World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Modulating the immunosuppressive tumor microenvironment: Multi-synergistic cancer therapeutic approach with oncolytic viruses

Michael Tosin Bayode [1, *], Olamide Joshua Babatunde [1], Prosper Obed Chukwuemeka [2], Henry Nnaemeka Ogbonna [3, 4], Chibuzo Valentine Nwokafor [3, 5], Sunday Ayodele Alonge [6], Christopher Busayo Olowosoke [2] and Arinola Harriet Oshokoya [7]

[1] *Department of Microbiology, Federal University of Technology, P.M.B. 704, Akure, Nigeria.*
[2] *Department of Biotechnology, Federal University of Technology, P.M.B. 704, Akure, Nigeria.*
[3] *Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.*
[4] *University of Bath. Claverton Down, Bath. United Kingdom.*
[5] *University of the West of Scotland, Lanarkshire, Glasgow. United Kingdom.*
[6] *Bamidele Olumilua University of Education, Science and Technology, Ikere, Ekiti-State, Nigeria.*
[7] *Department of Microbiology, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.*

World Journal of Advanced Research and Reviews, 2024, 21(01), 543–559

Publication history: Received on 07 November 2023; revised on 29 December 2023; accepted on 01 January 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.1.2585

Abstract

Most patients with complex malignancies show a high level of toxicity and limited long-lasting responses to current conventional therapies. In contrast, the immune system has the intrinsic potential to distinguish between self and non-self (foreign or different) cells, including cancer cells, and successfully eliminate them. Even after T and NK cells successfully navigate sophisticated surveillance paths studded with diversion networks, processes, and impediments, they must overcome the impacts of a highly neutralizing and immune-suppressive destination known as the tumor microenvironment (TME). A comprehensive understanding of these TME events, immune system stimulative OVs functions, and synergistic possibilities with other immune activating strategies will provide insight and present a unique opportunity for improved therapeutic efficacy against cancer. The synergistic potential of combining oncolytic viruses with immune checkpoint inhibitors merits further exploration. In particular, focusing on the PD-1/PD-L1 (programmed cell death) axis may hold promise in amplifying antitumor immune responses and thereby bolstering therapeutic outcomes.

Keywords: Oncolytic viruses (OVs); Cancer; Immunotherapy; Tumor microenvironment (TME); Immunosuppression; T-cells

1. Introduction

Recent and pertinent literature was systematically identified through a rigorous search strategy and meticulously scoured using a combination of targeted keywords such as "oncolytic viruses," "tumor microenvironment," "immunosuppression," and "cancer therapy" [1]. The inclusion criteria encompassed studies exploring the intricate interplay between oncolytic viruses and the tumor microenvironment, focusing on immunosuppressive mechanisms and therapeutic outcomes. The selected studies underwent meticulous quality assessment based on established evaluation criteria, underpinning the reliability and validity of the conclusions of the selected reviews [2]. According to Global Cancer Statistics 2020 [3], a projected 19.3 million cases of cancer occurred in 2020, and approximately 10 million died from breast cancer in females, leading to the most diagnosed cancer at 11.7% [4; 5]. Cancer is the leading cause of morbidity and mortality worldwide [6; 7]. Cancers are sophisticated, dynamic, and engage in mutualistic

* Corresponding author: Michael Tosin Bayode https://orcid.org/0000-0001-9990-3805

interactions with cells in their surroundings to progress, metastasize, and develop resistance to treatment [8]. Immunosuppression and evasion have been linked to cancer cell proliferation and metastasis [9]. In addition to intrinsic tumor resistance mechanisms, the tumor microenvironment (TME), which includes immunosuppressive immune cells and pathways, has been found to significantly impede numerous cancer therapy approaches [10]. The tumor microenvironment (TME) is a sophisticated niche of cells that surrounds cancer and influences its development, epigenetics, dissemination, and immune evasion (hampering antitumor immunity). The events that occur within the TME are linked to the survival of tumors within the body. Therefore, while developing new therapies and medical interventions for cancer patients, it is critical to address several aspects of the TME [9, 10].

The sophistication of the mammalian immune system in its complex but effective network of interactions among specialized innate and adaptive cell types that can collectively distinguish between self and non-self entities has provided a foundation for improved and efficient global cancer research efforts [11-13]. Immunotherapy, which involves turning on this complex machinery of the immune system network to target tumors, has been a highly regarded therapeutic option for many years and was unsuccessful in the early days. However, in recent years, it has shown a great deal of success as a traditional cancer treatment [14]. Some important examples of immunotherapy approaches include immune checkpoint inhibitors (CPI), oncolytic viruses, cancer vaccines, lymphocyte-activating cytokines, and CAR-T cells. Among these, the most successful and widely adopted in clinical cancer therapies involves blocking popular immune checkpoints, such as PD-1, PD-L1, and CTLA-4, while recently reported targets also include inhibitory lymphocyte activation gene (LAG-3), TIM-3, and V-domain Ig suppressor of T cell activation (VISTA), as well as classes of stimulatory inducible co-stimulatory pathways (ICOS, 4-1BB, and OX40), indicating a more promising future [14]. The fact that they are mostly successful in patients with comparatively low tumor burden in their early stages, demonstrating that immunosuppressive mechanisms have not advanced, represents a significant barrier that still exists. The heterogeneity of tumor types, mounting evidence of immune escape mechanisms employed by tumors and their microenvironment, and some observed treatment bottlenecks within the TME point to the need for more effective immunomodulatory agents to produce a more reliable and long-lasting therapeutic response against a broad range of cancers [9]. This therapeutic approach aims to enhance anti-tumor immunity by reprograming the immunosuppressive tumor microenvironment towards $CD8^+$ T-cell-biased anti-tumor immunity by increasing the proportion of colorectal cancer patients who benefit from immunotherapy. Tumor metabolism barometer dynamics via calorimetry studies can be used to probe the metabolic activity of malignant neoplastic cells, enabling researchers to probe the intricacies of cancer metabolism and detect alterations in the metabolic pathways of tumor cells [15]. However, both enhanced immunotherapeutic enhancement of anti-tumor immunity and tumor-metabolism gauge approaches are used in cancer research and have the potential to revolutionize our understanding of cancer biology and its implications for the advancement of personalized cancer therapies.

Any treatment that aims to reduce immunosuppression, such as CPI and CAR T cells, must be administered in conjunction with other therapies that boost immune responses or block other suppressive components of the TME such as the myeloid cell compartment. Immune-activating therapy using oncolytic viruses offers a special alternative for reducing the impact of immunosuppressive cells, events, or components because of their dynamic and mechanistic role within the tumor. Researchers worldwide have considered using OVs therapy to boost the effectiveness of immunotherapies, particularly when treating immunosuppressive TME [16, 17; 10]. We present a critical and comprehensive analysis of recent developments in the use of oncolytic virotherapy to alter the immunosuppressive TME, in addition to providing additional insights into various strategies for maximizing the therapeutic potential of OVs. Here, we discuss how engineered OVs expressing pro-apoptotic genes, chemotactic cytokines and chemokines, immune co-stimulatory genes, tumor suppressor genes, and TAA overexpression enhance immune responses against tumors. This review describes how over-expressed TAAs, up-regulated APC activities, and cytokine signaling lead to increased trafficking of T cells, NK cells, and CAR-T cells, and how combining immunotherapies with the modulation of innate antiviral responses (IFN and NK cells) against OVs by potent inhibitors can enhance effective viral tumor destruction.

The central hypothesis of modulating the dynamics of the immunosuppressive tumor, which elicits a multi-synergistic cancer therapeutic approach with oncolytic viruses, posits the potential to effectively remodel the immunosuppressive tumor microenvironment (TME) and thereby enhance the efficacy of cancer therapy. By harnessing the unique attributes of oncolytic viruses, including their tumor selectivity, cytotoxicity, and ability to trigger immunogenic cell death (ICD), researchers have aimed to disrupt the intricate network of immunosuppressive signals present within the TME. This approach is envisaged to overcome the limitations of conventional cancer treatments and pave the way for more robust clinical outcomes. While previous studies have probed the impact of oncolytic viruses on the TME, this comprehensive review aims to amalgamate the existing literature, pinpoint emerging trends, and uncover novel avenues for synergistic therapeutic interventions.

2. The tumor microenvironment (TME)

According to Labani-Motlagh et al. [10], the tumor microenvironment (TME) is a diverse and complex milieu composed of heterogeneous cell types and many substances that are released by stromal, tumor, and immune cells. This environment is packed with a variety of suppressive cells, including regulatory T (Treg) cells, cancer-associated fibroblasts (CAFs), M2 phenotype macrophages, regulatory B cells, myeloid-derived suppressor cells (MDSCs), immune-recruited cells, cytokines, chemokines, and secreted factors in the extracellular matrix, all of which are critical for tumor epigenetics, differentiation, and immune system evasion (Fig. 1) [18]. The improvements and invention of more efficient technologies and techniques in recent years have begun to enhance our understanding of the events and complex interactions occurring within a heterogeneous tumor environment. Despite this, there is still work to be done in utilizing this knowledge for efficient tumor killing. Immunologically "cold" or immunosuppressive tumors continue to be of great concern to researchers worldwide and have taken center stage in the field of immunotherapy research. Tang et al. [18] listed the distinguishing characteristics of an immunosuppressive TME: heterogeneity of constitution, absence of tumor antigen, defects in antigen-presenting cells, impairment of T-cell infiltration, enhancement of immunosuppressive metabolism, and activation of immunosuppressive signaling pathways.

