Developments of Wild Type Oncolytic Viruses for Modifying the Antitumor Immune Response

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Abstract:
Oncolytic virotherapy shows promise as an anticancer agent with its field having grown considerably since its birth in the 20th century. Unfortunately, there are still many challenges that face oncolytic viruses (OV) that should be further studied to improve oncolytic viruses' potency. Challenges faced in the field of oncolytic virotherapy are: elucidating the factors in viral oncoselectivity, improving the clinical efficacy of OVs, reducing adverse events from OV treatment. A promising strategy that is currently being researched to improve OV treatment is combining OVs with another cancer therapeutic. A substantial barrier to the treatment of tumors is the immunosuppressive nature of the tumor microenvironment. Oncolytic viruses have demonstrated the ability to counteract this environment to boost immune response against tumors.

1. Introduction

The origins of oncolytic virotherapy (OVT) date back just over 100 years to 1904 where a woman's tumor receded after she experienced an influenza infection. Later, in 1912, Italian doctors discovered a correlation between the rabies vaccine and cervical cancer regression [1]. These events led to the first studies of oncolytic virotherapy. Throughout the 1950s and 1970s, multiple studies were conducted for using oncolytic viruses as a cancer therapy. Unfortunately, this therapy was ineffective without proper safety measures to control the virus within human patients. In the 1980s, however, attenuated and selective viruses were created using novel viral genetic engineering technology. In 1991, a modified herpes virus was able to safely improve the survival of mice with glioma. The first oncolytic virus (OV) to be approved by the FDA for market use was Talimogene laherparepvec (T-VEC), a modified herpes simplex virus [2]. Currently, there are many clinical trials ongoing researching the safety and efficacy of various OV and their combination with other cancer therapies.

Oncolytic virotherapy is a branch of immunotherapy that relies on the use of a virus that has been engineered to be, or naturally is, selective towards cancer cells [3]. These viruses called OV are able to infect, replicate in and kill cancer cells while sparing the non cancerous human cells[4]. Additionally, OV infection is thought to stimulate an antitumor immune response[5]. OVT is thought to synergize well with other cancer treatment methods and improve their efficacy, especially immune checkpoint inhibitors[6].

One significant barrier to OVT is the tumor microenvironment (TME). In solid tumors, The TME contains both physical barriers and an immunosuppressive environment that prevents an antitumor immune response. This is especially important in immunotherapies such as OVT that help coordinate an antitumor immune response.

Many different types of oncolytic viruses are being studied for their safety and efficacy in fighting cancer. The wild type oncolytic viruses we will focus on in this review are measles virus (MV), H-1 parvovirus (H-1 PV), reovirus, and Newcastle disease virus (NDV). These viruses have significant, but limited research on them; they are naturally oncoselective and generally

resemble their natural state with limited genome modifications. This review will not focus on herpes simplex viruses or adenovirus. These viruses already have significant literature covering them as oncolytic viruses and have a heavily engineered genome. We provided links to reviews covering each of these viruses: herpes simplex virus,[7] adenovirus,[8] and vaccinia virus(Xu et al. 2023). These oncolytic viruses show potential as a cancer therapy, but they face many challenges and require further research to reach their potential as a cancer fighting agent.

2. Categories of Wild Type OVs

A. Measles: Measles Virus (MV) is in the Paramyxoviridae family meaning that MV has a single stranded, enveloped RNA genome [9]. Most wild type MVs use the SLAM/CD150 receptor for cell entry tropism which is expressed on the surface of immune cells [10]. However, vaccine strains of measles virus use the CD46 protein for cell entry which is frequently on the membrane of tumor cells [11]. With a mutation of the H protein at amino acid 481 in tissue culture adaption, MVs can experience CD46 tropism for cell entry [12]. A 2010 phase I clinical trial using Edmonston MV, a laboratory strain of MV that binds to the CD46 receptor, demonstrated promising signs regarding the safety and efficient oncolytic measles virus as a monotherapy for recurrent ovarian cancer; the median overall survival (OS) of patients treated with Edmonston MV was 12.15 months which favorably compares the an expected OS of 6 months[13].

