Review Article

Surveying Progress: A review of immunotherapeutic strategies for cancer prevention and treatment

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Abstract

Immunotherapy has reshaped cancer treatment and revitalized the study of cancer immunology. Adoptive cell transfer (ACT) and immune checkpoint inhibitors (ICIs) are two types of immunotherapy that have generated durable clinical effects, although their efficacies vary, and only certain categories of cancer patients can benefit from them. Immune infiltrates in the tumor microenvironment (TME) have been proven to play an important role in tumor growth and alter clinical outcomes in cancer patients. Comprehensive characterization of tumor-infiltrating immune cells provides an insight into the processes of cancer immune evasion, perhaps widening the creation of novel therapeutic possibilities. However, the diverse and dynamic characteristics of the TME make the exact dissection of intratumoral immune cells difficult. In this review, we discuss how cancer immunotherapy relies on a variety of ways to boost tumor immunity and marks a paradigm shift in cancer treatment, since attention is now drawn to the "biologic passport" of the individual tumor rather than the site of origin of the tumor. Biological modifiers such as cytokines and vaccines, adoptive cell therapies, oncolytic viruses, and antibodies against immune checkpoint inhibitors such as the co-inhibitory T-cell receptor PD-1 and one of its ligands, programmed death-ligand 1, are among the cancer immunotherapies discussed here. We expect that this review will strengthen our understanding of the advancements in cancer immunotherapy, facilitate the elucidation of immune cell modulation in tumor progression, and direct the discovery and development of novel immunotherapies for cancer treatment.

Keywords: Immunotherapy; tumor microenvironment; immune cells; therapeutic approaches

Historical Background

Cancer immunotherapies have significantly improved patients' chances of survival and quality of life when compared to current standards of care (which include chemotherapy, radiation, and surgery), and today, immunotherapy has made a name for itself as a cutting-edge cancer treatment of a variety of cancer types, including metastatic diseases. William B. Coley, who is regarded as the inventor of immunotherapy and made the first attempt to use the immune system power to treat cancer in the late 19th century, was one of the early oncologists who used Surgery for cancer treatment in an effort to cause sepsis and a potent immunological and anti-tumor response (Iowa, 2006). Coleybegan was injected to more than a thousand patients with mixtures of live and inactivated bacteria, in 1891 (Decker and Safdar, 2006). These bacteria included *Streptococcus pyogenes* and *Serratia marcescens*. His bacterial concoction, which came to be known as "Coley's toxin, was the first known applications of active cancer immunotherapy. Nonetheless, oncologists adopted surgery and radiotherapy as an alternative standard treatment early in the 20th century due to the lack of a recognized mechanism of action for Coley's toxin and the dangers of purposefully infecting cancer patients with dangerous germs. Future aspects of cancer immunotherapy are some cancer vaccine, immune check point inhibitors, T-celltherapies, and other

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cytokines are being used for cancer treatment (Rosenberg et al., 2007). Currently, diagnosis and treatment are challenging aspects of present time. But the recent discovery of T cell immune checkpoints, such as CTLA-4 and PD-1(Di Trolio et al., 2015), propelled the field of immune-oncology into its current era and swa the awarding of the 2018 Nobel prize in Physiology or Medicine to Dr. Allison and Honjo.

Introduction

Despite the enormous amount of research and rapid developments in prevention, diagnosis and treatment, cancer remains one of the most difficult diseases to treat. As long as the fight against cancer remains an uphill battle, there will be an adamant drive for the development of aggressive therapeutics aimed at minimizing or inhibiting cancer cell proliferation and metastasis. Cancer (malignancy) comprises many different diseases, all characterized by uncontrolled proliferation of abnormal cells with capacity for spread to healthy organs and tissues. In the last decades, a number of therapeutic approaches are available for cancer treatment, including surgery, radiation, chemotherapy, and other strategies, some of which have been awarded Nobel prizes previously (Pabla and Dong, 2012). However, advanced cancer remains immensely difficult to treat, and novel therapeutic strategies are desperately needed. Despite remarkable scientific progress, attempts to develop generalizable new strategies against cancer proved difficult. The use of immunotherapy for cancer has become widespread as a therapeutic method in recent decades and has been used to treat both solid and hematological malignancies (Kaye, 1998; Finn, 2008).

Although the initial utilization of immunotherapy for cancer treatments dates back to the nineteenth century, it was the more recent scientific advances that have helped elucidate innovative approaches to implementing immunotherapies to eradicate and/or treat various cancers (D'Errico et al., 2017). Immunotherapeutic approaches utilize components of a patient's own immune system to selectively target cancer cells, thereby mitigating many of the side effects associated with traditional treatment options (Lotze et.al., 1985).

