Leveraging the Tumor Immune Cycle: Exploring Novel Immunotherapies For Cancer

Shivani Acharya[1]*

[1]Centennial High School, Address, Frisco, Texas, 75035, United States of America

*Corresponding author email: shivaniacharya700@gmail.com

Abstract

Cancer is a deadly disease caused by the mutation and uncontrolled proliferation of cells in the body. The human body defends itself against cancer through the tumor immune cycle, a process whereby the patient's immune system is able to detect and fight cancerous cells. This cycle has inspired the development of various immunotherapies, including checkpoint inhibitors and oncolytic virus therapy. These work to more effectively engage the immune system and the tumor immune cycle, inhibiting cancer growth and eliminating cancer cells in the body. After success with various immunotherapies like antibody drug conjugates and virotherapy, scientists have continued developing more complex and efficient immunotherapies. This paper explores immunotherapy and two novel therapies, oncolytic virus therapy and antibody-drug conjugates, as more effective means to fight cancerous cells. It then proposes their potential use in combination to overcome limitations of current treatments and more efficiently leverage the tumor immune cycle. These treatments could save the lives of countless cancer patients and warrant further study.

Keywords

Cancer, Immunotherapy, Tumor Microenvironment (TME), Immune System, Tumor Immune Cycle

Introduction

Cancer is a disease caused by the uncontrolled spread and growth of mutated cells in the body. Mutations are replication errors that affect the genetic makeup of the cells (1). Some errors are inherited from parents, as with familial or hereditary cancers, while others occur due to exposure to carcinogens or errors during normal cell division (2). When a cell's genes are mutated, it affects the gene's function, hence altering the way the cell works. Cancer is a result of multiple gene mutations; malignant tumors form when mutated cells divide uncontrollably and cluster (3). These cells can then break off from the initial (primary) tumor site and spread throughout the body, a process called metastasis, which further progresses the cancer (4).

Cancer can form anywhere in the body, depending on which type of cells are first mutated. These cancers are generally named after the tissues or organs in which they form. However, there are many key differences between cancerous cells and normal tissue cells. Cancer cells grow without the body's normal growth signals (5). Additionally, cancer cells ignore signals that inhibit growth or cause programmed cell death. Cancer cells hide from the immune system's defenses that are in place to eliminate foreign cells, and cancer cells signal blood vessels to grow in the tumor's direction for the tumor to obtain substantial nutrients and oxygen (6).

Conventional cancer treatments include chemotherapy and radiation. Chemotherapy is a cancer treatment that uses drugs to minimize and eliminate cancerous cells and hinder tumor growth. Unfortunately, chemotherapy has side effects due to its effect on healthy cells. This leads to unfortunate side effects for patients, such as hair loss, nausea, fatigue, and a weakened immune system (7). Like chemotherapy, radiotherapy uses radiation as a physical agent to damage cellular DNA, resulting in cell death (8). While both normal and cancer cells are affected by radiation, the goal of radiation therapy is to target cancer cells while minimizing damage to normal cells. While these treatments can be combined, their non-specific targeting and toxic side effects necessitate research into more targeted, safer treatment options.

Oncolytic Virus Therapy (OVT) and antibody-drug conjugates (ADCs) are two promising approaches in the evolving field of targeted cancer therapy. Virotherapy, such as OVT, uses genetically

engineered viruses to selectively infect tumor cells and stimulate an immune response (9). ADCs consist of monoclonal antibodies and cytotoxic agents, enabling precise and targeted delivery of chemotherapy while minimizing damage to healthy tissues (10). The potential synergy between these two approaches, particularly when used in combination, presents a compelling strategy for treating cancer.

Understanding the unique characteristics of cancers is crucial for developing effective and safe treatments, particularly for those that harness the body's immune system, which plays a key role in detecting and eradicating cancerous cells. The aim of this paper is to first provide an overview of the tumor immune system, discussing its role in cancer detection and elimination. It will then explore conventional first-generation immunotherapies, followed by next-generation therapies—specifically, oncolytic virotherapy and antibody-drug conjugates—and examine how they leverage tumor immunity. By exploring the current progress and limitations of research on these therapies, this review offers insight into their effective use against cancer.