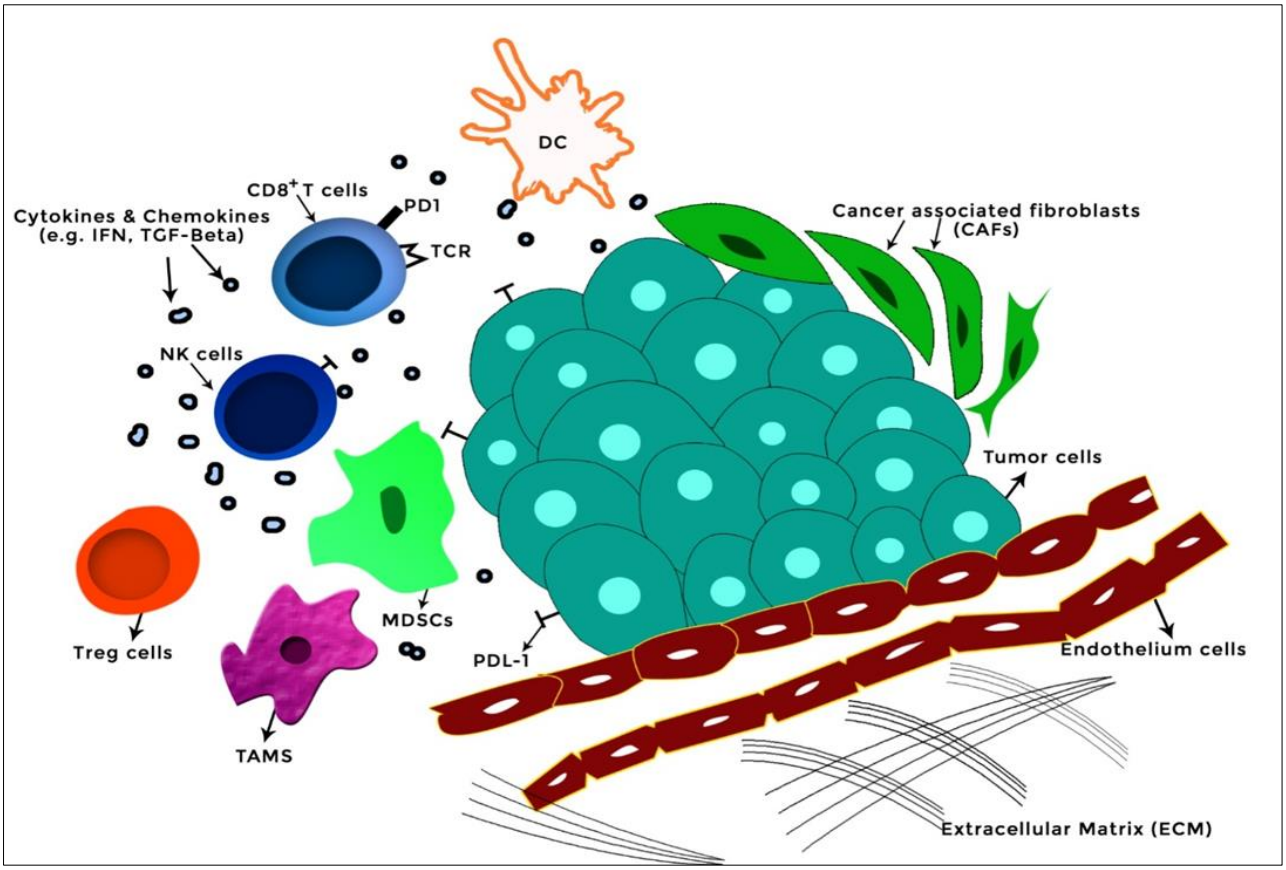

Figure 1 Cellular composition and events of immunosuppressive tumor microenvironment (TME). The immunosuppressive TME presents many barriers to immune cell (NK and T-cell) trafficking (high levels of CCL2, low levels of T cell chemotactic chemokines), T cell functionality through inhibitory cytokines (TGFβ and IL10), ligands (PDL1, etc.), and defects in antigen-presenting cells (APCs), such as dendritic cells (DCs). Many of these factors are expressed by tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), cancer-associated fibroblasts (CAFs), and tumor cells themselves

3. Review of the immunosuppressive TME events

The immunosuppressive tumor microenvironment refers to specific conditions within the tumor that foster immune evasion and tumor progression. This includes the presence of immunosuppressive cells, cytokines, and other factors that hinder effective antitumor immune responses [19]. The growth and progression of cancer generate a microenvironment that is highly immunosuppressive because of the interplay between the body's immune system, tumor cells, and tumor stroma [20]. Tumor cells bypass host immune surveillance through a variety of mechanisms,

including major histocompatibility complex (MHC) suppression to avoid being recognized by T cells; increasing the expression level of membrane proteins such as programmed cell death ligand-1 (PD-L1), which inhibits cytotoxic T cell activation, and then stimulates the secretion of regulatory cytokines, such as interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and other secreted molecules that are immunosuppressive, consequently inhibiting T cell activities, influencing the recruitment of immunosuppressive MDSCs and Treg cells, and aiding the transition of macrophages (TAMs) from an anti-tumor M1 to tumor-promoting M2 phenotype [21]. The immune system is neutralized by TAMs by upregulating the secretion of the regulatory cytokines IL-10 and TGF-β and releasing CCL22 to recruit more Tregs [20]. Arginase-1, which is produced by MDSCs, degrades l-arginine, which is required for T cell proliferation, and MDSCs downregulate T cell receptor signaling, which promotes T cell inactivation. MDSCs also aid in the recruitment of more Tregs by releasing chemokines such as CCL3, CCL4, and CCL5 [20]. Tregs inhibit the growth of early T cells by producing immunosuppressive mediators, or they block antigen presentation by DCs, which prevents the expansion of early T cells. Finally, they downregulate pro-inflammatory IL-12 signaling through the expression of a competitive receptor [21]. This could lower the levels of T cell-associated cytokines (e.g., IFN-γ, TNF-α, and IL-2) and subsequently suppress the activity of other antitumor immune effector cells [23; 24]. Anergic T cell distribution has been identified as a typical marker of an immunosuppressive TME, indicating a weak prognosis [25, 20].

Research has indicated that oncolytic viruses (OVs) can modulate the TME both naturally and through engineering, a process known as "cold-to-hot" tumor modulation. When using OVs to treat cancer, it is possible to target the inactivity of TME associated immune cells that characterize cold tumor states, which is linked to several previously described hallmarks [26]. A previous research has demonstrated that viral infection triggers a series of inflammatory events that activate the immune system (both innate and adaptive), changing the chemokines, cytokines, and cellular makeup of tumors [27]. Viral nucleic acids can activate cytoplasmic RNA and DNA sensors and Toll-like receptors (TLRs), which function as pathogen-associated molecular patterns (PAMPs) to activate type I IFN signaling through cytoplasmic MyD88 [27, 28]. Furthermore, OV infection can stimulate a response to danger-associated molecular patterns (DAMP) by the oncolytic release of ATP and high-mobility group box 1 (HMGB1) into the extracellular milieu and upregulation of calreticulin (CRT) on the cell surface [28]. The progression of these events in combination with type I IFN signals encourages DC maturation and recruitment, enabling them to collect tumor and viral debris that accumulate from virus-mediated destruction, deliver antigens back to lymph nodes, and eventually prime naive T cells for successful tumor elimination [29, 30]. Therefore, infection modifies the TME, cellular make-up of the tumor, and generated soluble mediators. OVs have been demonstrated that OVs significantly reduce the number of MDSCs and Tregs while simultaneously increasing the infiltration and activation of NK cells, DC (CD11c+), CD8 T cells, and macrophages of the M1 phenotype in various mouse models [27].

Oncolytic viruses work against cancer in monotherapies through a variety of mechanisms; however, it is intriguing that they have been specifically chosen to activate and heat up the immunosuppressive TME and/or target at least one or more of its major hallmarks for better treatment response [31]. The hallmarks include the absence of tumor antigens, dysregulated T-cell infiltration, defective antigen-presenting cell function, and immunosuppressive signaling pathway activation.

4. Oncolytic viruses and Oncolytic virotherapy

Oncolytic viruses (OVs) are a class of viruses that are either naturally occurring or genetically modified, and selectively infect and replicate within cancer cells. This replication can result in the lysis of cancer cells and release of tumor antigens, triggering an immune response against the tumor, as replicated by Russell et al. [32]. Viruses that have the power to stop unchecked growth or even eradicate cancer cells without harming healthy host cells are known as oncolytic virotherapies [10, 9]. It is not entirely novel to use viruses to treat cancer. Since the nineteenth century, numerous case reports or trials involving various viral strains have been widely reported [33, 34, 35, 36, 37]. However, the application of reverse genetics technology sparked a resurgence in virotherapy interest and accelerated the production of more potent tumor-specific oncolytic agents [34]. The observation that oncolytic viruses can kill tumor cells directly during replicative cycles has been the basis of earlier attempts to use them as cancer treatments. These efforts are frequently supplemented by engineered tumor tropism. However, more recent studies attribute greater potential to their ability to improve the tumor microenvironment and boost host antitumor immunity [38].

Four OVs currently have regulatory approval, and several others are undergoing clinical trials. Rigvir, an unmodified ECHO-7 picornavirus, was the first of its kind to be licensed anywhere in the world in 2004 for melanoma therapy. Georgia in year 2015 and Armenia in year 2016 both gave their approval, despite the lack of data on its efficacy [39, 40]. In November 2005, oncorine (H101), a genetically modified oncolytic adenovirus, was authorized in China for the treatment of patients with advanced nasopharyngeal cancer in combination with cytotoxic chemotherapy. Later, the drug Talimogene Laherparepvec (T-VEC) was approved by the Food and Drug Administration (FDA) in the United States

in October 2015 [41] for the treatment of patients with localized malignant melanoma. T-VEC is a modified herpes simplex virus type 1 (HSV-1), which incorporates two copies of the human cytokine granulocyte macrophage-colony stimulating factor (GM-CSF). The primary rationale for this approval was the pivotal phase III OPTiM trial [42], which showed a statistically significant improvement in overall survival. The most recent approval for DELYTACT, a modified herpes simplex virus, to treat brain cancers, such as glioblastoma, was approved in Japan in 2021 [40, 43]. As a result, oncolytic virotherapy continues to attract the attention of the cancer research community, as illustrated in Fig. 2.