B. H-1 Parvovirus (H-1 PV): H-1 PV is a single stranded, non-enveloped DNA virus [14]. H-1 PV is a parvovirus whose natural host is rats, therefore humans lack antibodies against H-1 PV. However, H-1 PV demonstrates little signs of cytolytic behavior towards non-tumor human cells[15]. H-1 PV is able to penetrate normal cells, but lacks the ability to replicate and perform cell lysis in normal cells [16]. H-1 PV expresses the oncotoxic protein, nonstructural protein 1 (NS1), which becomes upregulated in tumor cells due to tumor cells overexpressing phosphoinositide-dependent kinase-1, protein kinase B, and protein kinase C (enzymes involved in NS1 phosphorylation)[17]. In pre-clinical *in vitro* research, H-1 PV has demonstrated efficacy against pancreatic tumor cells in stand alone treatment [18]. In clinical trials, H-1 PV has shown a reasonable safety profile and promise in patient overall survival, although a double blind study is necessary to confirm these results[15].

C. Reovirus: Belonging to the Reoviridae family, Mammalian orthoreovirus type three Dearing strain (reovirus) is a non-enveloped, double-stranded RNA virus[19]. Reovirus does not replicate normal cells with it preferentially replicating in transformed cells. Rodent cell lines provided evidence that epidermal growth factor receptor pathways which are overexpressed on cancer cells helped facilitate reovirus infection[20]. Ras mutations, which promote uncontrolled cell growth, are found in approximately 30% of cancers, and Ras transformed cells have increased susceptibility to reovirus due to their downregulation of double stranded RNA activated protein kinase[21]. In multiple clinical trials, reovirus was demonstrated to be safe although with limited efficacy as a monotherapy [22–24]. However, reovirus

shows substantial promise in combination with other therapies such as chemotherapy and radiotherapy [25].

D. Newcastle Disease Virus (NDV): NDV is an avian paramyxovirus type I virus with an eveloped, single stranded RNA genome [26]. NDV has little pathogenicity in humans due to its high susceptibility to type I interferons (IFN). Since tumor cells have inadequate type I IFN signaling, they are more vulnerable to NDV infection [27]. NDV infection is facilitated through NDV haemagglutinin-neuraminidase (HN) and fusion protein (F) surface glycoproteins binding with sialic acid residues acting as a receptor on the surface of tumor cells [28]. Thus, IFN regulatory genes and sialic acid presence could be used as biomarkers for a tumor susceptibility to oncolytic NDV [29].In early 2000s clinical trials, NDV showed promise as an oncolytic virus demonstrating responses in a few patients and a prolonged progression free survival in 14 out of the 79 patients with manageable toxicities [30–32]. Currently, engineered NDVs are being developed to express proteins such as interleukin-12 (IL-12) and granulocyte-macrophage colony-stimulating factor (GM-CSF) with a clinical trial studying the safety and efficacy of an engineered NDV to express IL-12 in progress.

Virus	Family	Strain Derived from	Genome; Enveloped	Cell Entry Receptor	Oncotoxic Mechanism
Measles	Paramyxoviridae [9]	Human Vaccine [9]	Single stranded RNA; Yes[9]	CD46 and/or SLAM [11]	Induced autophagy or apoptosis[33]
H-1 Parvovirus	Parvoviridae [14]	Rat Pathogen [14]	Single stranded DNA; No[14]	Evidence towards sialic acid residues[34]	Induced lysosome dependent cell death, apoptosis, or necrosis[15]
Reovirus	Reoviridae [19]	Human Pathogen [19]	Double stranded RNA, No[19]	Not Identified	Induced necrosis, necroptosis, or apoptosis [35]
Newcastle Disease Virus	Paramyxoviridae[26]	Avian Pathogen [26]	Single stranded RNA; Yes[26]	Evidence towards sialic acid residues[29]	Induced apoptosis, autophagy, or necrosis [36]

3. Challenges for Wild Type OVs

Tumor Specific Tropism:
Since oncolytic viruses (OV) are live viruses, they carry an inherent danger for their ability to infect and kill non-cancerous cells. OVs such as H-1 Parvovirus (H-1 PV) and Newcastle Disease Virus (NDV) have a natural preference for tumor cells. This oncolytic preference of H-1 PV cannot be traced to one single factor but rather to many different factors throughout the life cycle of H-1 PV. Unfortunately, not all these oncoselective factors are specific to malignant cells and instead can be attributed to proliferating cells more generally. Such factors are cyclin A/CDK2 which convert H-1 PV's single stranded DNA genome into double stranded replicative forms which are essential for H-1 PV replication [37]. Since not all tumor cells are rapidly proliferating and non-cancer cells can be proliferating, H-1 PV infection could result in some undesired outcomes. Beneficially, these factors distinguish H-1 PV infection in rapidly proliferating tumors versus the generally dormant surrounding tissues [16].