The Immune System and the Tumor Immune Cycle

The immune system is the body's defense mechanism against infections, diseases, and foreign invaders (11). It consists of specialized cells, organs, and tissues that work together to eliminate the body's threats (11). Thoroughly understanding the immune system and the tumor immune cycle is necessary to overcome the obstacles that come with cancer treatment and immunotherapies.

There are two main branches of the immune system: the innate immune system and the adaptive immune system (12). The innate immune system is the body's first line of defense against pathogens. It is present at birth and lasts a lifetime. It has both an external division and an internal division (13). The external division consists of the body's physical barriers, such as skin, secretions, and mucous membranes (14). The internal division consists of innate immune cells and signaling chemicals known as cytokines and chemokines. The adaptive immune system, by contrast, can be considered the more specialized branch. It provides a targeted immune response against pathogens or foreign substances and importantly, can remember pathogens and how to eliminate them in the future (15).

The adaptive immune system consists mainly of two groups of immune cells: T cells and B cells (16). T cells are a critical part of the adaptive immune system, specializing in recognizing and responding to pathogens (17). Their main functions include destroying infected cells, coordinating the immune response, and keeping immune balance (17). Helper T cells (CD4+) secrete cytokines to activate B cells, cytotoxic T cells, and other immune cells (18). This boosts the body's immune response.Cytotoxic T cells (CD8+) target and kill pathogen-infected or mutated cells by recognizing antigens presented on their surfaces (19). They eliminate their targets by releasing molecules, such as granzymes and perforin, which help create pores in the target cell's membrane (19). This process triggers apoptosis, a type of programmed cell death (20). Regulatory T cells (Tregs) control the immune response and help prevent excessive inflammation and autoimmunity (21). Furthermore, memory T cells promote long-term immunity against previously encountered pathogens and enable a more efficient immune response upon reexposure (22).

B cells are another type of white-blood cell (lymphocyte) that play a necessary role in producing antibodies (23). Through the unique receptors on their surface, they can distinguish and bind antigens (23). Following activation, B cells differentiate into two key categories. Plasma cells produce and distribute antibodies throughout the blood, neutralizing the threat posed by pathogens and preventing further harm (23). Antibodies bind to pathogens, physically blocking them from infecting cells. This process is called neutralization (23). Pathogens can also be coated by antibodies, marking them for phagocytosis, a process performed by macrophages and neutrophils (24). This process is opsonization. Memory B cells "remember" the antigen, which results in a better response if ever re-exposed to that pathogen. It makes the immune response faster and more efficient in the future.

The immune system often engages in a cycle specially designed for recognizing and eliminating tumor cells with a sequence of events known as the tumor immune cycle (Figure 1). Although these steps each have their purpose, their interconnected synergy is what boosts their efficiency in eliminating tumors from the body (25).

The tumor immune cycle begins with antigen release and presentation (Step 1) (Figure 1). During apoptosis, tumor cells rupture, releasing tumor-associated antigens, tumor-specific antigens, and damage-associated molecular patterns (26). These antigens then attract antigen-presenting cells (APCs), through which they are processed and presented to T cells (Step 2) (26).

Next, T-cell priming and activation occur (Step 3) (Figure 1). Activated T cells proliferate and differentiate due to the antigens presented by the APCs (27). CD8+ cytotoxic T lymphocytes (CTLs) attack tumor cells upon activation while CD4+ helper T cells enhance the immune response by producing cytokines (27).