More recently, three distinct therapeutic modalities have revolutionized the field of Immune oncology: checkpoint inhibitors, adoptive T cell transfer, and bivalent antibodies. Immune checkpoint inhibitors, in particular, have demonstrated considerable promise in their recent approval for the treatment of melanoma, non-small cell lung cancer, and other cancers (Lotze et al., 1987; Rosenberg et al., 1994). Thus, with the inclusion of immunotherapy in cancer treatment regimens, it is imperative that oncology nurses are knowledgeable about the mechanisms of action, treatment regimens, and symptoms associated with these agents (Dutcher et al., 1999). Crosstalk between tumor, immune cells, and different environment cas sia complex process that will dictate the fate for anti-tumor or pro-tumor immunity. Meanwhile, with more than a dozen new molecules identified to be involved with signaling at the interface of T cells, the discovery of many more therapeutic leads is anticipated (Saul et al., 2017; Fyfe et al., 1995). This review highlights the emerging and evolving findings that contribute to the understanding of immune oncology as well as emphasizing the importance of relevant immunotherapies for potential therapeutic interventions for cancer treatment.

Diverse approaches to cancer immunotherapy or an exploration of different strategies and their applications

To repair or enhance the capacity of the immune system to detect and eliminate cancer cells, researchers are creating laboratory substances that are identical to immune system components. Immunotherapy has gained importance as a component of various cancer treatments over the past few decades, and new immunotherapy therapies are being evaluated and approved. Some cancer types respond more effectively to immunotherapy than others, while other tumors are treated with it alone, but seem to function best when combined with other forms of therapy.

Immune Checkpoint Blockade Therapy

The human immune system has the fundamental ability to discriminate “self” molecules from “non-self” molecules so that invading bacteria, viruses, and other dangers can be attacked and eliminated. Self-non-self-discrimination is achieved by both central thymic selection and peripheral immune regulation (Borrello et al., 2015). T cells have receptors that bind to structures recognized as non-self, and such interactions trigger the immune system to engage in defense. Additional proteins acting as T-cell accelerators are required to trigger a full-blown immune response. Many scientists have contributed to this essential basic research and have identified other proteins that function as brakes on T cells, inhibiting immune activation (Cohen et al., 2018). This intricate balance between accelerators and brakes is essential for tight control, ensuring that the immune system is sufficiently engaged in the attack against foreign microorganisms while avoiding excessive activation, which can lead to the autoimmune destruction of healthy cells and tissues (Schilling et al., 2015).

Immune checkpoints or immunosuppressive molecules play crucial roles in tissue protection, immunological response control, and immune tolerance maintenance (Chikuma, 2017; Crescioli et al., 2021). The immune system elucidates adaptive responses to cancer cells and neoantigens present in antigen-presenting cells (Milella et

al., 2015). Immune checkpoint inhibitors prevent receptors and ligands from binding to each other, thereby disrupting signaling (Chasalow et al., 2013). Some immune checkpoint proteins interact with their ligand clusters, which helps cancer cells to evade T cell-mediated death. These agents have recently demonstrated improved survival outcomes in adults with solid tumors in clinical trials and have subsequently been approved for the treatment of several disease types, including melanoma. The two main checkpoint proteins that are responsible for immune excavation are (CTLA-4) named cytotoxic T lymphocytes associated, and the other one is (PD-1) named programmed cell death protein, these are the receptors expressed on the surface of cytotoxic T cells (Sloan et al., 2017). (CTLA-4) binds to the C80 (CD80) or B7-1 and C86 (CD86) or B7-2 ligands, and other checkpoint proteins (PD-1) bind with (PDL-1) ligand on APC, which dysregulates immune cell function and helps in the negative control of immune T cells (Ayers et al., 2017). The FDA-approved immune checkpoint inhibitors include the anti-CTLA-4 agent ipilimumab, the anti-PD-1 agent nivolumab, and the Pembrolizumab and anti-PDL-1 agent atezolizumab and durvulamumab (Huang et al., 2021). These checkpoint inhibitors bind to their respective ligands and control the negative regulation of immune T-cell responses. Therefore, an effective immune response is directed toward cancer cells and terminates them from proliferating to other tissues in the body. Successful trials of this immunotherapy brought hope for cure and survival in patients with various cancers (Hu et al., 2021).

Adoptive T cell transfer therapy

Adoptive cellular therapy (ACT) traditionally involves three different approaches: infusion of tumor-infiltrating lymphocytes (TIL), genetically modified T cell receptor (TCR) therapies, and chimeric antigen receptor (CAR)-modified T cells. The most successful ACT is CART cell therapy (CAR-T), which now carries a multitude of FDA-approved indications and is being utilized as the standard of care worldwide for a variety of hematologic malignancies (Southam et al, 1999).

