Oncolytic Viruses, An Emerging Anti-Cancer Immunotherapy: Current Achievements and Future Directions

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Abstract. Oncolytic viruses (OVs) are currently influencing biological cancer therapy. It is a recently created immunotherapy that has been approved to treat cancer and can promote the death of specific cell types to promote antitumor immunological effects. Given the complicated conditions in the tumor micro environment (TME), trials involving the use of OVs demonstrated that OVs could potentially be utilized independently or in combination with other therapies like radiotherapy, chemotherapy, immune checkpoint inhibitors, as well as surgery. While immune suppression against tumors is of critical importance in OV therapy, concurrent antiviral immune responses should also be taken into consideration. Because of this, antiviral immune responses limit OV infections and replication, which also restricts the oncolytic effects of OVs. Recent studies on the operation and mechanics of OVs and how they are employed in clinics has produced results that are encouraging for the future. This review outlined the traits and biological categories of potential OVs, presented the findings of clinical trials, and discussed combinations with other forms of cancer therapy.

Keywords: Oncolytic viruses, glioblastoma, cancer treatment, immunotherapy.

1. Introduction

Tumor has been one of the main death causes around the world and scientists have been improving the treatment therapy of cancer for decades [1]. Although a number of cancer treatment options (such as surgery, chemotherapy and immunotherapy) have been employed in clinical practice, cancer-related mortality continues to rank among the world's top causes of death, and over 600,000 cancer deaths are expected in the US [2]. Tumor mutations may result through cellular pathway corruption, accumulation, disruption, dysregulation, and finally evasion of cellular regulatory mechanisms and loss of apoptosis. However, the particular alterations that tumor cells go through to ensure they are successful in growing also make them vulnerable to viral infection [3]. Due to the occasionally and various reasons for mutate, the treatment is quite different for specific cancer and individuals. As a result, oncolytic virus, immunotherapies, focused on cellular specificity, comes to be a new trend therapy.

Oncolytic viruses (OVs), which use native or genetically altered viruses that specifically reproduce within tumor cells, represent a promising new class of anticancer immunotherapies. They take advantage of a particular replication-competent virus' inherent capacity to selectively infect and lyse tumor cells while sparing normal, healthy cells. Given the ability of OV to cause ICD naturally occurring in cancerous cells, natural viruses with oncolytic properties can be screened. Additionally, they can be artificially altered by removing or inserting gene sequences to improve tumor selectivity, boost immunogenicity, strengthen replication and lower pathogenicity [4]. Following construction, the increasing appearance of tumor-specific receptors or antigens would give genetically modified viruses more desirable modification options for improved targeting accuracy and with higher efficacy for transporting specific medications. For instance, Oncorine (H101), the first oncolytic virus was approved by the Chinese SFDA for the treatment of nasopharyngeal carcinoma in conjunction with chemotherapy following the completion of a phase III clinical trial in November 2005. It subsequently received a GMP certificate in August 2006 [5]. Subsequently, the third-generation recombinant type 1 oncolytic herpes simplex virus Teserpaturev for the treatment of glioblastoma was approved in Japan, which can also treat several solid tumors [6].

There are obstacles to putting OVs into widespread use, despite the fact that they are an innovative revolutionary tumor therapy strategy with less side effects that selectively form replication and destruction to carcinoma cells, at the same time, leaving normal cells uninjured. OVs can lyse the tumor cells with peculiar receptor on membrane or in the cellular, or OVs may target on the TME of tumor. Other mechanisms may include the specific gene knockdown in the virus vector, or weaken the anti-virus effect of host immunity. Considering the immunity combination effect of anti-tumor and anti-virus, the standard of filtering and designing of OVs are quite flexible and universe, and TME should be taken into consideration as well.

In this article, the employment and obstacles of OVs will be comprehensively provided and discussed. Furthermore, the advanced combination of OVs and other therapies will be discussed as will. Attention must be paid in full to the proper choice of combination medicines considering results for use in cancer treatment as well as ongoing clinical management in this area. These cases have great significance since they can offer helpful knowledge and direction for the generation of more sophisticated, capable oncolytic viruses.

