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Review Article

Immunotherapy: the Mega Weapon to Cure Cancer

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Abstract

Objective: Cancer is one of the most complex genomic diseases that can gain abilities to resist different therapies. These capabilities, known as the hallmark of cancer, allow specific and personalised therapies such as immunotherapy.

Materials and methods: This review paper discusses how different immunotherapies, such as immune checkpoint blockade, chimeric antigen receptor (CAR) T-cell, and Oncolytic viral therapy, which are currently being used and researched to overcome cancer cell capabilities by using the patient's immune system.

Results: Immune checkpoint blockade therapy is used to block immune inhibitory pathways using anti-PD-1 receptor and anti-CTLA-4 receptor antibodies, which make lymphocytes more responsive towards cancer cells. Then, it is discussed how CAR T-cells are designed to make cancer antigens more easily identified by T-cells for a more specific immune response. Furthermore, it is shown that oncolytic viruses directly destroy cancer cells and, indirectly, make them more vulnerable to the immune system.

Conclusion: It is proposed that oncolytic viral therapy is a bridge between Immune checkpoint and CAR T-cell therapies for a more effective and more specific immune response towards cancer.

Keywords: Immunotherapy; Cancer; Immune Checkpoint Blockade; Viral Therapy

Introduction

Cancer is the disease of the genome. Cancer cells are self-centred cells that reproduce uncontrollably and stop functioning as they should in a specific organ. Most cancer types progress through five different stages (1). Organ cells start from a premalignant status and progress to stage IV (metastasis), in which cancer cells have invaded other organs (2). When a cell becomes premalignant, it means it has acquired gene mutations or gene activation of a few genes, which can potentially lead to over replication. These mutations can be called abilities in a way that cancerous cells gain over time at every stage, and with each capability that they gain, they become more invasive and more unstable (3). A total of 606,520 deaths are expected in 2020, only in the US, as a result of cancer (4). The earliest description of cancer dates back to 3000 BC, which was written in ancient Egypt, in which was noted to be untreatable (5). Since then, many therapies have been developed to treat this disease. In modern times, chemotherapy, radiotherapy, and cancer removal surgery have saved millions of lives. However, many people still die due to having more aggressive cancer types and

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metastasis as a result of late diagnosis or fast progression of the disease. Cancer cells continuously evolve to survive on their own. This means that cancer cells become multi-drug resistant by gaining the ability to pump drugs out by activating a family of ATP-dependent transporters (6). This is why general chemotherapy was mixed with targeted chemotherapy. However, cancer cells also evolve to evade targeted treatments by changing the drug target structure. For instance, imatinib is used for chronic myelogenous leukaemia, but overtime BCR-ABL protein structure changed so that imatinib cannot inhibit its ATP binding site (6). Cancer cells gain twelve capabilities that allow them to grow, resist different treatments, and become metastatic. Some of these phenotypic abilities are as follows: evading growth suppressors, inducing angiogenesis, resisting cell death, sustaining proliferative signalling, and avoiding immune destruction (7).

Many different therapeutic strategies have been developed to tackle these cancer capabilities. Consequently, a new type of oncology treatment has emerged, known as personalised cancer therapy. In this strategy, cancer capabilities are found by cancer genome sequencing, and accordingly, the patient is administered medication that is not bypassed by the cancer cells (8). This implies that cancer can relapse with a more vicious type (more phenotypic abilities) or progress to metastasis within the patient. Therefore, in the past decade, scientists have undertaken extensive research on immunotherapy. In personalised immunotherapy, the patient's immune system is used or assisted in detecting cancer cells better (9). Our immune system detects and destroys cancer cells every day from birth. When a cell becomes cancerous, one of the main capabilities it has gained to survive is to camouflage and not be detected by the immune system. Hence, much advancement such as immune checkpoint blockade, CAR T-cell therapy, and oncolytic viruses (OVs) have been developed to aid in increasing detection, targeted cancer cell destruction, and loss of capabilities in cancer cells. This paper aims to provide a comprehensive review of these therapies and to discuss how these therapies can complement each other to cure this formerly known untreatable disease.