As their name implies, T cells, which help to activate the immune response and terminate the cell infected by pathogens, are the backbone of CART cell therapy (Rosenberg et al., 1994). Currently, available CAR-T-cell therapies are customized for each patient and re-engineered in the laboratory to produce proteins on their surface, called chimeric antigen receptors (CARs, and bind to specific proteins or antigens on the surfaces of cancer cells (Perica, 2015). CARs recognize. After revamped T cells have expanded into millions in the laboratory, they are infused back into the patient, and the CAR-T cells will continue to multiply in the patient's body. With guidance from their engineered receptors, recognize and kill cancer cells that harbor the target antigen on their surfaces (Garrido, 2010)

Antibody/ligand-based Therapies

Several methods and mechanisms have already existed that are responsible for attaining ligand-mediated control of

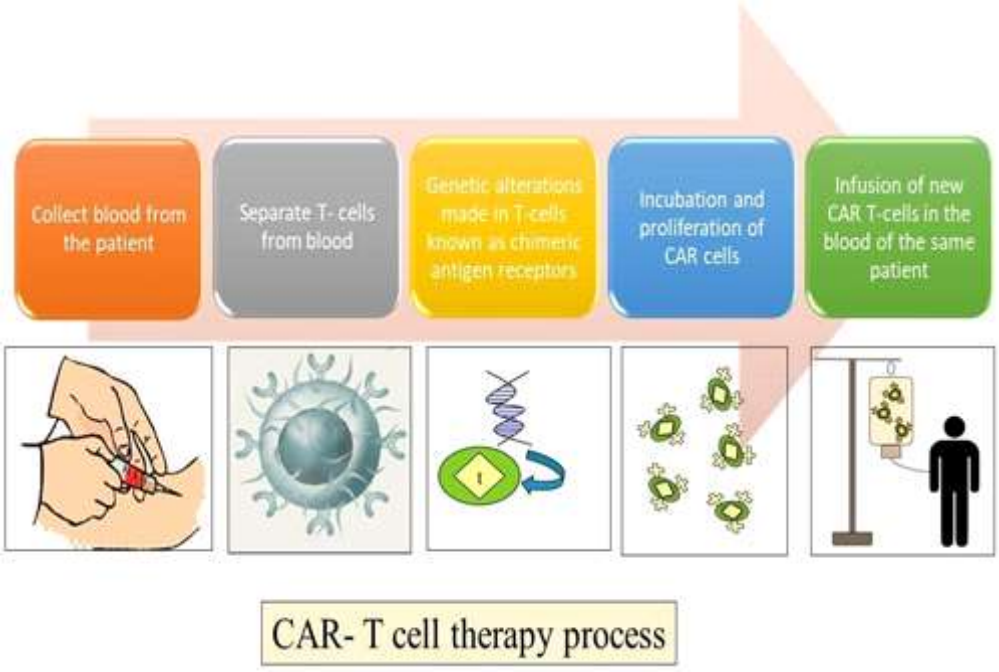

Figure1: Procedure of formation of Chimeric antigen receptors T cell therapy. The process involves the formation of genetic engineered T- cells of the patient from which blood was extracted and is unique for each individual.

disease suppression showing this therapy is highly effective and useful, and the foundation for antibody and ligand engineering and design is provided by mAbs and natural ligands, which characterize their very effective role in immunity. The main goal of ligand-based therapeutics is to remove or neutralize disease-causing pathogens or malignant cells. These are carried out by three main mechanisms of action: a) inhibition of the function of certain molecules, (b) targeting particular malignant or cancer-causing cells, or (c) acting as antibody markers/signaling molecules.

Selecting an appropriate targeting ligand is an essential step in producing antibodies because of the complicated collection of interactions that occur between these antibodies and their associated receptors for effective target-tracking applications. Several factors should be taken into consideration, including the degree of receptor expression and the involvement of receptor-mediated internalization, the use of ligands other than antibodies, and the use of complete or fragmented antibodies, all of which play a role in the binding affinity of the targeting molecule. (45) For most therapies, the target antigen/receptor should preferably be expressed at a high density on the target cell surface to enable accurate selectivity (Brekke et al., 2003). Additionally, avoiding targets with considerable heterogeneity may reduce off-target effects. Targets that are shed are not preferred as they may compete with cell-bound targets, limiting the therapeutic effects of treatment (Damelin et al., 2015).

Non antibody ligands are frequently accessible, inexpensive to produce and simple to handle. Examples include tumor necrosis factor (TNF) and TNF-related apoptosis-inducing ligand (TRAIL) (Mathew and Verma, 2009). The biggest drawback is that they express themselves on sick cells somewhat non-selectively, making antibodies the preferred targeted delivery agent (Kovtun et al., 2006). The identification and selection of antibodies and antibody derivatives with a high degree of specificity and a broad range of binding affinities for target tissues/cells have also been improved by recent advances in antibody engineering and phage display.

