but this secret military trial at Yale University paved the way for chemicals in treating cancers and developing the field of cancer chemotherapy for treating a variety of cancers (7)

Chemotherapy primarily works by preventing the cancer cells from further growth and division. Cancer cells usually divide and grow at a much-accelerated rate than normal cells and physiologically possess very high endogenous stress. (8)

The Cancer immunotherapy, which has sparked the most interest, involves antibodies to inhibitory immune checkpoint molecules. Although they have produced dramatic results in only a subset of this is an open-access article licensed under the terms of Creative Commons

Cancer immunotherapy (CI) is rapidly advancing and can now be considered to be the "fifth pillar" of cancer therapy, joining the ranks of surgery, cytotoxic chemotherapy, radiation, and targeted therapy. The CI, which has sparked the most interest, involves antibodies to inhibitory immune checkpoint molecules. (9,10)

In a recent meta-analysis of ipilimumab, a monoclonal antibody that targets cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), a type of immune checkpoint receptor or negative regulator of T-cell immune function, more than 20% of patients with metastatic melanoma who received a single round of treatment were alive 10 years later with no evidence of disease (11)

Many strategies for inducing an antitumor response against cancers have been developed. Conventional treatment modalities include surgery, radiotherapy, and chemotherapy, each of which has had advantages and disadvantages with limited success in improving clinical outcomes. (12)

Tumor cells construct an immunosuppressive environment to promote tumor growth and immune evasion mechanisms through mechanisms such as inhibiting the Th1 cells, which in turn induces cytotoxic T cell differentiation and a Th2 antagonistic response. Designing a cancer immunotherapy with appropriate delivery modalities will overcome the drawbacks associated with cancer (13)

Cancer employs a variety of strategies to evade the immune system, including delaying or even stopping antitumor activities. These immune-evading mechanisms overpower the natural immune system's antitumor activity and promote tumor formation and metastasis. (14)

The 2018 Nobel Prize in Physiology or Medicine was awarded to James Allison and Tasuku Honjo for their "discovery of cancer therapy through inhibition of negative immune regulation." Specifically, the Nobel Prize was awarded for the identification of immune checkpoints (i.e., cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death/ligand 1 (PD-1/PD-L1)), which led to the development of antibodies targeting these checkpoints for anticancer treatment (15)

However, due to poor tumor targeting and weak killing ability, they are only used for adjuvant therapy. Immunologic effector cells in nonspecific ACI include dendritic cells (DC), natural killer cells (NKC), cytokine-induced killer cells (CIK), tumor-infiltrating lymphocyte (TIL), lymphocyte-activated killer cells (LAK), macrophage-activated killer cells (MAK), etc. The immune cells in specific ACI are induced by specific tumor antigen stimulation and specific stimulating factors, including TIL therapy, T cell receptor -T (TCR-T), and Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) (16)

The main effector cells are CD8+ + T cells and CD4+ + T cells. This kind of therapy has strong specificity, strong targeting, high lethality, small side effects, and no drug resistance, so it can be used in some advanced patients or patients with no response to other curative effects. TIL therapy is only used for melanoma temporarily due to its difficulty in separating and collecting, and CAR-T therapy is mostly used for blood tumor treatment (17)

NK cells are toxic natural immune cells whose surface is mainly composed of activated killer activation receptors (KARs) and killer inhibitory receptors (KIRs). NK cells recognize that normal cells are generally dominated by inhibitory receptors and avoid killing, while NK cells can quickly respond to virus infection and tumor occurrence. (18)

In addition, activated cytokines such as IL-2 and IL-5 mediate and promote the activation of NK cells. Antibody-dependent cell-mediated cytotoxicity (ADCC) enables NK cells to recognize and kill antibody-coated tumor cells. Newly developed BiKE and TriKE molecules could improve the effectiveness of ADCC (19)

However, tumor cells still possess mechanisms that inhibit NK cells, enabling them to achieve immune escape. Firstly, tumor cells secrete MICA and MICB proteins, and relevant targeted antibodies have been developed and achieved certain results, eg, mAb 7C6 (20)

History

Immunotherapy was noted 3,000 years ago in Egypt (21)