Introduction

Immune checkpoint blockade: Immune cells such as T-cells, B-cells, APC, and NK cells are continually scanning somatic cells to identify cancer cells and destroy them by inducing apoptosis and secreting cytotoxins. This process of scanning is carried out by a series of immune checkpoint receptors present on T-cells, such as PD-1, CTLA-4, and CD-28 receptors (10). T-cells scan somatic cells by binding their T-cell receptors (TCR) to the major histocompatibility complex (MHC) of the self-cell, which is followed by PD-1 receptor present on T-cell binding to the PD-L1 ligand present on the same cell (11). These bindings will signal the inhibition of T-cell activation, which means the bound cell to the T-cell is non-cancerous or a cancer cell over expressing PD-1 and being recognised as self (Figure 1A) (12). Similarly, CTLA-4 receptors of the T-cell are attached to a dendritic cell or an APC (Antigen-presenting cells) to T-cells for antigen recognition and processing (9). When an APC is attached to the T-cell to present an antigen sample, it expresses different subtypes of B7 ligands (CD-80 and CD-86) (13). These subtypes of B7 compete to bind to CD-28 and CTLA-4 receptors on T-cells, depending on their expressed concentration on the APC (13). If B7 binds to CTLA-4, T-cell proliferation is inhibited, and if it binds to CD-28, the T-cell is activated (13, 14). This T-cell activation then leads to cytokine release for clonal expansion, T regulatory cell inhibition, and lymphocyte migration to the site of tumour or infection (14, 15). Thus, due to this immune checkpoint system, most cancer cells are identified and destroyed by the immune cells. However, based on the hallmarks of cancer, one of the expected abilities that cancer cells gain is increasing expression of PD-L1 and B7 ligands, which results in immune suppression (7, 13). Then, this immune inactivity towards the cancer cells leads to cancer progression. Currently, there are a few humanised antibodies developed that bind to the PD-1 receptor, blocking it, such as Nivolumab, Pembrolizumab, and Cemiplimab (16-18). Whilst for CTLA-4 blockade, monoclonal antibodies like Ipilimumab have been developed (19). These are known as Immune checkpoint blockade therapies, which help T-cell activation towards the cancer cells (Figures 1B and 1C). These drugs have been approved by the FDA and are currently being used clinically to treat many cancer types such as leukaemia, prostate cancer and sarcoma (20-22). However, PD-1 blockade alone is inefficient for solid tumours and progressed cancers (surpassing stage 3); consequently, a combination of PD-1 and CTLA-4 blockade therapy is currently being used as a more aggressive treatment (20).