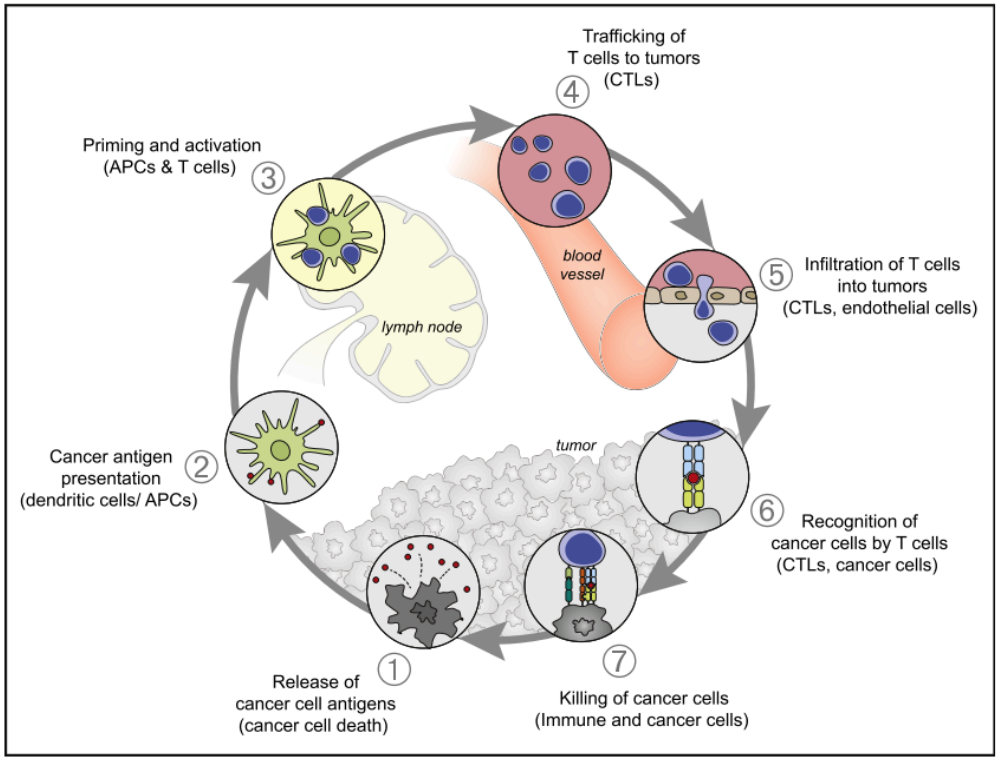

Figure 1. The Tumor Immunity Cycle. The steps the immune system takes in identifying and eliminating cancerous cells. Used with permission under Creative Commons Attribution 4.0 (CC BY 4.0). (25).

In the next phase (Step 5), activated T cells migrate and eventually infiltrate the tumor microenvironment (Figure 1). Tumors can develop immunosuppressive barriers to impede infiltration

ability (27). Due to antigen presentation, T cells recognize the cancerous cells expressing their target antigen (Step 6) (28). Cytotoxic T lymphocytes bind to specific MHC I molecules and eventually release perforin and granzymes (28). This results in tumor cell death through apoptosis (Step 7).

First-generation Immunotherapies

Based on the known mechanisms of tumor immune interactions, a new class of therapy has recently been tested in the clinic, known as immunotherapies. The goals of immunotherapy are to engineer and strengthen immune cells to fight tumors and build long-term antigen memory. Below, I will detail common types of immunotherapy, including immune checkpoint blockade and cell therapies.

Immune checkpoint inhibitors (ICIs) use engineered monoclonal antibodies to specifically recognize and bind to antigens on the surface of cancer cells (29). Once bound, they can interfere with signals that promote tumor growth or survival, directly block receptors, or tag cancer cells for destruction by the immune system (29). However, tumors can evade this by reducing the MHC molecule presentation and through the use of inhibitory proteins like PD-L1.

The main principle of immune checkpoint inhibitors is their ability to produce a physical blockade of inhibitory pathways that cancer cells take advantage of to evade the immune system (29). Certain immune checkpoints, such as PD-1/PD-L1 and CTLA-4, are necessary in maintaining the immune system's balance as they prevent the overuse of T cells and inhibit an unnecessary immune response (29). Commonly, cancer cells have excess PD-1, which binds to the corresponding receptor on a T cell, inhibiting immune activation (30). Checkpoint inhibitors block this from happening, ensuring the immune system can activate if necessary.

However, ICIs come with some challenges. The main problem is that they interfere with the immune system's natural regulation. Since they block the regulatory pathways, the immune system can sometimes hyperactivate, which can cause autoimmune side effects (31).

Another challenge is the adaptability of the tumor itself. One example is primary resistance. Neoantigens are proteins that have been mutated, making them recognizable by the immune system (32).

When tumors have too few neoantigens or insufficient T-cell infiltration, they naturally trigger a weaker immune response, resulting in primary resistance. Because of the scarcity of immune response pathways, the ICIs have nothing to block, making them useless in this situation.