In 1868, Busch intentionally infected a cancer patient with erysipelas, and following infection, documented that the patient's tumor decreased in size. Fehleisen repeated this treatment in 1882 and obtained similar results; he eventually identified *Streptococcus pyogenes* as the causative agent of erysipelas (22)

The first scientific attempts immune response against cancer can be attributed to German physicians, Fehleisen and Busch (23)

Father of immunotherapy---Coley used the power of the immune system to treat cancer patients in the late 19th century. (24)

Coley reported a significant number of regressions and cures in more than 1000 patients, many of whom had sarcomas (25)

The role of T-cells was recognized by Jacques Miller (26)

Thomas and Burnet proposed the concept of cancer immunosurveillance (27)

The theory of cancer immunosurveillance suggests that lymphocytes could act as sentinels to identify and potentially eliminate cells transformed by mutations (28)

This concept is now incorporated as a component of cancer immunoediting, whereby the immune surveillance system can "shape" the immunogenicity of tumor cells, which are not initially eliminated (29)

The theory of immune surveillance re-emerged in 1974, when Stutman demonstrated that nude mice with impaired T-cell function develop cancer more readily than wild-type mice (30)

Natural killer (NK) cells were identified, providing an additional cellular, anti-tumor, and virus mediator (31,32)

Schreiber, Dunn, Old, and their teams proved that T-cells were able to provide anti-tumor surveillance and immune responses (33,34)

Human tumor antigen recognized by T lymphocytes in 1991 (35)

Coley's principles were shown to be correct when Morales *et al*. established the effectiveness of BCG for the treatment of superficial bladder cancer (36)

Immune System

The immune system comprises the innate and adaptive immune systems. The innate immune system includes dendritic cells (DCs), natural killer cells (NK), macrophages, neutrophils, eosinophils, basophils, and mast cells. Innate immune cells do not require prior stimulation by antigens and act as a first line of defense against foreign antigens. The adaptive immune system includes B lymphocytes, CD4+ helper T lymphocytes, and CD8+ cytotoxic T lymphocytes, and requires formal presentation by antigen-presenting cells (APCs) for its activation. The adaptive immune system generates antigen-specific T- and B-cell lymphocytes. (37)

The immune system in every human body comprises special cells that constantly patrol the body for intruders. When they come across a damaged or cancerous cell, they destroy it. This

keeps cancerous tumours under check from growing. However, cancerous cells constantly look for ways to dodge the immune system defences. Through immunotherapy, one can strengthen the immune system's ability to fight cancer cells, apart from targeting and destroying specific proteins or receptors on cancer cells to prevent them from outsmarting the immune system.

Chemotherapy

In most situations, the drugs used to treat cancer are cytotoxic agents, ie, drugs that kill dividing cells (commonly referred to as chemotherapy). There are roughly 30-40 standard chemotherapeutic agents in common usage. They selectively damage cells that are rapidly dividing. Since tumour cells are normally in a state of rapid division, this explains the ability of these agents to reduce tumour growth and, in some cases, bring about tumour shrinkage. Some normal cells in the body are also dividing rapidly(For example, bone marrow, gut epithelium, and hair follicles). These cells are also killed by cytotoxics, which results in chemotherapy toxicity.

The aim is to kill more cancer cells than normal cells. This is called the therapeutic window due to the cancer cells being more sensitive to cytotoxics than the normal cells.

Introduction To Immunotherapy

Chemotherapy suppresses the immune system to kill cancer cells, while immunotherapy utilizes the body's own immune system to help recognize and kill the tumor. Another difference between the two treatments is predictability. Chemotherapy is highly predictable in its effects on patients, as clinicians have decades of experience treating patients with it. Immune-related toxicities are different and distinct from chemotherapy.

Some side effects of immunotherapy can include joint aches and pain, shortness of breath and colitis, pneumonitis, and myocarditis. The timing of those toxicities is unpredictable with immunotherapy, which can occur anywhere from the same day as treatment to many months and years after treatment has stopped. A variety of organ systems of the body can become inflamed as a reaction to the immunotherapy treatment. Immunosuppressive medicines can help treat the inflammation, while specific medicines are used to target the inflammation of specific organs.