Antibodies used for immunotherapy are very beneficial, as they increase binding affinity through multiple binding sites on one molecule. Additionally, antibodies have an Fc domain that interacts with other immune cells to naturally enhance the immune response through complement-and antibody-dependent cytotoxicity. Over extended storage times, whole antibodies may also be more stable than antibody fragments (Beck et al., 2017). Despite their benefits, all antibodies have drawbacks. For example, they frequently connect to normal tissues via Fc receptors on macrophages, leading to significant liver and spleen uptake and possible enhanced immunogenicity. The Fc domain and complement-activating region are absent from Fab and scFv (single-chain variable fragments), which lowers their immunogenicity potential. Additionally, owing to their small size, they are better able to penetrate cells, which is a desirable side effect of several treatments. Additionally, scFvs are desirable options because of their simplicity in manufacturing and identification, such as using Escherichia coli fermentation or phage display, as well as their low immunogenicity (Mathew et al., 2009; Ahmad et al., 2012).

Therapeutic Monoclonal Antibody

Monoclonal antibody (mAbs) is a type of targeted drug therapy. They function in different ways to kill cancer cells and stop their growth and are designed to interact with specific targets (Jones et al., 1986). Monoclonal antibodies are a special type of protein designed to attach to specific targets found in cancer cells, while some monoclonal antibodies mark carrier cells so that they can be better seen and destroyed by the immune system. Other monoclonal antibodies directly stop the growth of carrier cells or cause them to self-destroy.

The monoclonal antibodies are formed by using hybridoma technology in which the mortal spleen cells are fused with immortal myeloma cell. Through this technique, first mouse antibodies for the human therapeutics were formed, but after its administration, the human body developed HAMA (human anti-mouse antibody) (Baer et al., 2009). Though this problem was resolved using the genetic engineering method and new humanized monoclonal antibody was formed which can now be used in various cancers like breasts, colon, lymphomas, and many others. But treatment of cancer using Mab can lead to various other side effects, some of them being fatigue, fever, headache, trembling, pain, and bleeding.

Three primary processes underlie the effectiveness of mAbs as cancer immunotherapies (Berube et al., 2013). These include the following mechanisms: resistance of factors and receptors that stimulate the signal pathways used by cancer cells to divide and angiogenically; antibody-dependent cellular cytotoxicity (ADCC), which involves the presence of target monoclonal antibodies formed from either chimeric or full human antibody elements that bind to specific tumor-linked antigens; and complement-dependent cytotoxicity (CDC), which is caused by complement activation (Oganesyan et al., 2014).

The Fc receptors of immune cells like macrophages and natural killer (NK) cells identify cell-bound mAbs in the ADCC pathway after the mAb first attaches to antigens on the surface of target cells like tumor cells. When receptors cross-link, cytotoxic substances like perforin and granzyme are released into lytic synapses (Hua et al., 2014). Finally,

Table 1. Examples of the monoclonal antibodies along with their mechanism involved

Mechanism involved	Drug name
Antibody-Dependent Cellular Cytotoxicity (ADCC)	Rituximab, Pertuzumab, Cetuximab and Transtuzumab
Complement-Dependent Cytotoxicity (CDC)	Rituximab, Ofatumumab, Alemtuzumab and, Cetuximab
Non- Conjugated mAb	Transtuzumab and Alemtuzumab
Drug Conjugated mAb	Gemtuzumabozogamicin
Radioactive Conjugated mAb	Ibritumomab thiuxetan /tiuxetan

apoptosis causes tumor cells to die. In contrast, in the CDC approach, the mAb attaches to membrane-surface antigens on the target cell, which triggers a complement cascade that involves complement interacting with the mAbs. Complement binding results in the induction of a membrane attack complex, and the target cell is lysed by the complement system once it is activated (Sause, et al., 2016; Larocca et al., 2008).

Numerous monoclonal antibodies (mAbs) used in cancer immunotherapy identify and adhere to an antigen on the surface of cancer cells, inhibiting certain downstream signaling pathways and cell proliferation). There are some Monoclonal antibodies that are effectively used in cancer immune therapy: Trastuzumab, Pembrolizumab, Rituximab, Nivolumab, and Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy.