Another example is acquired resistance. This only occurs after exposure to ICIs. Tumors can adapt and eventually hide themselves from the immune system (33). This could be achieved by reducing certain proteins like PD-L1 (33). This reduces their susceptibility to being affected by T cells. Others form mutations in the antigen-presenting pathways, which, again, hinder the immune system's ability to detect the antigens. Tumor resistance is one reason ICIs are often not successful long-term. Thus, exploration of other strategies to overcome or address tumor resistance is warranted.

Another conventional immunotherapy being developed is chimeric antigen receptor (CAR)-T-cell therapy. CAR-T-cell therapy involves the genetic engineering of the immune system's T cells that improves their ability to recognize and eliminate cancer cells (34). The T cells are taken from the bloodstream and engineered in a lab to express a receptor that targets specific cancer antigens, known as a "CAR". These engineered CAR-T cells are produced in large numbers, and then they must be inserted back into the body. This is usually done through a viral vector. CAR-T-cell therapy also has future benefits as the cells can reproduce, increasing the amount of these enhanced immune cells in the body (34).

Despite these advances and benefits, several risks and challenges are associated with CAR-T-cell therapy that limit its use and effectiveness. When the enhanced cells multiply within the body, an excess of cytokines is produced (34). Cytokine release syndrome (CRS) is a common side effect. It is a life-threatening inflammatory response that occurs when excess cytokines trigger high fevers, low blood pressure, breathing difficulty, and organ stress (34). Furthermore, immune effector cell–associated neurotoxicity syndrome (ICANS) is also a side effect. In this syndrome, cytokines cause brain inflammation, which can cause confusion, headaches, speech problems, and seizures (34). Taken together, these challenges with ICIs and CAR-T cells may be overcome by next-generation immunotherapies such as oncolytic virus therapy and antibody-drug conjugates.

Next-generation Immunotherapies

Oncolytic Virus Therapy

Oncolytic Virus Therapy is a type of cancer treatment that uses viruses to infect and kill cancer cells while sparing healthy cells. OVs also stimulate the immune system to recognize and attack tumors (35). A virus is a microscopic invader that can infect cells and reproduce inside host cells. Although it is common knowledge that viruses should be avoided, however, the properties of viruses can be embraced to engineer an efficient immunotherapy.

Historically, the idea of OVs started when doctors noticed that some cancer patients improved after natural viral infections, but modern OV therapy only became possible once scientists learned how to genetically engineer viruses to be safer and more tumor-selective. Oncolytic viruses are engineered in the lab, starting with a virus that can infect human cells, such as herpes simplex virus type 1 (HSV-1), adenovirus, vaccinia virus, reovirus, measles virus, Newcastle disease virus, or modified poliovirus (36). Scientists then genetically edit the virus by deleting genes that make it harmful to normal cells, changing parts of the virus so it targets cancer cells better, and sometimes adding immune-stimulating genes. The main FDA-approved oncolytic virus in the United States is T-VEC, also called talimogene laherparepvec (37). It is made from a modified HSV-1 virus, which is the same type of virus that can cause cold sores. In the lab, researchers weakened the HSV-1 virus by removing certain viral genes and added the GM-CSF gene, which helps activate immune cells against the tumor (37). T-VEC is injected directly into melanoma tumors, where it replicates inside cancer cells, causes them to burst, and releases tumor signals that help the immune system recognize the cancer (38). T-VEC became the first and only FDA-approved oncolytic virus therapy in 2015 for certain melanoma lesions that cannot be fully removed by surgery (38).

The next step is inserting the virus into the body through an injection. This injection is based on the cancer; if the cancer has metastasized, it will enter the body through an intravenous injection. Otherwise, the virus will be directly inserted into the tumor via an intratumoral injection (35).

Taking advantage of cancerous cells' impaired antiviral defenses, the virus specifically targets tumor cells because of their specific surface receptors, abnormal signaling pathways, etc. while skipping over regular healthy cells. There are a few additional ways that the virus can look past the healthy cells and focus on cancerous/mutated cells. One example of this is that the rapid replication of cancerous cells attracts the attention of viruses as the viruses aim to find a host cell they can replicate in easily (35). Another is the specific engineered genetic modifications made to the viruses before entering the body. For instance, T-VEC is a herpes simplex virus that has been modified. The genes, ICP34.5 and ICP47, are deleted and the gene, GM-CSF has been added (37). This gene is added to help enhance the immune response.