2. The current treatments for tumor

2.1. Radiotherapy and chemotherapy

Up to now, radiotherapy (RT) and chemotherapy (CT) continue to be the first choice to treat cancer. After X-ray discovered in 1895, radiation therapy was first employed to clinic use in 1986, and now RT still is one of main cancer treatment, in over 50% cancer patients [7]. Multiple factors affect the clinical outcome after radiotherapy, including the type of radiotherapy, administration regimen, delivery technique, and biological property of the tumor and normal tissue. Because above factors tend to have serious side effects on human body if unsuitable or over used. A wide range of cancers can be treated with radiotherapy alone or more frequently coupled with surgery or chemotherapy. Radiotherapy takes an essential part in treating most advanced head cancers, which is considered to be an essential component of multidisciplinary therapy. It has a wide range of capabilities for adaptation in preoperative, primary, complementary, and palliative care. A fundamental characteristic of cancer is gene instability, which is also associated with a higher susceptibility for DNA damage buildup. Despite the fact that this hypothesis explains therapies like DNA-damaging chemotherapy and radiation therapy, they can have serious adverse reactions and seriously harm healthy tissue [8]. The most adopted radiotherapy method for treating head cancer is intensity-modulated radiotherapy, or IMRT. Plenty rotating beamlets of various forms and intensities are employed to create an optimum radiation plan, adapting surrounding volumes of varying shapes and targets those regions of cancer involvement, meanwhile, avoiding key anatomical structures [9].

2.2. Biological therapy

The therapeutic effectiveness of RT and CT comes with serious side effects, so there is a growing focus on using these therapies as an alternative to less harmful and painful biologic therapies, although biologic therapies can be more complex and expensive. Among them, CAR-T therapy, virus vaccine, ICI therapy and oncolytic virus are emerging novel therapies to treat cancer. The following biological therapies are mainly aimed at the treatment of GBM. The CAR-T treatment is initially introduced. Single-stranded variable segments (SCFVS), hinges with a diversity of flexibility and length, transmembrane (TM) regions, several signaling intracellular domains connected with T cell signaling, and extracellular regions with tumor-binding parts build up the chimeric structure known as the CAR. The benefit of CAR T therapy is that it eliminates the requirement for MHC to deliver antigens and initiate an adaptive immune response. This benefit also stems from the fact that target epitopes are effectively presented without dependence on MHC. Interleukin (IL) 13R2 (IL-13Ra2), epidermal growth factor receptor variation III (EGFRvIII) and ephrin-A2 (Her2) have been used as targeting positions in a number of clinical CAR T cell treatments evaluated against GBM, with mixed but instructive outcomes [10, 11]. In spite of some promising results, the heterogeneity of GBM is the

main obstacle to GBM CAR T therapy, and the fact that technologies based on CAR are capable of targeting whatever clone groups makes them difficult to use. Immune checkpoint inhibitor therapy is the second. immunological checkpoints exist to reduce or halt immunological activity in order to stop autoimmunity and preserve self-tolerance. Tumors, however, can choose immunological checkpoint routes to avoid immune monitoring. Immune checkpoint inhibitors like CTLA4, PD-L1, as well as PD-1have the ability of boosting immunological responses that are anti-tumor while make it possible for T cells to more efficiently kill cancer cells [12]. The possible benefit of immune checkpoint blocking treatment for GBM was extensively researched given the success of many solid tumors. In contrast to other kinds of tumors, GBM showed a low prevalence of somatic mutations and inadequate T cell infiltration, limiting the possible immune checkpoint blockade availability. More importantly, the use of cancer vaccine treatments in prevention as well as therapy has shown considerable promise [13]. Cancer vaccines are made to target tumor-associated antigens in GBM (glioblastoma) with the aim to trigger an immune defense against the cancer. Due to the scarcity of GBM-specific antigens, patient enrollment is constrained since GBM antigen targets are frequently tumor-associated antigens. brain tumor Because the tumor is restricted to the brain and has no distant metastases, as well as being primarily surrounded by post-mitotic cells, GBM is one of the malignancies that is most amenable to oncolytic viral therapy. An active cell cycle is required for co-replication [12].