Antibody – Drug Conjugates

An antibody-drug conjugate (ADCs) can be used to select ablating cancer cells by combining the specificity of a monoclonal antibody (mAb) for a target antigen with the delivery of a highly potent cytotoxic agent and is a form of targeted immunotherapy. They are composed of three components: a monoclonal antibody (mAb) and cytotoxic payloads made from a chemotherapy agent, which are connected together using a chemical linker (Weiner et al., 2016). Conjugated mAbs, also known as labeled, loaded, or tagged antibodies, are radioactive particles that are combined with chemotherapy drugs. These monoclonal antibodies deliver the therapy directly to the cells that need it the most and decrease the damage to normal cells within the body (Amiri-Kordestani et al., 2014).

Four antibody-conjugates currently have FDA approval for the treatment of solid tumors: trastuzumab emtansine and trastuzumab deruxtecan, anti-HER2, enfortumab vedotin, targeting Nectin-4, and Sacituzumab govitecan, active against Trop-2. Tubulin polymerization promoters target the β-subunits of tubulin dimers to perturb microtubule growth, and they are exemplified by auristatin derivatives monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF). Among the 14 approved drugs, five used MMAE/MMAF as payloads (Herrera et al., 2018)."

Immunotoxins

Immunotoxins are proteins used to treat cancers and are composed of an antibody fragment linked to a toxin. The immunotoxin binds to a surface antigen on a cancer cell, enters the cell via endocytosis, and kills it. The most potent immunotoxins are produced by bacteria and plants. Immune substances bind to specific proteins or receptors in some cancer cells. This allows the linked toxic substances to enter cancer cells and kill them without harming nearby healthy cells. The toxic moieties of immunotoxins have been derived from bacteria, fungi, plants, and even animal toxins (Cao et al., 2012) whereas growth factors, monoclonal antibodies, cytokines (Aruna, 2006) and cancer-specific cell-penetrating peptides (CPPs) (Kersemans and Cornelissen, 2010) have been used as targeting moieties. Among bacterial toxins, Vibriocholera toxin (Soleimani et al., 2016), Shiga toxin, Pseudomonas exotoxin, and DT (Jahanian-Najafabadi et al., 2012) have been used as either immunotoxins or other forms of targeted toxins. Among these, DT is the most widely used owing to its easy expression, high activity, and minimal side effects in humans (Vallera et al., 1999).

Diphtheria toxin is a single-chain, 62 kDa protein consisting of 535 amino acid residues that are produced by Corynebacterium diphtheria containing lysogenic beta phage (Holmes, 2000). DT mediates its cytotoxic effects by inhibiting protein synthesis in susceptible cells (Liu et al., 2000). DT is a Y-shaped molecule containing two functionally different regions, A and B where A fragment (located at the N-terminus) includes a catalytic domain (C domain; 22 KDa, residues 1–193) that inhibits protein synthesis within eukaryotic cells and B fragment (located at the C-terminus), on the other hand, consists of two domains, a transmembrane domain (T domain, 22 KDa, residues 201–384), and a receptor-binding domain (Vaclavkova et al.,

2006; Choe et al., 1992). Truncated forms of DT have been successfully used to generate recombinant immunotoxins for cancer treatment (Collier, 2001). Genetic substitution of the native DT R domain with cytokines, growth factors, cancer-specific CPPs, and generally any ligands specific for cancer cell antigens has resulted in the formation of fusion proteins that retain the functions and activities of their constituent parts (Shapira and Benhar, 2010).

Targeted therapy is an emerging method for cancer therapy and is expected to replace conventional therapies in the future. For effective cancer treatment, it is necessary to directly direct the killing agent toward the surface molecules of tumour cells. Immunotoxin molecules are highly potent agents in cancer therapy as they contain selective binding domains (Beilhartz et al., 2017).

Radioimmunotherapy/ radioimmuno conjugates

A tailored cancer treatment called radioimmunotherapy (RIT) combines radiation therapy with immunotherapy, which mimics immune system cells' activity through precision targeting. A form of radiation treatment that involves injecting the patient with a radioactive material attached to a monoclonal antibody. Cancer cells and other substances in the body can be bound by monoclonal antibodies. Radiation released by the radioactive chemical may aid in the death of cancer cells. A little amount of radioactive material (radionuclide) and a molecule created in a lab (monoclonal antibody) are joined in radioimmunotherapy (RIT). As a radiopharmaceutical, this monoclonal antibody-radionuclide mixture is referred to. Antigens and cell receptors are two examples of particular cell characteristics that monoclonal antibodies may identify and bind to. The radiopharmaceutical binds to cancer cells when administered intravenously to a patient, attaching to them and sending a powerful dose of radiation to the tumor. Patients usually get one or two RIT treatments. An intravenous injection of a monoclonal antibody that is not radioactive (or cold) is given to the patient prior to the start of treatment. This antibody adheres to other parts of the body and shields them from the radioactive antibody utilized in the therapy. It might take up to 4-5 hours to finish this infusion. The therapeutic radioactive monoclonal antibody was infused for a shorter period of time after another non-radioactive monoclonal antibody infusion the next week. It can take an hour to set up and administer this infusion because it is substantially shorter.