Reovirus is a human pathogen that has very mild human infections, but it preferentially replicates and lyses in transformed cells because of factors which include epidermal growth factor which stimulates Ras signaling pathways [38]. Ras mutations in tumor cells increase their proliferation. Ras signaling enhances the antitumor tropism of reovirus due to its ability to enhance reovirus transcription [39]. While reovirus benefits from Ras mutations, reovirus can be effective in Ras independent cancers. So far, no factors determining reovirus efficacy in non-Ras tumor cells have been elucidated [40]. Further research must be conducted to determine these factors for more effective reovirus treatment.

Measles is a highly infectious human pathogen and must be attenuated before it is safe to use in humans. Oncolytic Measles Virus (MV) are derived from laboratory strains of MVs which are mutated to experience cell entry tropism from CD46 protein, an overexpressed transmembrane protein on tumors, in order for the MV to have oncoselective properties. CD46 is expressed on all human cells which creates a reasonable safety concern when used in humans. Future MV strains could potentially be developed with binding domains that spare non malignant cells with low CD46 expression [41].

Efficacy:
While OVs show promise in *in vitro* transformed cell lines and in improving overall survival, there is still a long way to go in terms of efficacy for OVs as a monotherapy. Several clinical trials have been conducted regarding the efficacy of various OVs. One trial used H-1 PV to treat progressive primary or recurrent glioblastoma. They found a median overall survival of 15 months which is greater than the expected overall survival

of recurrent glioblastoma of 9 months [42]. While this demonstrates some potential for H-1 PV in regards to efficacy, no progression free survival lasted for more than 6 months. Thus, this therapy still has much to improve in its efficacy [16]. A clinical trial studying the use of reolysin (reovirus therapy) in 12 patients with multiple myeloma found no objective response in patients treated with reolysin, and the longest period of stable disease for one of the patients was 8 months. The authors of the trial proposed three different factors that might have contributed to an inadequate clinical response: 1) unable to overcome inherent viral resistance to cytolysis, 2) lack of an OV related antitumor immune response, 3) inaccurate dosing [43]

Adverse Events (AE):

OVs are generally safe. With intravenous reovirus treatment, the most common adverse effects are grade 1 or 2 flu like symptoms, and in a phase I trial, no grade 3 or 4 AEs were observed. Reovirus treatment is considered to be safe for a broad range of cancers including, prostate cancer, malignant glioma, metastatic colorectal cancer, multiple myeloma and solid cancers [43]

Additionally, a 2012 study using MVs to treat 37 patients with ovarian or peritoneal cancer found that 5 out of the 37 patients experienced serious adverse events (adverse events requiring hospitalization) while all patients received some form of minor adverse event. The most common adverse events regarding both minor and serious were gastrointestinal disorders (such as abdominal pain, diarrhea, and nausea) and general disorders (flu-like symptoms). It is important to note that this study gives no analysis on the cause of these adverse events. The common adverse effects mentioned are also common symptoms of cancer (especially ovarian and peritoneal cancer). Thus, these adverse effects should not necessarily be attributed to the oncolytic measles virotherapy. Even if these adverse effects were not directly resulting from the oncolytic measles virus, they are still important in determining the safety and efficacy of the treatment [44].

Another clinical trial studied the use of oncolytic measles virus in treating 29 patients with multiple myeloma. The grade 3 or 4 adverse effects that were recorded and deemed to be possibly related to treatment were neutropenia (n=9); leukocyte count decreased (n=5); thrombocytopenia (n=2); and CD4 lymphocytes decreased, anemia and lymphopenia (each n=1). One patient experienced left ventricle failure that could have been related to treatment [45].