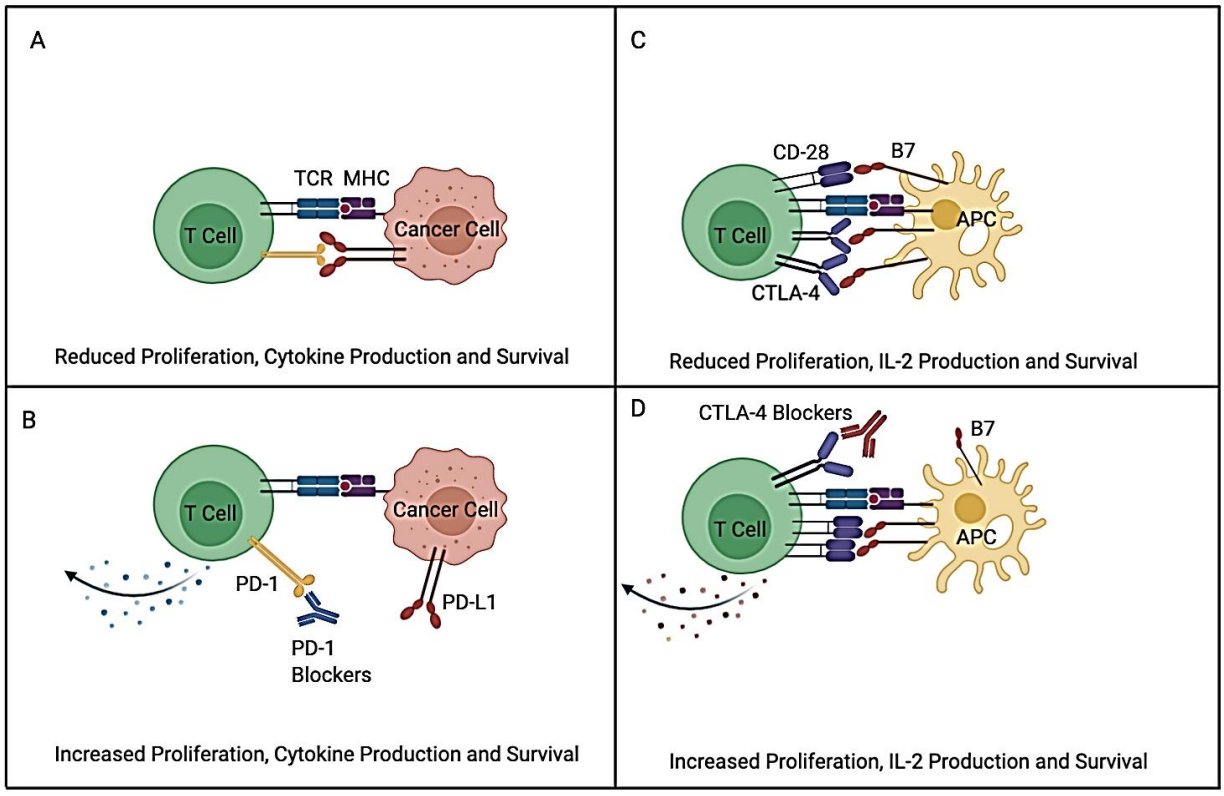

Figure 1: PD-1 and CTLA-4 immune checkpoint regulation
A) Attachment of PD-1 receptor to PD-L1 ligand increases T regulatory cell proliferation and reduced CD8 T-cell proliferation and survival with reduced cytokine production. B) PD-1 blockade results in cancer cell detection, increased CD8 T-cell proliferation, cytokine release and T regulatory cell deactivation. C) Higher number of CTLA-4 binding to B7 than CD-28 results in CD8 T-cell inactivation, T reg cell activation reduced IL-2 production and cancer progression. Blockade of CTLA-4 causes T reg inactivation, cancer detection, CD8 T-cell proliferation and increased IL-2 secretion (10). "Created in BioRender. Rt, Z. (2026) https://BioRender.com/og0jcpo ".

For instance, for the treatment of Metastatic Esophagogastric Cancer, a group of patients who received combination therapy had a 9% higher progression-free survival rate than the group of patients who only received PD-1 blocker over 12 months (19). It also should be noted that these immune checkpoint blockade therapies are not free of risks and may lead to autoimmune diseases due to blockade of PD-1 and CTLA-4 receptors, which act as T-cell off switches (23).

CAR T-cell: T-cells are one of the primary lymphocytes that scan the body for cancer cells and destroy them if identified. However, in some people, their immune system does not recognise or does not fully respond to cancer cells, which is due to their genetic make-up, genome composition, and epigenetic regulation (24). Previously, it was shown that this lack of response could be due to immune checkpoint inhibitory pathway activation, but there are other reasons for this lack of response. There are many genes that regulate transcription of many surface receptors and cytokine production of lymphocytes other than PD-1 and CTLA-4, such as IL-2R (α, β, and γ) and TCR (CDR3 α, β, γ, and δ control VJ and VDJ recombination) (15, 25).