A rigorous preclinical and clinical search for effective clinical candidates is currently ongoing, and spans both RNA and DNA virus families of either unattenuated or attenuated forms [42]. Members of the families adenoviridae (such as ONYX-015), herpesviridae (such as T-Vec, NV1020, and G207), and poxviridae are some of the DNA viruses that are most frequently studied (including myxoma viruses and some strains of vaccinia virus such as pexastimogene devacirepvec) as stated by Ajina and Maher, [38]. Reoviridae family members (such as reolysin, an unmodified type 3 Dearing strain reovirus), Picornaviridae members (such as the coxsackievirus CVA21 or the polio/rhinovirus recombinant PVSRIPO and Seneca Valley virus), Togaviridae members (particularly using specific alphavirus strains such as M1 and Sindbis AR339), rhabdoviruses (such as vesicular stomatitis virus (VSV)), and paramyxoviridae (including Newcastle disease virus (NDV) and measles viruses) [39].

5. Multi-mechanistic monotherapeutic action of oncolytic viruses

In theory, most cancer cells are especially vulnerable to viral infection, and this natural proclivity serves as the basis for the use of OVs as an important emerging antitumor treatment to selectively infect and kill cancer cells while posing no serious pathogenic threat to the host [44]. Oncolytic viruses target tumors in a phasic manner with the intention of mechanistically eliminating them with the least possible toxicity. The first and most distinctive characteristic is that they are oncotropic or possess the ability to selectively target and kill cancer cells without harming host cells, a property referred to as oncotropism [26]. These OVs activate the antitumor immune response, clearing away infected cell debris and subsequent tumor infection, frequently following and successfully completing the initial stage of oncotropism [26; 20]. Exogenous therapeutic genes can be genetically inserted into OVs to control tumor growth or induce tumor-specific immune function, resulting in high therapeutic effectiveness and low toxicity [20].

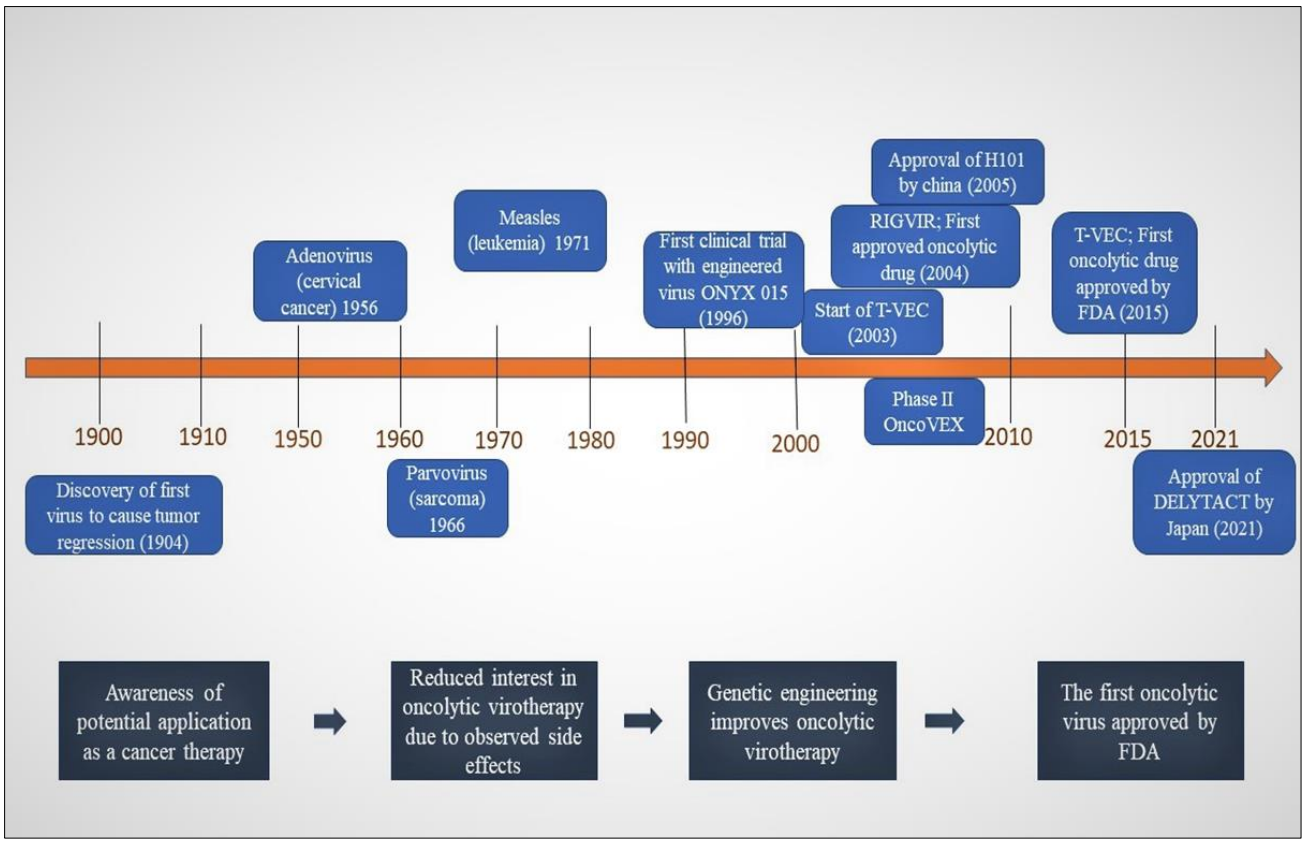

Figure 2 Historical development of viruses in oncolytic virotherapy cancer treatments

6. Drawbacks and Limitations of Oncolytic Virus Therapy

Efforts to scale up the therapeutic application of oncolytic viruses encounter significant challenges. Firstly, achieving optimal transduction efficiency across all tumor cells remains an ongoing challenge, impairing the uniformity and effectiveness of treatment [45]. The host's immune system can mount antiviral responses, leading to neutralization or clearance of virus particles, thereby diminishing treatment efficacy as demonstrated by Prestwich et al. [46]. The intricate heterogeneity of the tumor microenvironment poses a formidable obstacle, impeding consistent therapeutic responses and necessitating tailored interventions as observed by Quail and Joyce, [47]. The pre-existing immunity within the patient population towards the oncolytic virus can attenuate treatment efficacy and limit its therapeutic potential [48].

7. Selective oncolytic tumor tropism

Tumor cells go through a variety of physiological and genetic changes during oncogenesis that set them apart from healthy host cells. The evasive ability of malignant cells to escape immune system-mediated destruction, the development of hypoxic environments, the acquisition of defects or changes in cellular signaling pathways, changes to cancer cells' metabolism, and changes to aberrant tumor cell receptors are a few of these inherent cancer hallmarks [49, 50, 26, 20]. A few abnormal cell surface receptors allow for viral binding, making them essential for viral oncotropism and the ability of the infected cell to allow for viral intracellular replication. Neoplastic cells may have surface receptors that are distinct from those found on other cells that are viral targets particularly some bearing characteristics of malignant phenotypes such as over-expression of CD155, CD46, and I domain integrin 21, which serves as an important viral selectivity and entry receptor for measles viruses, poliovirus, echoviruses binding to CD-155. Examples include Herpes virus binding to over-expressed HVEM and Nectin co-receptor of malignant cells and Sindbis virus that recognizes high-affinity laminin receptor overexpressed in many cancer [49, 50]. Furthermore, by binding to the widely expressed LDL receptor, some viruses, like the vesicular stomatitis virus (VSV), exhibit a remarkable robust and pantropic selectivity. As a result, the tumor tropism of VSV depends on the susceptibility of malignant cells to viral infection rather than receptor specificity [49, 50].

Additional ways for OVs to target cancer cells only while totally disregarding their healthy counterparts include defects or changes in anti-viral pathways, cellular signaling pathways of tumor cells, such as disruption of cell cycle regulation, proto-oncogenes activation, and inactivation of tumor suppressor genes. For instance, genetically altered E1A and E1B genes of the adenovirus (Ad) selectively replicate in cells lacking the Rb or p53 tumor suppressor pathways, which is reported in 50% of malignant tumors [50, 51]. Furthermore, it has been demonstrated that cancer-specific mutations in cancer-related genes such as the genes responsible for the WNT signaling pathway proteins RAS, RB1, TP53, and PTEN make tumor cells more susceptible to viral infection [52, 53, 17].When compared to conventional treatments like chemotherapy, which have a high level of host cell toxicity, this level of selectivity and specificity enables the achievement of a strong cytolytic effect that is highly restricted to transformed cells [54, 53].