Another clinical trial studied the safety of H-1 PV in 7 patients with Pancreatic Ductal Adenocarcinoma (PDAC). There were 2 adverse effects out of the 91 total that were deemed related to the H-1 PV treatment which were moderately increased C-reactive protein. A total of 6 significant adverse effects were observed and none of them were attributable to the H-1 PV treatment, but instead were credited to PDAC [46].

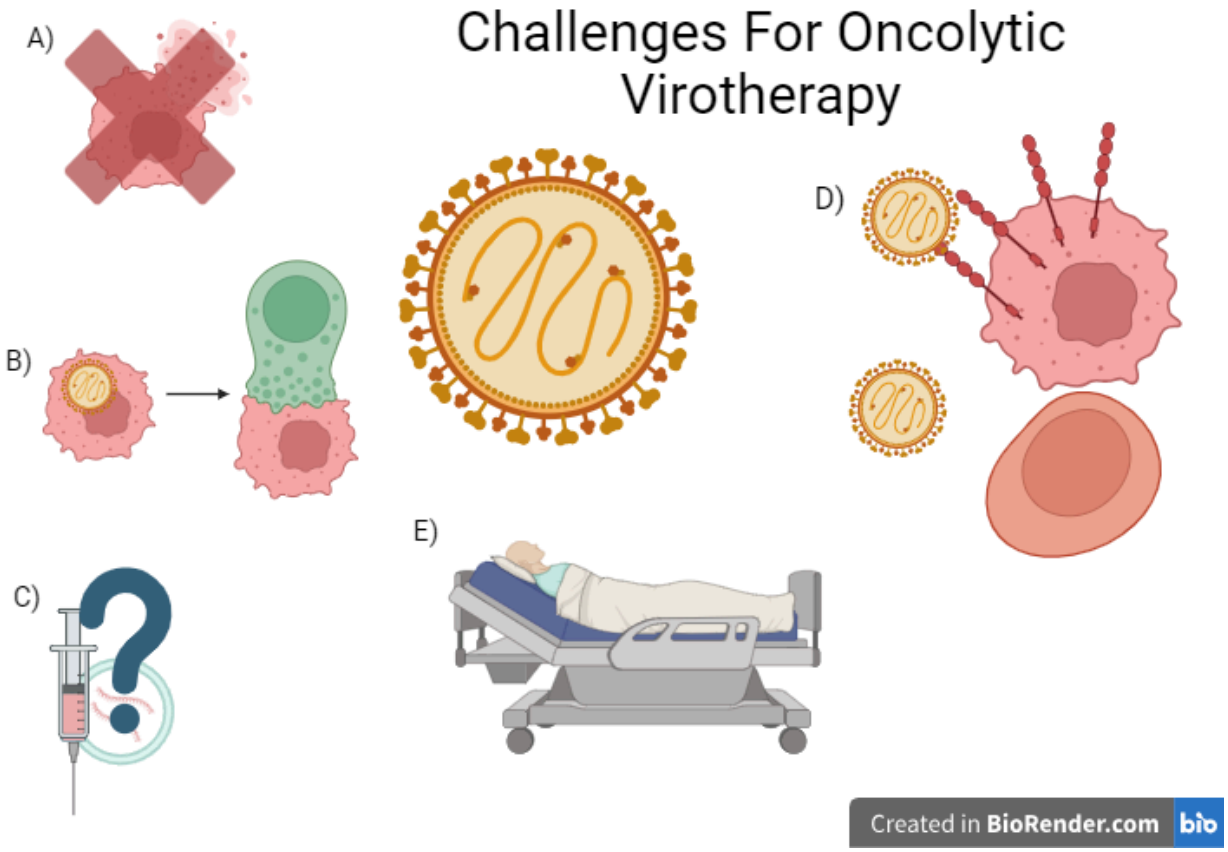

Figure Legend: Challenges for oncolytic virotherapy include A) inability to overcome inherent resistance to cytolysis B) lack of oncolytic related immune response C) inaccurate dosing D) attenuation of oncolytic virus to exhibit tumor specific tropism E) adverse events and serious adverse events