There are a few common modifications that occur in the lab at this stage. One is altering the virus's virulence for healthy cells by ensuring that its activation is contingent on certain factors found only in cancerous cells. Additionally, specific cancer-specific promoters encourage replication in only cancerous cells (39). Viruses can also be engineered to recognize specific surface proteins that are expressed highly on cancer cells and minimally on regular cells (39). The permeability of tumor cells makes it easier for viruses to enter, and viruses can be coated to evade the immune system, making their way to the tumor without falling victim to the body's immune response. Lastly, yet still notable, are the factors in the tumor microenvironment. Tumor environments are generally hypoxic, meaning they contain less oxygen (40). This and its immunosuppressive qualities make the tumor microenvironment a sufficient location for the flourishing of oncolytic viruses.

When inside the cell, the virus replicates rapidly, rupturing the cell. This rupture is called cell lysis and is a key part of spreading oncolytic viruses (41). The tumor antigens and virus particles are released into the tumor microenvironment, alerting the immune system. An immune response is activated when dendritic cells present the antigens to T cells (41).

Over the last decade, these OVs have increased in popularity. As of 2023, 4 OVs (Rigvir, Oncorine, Imlygic, and Delytact) have been FDA-approved for clinical use (41). They work to generate an initial localized antitumor immune response through direct lysis of the cells rather than the simulation of antitumor mechanisms. Through this mechanism, OVs support local antigen (neoantigen) release, tumor cell priming, activation, and ultimate tumor-directed killing. Researchers have focused on combination approaches to synergize with the mechanism of OVs (41). For instance, chemotherapy and OVs have been explored, and it was found that chemotherapy can enhance the effect of OVs in many ways. Chemotherapy can weaken tumor cells, making them more susceptible to viral infection, and chemotherapy can suppress the immune response, allowing the virus to be more effective in infecting malignant cells. However, the chemotherapy side effects are not absent in this approach. Fatigue, weakness, and hair loss are still common in this approach, making targeted chemotherapy a better route, as only malignant cells are impacted (42). Another developing therapy leveraging the immune system to fight cancer cells are antibody-drug conjugates.

Antibody-drug conjugates

Contrary to conventional chemotherapy, targeted therapy targets only cancerous cells rather than affecting healthy cells (42). It distinguishes between cells by looking for unique features only present in cancerous cells. A specific type of targeted chemotherapy is antibody-drug conjugates (ADCs). They contain three key components: a monoclonal antibody, a particular drug such as chemotherapy, and a linker protein (43). As discussed earlier, monoclonal antibodies are lab-engineered proteins that target and bind to tumor antigens (43). These are tumor-associated antigens that are heavily expressed on tumor cells but less expressed on healthy cells. Examples of tumor antigens often targeted in solid tumors are HER2, TROP, and Nectin-4 (44). Another tumor antigen, CD33, is a hematological antigen found on acute myeloid leukemia cells (45). When the antibody binds to its matching tumor antigen, the cell absorbs the ADC. This causes the linker protein to break down, eventually releasing the chemotherapy drug in the cell where it is needed. This is similar to the interaction of a lock and key, as the antibody acts as the "key"

that perfectly fits the "lock" (the cancer antigen), which opens the gate for the drug, such as chemotherapy, to enter the cell. These chemotherapy drugs are highly significant as they are thoroughly tested to ensure efficiency in cancer cell elimination. The linker protein is a vital part of this process as it holds the monoclonal antibody and the chemotherapy drug together throughout delivery (46). Additionally, it is responsible for the precise release of the drug in the cancerous cell.