3. The classifications and characteristics of different oncolytic viruses

Considering the anti-tumor mechanisms, different types or subtypes of viruses are studied because of their different pathological efficacies. The DNA or RNA viruses that give the formation of oncolytic viruses can be single-stranded or double-stranded, depending on the nucleic acid type. Although OVs have similar characteristics, different viruses are used in different ways to create OVs. The most widely utilized viruses are those with dsDNA and ssRNA. Examples of dsDNA viruses include herpesvirus, adenovirus and vaccinia virus. ssRNA viruses can also be separated into positive and negative viruses. In a plus-stranded ssRNA virus, the virus multiplies inside the cell and the host cell's ribosomes immediately translate the post-transcriptional genetic material into proteins. Contrarily, ahead of protein translation can occur, negative ssRNA viral genetic material needs to be transcribed into righteous RNA since it possesses a complementary nucleic acid to mRNA of virus. Here, several most commonly used viruses are introduced.

3.1. Herpesvirus

One of the most popular and potential vector viruses is the herpesvirus. The dsDNA of the herpes simplex virus (HSV), which has a pair of distinct types, HSV-1 and HSV-2, is wrapped and covered by the tegument. Seven HSV-based oncolytic viruses have been tested and developed, but the manufactured T-VEC is the first to be given EMA and FDA approval for human usage after successfully completing phases I, II, and III of clinical studies. ICP34.5 is replaced with two copies of the human granulocyte macrophage colony-stimulating factor (GM-CSF) gene, while ICP47 and ICP34.5 are removed. Viral proliferation is prevented in healthy cells by activation of protein kinase R (PKR) and subsequent phosphorylation of eukaryotic initiation factor 2 (eIF2). The pathway of PKR-eIF2 is disturbed in cancer cells, leading to unchecked cell growth and unrestricted viral replication. ICP47 promotes HSV1 growth by reducing the immunological injury brought on by the host cell [14]. In figure 1, removal of ICP47 can therefore improve MHC1 expression on cancer cell surfaces, boost tumor antigen expression by infected malignant cells, and cause the immune system to destroy viruses in normal cells. To encourage dendritic cells to develop into T cells, which will then activate the immune system to specifically destroy tumor cells, GM-CSF is altered into T-VEC.

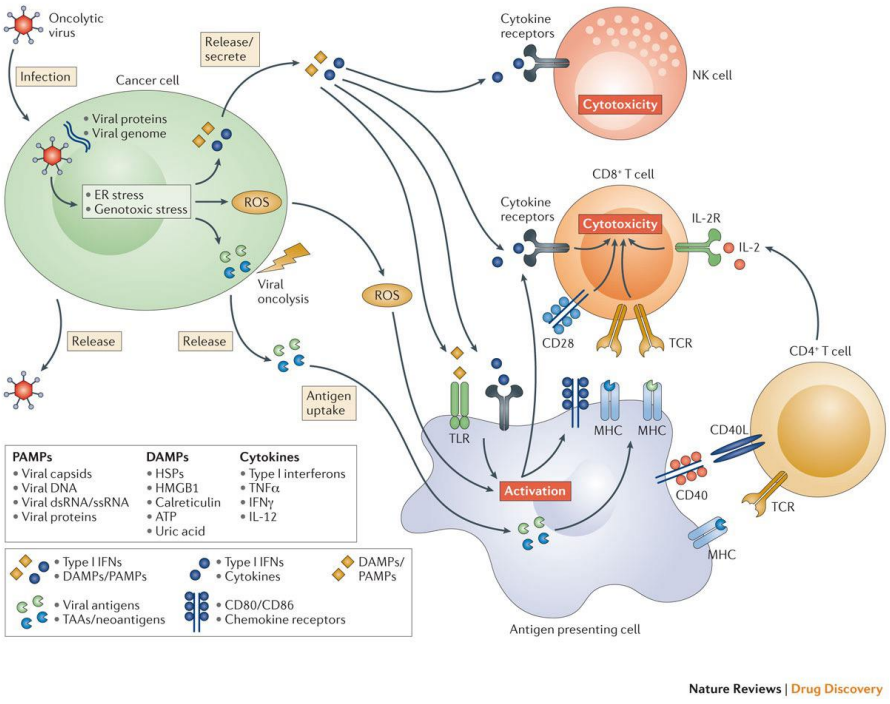

Fig. 1 Mechanisms of oncolytic viruses exploiting cancer immune evasion pathways [14].