4. Oncolytic Viruses effects on the Tumor Microenvironment

The Tumor Microenvironment:
The presence of tumor infiltrating immune cells such as cytotoxic T cells (CTL) and natural killer (NK) cells are correlated with a better prognosis in tumors [47]. Tumor microenvironments (TME) that contain numerous infiltrating immune or T cells are inflamed or “hot”. Consequently, tumors possess the ability to bypass the normal immune response of systematically recognizing and killing malignant cells due to the cytotoxic behavior [29]. For one, the fibrogenic extracellular matrix and the cancer associated vasculature are two physical barriers that work to prevent T cell infiltration into the tumor [48]. Additionally, the TME contains many immunosuppressive molecules such as growth factors (prominently transforming growth factor-β), cytokines (mainly interleukin-10 and interleukin-4), chemokines, matrix-remodeling enzymes, and metabolites [49]. These molecules can be secreted by transformed tumor cells, and infiltrating immune cells such as immunosuppressive regulatory T cells, myeloid-derived suppressor cells, and tumor associated fibroblasts.

OV facilitated Immune Response within the TME:
Oncolytic Viruses (OV) contain the ability to change uninflamed or “cold” tumors to “hot tumors. Upon tumor cell lysis, OVs release molecules with pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)[50] which cause an inflammatory effect and activate immune response. PAMPs and DAMPs are recognized by pattern recognition receptors (PRR) on dendritic cells, macrophages, other immune cells, etc.. When stimulated by PRRs, the dendritic cell releases inflammatory and antiviral cytokines [51]. One major consequence of dendritic cell activation is the release of the cytokine type I IFN, IFN-β, which leads to CTL activation [52]. Furthermore, neoplastic transformation usually causes antiviral immune system deficiencies, meaning that cancer cells are unable to secret type I IFNs, but within the TME there may be a small percentage of cancer cells that retain the ability to secret these cytokines. Type I IFNs cause both desirable and undesirable effects in the TME [53]. Undesirably, type I IFNs are potent antiviral cytokines that prevent replication and facilitate elimination of OVs. Desirably, type I IFNs facilitate oncolytic immune response. Type I IFNs have anti-angiogenic effects and are able to stop tumor proliferation [54]. Type I IFNs also may be able to facilitate anti tumor immune response because they are regulators to CTL and NK activation. The secretion of type I IFNs differs between different OVs, i.e NDV induces considerable IFNs [55] while H-1 PV induces little IFNs [56] meaning that it lacks both desirable and undesirable type I IFN induced effects.

Endothelial Cells:
Solid tumors need a constant blood supply in order to proliferate and metastasize [57]. To achieve this blood supply, tumor vascularization and angiogenesis are promoted by vascular endothelial growth factor (VEGF) [58]. Not only does VEGF promote tumor angiogenesis, but additionally, it is thought to repress immune antitumor response [59]. VEGF signaling pathways can be exploited by viruses [60–62]; reducing VEGF has been shown to decrease OV infection in tumor-associated vascular endothelial cells [63]. In pre-clinical *in vivo* models, OV treatment to tumors with baseline high VEGF levels showed significant ability to disrupt tumor vasculature and infect tumor-associated vascular endothelial cells. There was a 90% decrease in perfusion recorded throughout these tumors, while adjacent normal cells showed no change in perfusion. Disrupting tumor perfusion is often followed by durable tumor necrosis. These anti-angiogenesis effects were observed preceding widespread tumor OV infection [64]. In a clinical trial, high dose OV treatment infected tumor-associated vascular endothelial cells in 5 out of 8 patients, while all patients with low dose OV treatment showed no infection in tumor-associated vascular endothelial cells. OV infection was found in tumor-associated vascular endothelial cells in patients with diverse histologies including colorectal carcinoma, ovarian carcinoma, and leiomyosarcoma. Control samples of non cancerous cells and pre OV treatment tumor cells were negative for OV infection. A separate phase II clinical trial revealed acute disrupted perfusion in liver tumors treated with OVT using MRI imaging. Acute disruption of perfusion was demonstrated in both intratumoral and intravenous injection and was also found in small, distant tumors [64].