These mutations affect tumour antigen recognition and lymphocyte activation and survival (25). Therefore, when these genes are downregulated, cancer cells are not recognised and continue to progress. In order to overcome this problem, scientists have been working on a new technology called CAR T-cell therapy. In this TCRs of the T-cells are designed for a specific tumour antigen as receptors called CARs (Figure 2A) (26). Then, the genetic code for this CAR is transferred ex vivo to the patient's T-cells using Lentiviruses and other nanoparticles (27). The advancement in this technology has created new generations of CARs, which have signalling capability for T-cell activation (28).

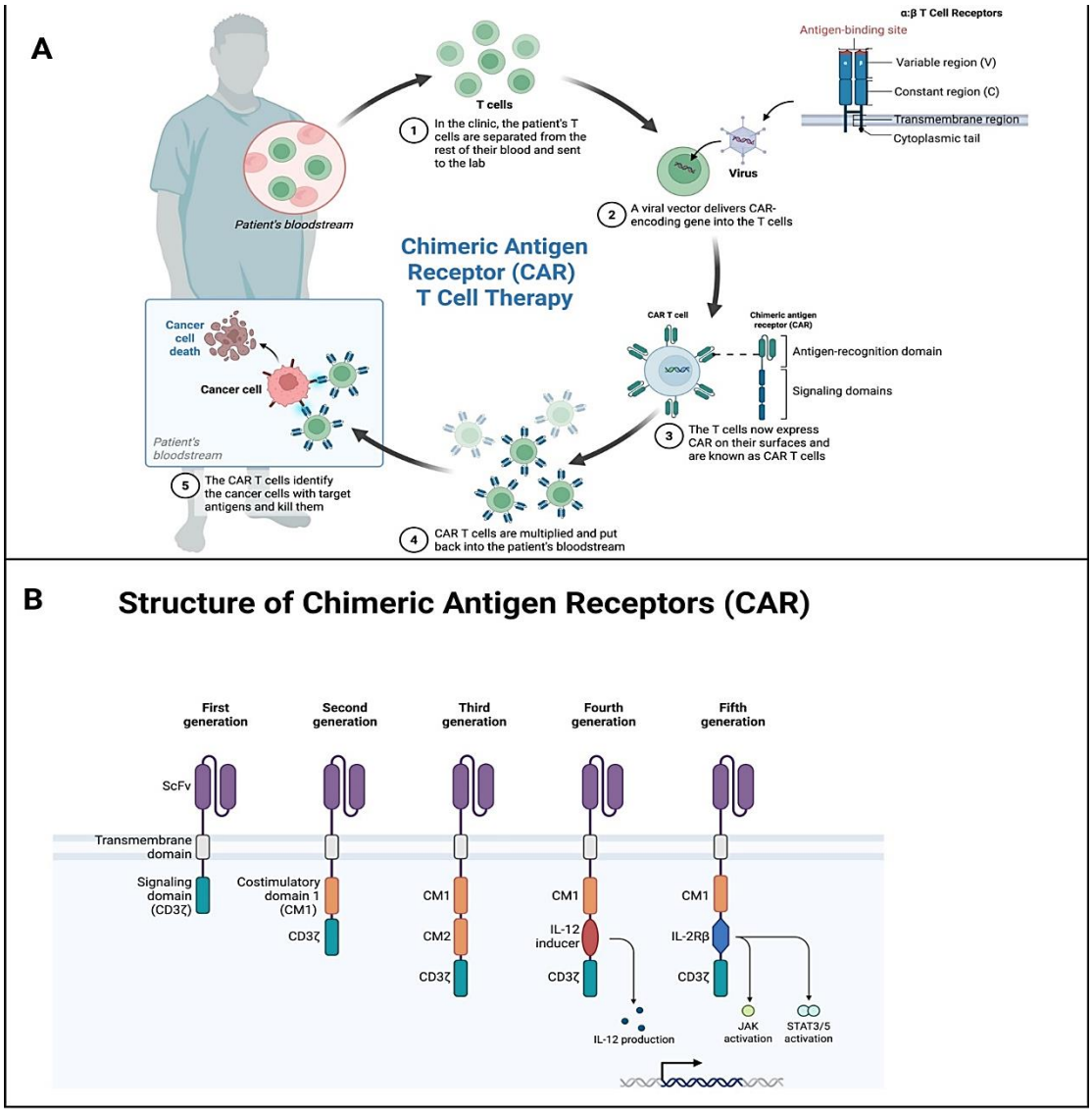

Figure 2: Chimeric antigen receptor design and CAR T-cell administration.
A) CAR is designed based on cancer specific antigen antibody's variable region, and its gene is delivered to the T-cells via AAV vectors before CAR T-cells' administration to the patient. B) First-generation CARs were designed by fusing CD3ζ signalling protein (intracellular domain) to the variable fragment (extracellular domain) for T-cell activation. Second and third-generation CARs have additional CD1 and CD2 intracellular signalling proteins that were fused to first-generation CAR. In fourth and fifth-generation CARs extra inducible IL-12 and IL-2Rβ chains were infused with second-generation CARs (26). "Created in BioRender. Rt, Z. (2026) https://BioRender.com/ozv6hj7 ".

These signalling capabilities can be added to CARs intracellular domain to make up for signalling pathways that patients' T-cells lack, such as IL-12 (29). Currently, three generations are being utilized in clinical trials, and further generations four and five are being developed in mouse models capable of inducing the production of one or more cytokines (Figure 2B) (28). CARs target tumour-specific antigens that are typically overexpressed in different cancer types. For instance, Anti-CD19 is CAR T-cell therapy that has been made to treat acute lymphatic leukaemia since CD19 is overexpressed on B cells in this disease (30). Multiple CARs are developed for different cancer antigens in order to treat different types of cancer, as shown in Table 1 (31). However, since these targeted antigens are expressed and presented at different levels, unfortunately, CAR T-cell therapy may occasionally lead to autoimmune diseases, cytokine release syndrome, and neurotoxicity (28).

Table 1: Some examples of CARs developed for solid tumors (31)

Targeted antigen	Disease	Vector	CAR Generation
FRa	Ovarian cancer	Retrovirus	First
Mesothelin	Pancreatic cancer	mRNA	Second
c-MET	Breast cancer	mRNA	Second
EGFRvlll	Glioblastoma	Lentivirus	Second
CEACAM5	Colorectal cancer	Retrovirus	First
CEA	Colorectal cancer	Lentivirus	Second
GD2	Neuroblastoma	Retrovirus	First
CD133	Colorectal cancer, Pancreatic cancer, Hepatocellular carcinoma	Lentivirus	Second