Blocking one protein supercharges the immune system against cancer

Researchers have discovered a way to make the immune system's T cells significantly more effective at fighting cancer. By blocking a protein called Ant2, they were able to reprogram how these cells consume and generate energy -- essentially rewiring their internal power supply. This shift makes T cells more active, resilient, and better at attacking tumours. The findings open the door to new treatments that could strengthen the body's own immune response, offering a smarter, more targeted approach to cancer therapy. (39)

Adaptive Cell Therapy

Adoptive cell therapies (ACTs) have existed for decades. From the initial infusion of tumor-infiltrating lymphocytes to the subsequent specific enhanced T cell receptor (TCR)-T and chimeric antigen receptor (CAR)-T cell therapies, many novel strategies for cancer treatment have been developed. Owing to its promising outcomes, CAR-T cell therapy has revolutionized the field of ACTs, particularly for hematologic malignancies. Despite these advances, CAR-T cell therapy still has limitations in both autologous and allogeneic settings, including practicality and toxicity issues. To overcome these challenges, researchers have focused on the application of CAR engineering technology to other types of immune cell engineering.

CAR T-cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is one class of ACT in which a patient's T cells (a type of immune cell) are isolated from blood and genetically modified to make a protein called CAR that recognizes cancer cells. The modified T cells are then infused back into the patient, where they will seek out and kill cancer cells. The FDA has approved CAR T-cell therapy for many blood cancers, but it has so far been ineffective against solid tumors.

TCR T-cell Therapy

Another type of ACT is T-cell receptor (TCR) therapy. In this treatment, T cells from a patient's blood are genetically modified in the laboratory to make a protein called TCR before being infused back into the patient. The TCR protein helps the T cells seek out the patient's cancer cells more effectively and triggers them to attack the patient's cancer cells.

TIL Therapy

A third type of ACT, called Tumor-infiltrating Lymphocyte (TIL) therapy, uses T cells that have already made their way into tumours; these T cells are referred to as tumor-infiltrating lymphocytes (TILs).

For TIL therapy, part of the patient's tumor is surgically removed, and the TILs from within it are isolated, grown in the lab, and delivered back to the patient. Unlike the other types of ACT, TIL therapy does not require genetic modification of the patient's immune cells. TIL therapy is approved to treat certain melanomas.

Game-changer In Cancer Treatment: New Antibody Therapy

Cancer immunotherapy is a recent medical achievement, providing an additional pillar for cancer therapy. The greatest challenge in cancer therapy is to eradicate cancer cells with minimal damage to normal cells. Targeted therapy has been developed to meet that challenge, showing a substantially increased therapeutic index compared with conventional cancer therapies. Antibodies are important members of the family of targeted therapeutic agents because of their extraordinarily high specificity to the target antigens. Therapeutic antibodies use a range of mechanisms that directly or indirectly kill the cancer cells. Early antibodies were developed to directly antagonize targets on cancer cells. This was followed by advancements in linker technologies that allowed the production of antibody-drug conjugates (ADCs) that guide cytotoxic payloads to the cancer cells. Improvement in our understanding of the biology of T cells led to the production of immune checkpoint-inhibiting antibodies that indirectly kill the cancer cells through activation of the T cells. Even more recently, bispecific antibodies were synthetically designed to redirect the T cells of a patient to kill the cancer cells. (38)

Immunotherapy Is The New Era In Cancer Treatment

Immunotherapy helps in killing the cancer cells and boosting the immune system. There are several ways to treat cancer – from surgery to chemotherapy. Cancer is a disease in which some of the body's cells start to grow uncontrollably and spread to other parts of the body. Hence, it needs external help in controlling the growth. Immunotherapy is one of the processes that has shown positive results in controlling cancer. It is the process when the substances made by the body or in a laboratory are used to boost the overall immunity of the body, which further helps in finding and destroying the cancer cells. Addressing this, Dr. Sewanti Limaye, Director, Oncology and Precision Medicine, Sir HN Reliance Foundation Hospital, spoke to HT Lifestyle, and said, "Decoding of the human genome in the early 2000s brought about revolutionary changes in cancer treatment with the discovery of cancer-related genetic pathways that could be targeted with novel drugs, also known as targeted therapy. The other landmark development in cancer treatment

happened with the arrival of Immunotherapy in 2010. These drugs are designed to stimulate the body's own immune system to fight cancer. They are better tolerated with minimal side effects; however, severe toxicities could be seen in nearly 5%."(40)