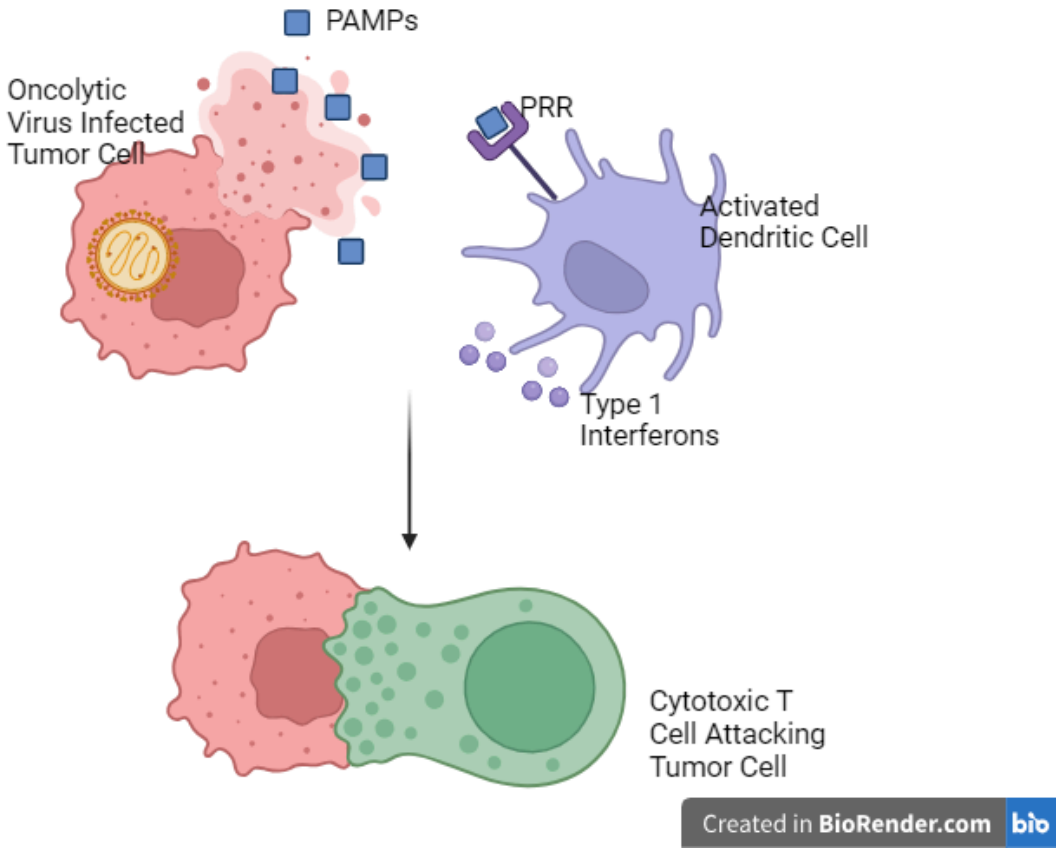

Figure Legend:
A tumor cell lyse during oncolytic virus infection. This releases pathogen-associated molecular patterns (PAMP) which are detected by pattern recognition receptors (PRR) on dendritic cells which activate them. Activated dendritic cells release type 1 interferons that cause cytotoxic T cell activation. These activated cytotoxic T cells are able to recognize and eliminate cancer cells.

5. Combination Therapy:

Combination Therapies

One promising approach to improving the efficacy of OVT is combining OVs to synergize with another cancer therapeutic - called combination therapy. There are a wide range of promising combinations involving OVT, including combining OVT with immune checkpoint inhibitors, chemotherapy, or targeted/small molecule therapy(Zhu et al. 2022).

Immune Checkpoint Inhibitors:
The overexpression of immune regulatory receptors such as PD-L1, PD-1, and CTLA-4 can create an immunosuppressive state in the TME. Immune checkpoint inhibitors (ICIs) bind to these receptors, preventing their immunosuppressive function in TME. ICI response is dependent on T cell infiltration, due to their direct effect in preventing immune regulatory receptors from being activated on T cells. Thus, the presence of antigen presenting cells and

tumor infiltrating lymphocytes within the tumor are associated with ICI efficacy. Consequently, low immune infiltration has a negative impact on ICI response [65]. OVs have a natural ability to increase immune infiltration because they stimulate antigen presenting cells through the release of pathogen-associated molecular patterns. These APCs then activate T cells allowing for antitumor immune response [66]. Since OVT increases immune response within the tumor, it shows promise as a potent combination with ICIs [67].