3.2. Adenovirus

Oncolytic viruses based on adenoviruses have taken advantage of p53 inactivation in the majority of cancer cells to maintain replicating. Oncorine (also referred to as H101), the first recombinant oncolytic adenovirus, received approval from the CFDA in late 2005 to be used in conjunction with chemotherapy to treat nasopharyngeal cancer [15]. However, rather than inducing antitumor immunity, the oncolytic medicines' ability to treat cancer is mostly attributed to their inherent oncolytic properties.

3.3. Vaccinia virus

The vaccine virus has a sizable dsDNA genome (about 190 kb), and it belongs to the family of poxviruses. The vaccinia virus multiplies only in the nuclear compartment of infected cells, allaying worries about the potential for insertional mutagenesis. Additionally, vaccines can infect a variety of types and are particularly tropic for tumor cells [16].

4. The mechanism of OV treat tumor

Oncolytic virotherapy, divided into two groups: replication-competent OVs that specifically infect and replicate in cancer cells to kill tumor cells, and replication-deficient viral vectors used as delivery systems for therapeutic genes, represents a promising form of immunotherapy for the treatment of GBM. To promote fast and targeted replication, genetically manufactured OVs are engineered to specifically target pathogen-associated antigens present on tumor cells. At a certain point, the viral infection and amplification set off host immune reactions that kill cancer cells. Different types of viruses have different OV therapy strategies. For decades, the main cancer treatment mechanism of OV treatment has been direct lysis of infected cells [4]. The prevalent idea states that antiviral responses prevent OV infection and proliferation. Some of these reactions that mitigate their oncolytic effects include the early elimination due to NK cells' antiviral function, the transfer of viral antigens

by mature DC to CD4+ helper T cells, the production of antibodies that are neutralizing by B cells, and the fatal effect caused by CTLs. Three factors contribute to oncolytic viral efficacy: tumor development, immunological activation, and viral reproduction [17].

4.1. Apoptosis

The following three components contribute to the death inducing signaling complex (DISC) of apoptotic mechanisms and the death receptors in discussion are Fas, TNF- R and TRAIL-R, which are modulated by viral infection through death receptor-mediated pathways [18]. The main reasons why viruses are able to control death receptor-mediated apoptosis are the multiplication of apoptotic receptors as well as ligands that are located on the cell membranes of hosts that are infected and increased sensitivity to this apoptosis signal. Death receptor-mediated apoptosis is a powerful means of virus-induced cell death and progeny transfer. A fascinating aspect, nevertheless, may be that as oncolysis progresses, apoptosis increases and tumor cells keep proliferating, despite results that it is initially repressed quickly. In the early stages, several viruses can influence particular aberrant signaling pathways in tumor cells to suppress apoptosis, giving the virus enough time and space to replicate and grow.

4.2. Pyroptosis

OV may be utilized to induce pyroptosis in cells that are malignant, which causes a powerful immunological response as well as a decrease or eradication of the tumor. Multiple cancer cell types have been successfully prevented from proliferating and metastasizing by altering the pyroptotic process that causes inflammatory destruction of cells, which may one day be used as a cancer therapy method. ASC, which can also be referred as apoptosis-associated speck-like protein featuring the activation of caspase as well as recruitment domains, is a bipartite protein, found in inflammatory vesicles made up of NLR or ALR, and has been discovered that it binds to Caspase-1 and initiates the caspase chain reaction, which finally results in the gas phase cortex being cracked and pyrodeath. The trigger above causes cancer cell membrane to become porous, which causes the cell to burst and die. Additionally, it was discovered that pyroptosis releases a number of DAMPs and proinflammatory cytokines, including IL-1 and IL-18, launching an adjuvant immune response against the tumor. Additionally, Gasdermin D (GSDMD) is degraded into its active component, the N-terminal fragment, then ruptures the membrane of plasma and results in pyrosis [19].