The Immune System's Role In Eliminating Or Controlling Malignant Cells

As a brief background review, the immune system is classically considered to be comprised of the innate and adaptive arms, although this is a simplification since these arms have overlapping functions and are intimately related. The innate immune system includes dendritic cells, natural killer cells (NK), macrophages, neutrophils, eosinophils, basophils, and mast cells. Innate immune cells do not require prior stimulation by antigens and act as a first line of defence against foreign antigens. (41)

The adaptive immune system includes B lymphocytes, CD4+ helper T lymphocytes, and CD8+ cytotoxic T lymphocytes (CTLs), and requires formal presentation by antigen-presenting cells (APCs) for its activation (42)

The adaptive immune system generates antigen-specific T- and B-cell lymphocytes. The immune system is highly variable between individuals but relatively stable over time within a given person (43)

Each cell is estimated to experience over 20,000 DNA-damaging events each day, which are normally repaired by specific DNA repair pathways with no lasting effects (44)

Cells that are not repaired and which acquire malignant or potentially malignant changes are then usually recognized and killed by the tumour immunosurveillance system. This involves predominantly cell-mediated mechanisms that can differentiate between self and non-self antigens. Since a malignant cell can have more than 11,000 genomic mutations, many new tumor-associated antigens (TAAs) may be expressed (45)

TAAs include products of mutated proto-oncogenes, tumor suppressor genes, overexpressed or aberrantly expressed proteins, tumor antigens produced by oncogenic viruses, oncofetal antigens, altered glycolipids and glycoproteins, and cell type-specific differentiation antigens. These new TAAs, or fragments thereof, are presented on the cell surfaces with their major histocompatibility complex (MHC) molecules (46)

However, recognition of an antigen-MHC complex by a T-cell antigen receptor is insufficient for the initial activation of naive T-cells, requiring additional costimulatory signals that are provided by the engagement of the CD28 receptor on the T-cell surface with B7 ligand molecules (two of which are CD80 and CD86) on the APCs (47)

This CD28 receptor/B7 ligand combination or "immunological synapse" stimulates the proliferation and function of the T-cells. (48)

Many other receptor/ligand combinations are possible between activated T-cells and other cells, including tumor cells, and some of these interactions are inhibitory, such as PD-1/PD-L1 and CTLA-4/B7, and are discussed later in this monograph (49)

Some malignant cells can evade the tumor immunosurveillance system by manipulating their own characteristics as well as the cells in their microenvironment to become "successful" tumors; these evasive mechanisms represent the major area of interest in current CI research (50)

The concept that the immune system is capable of detecting and killing nascent "non-self" malignant cells was first developed by Burnet and Thomas in their cancer immunosurveillance hypothesis (52)

The concept was not accepted initially, but it is now considered a component of cancer immunoediting, whereby the surveillance system can determine or "shape" the immunogenicity of the tumour cells, which are not eliminated initially (53)

CONCLUSION

Cancer cells are produced in the body all the time, but most of these cells are taken care of by the body's immunity. When the body's immunity is good, these cells are killed by the immune cells. However, there are various reasons why this process fails and why cancer occurs. If the body's immunity fails or the cancer cells develop a protective mechanism due to which their antigens are not exposed to the immune cells, they don't get killed. Immunotherapy involves strengthening the body's immunity by various mechanisms-either by giving antibodies like rituximab or trastuzumab; by giving checkpoint inhibitors; or taking out the cells from the body and re-engineering them in such a way that they can fight cancer.

Till now, cancer is treated with surgery, chemotherapy, and radiation therapy, but they have limitations. For example, surgery may not be possible in large, inoperable tumours. At times, the tumours are operable, but the cancer has spread to other parts of the body, and thus the local treatment doesn't work. The same holds true for radiation therapy. Chemotherapy kills cells across the body, but again, there are chances that the cells develop resistance. Initially, we started offering immunotherapy only in advanced and relapsed cancers, but now many patients are getting this therapy upfront.

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