In preclinical models, reovirus in combination with anti-PD-1 therapy allowed natural killer cells to more effectively recognize and kill reovirus infected tumor cells and increase CTL response through the reduction of regulatory T cells [68]. A clinical trial that studied the use of ICIs in combination with Pelareorep, a reovirus based therapy, and chemotherapy on pancreatic ductal adenocarcinoma found the toxicities of this combination to be manageable with only 2 out of 11 patients experiencing grade 3 or 4 toxicities. 3 out of 10 patients had a stable disease or partial response. This clinical trial concluded that this combination was safe and that it had efficacy promise, warranting further study [69]. Newcastle disease virus, parvovirus, and measles virus have all been researched in combination with ICIs in pre-clinical trials, and clinical trials are expected to be conducted in the near future [70]. A combination of T-VEC and pembrolizumab were studied in a randomized, double blind, and placebo controlled phase III clinical trial. This trial concluded that the combination of T-VEC and pembrolizumab demonstrated no benefits to patients overall survival and progression free survival when compared to a pembrolizumab control. While T-VEC is not the focus of the review, this study qualifies the extent to which this combination demonstrates promise (Chesney et al. 2023).

Chemotherapy:

A promising combination that is being explored is combining OVT with chemotherapy. The combination of OV and chemotherapy demonstrate promise in non-small cell lung cancer lines for their ability to synergize with chemotherapeutic agents improving OV induced cell death[71]. Additionally, this combination has the potential to lessen the dose and duration of the chemotherapy treatment, consequently decreasing side effects and the chance of drug resistance [65]. A 2011 phase I clinical trial studied the combination of reovirus and Gemcitabine, a chemotherapy agent. It concluded that this combination was safe with a full dose of Gemcitabine, but it highlighted an interesting problem. Gemcitabine has the ability to damage the humoral and anti-reovirus immune response. These damages increase the ability for a virus to infect normal cells leading to increased OV related side effects, but they also may improve the OVs ability to infect tumor cells [72].