8. Induction of antitumor immune responses

A combination of antiviral pathways required for viral eradication and immune responses activated by recognition of tumor-associated antigens (TAAs), cellular epitopes, and neoantigens from the virus-infected tumor cell must work in harmony for oncolytic virotherapy to be effective [55, 26]. Tumor-associated antigens (TAAs), neoantigens, pro-inflammatory cytokines, chemokines, and other danger signals (danger-associated molecular pattern (DAMP) and pathogen-associated molecular pattern (PAMP) are released through the various mechanisms by which OVs lyse tumor cells during the lytic stage of selective viral tumor tropism. This promotes immune cell activation and recruitment within the tumor microenvironment (TME) consequently inducing T cells to attack uninfected tumor cells/secondary tumor and viral infected cell [55, 17]. Tumor cells are infected by OVs, which then control the cell's protein synthesis to produce viral macromolecules. However, this also causes "danger signals" to be expressed and recognized, which leads to a series of signaling events that end with the release of cytokines and DAMPs [56, 55, 57]. Additionally, after OVs cause oncolysis, infectious viral progeny, such as viral particles and PAMPs are released, causing them to infect and replicate in nearby tumor cells [56, 55, 26]. Each of these processes makes a significant local and systemic contribution to the stimulation and induction of anti-cancer immune responses.

TAA and neoantigen processing, effective cross-presentation to T cells, and the subsequent induction of antitumor and antiviral immune responses are all made possible by the activation and maturation of APCs such as dendritic cells (DCs). On the other hand, due to immunosuppressive regulatory elements and mechanisms present within the TME as well as premature viral clearance, OVs typically only stimulate weak tumor-specific immune responses [56, 26]. With the

development of genetic engineering techniques, scientists have been able to enhance the immunogenic effects of OVs and encode the OVs with different cytokines, immuno-modulators, and TAAs. Better therapeutic effects have been observed when the anti-tumor effectiveness of OVs expressing cytokines like TNFα, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, IL-4, IL-12, IL-18, and IL-24 has been evaluated. In numerous successful clinical trials, it has been shown that three viral vectors—namely, Ad, HSV, and VV engineered with GM-CSF expression can enhance antitumor immunity and cytotoxicity [56, 26]. In phase III trials for melanoma and head and neck cancer, the FDA approved (T-VEC), an oHSV-1 that expresses GM-CSF. These studies were the first to show that OVs immunotherapy was effective, with a response rate of around 30% against systemic disease following local injection into tumors. Fms-like tyrosine kinase-3 ligand (FLT3L), similar to GM-CSF is also a powerful growth factor capable of attracting and proliferating DCs in vivo [55, 58]. Additionally, OVs induce immune stimulation through a variety of inherent mechanisms, including altering the tumor microenvironment (TME), inducing immunogenic cell death, and the effects of genetically modifying OVs by providing them with therapeutic transgenes [26]. Furthermore, OVs are one of the most well-known stimulators of immune cell deaths (ICDs), and they do so by stimulating apoptosis, which is a result of autophagy and endoplasmic reticulum stress. However, they can also trigger ICD to a lesser degree through virus-stimulated necrosis, pyroptosis and necroptosis [59, 60, 61, 62, 63].

As previously discussed, during selective viral oncolysis, OVs kill cancer cells by enabling cell lysis. This is eventually followed by the release of infectious viral progeny that spread to nearby tumor cells (amplification of oncolysis), as well as sub-products like viral particles, DAMPs, PAMPs, tumor cell debris, and tumor-associated antigens (TAAs), which can all promote virus initiated ICDs, and both local and systemic induction of anti-cancer innate and adaptive immune responses (Fig. 3) [59, 64, 44, 26, 65]. Better expression of viral antigen, TAAs, neoantigens, pro-inflammatory cytokines, and chemokines on the surface of tumor cells is made possible by this, which promotes immune cell activation and recruitment within the tumor microenvironment and subsequently induces T cells to attack uninfected tumor cells/secondary tumors [56, 50, 17]. However, the host's initial reactions against OVs can have a big impact on the interplay between the immune system and OV therapy allowing for a strong immune response within the TME. One such reaction is the typical antiviral response of normal cells, which may, however, directly inhibit OV replication in tumor cells. Type I IFN and NK cell-mediated innate immune response are the main contributors to this reaction, and both have been described to reduce the efficiency of OV therapy [59, 66, 26]. Increased endogenous IFN signaling and OV therapy resistance have been linked in a number of studies. For instance, one study of stimulator of IFN genes (STING) activity in MPNST cell lines found that down-regulating STING made the cells more susceptible to OV infection and cell-to-cell transmission [67]. It was also noted that the administration of oncolytic HSV in a glioblastoma model caused an immediate activation and recruitment of NK cells, which led to viral clearance and decreased anti-cancer efficacy. Further research was done to demonstrate that TGF-b and oncolytic HSV combined dysregulated intracranial activation of NK cells, their recruitment, and function, allowing for increased viral replication and improved mouse survival in both xenograft and syngeneic glioblastoma models [26]. The outcome of OVs-dependent tumor regression may be improved by focusing on IFN signaling genes, its downstream proteins, or any of its components, which have been identified as important regulators of tumor resistance to OV therapy. This could be achieved through the use of IFN signaling modulators/inhibitors or as a combination therapy with OVs in cancer treatments. In a related manner, future OV treatment could benefit from the use of NK cell activation modulators (Fig. 3). Another method for treating tumors effectively involves preventing the over-activation of NK cells, which have been exposed to OV viral clearance and low potency of OV in the TME. IL-2 and IL-12, effector cytokines that activate NK cells, could also be inhibited in this situation. However, there is evidence of partial and complete tumor regression in some patients with innate NK cell natural and intervening responses, demonstrating the importance of NK cells in the immune response against tumors. In order to prevent total inactivation of the NK cell response to the tumor itself within the microenvironment, the proper balance must be struck in this instance.

9. Transgene delivery system

It is possible to selectively engineer OVs to carry and deliver specific genes that are necessary for either enhancing immune function or eliminating the tumor. This is another technique used in OV therapies, which involves inserting host cytokines, other immune-regulatory genes, or even some apoptotic and cell cycle regulation genes into the OVs' genome. This creates transgene-armed OVs that are intended to produce particular proteins of interest locally within the virus-infected TME. The TME can be modified to address issues with defective antigen presentation and impaired T-cell infiltration by engineering OVs to activate both DCs and T cells (Fig. 3) [26]. Genetically modified OVs can specifically change metabolic and immunosuppressive signaling pathways. One such metabolic checkpoint that has been targeted by researchers using engineered OVs is the COX2/PGE2 pathway [38]. Additionally, engineering OVs can be used to modify the structure of the TME, as was observed when an oncolytic adenovirus was equipped with the ability to express the endopeptidase matrix metalloproteinase 8 (MMP-8), which can degrade tumor-associated ECM. MMP-8 is a zinc- and calcium-dependent enzyme. In human NSCLC and PDAC xenograft models, the virus's rapid spread

was shown to be improved by MMP-8. Additionally, infection of PDAC tumors in nude mice with a recombinant vaccinia strain (GLV-1h255) showed a decrease in type IV collagen within the TME when the recombinant vaccinia strain was equipped with MMP-9, a related zinc-metalloproteinase [38].

Chemokines, cytokines, tumor-suppressor genes, inhibitory and co-stimulatory receptors, pro-apoptotic genes, anti-angiogenic transgenes, TAA-like tumor vaccines, immune ligands, and mixtures of any of these are just a few examples of the various possible transgenes (Table 1). Most of these transgenes are intended to trigger an immune response against tumor or to induce cancer treatment with low levels of immune cells [68, 17]. For instance, oncolytic adenovirus (Ad) vectors are a promising form of gene therapy for the treatment of cancer. This was demonstrated by the co-expression of IL-12 and IL-18 by an oncolytic adenovirus. The differentiation of T cells expressing IL-12Rβ2 or IL-18Rα improved tumor-specific immunity, according to the research on the engineered Adeno OVs [68]. Adenovirus-mediated decorin expression has also been used to trigger p53 activation and mitochondrial apoptosis, which kill cancerous cells [69]. However, reports indicate that one of the most promising cancer treatment methods is cytokine immune-gene therapy [49, 69, 70].

Given that the function of APCs is frequently hampered in the cancer microenvironment and that immune-stimulatory genes like those encoding TNF-a and GM-CSF play crucial roles in T cell migration and homing, novel methods to facilitate the recognition and presentation of TAAs are urgently needed. In an effort to create more powerful OVs capable of overcoming the immunosuppressive TME and enhancing oncolysis, many OVs have been altered to express these transgenes (Fig. 3).

10. Cytokine and chemokine immune-gene OVs therapy

Cell signaling and trafficking within the body depend on cytokines and chemokines. With regard to the immunosuppressive TME, they offer researchers the distinctive, varied, and promising property of enhancing OVs and immune functions. They can have a range of pleiotropic effects that promote anti-tumor responses; however there is some cellular complexity involved. Major Cytokines that have been used extensively in OVs to date include IL-2, IL-6, IL-12, IL-15, IL-21, IL-24, and GM-CSF, all of which are crucial for stimulating various immune system components. IL-2 is crucial for promoting T cell expansion and can also activate Tregs, but it has significant side effects on humans. However, membrane-bound IL-2 was engineered to be expressed in VV in an effort to reduce the toxic side effects, and its anti-tumor efficacy was comparable to that of the virus expressing free IL-2 [71]. Both GM-CSF and IL-12 have been used in numerous clinical trials in combination with OVs and other treatments, with IL-12 having been shown to produce more potent anti-tumor effects than GM-CSF (Table 2) [26]. IL-15 is less harmful than IL-2 and solely stimulates T cells and NK cells. As an alternative, several chemokines, including as CCL2, CCL5, CCL19, CXCL11, CXCL9, and CXCL10, are also frequently included within OV genomes. These chemokines increase Th1 leukocyte infiltration and T cell trafficking to the TME [26]. It has been shown that chemokines generated by cancer cells and their stroma can influence proliferation and metastasis of tumor cells as well as immune cell infiltration [10]. In colorectal cancer, for instance, CXCL16 and its receptor (CXCR6) promote CD4 and CD8 T cell influx [72]. Also, evidence from breast and ovarian cancer shows that CCL22 modulates Treg accumulation in the TME [10]. These constitute more chemokines that can be inserted into OVs and used to modulate the TME.