Scientists have been more engaged in OVs-mediated oncolytic immunogenicity owing to extensive study of OVs and their underpinning procedures. Viral offspring, TAA, DAMP signals, pathogen-associated molecular pattern (PAMP) are all released after the tumor cell lyses, and subsequently resulting to tumor immunogenic cell death. Important signals like DAMP and PAMP connect to sites like the ones called toll-like receptors (TLRS), activating immunity that is innate, which are involved in signaling. Furthermore, natural killer (NK) and developed DCs are boosted, and it is found that these cells help OV get rid of tumors. Antigen-presenting cells (APCs) specifically capture TAAs and tumor neoantigens (TNAs) to activate adaptive immunity. Once T cells that target the tumor have been primed from lymph nodes that are draining to exert tumor immunological activity in the main site, CD4+ and CD8+ T cells are activated. Either as a platform or independently, OVs might promote the synthesis of inflammatory substances. Even with ICD, OVs can support the antitumor immune system's operation. Cytokines and chemokines are released as part of the promotion. Cytokines are numerous soluble proteins or glycoproteins with modest molecular masses that work by communicating between cells to control immune response, cell differentiation, and proliferation. Numerous cytokines that are proinflammatory have been thoroughly studied to serve as the accessory the transgenic in OV regulation since more cytokines are believed to actively contribute to initiating and maintaining immune responses in malignancies. Chemotactic cytokines called chemokines are produced, attracted to, and control migrating movement of immunological cells. These chemokines control cellular movement and interactions inside the TME to facilitate an effective immune response against malignancy. In order to generate a protumorigenic the

environment, they also orchestrate the gathering of immunological cells. Strong T-cell-attracting chemokines were once thought to assemble into OVs and essentially contribute to activating the tumor immunological environment. Even while OVs have the capacity to combat tumors, the concurrent antiviral immune reactions cannot be disregarded. The principle of antiviral activity states that viral removal occurs through the swiftly antiviral functions of NK cells, antigen from the virus delivery by mature DC to CD4+ helper T cells, the ensuing production of antiviral antibodies that neutralize by B lymphocytes, and the toxic effect of CTL limit the spread of infection and development of OV, and thereby limit the oncolytic effect. One area where scientists are working hard is arming transgenes to dampen the virus-fighting response from the immune system. BV49.5 was created by replacing 34.5 genes with the bovine herpesvirus UL49.5 and US11 genes in the oHSV-1, in order to inhibit antiviral immune system recognition of CD8+ T cells by disrupting the transporter related to antigen processing. In animal models, it has been demonstrated that the inclusion of TAP inhibition in the therapy of bladder and breast cancer has a substantial effect. According to the discussion previously mentioned, it shows necessity to carefully control anti-viral resistance during OV changes, keep a delicate equilibrium between the anti-viral and anti-tumor immune systems, while avoiding negative effects, encourage and maintain sustainable infection and replication aimed at anti-cancer immune system function.

4.3. Anti-angiogenesis

Regarding the OVs that are directed towards TME, they mostly focus on angiogenesis. One of the characteristics of the majority of malignancies is persistent aberrant angiogenesis, which is fueled by the need for the transport of nutrients and metabolic exchange. Major factors limiting the administration of anti-cancer drugs and white blood cells, especially the infiltration of immune cells in white blood cell delivery, include stress and kinked blood circulation circumstances. Hypoxia Acidic and a hypoxia TME also inhibit the proliferation and spread of OV. Controlling growing vascularization is the aim when using conventional OV construction equipped with anti-angiogenic armaments. Currently, a number of OVs have been identified and evaluated that have a propensity to infect tumor-associated endothelium tissues. Even while the strategy focusing on the tumor vasculature is not the fundamental component of OV alteration yet could represent a useful anti-cancer therapy if the malignancy becomes significantly impacted by aberrant neovascularization [4, 20].