Nevertheless, even with such adverse effects, this study has shown a promising success rate of 68% to 93% with a low relapse rate of 40% to 50% of patients (32).

Oncolytic Viruses: Viruses are small particles that carry a small genome and are responsible for many diseases. These are capable of causing disease by entering a host cell and disturbing the cell's normal function by using the cell's machinery to transcribe and translate its genome. This characteristic of viruses allows scientists to apply them as vessels to transfer specifically designed viral genomes into the cancer cells, also known as OVs. Such viruses can be configured to have a cancer-specific surface protein, which will allow them to infect cancer cells solely (33, 34). In order to make this viral infection and expression, more specific cancer distinct promoters are used in their designed genome; therefore, in case of entry to healthy cells, they will not be expressed (33). These viral vectors lack disease-causing genes, so they are unable to cause illness in patients. Many different genes can be inserted into the viral vector which will destroy cancer cells; these occur through two primary mechanisms, tumour tropism and tumour cell lysis (35). Viral replicative genes lead to tumour cell lysis due to viral particle production and assembly (Figure 3A) (36). On the other hand, tumour tropism can be a bridge between many cancer therapies, such as CAR T-cell therapy and immune checkpoint blockade therapy. It can also take away the abilities that tumour cells have gained, as mentioned is a crucial quality of cancer. For instance, Oncolytic adenovirus can carry a p53 gene aimed for cancers with p53 tumour suppressor gene mutation to induce apoptosis in them (Figure 3E) (37). Another example of tumour tropism would be the introduction of an anti-PD-1 receptor antibody gene (Figure 3C) (38). In a mouse animal model, oncolytic viral therapy was used to treat five mice in which anti-PD-1was detected, and four of them had reductions in tumour size and volume with 80% success rate (39). OVs are capable of altering the microenvironment of the tumour by suppressing angiogenesis and establishing production of prodrug activating enzymes such as Vasculostatin and yeast cytosine deaminase uracil phosphoribosyltransferase (yCD–UPRT) (Figures 3D, 3G) (40, 41). Last but not least, OVs can be designed to carry genes that produce IL-12, which promotes clonal expansion and T-cell activation, expressing specific membrane-bound antigens on cancer cells (Figures 3F, 3B) (42). For instance, CLDN6 is only expressed in early stages of embryonic development and not in adult cells (43). Expressing CLDN6 in cancer cells via OVs, flags cancer cells and makes them easy targets for the immune cells to identify (43-45). Thus, oncolytic viral therapy directly kills cancer cells and, through the tumour tropism mechanism, makes cancer cells a better target for the immune system in addition to creating an overall harsh environment for them to survive.