Table 1 Some selected transgenes and their mechanisms [14, 65]

Targeted Mechanism	Genes
Cytokine and chemokine	IL-2/IL-15/IL18/IL-21, IFN (α, β or γ), GM-CSF, CCL21, CCL5, CXCL10, CCL20, CXCL4L1, CXCL16, CXCR6, CCL22.
Tumor-associated antigens	CEA, PSA, hDCT, CLND6
Co-stimulatory molecules	OX40, CD40, CD28, CD30, ICOS, and 4-1BB
Immune checkpoint blockers	CTLA4, PD-1, LAG3, TIGIT, TIM3.
Tumor suppressor genes	P53, Rb, PTEN, P16
Pro-apoptotic proteins and genes	Apoptin, SMAC, TRAIL
Anti-angiogenesis	VEGI, VEGF promoter-targeted transcriptional repressor zinc finger protein, VEGF promoter-targeting transcriptional repressor (KOX), fibroblast growth factor receptor, plasminogen kringle 5, vasculostatin

11. Targeting Immune evasive mechanism of tumor cells

The reduced response of immune cells within the tumor milieu is mostly due to the immune-evasive characteristics of tumor cells, one of the cellular hallmarks of cancer. Several checkpoint molecules, including PD1 and CTLA-4, are activated by tumors. This immune checkpoint system must have developed to restrict diseases induced by the immune system, perhaps especially during viral infections, but also limits the immune response and the monitoring of CTLs against cancer cells [73, 74].

The prognosis of patients with advanced cancer has significantly improved thanks to anti-PD-1/PD-L1 and anti-CTLA-4 medications that target immune checkpoint molecules. Nevertheless, a number of recent studies have found conflicting, but solid evidence of non-negligible defects in immunological check point targeting strategies that may reduce their therapeutic efficacy [18]. Since then, researchers have started combining OVs with several checkpoint blockers to heat up "cold" tumors (Fig. 3). Preclinical studies have inspired several clinical trials that examine inhibitors/blockers of immune activation checkpoints in combination with various OV platforms. Recent research into these is beginning to yield even more promising results. Recent phase I studies evaluating T-VEC combined with antibodies against PD1 or CTLA4 provide evidence for this strategy (Table 2) [17]. Intratumoral injection of melanoma lesions with T-VEC led to noticeably higher levels of tumor-infiltrating lymphocytes in a trial using the PD1 antibody pembrolizumab, particularly interferon-(IFN)-producing CD8+ T cells. Further evidence that the PD1-PDL1 pathway was a crucial target to alter in this environment came from the rise in PDL1+ cells in the TME. Circulating CD4+ lymphocyte and CD8+ lymphocyte counts increased in Talimogenela herparepvec-treated patients, increasing the chance of systemic immunological responses [17].

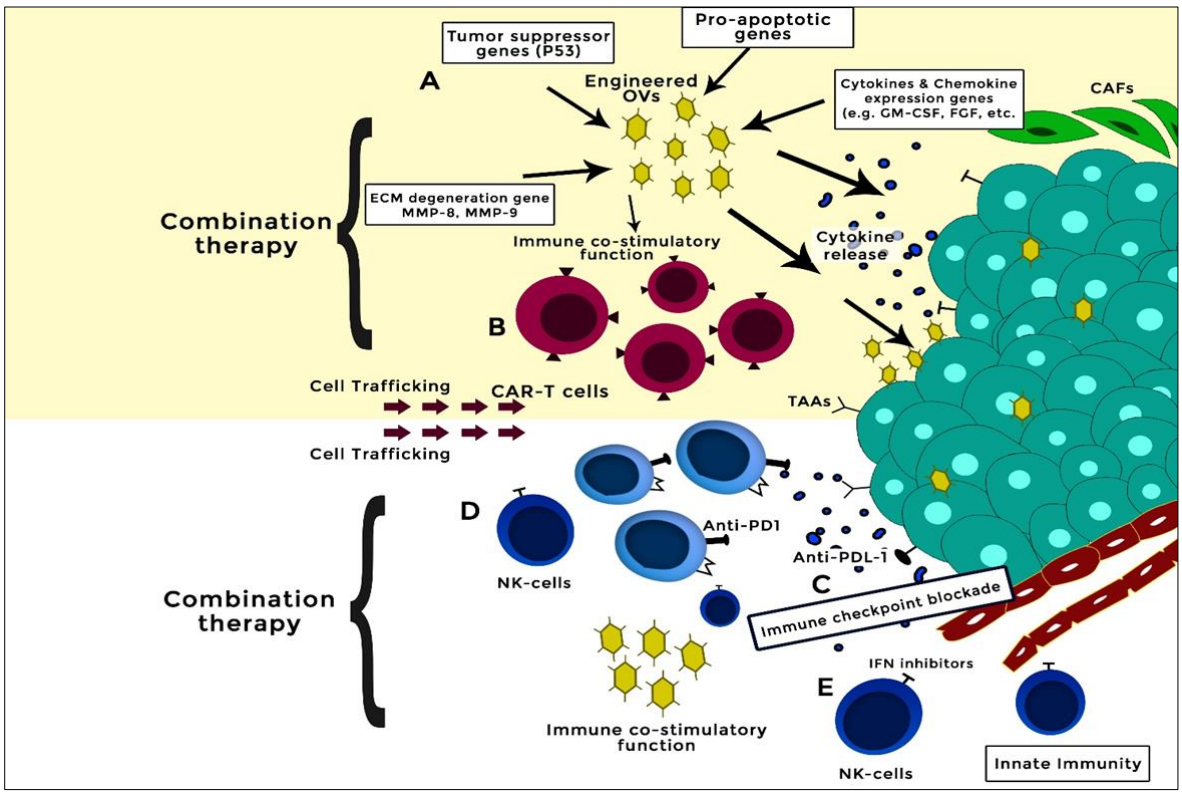

Figure 3 Dynamic interactions of oncolytic viruses (OVs) with immune stimulatory interventions within the immunosuppressive TME. Oncolytic viruses (OVs) can enhance anti-tumor immune responses through multiple mechanisms; A: Selective viral oncolysis by engineered OVs to express pro-apoptotic genes, chemotactic cytokines and chemokines, immune costimulatory genes, tumor suppressor genes, collagen degrading protein (ECM) genes and over expressions of TAAs. B: Increased CAR-T cells trafficking in response to over expressed TAAs, cytokine release and other viral induced events in step A. C: Combination therapy of immune checkpoint inhibitors (ICIs)/ engineered OVs to express certain ICI genes, with NK and T cells, and CAR-T cells in step B leading to improved immune cell trafficking for tumor destruction. D: Increased response of T cells and NK cells to step A induced by OVs and upregulated APC activities from cytokine signaling. E: Augmentation of the innate anti-viral responses (IFN and NK-cells) against OVs through potent inhibitors to cause effective tumor killing

Furthermore, Twumasi-Boateng et al. [17], described a more promising and compelling alternative approach which have had less attention in the scientific community's research efforts. This entails modifying OVs to encode ICIs (Table 1), possibly lowering the need for combination therapy. The distinctive selectivity mechanisms of OVs for tumor could increase localized production of ICIs, which would offer a superior safety profile to systemic administration (Fig. 3). ICIs that target CTLA4 and the PD1-PDL1 axis are currently the most clinically developed and being researched. Agents targeting more immune checkpoint molecules such as OX40 (also known as TNFRSF4), inducible T cell co-stimulator (ICOS), V-domain immunoglobulin suppressor of T cell activation (VISTA), gluco-corticoid-induced TNF receptor-related protein (GITR; also known as TNFRSF18), and newly emerging ones such as TIM-3, inhibitory lymphocyte activation gene (LAG-3) are reportedly under active research and may add to the armory of future immunotherapy (Table 1) [14, 17].

12. Enhancing T-cell Function: Chimeric antigen receptor (CAR)-modified T (CAR-T) cells

The DC/APC-MHC complex is always responsible for inducing T cell responses by presenting specific epitopes to naive T cells that are expressing a corresponding T cell receptor (TCR). Methods to improve the presentation and detection of TAAs are needed due to the fact that APC function is commonly impaired in TME. For instance, tumor-intrinsic oncogenic signals like the β-catenin pathway may prevent the recruitment of APC to tumors in vivo, leading to immunologically "cold" tumors. T-cell priming is a crucial and effective strategy that has already been studied by global research efforts. Antigen-presenting cells (APCs) that have undergone appropriate antigen loading and functional maturation are necessary for this complicated process [17]. As an alternative, chimeric antigen receptor (CAR)-modified T cells (CAR-T cells) therapy is another immunological intervention that has been applied thus far [38; 9].

Chimeric antigen receptors (CARs) improve T lymphocytes' antigen specificity, and their efficacy in treating cancer has been examined in several clinical investigations. CARs have a significant advantage over conventional T cell receptors in that they can target cancer cell surface antigens without the aid of the MHC [74]. The problem of T cell malfunction and its relation to the TME are addressed by this kind of therapy. Since their introduction, CD19 CAR-T cells have become the most widely used adoptive CAR-T cell therapy for B cell malignancies, with remarkable success in clinical trials. As a result of these findings, the FDA has given its approval of CD19 CAR-T cell medicines "Kymriah and Yescarta". As it stands, an autologous T-cell product is currently being made by stimulating and expanding T cells derived from patients' peripheral blood mononuclear cells [38, 9].