5. The clinical trails of OV Combination therapy

Future combination therapy using OV and medicines is one of the critical development avenues in this area. The most prevalent combination methods with OV at the time are chemotherapy, radiation, and targeted immunotherapy. Additionally, in contrast to conventional therapeutic options, OV has constrained toxic properties. Currently, there is well-established preclinical model evidence that shows OV's anti-tumor activity is increased when coupled with other systemic treatments involving chemotherapy and cell therapy. The OV is appropriate for tumors at different stages, and the variety of its administration techniques makes it appropriate for combined administration. There is growing evidence that combining chemotherapeutic drugs with OVs can enhance the cancer-fighting properties of various human-derived xenogeneic alive models of cancer. The two advantages of this synergy are that it can use fewer OVs in the same amount of time and space while simultaneously reducing the likelihood of undesirable responses. By doing so, the risk of the medicine's side effects on the body and medication resistance emerging in cancer cells are both diminished.

Among other combo therapies, the potential of OV in conjunction with immune therapy is the most encouraging. For instance, in tumors with low immune cell infiltration, ICIs frequently perform less well than OVs, which have been demonstrated to promote the infiltration of lymphocytes into the TME. Additionally, local levels of PD-L1, particularly varies between patients and tumors, may affect how well ICIs work in a particular area. Numerous OVs were also discovered to boost PD-L1

and PD-1 activity, most likely as a result of subsequent IFN production brought on by the invasion of viruses. OVs may therefore be able to at least partially reverse ICI resistance. In animal models, it has been demonstrated that ICIs and OVs may work in harmony. When virus engineering is used to create an oncolytic HSV in murine glioma models [21], with many trials utilizing modified HSV constructs currently underway or completed, clinical strategies are moving much more swiftly now. Patients with GBM have participated in or are currently enrolled in trials for the following substances: HSV-1716 (NCT02031965), G207 (NCT00028158, NCT02457845 and NCT03911388). In a Phase I-IIa trial including patients with GBM (UMINCTR: UMIN000002661), the security of G47 injected into the brains of humans was established. Third-generation oncolytic HSV-1 is G47. The subsequent investigator-initiated phase II research study in individuals with GBM has just been successfully completed (UMIN-CTR: UMIN000015995). The underlying tumor histology and patient-specific immunological variables may both have an impact on the action of OVs and ICIs. In Japan, G47 (Teserpaturev) was granted restricted and time-limited authorisation in June of 2021 for the treatment of malignant brain tumors based on its positive results of this phase II trial. Additionally, Individuals with glioblastoma are anticipated to benefit from ongoing Phase I and Phase II trials utilizing transgenic oncolytic adenoviruses in conjunction with standard medical therapy or immune checkpoint inhibition [22]. Additionally, adenoviruses were genetically modified to create the adenovirus vector aglatimagene besadenovec (AdV-tk), which encodes the HSV a compound called thymidine kinase gene. This was followed by antiherpetic drugs, such as valaciclovir, which act as nucleotide analogous signals and insert sequences during tumor division, destroying cells that are malignant [12]. Particularly when utilized alongside immune therapy, the most contentious combination technique at the moment, conjugated therapy for OV is a highly effective method of treating OV. There are now many clinical trials being done on OV combination medicines with different immunotherapies are being conducted globally. The overall performance is inspiring, albeit that the vast majority of the outcomes are mainly published at congresses.

6. Summary

Oncolytic viruses have been applied to the preclinic and clinic trails so far and the immune efficiency of OVs prove to be strong, showing broad application prospects. The utilization of OV therapy now mainly is performed on solid tumor like glioblastoma, and because of its strong immunogenicity, the total amounts of viruses reaching tumor sites are shown to be reduced obviously. Thus, the efficiency of OVs declines. In attempts to increase the safety of OVs, the variations and characteristics of natural viruses have been evaluated. Numerous viruses have been modified to carry medications or particular genes that increase their infectiousness and anti-tumor effects. Moreover, adopting combination therapy to OV therapy is the trend to enhance the effectiveness of viruses, as well as reduce the side effect of treatment. As a result, it needs to keep a balance to select safe and stable virus vectors, which requires additional clinical studies to confirm the biological validity safety of OVs and enhance OV therapies. Thus, oncolytic viral immunotherapy opens the door to an entirely new, highly promising class of medications for the treatment of cancer patients.

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