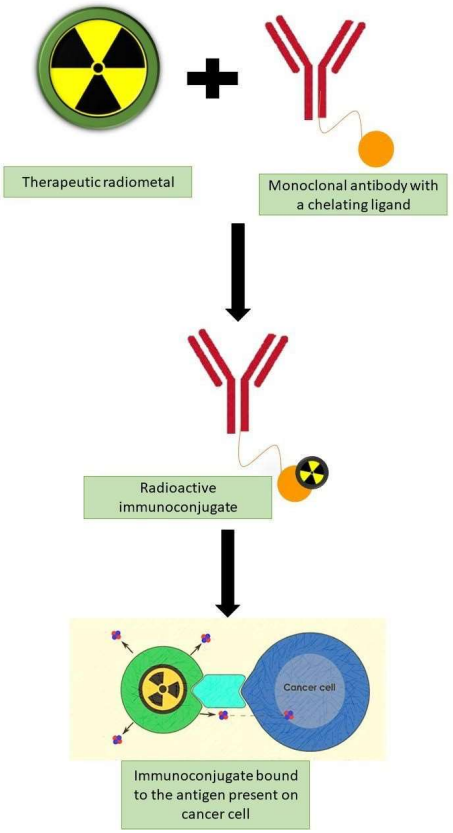

Figure 2: Formation of radioimmunoconjugates for radioimmunotherapy.

Radiopharmaceuticals are used to diagnose certain medical problems or treat certain diseases. They can be administered to patients in several different ways. The most common radioisotope used in diagnosis is technetium-99 (Tc-99), with some 40 million procedures per year, accounting for about 80% of all nuclear medicine procedures and 85% of diagnostic scans in nuclear medicine worldwide. CD20 is an excellent target for the treatment of B-cell lymphoma. Gallium-67 citrate (67Ga), the most widely used tumour-seeking radiopharmaceutical, seems to have the greatest value in detecting bronchogenic carcinomas irrespective of cell type, and depending on the type of radioactive compound used, the resulting energy can penetrate the cell bound to the radiopharmaceutical as well as approximately 10 to 30 cells surrounding the cell. This increases the number of cancer cells that can be killed using a single radiopharmaceutical molecule. Arsenic-74 is used to detect small tumors in the body. Cobalt-60, boron-10, and iodine-131 have been used for the treatment of brain tumors.

Cancer Vaccine/Treatment Vaccine

Vaccines are drugs that support the immune system. They teach the immune system to identify and eliminate dangerous microorganisms and cells. Cancer vaccines, which help in cancer prevention and treatment, are currently available. Vaccines that can shield healthy individuals from contracting specific virus-related malignancies. These vaccines shield the body from these viruses, much like the immunizations for the flu or chicken pox.

The U.S. Food and Drug Administration (FDA) has approved two types of vaccines that help to treat cancer: the

HPV vaccine. This vaccine provides protection against HPV; if the HPV virus holds the human body for a long period of time, it can cause some types of cancer (Morales et al., 1976). For the sake of public safety and protection, FDA-approved HPV vaccines to prevent cervical, vaginal, and vulvar cancers, anal cancer genital warts HPV can also cause other cancers and not oral cancer. This vaccine provides a shield against the hepatitis B virus (HBV), which is responsible for liver cancer.

As immunotherapeutic resources, therapeutic cancer vaccines are utilized to treat a disease that is already active. In cancer immunotherapy, only two therapeutic vaccines have been authorized (Lamm et al., 1980). These consist of Sipuleucel-T (Provenge), a dendritic cell (DC)-based vaccination for the therapy of castration-resistant prostate cancer, and the Bacillus Calmette-Guerin (BCG) vaccine for the treatment of early-stage bladder cancer. Following evidence that intra vesical instillation of this bacteria might arrest disease development and recurrence of NMIBC, the use of BCG for the treatment of high-risk NMIBC was approved. Following the removal of the tumors, BCG is infused into the bladder once a week for six weeks as part of the therapy. A few genitourinary tract side effects of BCG treatment include cystitis, bladder ulceration, penile sores, prostatitis, and kidney infection (Liu et al., 2019).

In castration-resistant prostate cancer patients, the Sipuleucel-T vaccine stimulates cellular immune responses against prostatic acid phosphatase (PAP) by the use of autologous DC. Antigen-presenting cells (DCs) have the capacity to effectively prime and activate T lymphocytes in response to particular antigens. They display processed antigenic peptide: HLA complexes to T lymphocytes while expressing class I and class II HLA molecules. In order to activate patient DCs, process PAP antigenic epitopes, and express antigenic peptides, HLA complexes, and costimulatory molecules, the vaccine is made by incubating patient DCs with a fusion protein made of PAP coupled to granulocyte-macrophage colony-stimulating factor. The patient is subsequently given activated DCs again, which will present antigens and trigger T cell reactions against PAP protein (Grimmett et al., 2022).