The anti-CD19 CARs are already in therapeutic use for patients, and Ajina and Maher [38] enumerates many other CARs that have shown efficacy in the haemato-oncology field. Some of which includes clinical candidates like CARs developed to target relapsed B-cell lymphomas and leukemias (predominantly targeting CD22 but also CD133 or TSLPR) [72], multiple myeloma (actively targeting BCMA but also CD19, CD138, CD38, SLAMF7, or CD229) [75] Hodgkin's lymphoma (CD30) [76], and T-cell lymphomas and leukemias (CD7 or CD5) [77]. Current research suggests that CARs that target solid tumors may be successful, despite the fact that there has been little advancement in their use. The ErbB family (including EGFR and HER2 (Table 2) is now being investigated in early phase trials, as are B7-H3, CD133, CD70, GD2, EpCAM, IL13Ra2, L1CAM, mesothelin, PSCA, and PSMA [38].

Furthermore, CARs can be designed to specifically target immune-suppressive TME cells like CAFs, for example, by targeting FAP [78], which, when combined with OVs therapy, can improve the function and impact of CARs within the TME (Fig. 3). Based on the long-term effects of OV-derived type I interferon response, a combination of CAR T-cell and OVs therapy should change a TME from one that is immunologically "cold" to one that is "hot/active," therefore increasing the likelihood of CAR T-cell entrance, activation, and proliferation [38]. For example, preclinical investigations involving numerous OVs have shown a common ability to elicit an upregulated type I IFN signaling in the tumor milieu, as previously illustrated [79]. Along with this capability, type I interferons have the potential to negatively regulate cellular proliferation, which is essential for modulating the TME. This property makes the TME more receptive to host innate and adaptive immunity, making it potentially exploitable when considering combination strategies with CAR T-cell therapy [38]. In a multi-synergistic combination, a clinical trial has been described to utilize adenovirus (CAdVEC) with genetic modifications to express stimulatory cytokine IL-12, with both HER 2 CAR T-Cells and anti-PDL1 (Table 2). Three signals must be present for effector T-cells to respond effectively after engaging the target cell: signal 1 is activation of T cell receptor (TCR), signal 2 is engagement of co-stimulatory receptors with professional antigen-presenting cells' cognate ligands, and signal 3 is frequently provided by generation of local pro-inflammatory cytokines. In the second or third generation, CARs will imitate Signals 1 and 2. When these cells are exposed to stimulating cytokines during ex vivo development, signal 3 is initially produced. In fourth-generation constructs, signal 3 may be further boosted by making CAR T-cells capable of secreting their own cytokines or by modifying their reaction to them [38]. Type I interferons may also deliver signal 3, and if they are delivered by OVs during tumor tropism, they may increase the efficacy and safety of CAR T-cell therapy, allowing it to work to its fullest potential in the TME [38]. Clinical

trial data using 4-1BB endodomain-containing second-generation CARs revealed the significance of type I interferons in CAR T-cell therapy. These studies demonstrated a connection between the downstream activation of tumor necrosis factor receptor-associated factor 2 (TRAF2) and the induction of IFN gene expression as well as the formation of autocrine signaling via interferon receptors on the CAR T-cells themselves [38; 80].

Table 2 Some related clinical trial updates on OVs with engineered targeted/combination therapies on https://clinicaltrials.gov

Viral backbone	Name	Genetic modification	Combination therapy	Indication(s)	Phase/Status	NCT identifier
Adenovirus	CAdVEC	Engineered expression of IL12	HER2 CAR T-cells anti-PDL1	Bladder, Head and Neck, salivary gland etc. Solid tumors, melanoma, and prostate cancer	I/Recruiting	NCT03740256
	ONCOS-102 (GMCSF)	Engineered Expression of GM-CSF	Pembrolizumab	Metastatic cancer and Epithelial Tumor	II/Terminated	NCT03514836
	NG-641 (CXCL9/ CXCL10/IFNα)	Oncolytic Transgene Expressing Adenoviral Vector FAP-TAc antibody with CXCL10/IFNα/ CXCL9 (Immune enhancers).	None		I/Recruiting	NCT04053283
	LOAd703	Oncolytic adenovirus serotype 5/35 encoding 4-1BBL and (TMZ-CD40L Immune co-stimulatory molecules)	None Anti-PD-L1 (Atezolizumab)	Ovarian cancer, Pancreatic Adenocarcinoma, colorectal cancer and biliary carcinoma	I/II/Recruiting I/II/Recruiting	NCT04123470 NCT03225989
Vaccinia Virus	Pexa-Vec (JX-594)	Thymidine kinase gene-inactivated, engineered GM-CSF expression and beta galactosidases	Anti-PD-L1 (Durvalumab) Anti- CTLA-4 (Tremelimumab) Anti-PD1 (Cemiplimab)	Colorectal carcinoma, refractory cancer Renal cell carcinoma	I/II/Active I/II/Recruiting	NCT03206073 NCT03294083
	TG6002	Thymidine kinase and ribonucleotide reductase deletions and transgenic	5FC (chemotherapy prodrug)	Glioblastoma and brain cancer	I/II/Recruiting	NCT03294486

		expression of yeast FCU1				
Measles Virus	MV-CEA	Engineered expression of carcinoembryonic antigen	Therapeutic surgery	Recurrent Glioblastoma multiforme	I/ Recruiting	NCT00390299
Coxsackie Virus	CAVATAK		Pembrolizumab (anti-PD1) Ipilimumab (anti-CTLA4)	Melanoma	I/ Recruiting	NCT02565992 NCT02307149
HSV-1	T-VEC	ICP47 and ICP34.5 deletions and transgenic GM-CSF expression	None	Melanoma	III/ Terminated	NCT02288897
	TBI-1401 (HF10)	Spontaneous deletion in the UL56 promoter	Ipilimumab (anti-CTLA4)	Melanoma	II/completed	NCT03153085

13. Conclusion

The extreme host cellular toxicity associated with conventional cancer therapies continues to be a major obstacle in the fight against cancer globally. However, the immune system offers the crucial intrinsic target specificity required, improving treatment effectiveness, and lowering host cell toxicity. With numerous great preclinical and early clinical trial outcomes and evidence, the increase in interest in cancer immunotherapy techniques has been strongly expanding. Within a highly varied and complex TME, OVs give us an extra layer of selectivity for tumor cells and a helpful amplification of the immune system's response to cancer. To have better success in the global research scene, it is also possible to further enhance this interaction between OVs and the immune system.

Finally, all our review of literature and research findings lead to the idea that future cancer therapeutics research, particularly those aimed at resolving the immunosuppressive TME, would begin to include targets of newly found and understood TME players, both immune and non-immune components. For instance, antibodies that block chemokine receptors may be used to restrict the entry of suppressive myeloid lineage cells such as M2 phenotype macrophages into the tumor milieu. These agents could be highly effective in applications that integrate OVs and CPIs. Such agents could be of tremendous use in applications that work in tandem with OVs and CPIs. Agents that inhibit angiogenesis may also be of relevance because they not only reduce blood flow to tumor cells but also regulate otherwise dysregulated vasculature in tumor tissue. It is possible that a normalization of this kind will make it possible for improved lymphocyte adhesion, and migration into the site of the tumor. The advancement of modern molecular technologies, along with a greater knowledge of the diversity and events inside the TME, presents a one-of-a-kind opportunity for improved therapeutic efficacy.

Future investigations should delve into innovative strategies that surmount immune evasion mechanisms which curtail the effectiveness of oncolytic virus therapy within the tumor microenvironment. These strategies may encompass combinatory approaches targeting multiple immunosuppressive pathways simultaneously, thereby potentiating therapeutic efficacy. The development of precision medicine-based treatment strategies is a pressing avenue for research. By tailoring therapeutic interventions to individual patients, considering tumor-specific characteristics and unique immunological profiles, researchers can potentially enhance cancer treatment response rates. The synergistic potential of combining oncolytic viruses with immune checkpoint inhibitors merits further exploration. Particularly, focusing on the PD-1/PD-L1 (programmed cell death ligand) axis may hold promise in amplifying antitumor immune responses and thereby bolstering therapeutic outcomes.

Abbreviations

TME- Tumor microenvironment; OVs - Oncolytic viruses; LAG - Lymphocyte Activation Gene; VISTA -V-domain Ig suppressor of T cell activation; ICOS - Inducible co-stimulatory pathways; MDSCs - Myeloid derived-suppressor cells; CAFs - Cancer-associated fibroblasts; MHC - Major Histocompatibility Complex; PD-L1 - Programmed cell death ligand-

1; IL-10 - Interleukin-10; TGF-β - Transforming growth factor-β; TAMs - Transition of macrophages; PAMPs - Pathogen-associated molecular patterns; DAMP - Danger-associated molecular pattern; HMGB1 - High-mobility group box 1; CRT – Calreticulin; FDA - Food and Drug Administration; T-VEC - Talimogenela herparepvec; HSV-1 - Herpes simplex virus, type 1; VSV - Vesicular stomatitis virus; TAAs - Tumor-associated antigens; DCs - Dendritic cells; FLT3L - Fms-like tyrosine kinase-3 ligand; ICD: Immunogenic Cell Death; PDAC: Pancreatic Ductal Adenocarcinoma; STING - Stimulator of IFN genes; Tregs - regulatory T cells; MMP-8 - Matrix metalloproteinase 8; LAG - Lymphocyte activation gene; TCR - T cell receptor; TLR – Toll-like receptors**;** APCs - Antigen-presenting cells; CAR-T cells - Chimeric antigen receptor (CAR)-modified T cells; CAR-T cells - Chimeric antigen receptor-modified T cells; TRAF2 - Tumor necrosis factor receptor-associated factor 2; IL- Interleukin; NK- Natural killer cells; IFN- Interferon

Compliance with ethical standards

Acknowledgments

Authors cherish the literature reviews of scholars cited in the review article.