Results

Scanning somatic cells to identify cancer cells and destroy them is carried out by a series of immune checkpoint receptors present on T-cells. Immune checkpoint blockade therapies are not free of risks and may lead to autoimmune diseases due to blockade of PD-1 and CTLA-4 receptors, which act as T-cell off switches (23). Multiple CARs are developed for different cancer antigens in order to treat different types of cancer, as shown in Table 1 (31). However, since these targeted antigens are expressed and presented at different levels, unfortunately, CAR T-cell therapy may occasionally lead to autoimmune diseases, cytokine release syndrome, and neurotoxicity (28). Nevertheless, even with such adverse effects, this study has shown a promising success rate of 68% to 93% with a low relapse rate of 40% to 50% of patients (32).

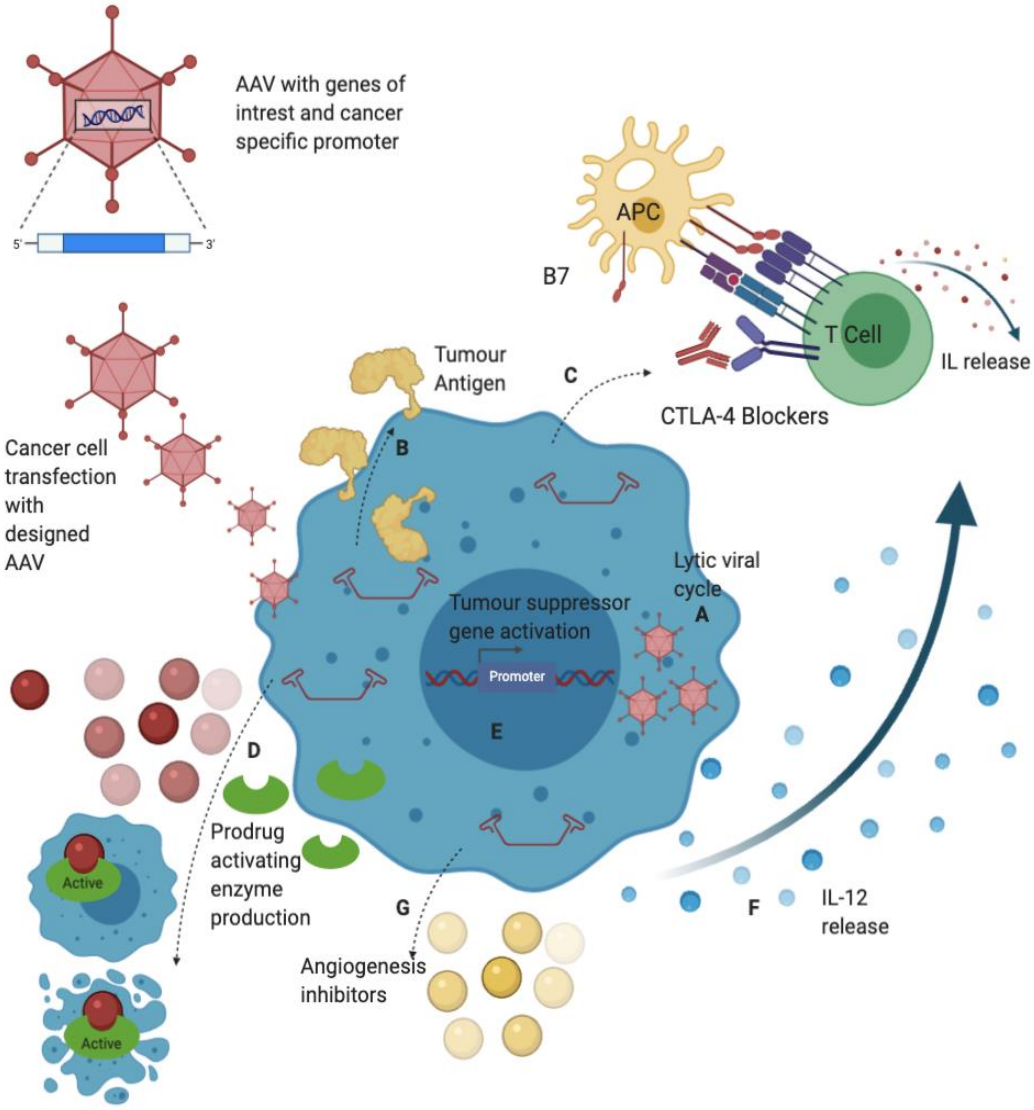

Figure 3: Oncolytic virus different applications for cancer therapy.
A) Viral replication leads to cancer cell stress and death. B) Membrane bound tumour cell specific antigen production. C) Anti-PD-1 antibody production. D) Prodrug activating enzyme production. E) Tumour suppressor gene activation. F) IL-12 expression and release. G) Angiogenesis inhibitor drug production. All these expressions happen by the cancer cell due to the viral vector transfection (33). "Created in BioRender. Rt, Z. (2026) https://BioRender.com/zvht8my".

Oncolytic viral therapy directly kills cancer cells and, through the tumour tropism mechanism, makes cancer cells a better target for the immune system in addition to creating an overall harsh environment for them to survive.

Conclusion