Over the last several years, the use of antibody-drug conjugates has become more common. As of 2024, 15 ADCs are FDA-approved, and over 200 are in clinical trial stages (46). Additionally, 24 have reached Phase III clinical trials (46). In Phase III trials, HER2-targeted antibody-drug conjugates are the most extensively tested type and remain the most promising (46). First-generation HER2-directed ADCs, like gemtuzumab ozogamicin conjugates, had many limitations (46). First generations were the first group of ADCs made to target HER2. They had non-cleavable linkers and carried a maytansinoid payload. These limitations included heterogeneous drug loading and systemic toxicity; however, these first-generation HER2 ADCs gave proof of concept, and the next generation stemmed from it . Second-generation HER2-directed ADCs such as trastuzumab deruxtecan (T-DXd) have proven more efficient, stable, and effective (47). Trastuzumab deruxtecan has a payload that causes immunogenic cell death . This stimulates the release of tumor antigens and damage-associated molecular patterns. These act as danger signals and cause an immune response to be stimulated. A Phase III trial, DESTINY-Breast03, designated T-DXd as the standard in ADC therapy due to improved response rates (48). A recent example of a FDA approved ADC is DECNUPAZ (pivekimab sunirine-pvzy). In May of 2026, it was approved to treat adults with a rare blood cancer called Blastic Plasmacytoid Dendritic Cell Neoplasm (49). Before the introduction of the approved ADC, treatment for this disease consisted of intensive chemotherapy and possible stem-cell transplants. However, many patients experienced relapse following treatment. This made it crucial for another treatment option. Pivekimab sunirine-pvzy targets the antigen, CD123, which is a protein heavily expressed on BPDCN (49). The payload is part of the indolinobenzodiazepine pseudodimer class that chemically attaches to DNA and results in single-strand DNA breaks (49). This causes the cancer cell to stop functioning correctly and eventually triggers apoptosis. CADENZA was the

Phase 1/2 clinical trial that tested the drug in patients with these rare blood cancers. In the trial, patients developed notable responses. Among new patients, 69.7% had a complete response to treatment and the median response duration was 9.7 months (49). Thirteen patients, representing 39.4% of the group, were able to undergo a stem cell transplant after completing the study treatment (49).

Discussion

While both oncolytic virus therapy and ADC therapies are relatively new, they invite an exciting opportunity for combination therapy. Due to their complementary mechanism of action, if combined, they could produce a strong synergy that could enhance the overall efficacy of these treatments. ADCs work to enhance the tumor immune cycle, particularly in the early stages. They cause targeted cell death, which promotes antigen release, jump-starting this system and increasing immune interaction. OVs can play a significant role in the later parts of the process, as they induce immunogenic cell death. Through the combination of ADCs delivering specific toxic payloads to tumor cells while OVs infect the cells and stimulate an immune response, treatment could be a more definitive and efficient method of treatment. Thus, ADCs would offer more precise, specific tumor-cell targeting, while the oncolytic effect of OVs would help to spread the tumor antigens. In combination, ADCs and OVs could overcome the limitations of these therapies when administered alone. The combination would address unwanted off-tumor toxicity and acquired resistance due to antigen heterogeneity. It could also incite a more robust and diverse immune response against the tumor, creating a more effective and long-lasting anti-tumor effect.

However, several limitations are important to consider when exploring the potential combination of these approaches. For instance, several challenges inhibit the efficiency and success of oncolytic virus therapy. Our immune system is designed to eliminate all foreign threats. This includes oncolytic viruses that are meant to eradicate cancerous cells. It is essential to account for the fact that the immune system will be attempting to eliminate this virus before it has the chance to replicate within the tumor cell and rupture the cell. Scientists are currently experimenting and exploring ways OVs work despite the immune system.

In addition, although ADCs are recognized as a promising therapy, clinical trials have highlighted several limitations. A major challenge is antigen heterogeneity, which is the low and uneven distribution of the target protein. This may cause some cells to be overlooked or skipped over, leaving cancer in the body even after the therapy is done (46). Another notable hindrance of ADCs is off-tumor toxicity. This is because the surface protein being targeted by the ADCs can sometimes be expressed in noncancerous cells (50). When ADCs bind to these noncancerous cells, a cytotoxic can be released, damaging or killing the healthy cell. Overall, the constraints that come with OVs and ADCs highlight the need for a strategy that can increase the efficiency of these treatments.

In conclusion, this combination of ADCs and oncolytic virus therapy is a notable way to leverage the tumor immune cycle and induce a greater, potentially more durable antitumor immune response. A targeted approach, combined with oncolysis, invites an opportunity to fight cancer without the risks or side effects associated with more conventional methods. For instance, by potentially expanding the diverse repertoire of immunogenic antigens, this could diminish the likelihood of primary or acquired resistance. Additionally, the combination being more targeted through the use of cancer-cell directed antibodies could mitigate changes of off-target effects. Thus, the proposed combination of ADCs and virotherapy offers an exciting next phase in the fight against cancer.

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