Disclosure of Conflict of interest

The authors declare no competing interests

Author contribution

M. Bayode: Conceptualized, investigate, draft outline and literature review of original draft. O. Babatunde: reviewed and made illustrations. S. Alonge and A. Oshokoya: reviewed and edited the draft. H. Ogbonna, C. Nwokafor, C. Olowosoke and P. Chukwuemeka: reviewed, edited, supervised and corrected the draft. All authors read and approved the final manuscript draft.

References

[1] Zhang Q, Yu YA, Wang E, Chen N, Danner RL, Munson PJ, et al. Eradication of solid human breast tumors in nude mice with an intravenously injected light-emitting oncolytic vaccinia virus. Cancer Res. 2007, 67(20):10038-10046. https://doi.org/10.1158/0008-5472.can-07-0146

[2] Hemminki A, Kanerva A, Kremer EJ, Bauerschmitz GJ. Oncolytic adenoviruses for the treatment of human cancer: focus on translational and clinical data. Molecular Pharmaceutics. 2012, 9(8):2101-2113. https://doi.org/10.1021/mp100219n

[3] Sung YK, Kim SW. Recent advances in the development of gene delivery systems. Biomater Res. 2019, 23:1-7. DOI: https://doi.org/10.1186/s40824-019-0156-z

[4] Elekofehinti OO, Iwaloye O, Olawale F, Ariyo EO. Saponins in cancer treatment: Current progress and future prospects. Pathophysiol. 2021, 28:250–272. https://doi.org/10.3390/pathophysiology28020017

[5] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021, 71:209-49.

[6] Chukwuemeka PO, Umar HI, Iwaloye O, Oretade OM, Olowosoke CB, Oretade OJ, et al. Predictive hybrid paradigm for cytotoxic activity of 1, 3, 4-thiadiazole derivatives as CDK6 inhibitors against human (MCF-7) breast cancer cell line and its structural modifications: rational for novel cancer therapeutics. J Biomol Struct Dyn. 2023, 40:8518–8537.

[7] Olukunle OF, Olowosoke CB, Khalid A, Oke GA, Omoboyede V, Umar HI, et al. Identification of a 1, 8-naphthyridine-containing compound endowed with the inhibition of p53-MDM2/X interaction signaling: a computational perspective. Mol Divers. 2023:1-19. https://doi.org/10.1007/s11030-023-10637-3

[8] Kikiowo B, Ogunleye AJ, Iwaloye O, Ijatuyi TT, Adelakun NS, Alashe WO. Induced fit docking and automated QSAR studies reveal the ER-α inhibitory activity of cannabis sativa in breast cancer. Recent Pat Anticancer Drug Discov. 2021, 16:273-284. https://doi.org/10.2174/1574892816666210201115359

[9] Watanabe N, McKenna MK, Shaw AR, Suzuki M. Clinical CAR-T cell and oncolytic virotherapy for cancer treatment. Mol Ther. 2021, 29:505-520. DOI: https://doi.org/10.1016/j.ymthe.2020.10.023

[10] Labani-Motlagh A, Ashja-Mahdavi M, Loskog A. The tumor microenvironment: a milieu hindering and obstructing antitumor immune responses. Front Immunol. 2020, 11:940. https://doi.org/10.3389/fimmu.2020.00940

[11] Adeboboye CF, Oladejo BO, Adebolu TT. Immunomodulation: a broad perspective for patients' survival of COVID-19 infection. Eur J Biol Res. 2020, 10:217–224. http://dx.doi.org/10.5281/zenodo.3956771

[12] Opeyemi I, Paul O, Olawale F, Olorunfemi B, Elekofehinti OO, Kikiowo B, et al. Computer-aided drug design in anti-cancer drug discovery: What have we learnt and what is the way forward? Informatics in Medicine Unlocked. 2023, 47:101332. https://doi.org/10.1016/j.imu.2023.101332

[13] Oladejo BO, Adeboboye CF. Influenza Viruses: Targeting Conserved Viral Ha-Stem, Matrix and Nucleo-Proteins to Disarm a Resilient and Recurring Pandemic. InTech Open. 2022. http://dx.doi.org/10.5772/intechopen.104770

[14] Sharma P, Allison JP. The future of immune checkpoint therapy. Science (1979). 2015, 348:56-61. htts://doi.org/10.1126/science.aaa8172

[15] Bayode MT, Alabi MA, Ibisanmi TA, Okiti AF, Adebisi OO, et al. Isothermal calorimetry calscreener in the metabolism gauge of human malignant neoplastic cells: a burgeoning nexus in cancer biochemical metrology and diagnostics. Bull Natl Res Cent. 2023, 47(1):120. https://doi.org/10.1186/s42269-023-01097-8

[16] Kelly E, Russell SJ. History of oncolytic viruses: genesis to genetic engineering. Mol Ther. 2007, 15:651-659. https://doi.org/10.1038/sj.mt.6300108

[17] Twumasi-Boateng K, Pettigrew JL, Kwok YYE, Bell JC, Nelson BH. Oncolytic viruses as engineering platforms for combination immunotherapy. Nat Rev Cancer. 2018, 18:419-432. DOI: https://doi.org/10.1038/s41568-018-0009-4

[18] Tang T, Huang X, Zhang G, Hong Z, Bai X, Liang T. Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy. Signal Transduct Target Ther. 2021, 6:72.

[19] Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. Oncogene. 2008, 27(45):5904-5912. https://doi.org/10.1038/onc.2008.271

[20] Zhang Y, Li Y, Chen K, Qian L, Wang P. Oncolytic virotherapy reverses the immunosuppressive tumor microenvironment and its potential in combination with immunotherapy. Cancer Cell Int. 2021, 21:1-17.

[21] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011, 144:646–674.

[22] Fleming V, Hu X, Weber R, Nagibin V, Groth C, Altevogt P, et al. Targeting myeloid-derived suppressor cells to bypass tumor-induced immune-suppression. Front Immunol. 2018, 9:398. https://doi.org/10.3389/fimmu.2018.00398

[23] Chappert P, Leboeuf M, Rameau P, Lalfer M, Desbois S, Liblau RS, et al. Antigen-specific Treg impair CD8+ T-cell priming by blocking early T-cell expansion. Eur J Immunol. 2010, 40:339–350. https://doi.org/10.1002/eji.200839107

[24] Kim J-H, Kim BS, Lee S-K. Regulatory T cells in tumor microenvironment and approach for anticancer immunotherapy. Immune Netw. 2020, 20.

[25] Crespo J, Sun H, Welling TH, Tian Z, Zou W. T cell anergy, exhaustion, senescence, and stemness in the tumor microenvironment. Curr Opin Immunol. 2013, 25:214–221. https://doi.org/10.1016/j.coi.2012.12.003

[26] De Matos AL, Franco LS, McFadden G. Oncolytic viruses and the immune system: the dynamic duo. Mol Ther-Method Clin Develop. 2020, 17:349-358. https://doi.org/10.1016/j.omtm.2020.01.001

[27] Evgin L, Vile RG. Parking CAR T cells in tumours: oncolytic viruses as valets or vandals? Cancers (Basel). 2021, 13:1106. https://doi.org/10.3390/cancers13051106

[28] Wongthida P, Diaz RM, Galivo F, Kottke T, Thompson J, Melcher A, et al. VSV oncolytic virotherapy in the B16 model depends upon intact MyD88 signaling. Molecular Therapy. 2011, 19:150-158. DOI: https://doi.org/10.1038/mt.2010.225

[29] van Vloten JP, Workenhe ST, Wootton SK, Mossman KL, Bridle BW. Critical interactions between immunogenic cancer cell death, oncolytic viruses, and the immune system define the rational design of combination immunotherapies. J Immunol. 2018, 200:450-458. DOI: https://doi.org/10.4049/jimmunol.1701021

[30] Workenhe ST, Mossman KL. Oncolytic virotherapy and immunogenic cancer cell death: sharpening the sword for improved cancer treatment strategies. Mol Ther. 2014, 22:251-256.

[31] Phan M, Watson MF, Alain T, Diallo JS. Oncolytic viruses on drugs: achieving higher therapeutic efficacy. ACS Infect Dis. 2018, 4(10):1448-1467.

[32] Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nature Biotechnology. 2012, 30(7):658-670. https://doi.org/10.1038/nbt.2287

[33] Bierman HR, Crile DM, Dod KS, Kelly KH, Petrakis NI, White LP, et al. Remissions in leukemia of childhood following acute infectious disease. Staphylococcus and streptococcus, varicella, and feline panleukopenias. Cancer. 1953, 6:591–605. https://doi.org/10.1002/1097-0142(195305)

[34] Denton NL, Chen C-Y, Scott TR, Cripe TP. Tumor-associated macrophages in oncolytic virotherapy: friend or foe? Biomed. 2016, 4:13. https://doi.org/10.3390/biomedicines4030013

[35] Dock G. The influence of complicating diseases upon leukaemia. The Amer J Med Sci (1827-1924). 1904, 127:563. https://doi.org/10.1097/00000441-190412740-00001

[36] Pelner L, Fowler GA, Nauts HC. Effect of concurrent infections and their toxins on the course of leukemia. Acta Med Scand. 1958, 162:5-24. https://doi.org/10.1111/j.0954-6820.1958.tb17327.x

[37] Sinkovics J, Horvath J. New developments in the virus therapy of cancer: a historical review. Intervirology. 1993, 36:193-214. https://doi.org/10.1159/000150339

[38] Ajina A, Maher J. Synergistic combination of oncolytic virotherapy with CAR T-cell therapy. Prog Mol Biol Transl Sci. 2019, 164:217–292.