In summary, the hallmark of cancer has shown the capabilities that cancer gains to progress and to resist usual therapies such as chemotherapy and radiotherapy. Hence, immunotherapy has become more popular since it uses the best weapon against diseases, which is our immune system. Immune checkpoint blockade therapy development and implications make immune cells more responsive towards cancer cells by blocking inhibitory receptors such as PD-1 and CTLA-4. Next, it was demonstrated how CAR T-cell therapy trains T-cells to identify tumour-specific antigens readily and as a result, make the treatment more effective. CAR T-cells are designed using the variable region of cancer specific antibodies, which are fused with various signalling proteins to enhance tumour detection and destruction. Attention must be kept on how to overcome the

possible autoimmune disease side effects as a result of immune checkpoint blockade therapy. Finally, the way OVs, directly and indirectly, weaken and destroy malignant cells was able to be determined. OVs have tumour lysis and tropism capability, which reduces cancer cell survival and progression. OVs can be combined with immune checkpoint therapy and CAR T-cell therapy and act as a bridge between these two treatments.

For future applications, this review paper proposes to utilize all three therapies together to treat cancer. OVs can be designed to give rise to specific membrane tumour antigens that our own cells do not express, in addition to the production of immune checkpoint blockade antibodies. Furthermore, fourth-generation CAR T-cells can be designed for the tumour antigen coded by the OVs and an inducible IL-12 domain. This could theoretically increase the T-cell response to cancer cells expressing the antigen and limit their activation to the tumour microenvironment, and where only cancer cells are present. Thus, this combined therapy can increase immune response and infiltration towards cancer cells while reducing future off-target effects to become the mega weapon to cure cancer.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

None.

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