Immune System Modulators

A substance that stimulates or suppresses the immune system may help fight cancer, infections, or other diseases. Specific immune system modulators such as monoclonal antibodies, cytokines, and vaccines affect specific parts of the immune system. Immune modulation in cancer refers to a range of treatments aimed at harnessing a patient's immune system to achieve tumor control, stabilization, and potential eradication of the disease. A novel therapeutic drug class called immune checkpoint-blocking antibodies modulates T-cell pathways that regulate T cells and has the potential to reinvigorate an antitumor immune response. Ipilimumab was the first FDA-approved immune checkpoint antibody licensed for the treatment of metastatic melanoma (MM). It blocks a checkpoint molecule called cytotoxic T-lymphocyte antigen 4 (CTLA4).

Cytokines are major regulators of innate and adaptive immunity that enable the cells of the immune system to communicate over short distances. The use of cytokines to stimulate the immune system of patients with cancer has long been a significant therapeutic approach and still has a significant impact on clinical cancer research. They can also be created in a laboratory for the treatment of certain illnesses (Spaapen et al., 2014). Cytokine treatment for cancer may assist the immune system in eliminating cancer cells or in preventing their growth. Interleukins and interferons are two primary categories of cytokines used to treat cancer (Allen et al., 2012). Cytokines, as immune system proteins, can directly promote tumor cell death and influence the host immunological response to cancer cells. Cytokine-based immune therapy is a promising approach to cancer treatment (Cauwels et al., 2018).

Table 2: Various types of immune modulators can be loosely categorized in to: adjuvants, cytokines, and checkpoint inhibitors

Types of immune system modulators	Functions	Examples
Cytokines	Promote cytotoxic effect or cell identification of tumor cells by immune effector cells and stromal cells at the tumor site and improve antigen priming.	Aldesleukin (targetstheIL-2/IL-2R pathway Peg interferon alfa 2b (targets IFNAR1-pathway)
Checkpoint Inhibitors	Elicit new immune responses to combat cancer while enhancing those that are already in place to support the elimination of cancer cells.	Ipilimumab, Avelumab, Cemiplimab, Dostarlimab, and, Nivolumab (targets PD-1/PD-L1pathway), Relatlimab (targets LAG-3 pathway), and Tremelimumab (targets CTLA-4 pathway).
Adjuvants	Engage innate immune system pathways that can generate broader immunological responses and eventually encourage adaptive immune responses.	Imiquimod (targetsTLR-7) and, PolyICLC (targetsTLR-3).

Oncolytic Immunotherapy

Oncolytic viruses can specifically target, proliferate inside, and eradicate tumors (recently termed oncolytic immunotherapy). Oncolytic immunotherapy is thought to be the method of immunogenic cancer cell death (ICD), or virus-induced tumor cell death, which enables the immune system to identify tumor cells and offer a persistent antitumor response. Together, immune responses to the virus and ICD contribute to successful antitumor efficacy. OVs have an anticancer impact by either directly infecting and lysing tumor cells or by inciting an immunological response that results in an immune assault.

Oncolytic viruses are being developed for use in cancer treatment, including adenoviruses, herpesviruses, measles viruses, coxsackieviruses, polioviruses, reoviruses, poxviruses, and Newcastle disease viruses. Given the impaired viral sensing mechanisms of the majority of cancer cells, tumor-preferential replication may be 'normal.' Some cancer cells have higher levels of viral entry receptor expression, whereas some viruses do not seem to require particular receptors to infect their host. Some viruses have the ability to take advantage of dysfunctional intracellular signaling pathways, such as interferons, which are naturally inclined to multiply aggressively in tumor cells, similar to many other viruses. Their wild-type versions might theoretically be utilized in cancer treatment, as was the case in historical episodes. However, by making viruses tumor-specific ('oncolytic') through rational design, better patient outcomes are anticipated. Adenoviruses have undergone substantial modifications in recent years to combine potent anticancer activity with low toxicity.