[39] Alberts P, Tilgase A, Rasa A, Bandere K, Venskus D. The advent of oncolytic virotherapy in oncology: The Rigvir® story. Eur J Pharmacol. 2018, 837:117–126. https://doi.org/10.1016/j.ejphar.2018.08.042

[40] Rahman MM, McFadden G. Oncolytic viruses: newest frontier for cancer immunotherapy. Cancers (Basel). 2021, 13:5452. https://doi.org/10.3390/cancers13215452

[41] Food and Drug Administration (FDA). FDA Approves Talimogene Laherparepvec to Treat Metastatic Melanoma. 2015. https://www.cancer.gov/news-events/cancer-currents-blog/2015/t-vec-melanoma

[42] Sugawara K, Iwai M, Ito H, Tanaka M, Seto Y, Todo T. Oncolytic herpes virus G47Δ works synergistically with CTLA-4 inhibition via dynamic intratumoral immune modulation. Mol Ther-Oncol. 2021, 22:129-142. DOI: https://doi.org/10.1016/j.omto.2021.05.004

[43] Marelli G, Howells A, Lemoine NR, Wang Y. Oncolytic viral therapy and the immune system: a double-edged sword against cancer. Front Immunol. 2018, 9:866. DOI: https://doi.org/10.3389/fimmu.2018.00866

[44] Yamamoto M, Curiel DT. Current Issues and Future Directions of Oncolytic Adenoviruses. Molecular therapy. 2010, 18(2):243-250. https://doi.org/10.1038/mt.2009.266

[45] Prestwich RJ, Errington F, Ilett EJ, Morgan RS, Scott KJ, Kottke T, et al. Tumor infection by oncolytic reovirus primes adaptive antitumor immunity. Clinical cancer research. 2009, 15(13):4374-4383. https://doi.org/10.1158/1078-0432.CCR-08-0831

[46] Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. Cancer cell. 2017, 31(3):326-341. https://doi.org/10.1016/j.ccell.2017.02.009

[47] Breitbach CJ, Burke J, Jonker D, Stephenson J, Haas AR, Chow LQ, et al. Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans. Nature. 2011, 477(7362):99-102. https://doi.org/10.1038/nature10358

[48] Choi AH, O'Leary MP, Fong Y, Chen NG. From benchtop to bedside: a review of oncolytic virotherapy. Biomed. 2016, 4:18. https://doi.org/10.3390/biomedicines4030018

[49] Filley AC, Dey M. Immune system, friend or foe of oncolytic virotherapy? Front Oncol. 2017, 7:106. https://doi.org/10.3389/fonc.2017.00106

[50] Fukuda K, Abei M, Ugai H, Seo E, Wakayama M, Murata T, et al. E1A, E1B double-restricted adenovirus for oncolytic gene therapy of gallbladder cancer. Cancer Res. 2003, 63:4434–4440. https://doi.org/10.1038/cgt.2008.67

[51] Nguyen A, Ho L, Wan Y. Chemotherapy and oncolytic virotherapy: advanced tactics in the war against cancer. Front Oncol. 2014, 4:145. DOI: https://doi.org/10.3389/fonc.2014.00145

[52] Pikor LA, Bell JC, Diallo J-S. Oncolytic viruses: exploiting cancer's deal with the devil. Trends Cancer. 2015, 1:266-277. https://doi.org/10.1016/j.trecan.2015.10.004

[53] Bell J, McFadden G. Viruses for tumor therapy. Cell Host Microbe. 2014, 15:260–265. https://doi.org/10.1016/j.chom.2014.01.002

[54] Gujar S, Pol JG, Kim Y, Lee PW, Kroemer G. Antitumor benefits of antiviral immunity: an underappreciated aspect of oncolytic virotherapies. Trends Immunol. 2018, 39:209–221. https://doi.org/10.1016/j.it.2017.11.006

[55] Bai Y, Hui P, Du X, Su X. Updates to the antitumor mechanism of oncolytic virus. Thorac Cancer. 2019, 10:1031–1035. https://doi.org/10.1111/1759-7714.13043

[56] Torres-Domínguez LE, McFadden G. Poxvirus oncolytic virotherapy. Expert Opin Biol Ther. 2019, 19:561-573. DOI: https://doi.org/10.1080/14712598.2019.1600669

[57] Motalleb G. Virotherapy in cancer. Iran J Cancer Prev. 2013, 6:101.

[58] Achard C, Boisgerault N, Delaunay T, Tangy F, Grégoire M, Fonteneau J-F. Induction of immunogenic tumor cell death by attenuated oncolytic measles virus. J Clin Cell Immunol. 2015, 6. https://doi.org/10.4172/2155-9899.1000291

[59] Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018, 25:486–541.

[60] Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, Agostinis P, et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunol. 2014, 3:e955691.

[61] Lawler SE, Speranza M-C, Cho C-F, Chiocca EA. Oncolytic viruses in cancer treatment: a review. JAMA Oncol. 2017, 3:841-849. DOI: https://doi.org/10.1001/jamaoncol.2016.2064

[62] Serrano-del Valle A, Anel A, Naval J, Marzo I. Immunogenic cell death and immunotherapy of multiple myeloma. Front Cell Dev Biol. 2019, 7:50.

[63] Davola ME, Mossman KL. Oncolytic viruses: how "lytic" must they be for therapeutic efficacy? Oncoimmunol. 2019, 8:e1581528. https://doi.org/10.1080/2162402x.2019.1596006

[64] Zheng M, Huang J, Tong A, Yang H. Oncolytic viruses for cancer therapy: barriers and recent advances. Mol Ther-Oncol. 2019, 15:234-247.

[65] Marchini A, Daeffler L, Pozdeev VI, Angelova A, Rommelaere J. Immune conversion of tumor microenvironment by oncolytic viruses: the protoparvovirus H-1PV case study. Front Immunol. 2019, 10:1848. DOI: https://doi.org/10.3389/fimmu.2019.01848

[66] Lee JM, Ghonime MG, Cassady KA. STING restricts oHSV replication and spread in resistant MPNSTs but is dispensable for basal IFN-stimulated gene upregulation. Mol Ther Oncol. 2019, 15:91-100. DOI: https://doi.org/10.1016/j.omto.2019.09.001

[67] Kim SI, Park AK, Chaurasiya S, Kang S, Lu J, Yang A, Sivanandam V, Zhang Z, Woo Y, Priceman SJ, Fong Y. Recombinant orthopoxvirus primes colon cancer for checkpoint inhibitor and cross-primes T cells for antitumor and antiviral immunity. Molecular cancer therapeutics. 2021, 20(1):173-82.

[68] Hernandez–Gea V, Toffanin S, Friedman SL, Llovet JM. Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. Gastroenterol. 2013, 144:512–527. https://doi.org/10.1053/j.gastro.2013.01.002

[69] Yoon A-R, Hong J, Yun C-O. Adenovirus-mediated decorin expression induces cancer cell death through activation of p53 and mitochondrial apoptosis. Oncotarget. 2017, 8:76666.

[70] Liu Z, Ge Y, Wang H, Ma C, Feist M, Ju S, et al. Modifying the cancer-immune set point using vaccinia virus expressing re-designed interleukin-2. Nat Commun. 2018, 9:4682.

[71] Hojo S, Koizumi K, Tsuneyama K, Arita Y, Cui Z, Shinohara K, et al. High-level expression of chemokine CXCL16 by tumor cells correlates with a good prognosis and increased tumor-infiltrating lymphocytes in colorectal cancer. Cancer Res. 2007, 67:4725–4731.

[72] Ghobadi A. Chimeric antigen receptor T cell therapy for non-Hodgkin lymphoma. Curr Res Transl Med. 2018, 66:43–49. https://doi.org/10.1016/j.retram.2018.03.005

[73] Melcher A, Parato K, Rooney CM, Bell JC. Thunder and lightning: immunotherapy and oncolytic viruses collide. Mol Ther. 2011, 19:1008-1016. DOI: https://doi.org/10.1038/mt.2011.65

[74] Harris DT, Kranz DM. Adoptive T cell therapies: a comparison of T cell receptors and chimeric antigen receptors. Trends Pharmacol Sci. 2016, 37(3):220-230.

[75] Ormhøj M, Bedoya F, Frigault MJ, Maus MV. CARs in the lead against multiple myeloma. Curr Hematol Malig Rep. 2017, 12:119-125. https://doi.org/10.1007/s11899-017-0373-2

[76] Ramos CA, Bilgi M, Gerken C, Dakhova O, Mei Z, Wu M-F, et al. CD30-chimeric antigen receptor (CAR) T cells for therapy of Hodgkin lymphoma (HL). Biol Bld and Marrow Transplant. 2019, 25:S63. https://doi.org/10.1002/hon.125_2629

[77] Scarfò I, Frigault MJ, Maus MV. CAR-based approaches to cutaneous T-cell lymphoma. Front Oncol. 2019, 9:259.

[78] Wang L-CS, Lo A, Scholler J, Sun J, Majumdar RS, Kapoor V, et al. Targeting fibroblast activation protein in tumor stroma with chimeric antigen receptor T cells can inhibit tumor growth and augment host immunity without severe Toxicity FAP-redirected CAR T cells. Cancer Immunol Res. 2014, 2:154-166. DOI: https://doi.org/10.1158/2326-6066.CIR-13-0027

[79] Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov. 2015, 14:642-462. https://doi.org/10.1038/nrd.2016.178

[80] Zhao Z, Condomines M, van der Stegen SJC, Perna F, Kloss CC, Gunset G, et al. Structural design of engineered costimulation determines tumor rejection kinetics and persistence of CAR T cells. Cancer Cell. 2015, 28:415-428.