Each kind of OV has a unique cellular entrance pathway that might influence effectiveness. For instance, the poliovirus penetrates cells via the poliovirus receptor CD155, which is highly expressed in a variety of tumor forms. Coxsackie and adenovirus receptor, or CAR, is expressed in different ways by tumor cells. To increase tumor cell selectivity, many OVs have been developed. Strong lytic features of the herpes simplex virus type 1 have led to the development of various variations, frequently by the deletion of the ICP34.5 neurovirulence and ICP6 (UL39) (ribonucleotide reductase) genes. In healthy, dormant cells, ICP6 is required for the creation of the nucleotide pool required for viral replication. One of the most prevalent deficiencies in cancer is the inactivation of the tumor suppressor p16INK4A, and deletion of ICP6 offers replicative selectivity for these cells. Reovirus similarly targets cells with activated ras signaling for oncolysis. OVs delivered locally are often well accepted. Mild flu-like symptoms, which may become more severe after systemic delivery and local response at the injection site are the most often reported side effects.

A strong opportunity exists right now to study the effects of combining immunostimulatory OVs with immune checkpoint inhibition in malignancies, which would significantly speed up the antitumor immune response while removing any potential obstacles to T-cell-mediated tumor killing. Many groups are developing new OVs that express checkpoint inhibitory antibody molecules. In situ expression might be possible as a result of this research, preventing negative side effects from antibody systemic distribution and enhancing the local immune response against tumor cells.

Conclusion

Cancer cells possess the ability to evade immune detection, and the immunosuppressive characteristics of the tumor microenvironment make tumor-infiltrating lymphocytes incapable of removing tumors in vivo. Immunotherapy

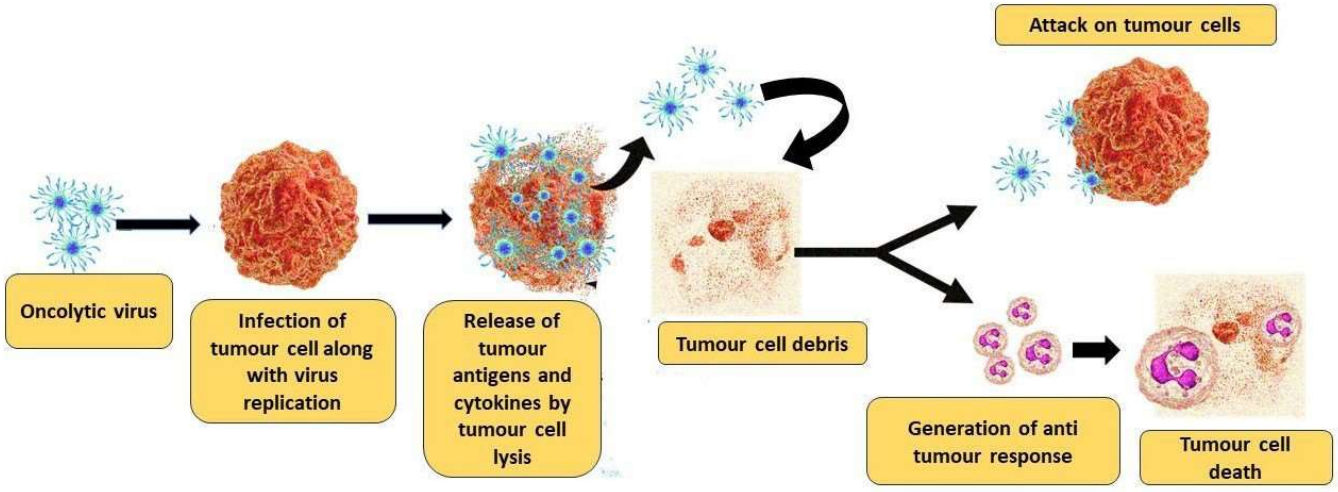

Figure 3: Antitumor mechanism of oncolytic virus

aims to combat immune suppression in the tumor microenvironment and activate the immune system's inherent capacity to combat and eradicate cancer. The last ten years have seen a significant shift in the treatment of patients with cancer due to cancer immunotherapy. Immunotherapeutic techniques have proven to be extremely effective in a wide range of contexts and individuals with previously impermeable diseases.

Novel engineering of CAR-T cells to facilitate enhanced trafficking and diminished immunosuppression within solid tumors may subsequently lead to improved outcomes. Cancer vaccinations have also made significant progress in recent years, and studies combining neoantigen vaccines with targeting the tumor microenvironment (TME) in particular offer the potential to open up this exciting field.

The age of immunotherapy has revolutionized the treatment of cancer. The challenges that lie ahead include determining why immunotherapy treatments work well in some tumors and patients but not in others, and understanding how tumors that were once responsive to treatment might develop resistance. To be effective, cancer immunotherapy must find ways to manipulate the immune system in the likely majority of patients who have little or no immune response to their tumors, even if the tumor microenvironment is an "immune desert" with no tumor-infiltrating T-cells.

However, there is still significant room for improvement, and efforts are currently underway to achieve more effective patient outcomes. With the development of an understanding of the biological genesis of diseases, the current knowledge of immunotherapies is believed to develop significantly and may be revolutionary in combating non-infectious diseases.

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