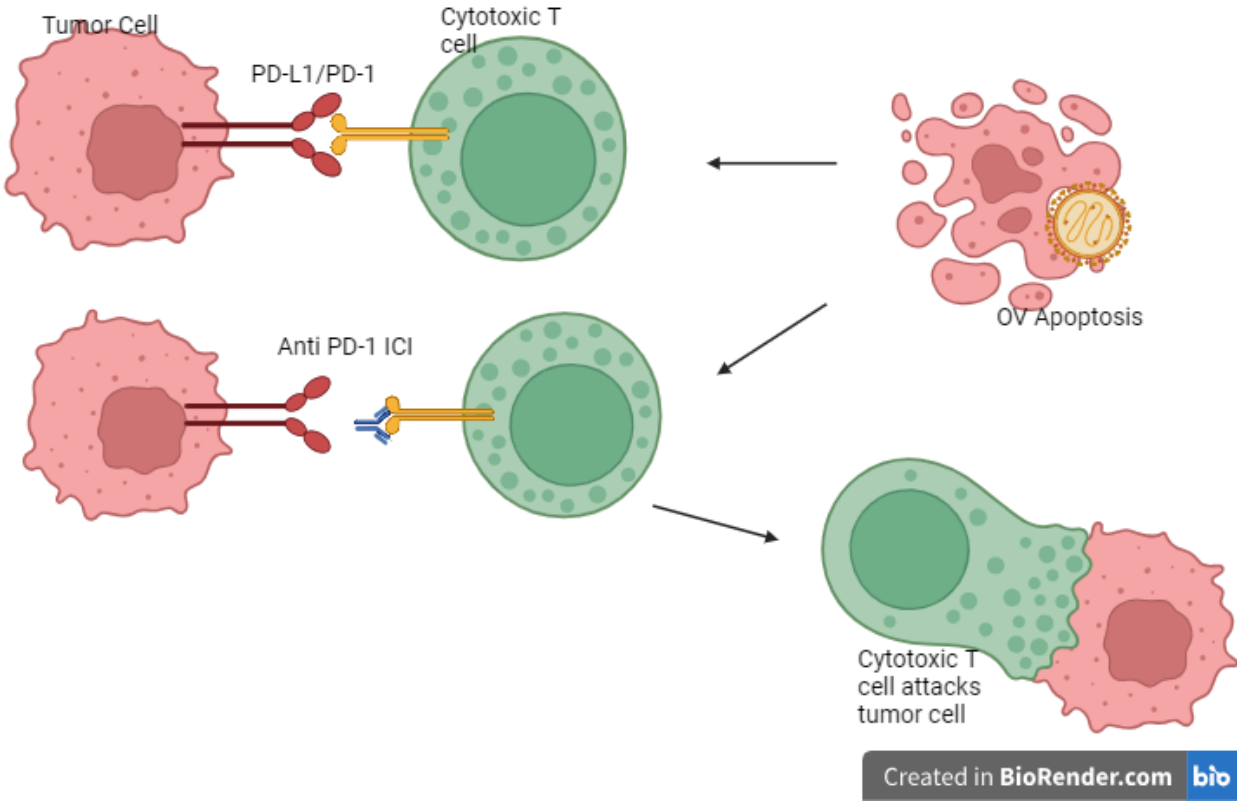

Figure Legend: Oncolytic Virus (OV) induced apoptosis leads to Cytotoxic T cell (CTL) activation. Programmed cell death protein 1 (PD-1) on the activated CTL binds with the programmed death-ligand 1 (PD-L1) on tumor cells inactivating it, but if an anti PD-1 antibody prevents PD-1 and PD-L1 from binding, then it prevents CTL inactivation. The activated CTL is able to attack tumor cells.

6. Conclusion and Future Perspective

The field of oncolytic virotherapy has exponentially progressed since its advent at the beginning of the 20th century. Various viruses have been studied in clinical and preclinical trials for their use as a cancer therapeutic including T-VEC which has been approved by the Food and Drug Administration for cancer treatment .

Unfortunately, as far as this field has come, there is still major progress needed in this field. For one, many of the details regarding OVs oncoselectivity are not fully understood or accounted for. For example, while reovirus's mechanisms to preferentially replicate in Ras mutated tumors have been thoroughly investigated, the mechanism for reovirus's preference in non-ras tumors have not been elucidated. Clinical trials using reovirus have had limited success in efficacy, and it should be considered that determining reovirus's oncoselective mechanisms would enable better designed trials to be conducted which could potentially help combat some of reovirus current modest efficacy as a

monotherapy. Furthermore, H-1 PVs mechanisms for oncotropism are not completely specific to cancer cells and can be stimulated in proliferating cells too. This adds an inherent safety risk for H-1 PV use in humans. These important details in OV mechanisms for tumor specific tropism could be elucidated and solved in order to improve the clinical efficacy and safety of OVs in the future.

Additionally, some OVs have struggled with clinical efficacy. H-1 PV and reovirus have shown promise in their use as a monotherapy, especially in animal models, but they both have failed to meet clinical endpoints and eradicate tumors. These failures raise concerns about OVs potential as a monotherapy. Some of the ways that researchers hope to improve the OVs clinical efficacy is by arming the virus with genetic information that boosts their ability to kill cancer cells or that better stimulates the immune system for an antitumor immune response. Another method to improve OV success is to engineer retargeted OVs that have more specific oncoselective mechanisms.

While OV monotherapy has its limitations, combination therapy is another attractive use of OVs. Since oncolytic viruses have very limited adverse events compared to more traditional cancer treatments, oncolytic virotherapy used in combination with chemotherapy is able to reduce the dose and side effects of chemotherapy mono treatment. Moreover, oncolytic virotherapy is able to facilitate an antitumor immune response allowing it to synergize with immune checkpoint inhibitors. ICIs prevent normal cells from suppressing immune cells, a function that is exploited by cancer cells to evade the immune system. In combination, OVs can stimulate an immune response to cancer cells while the ICIs boost the immune system against cancer. This combination is still in clinical stages, but shows promise as a cancer therapy.

A large limitation to the success of immunotherapy is the tumor microenvironment. The TME is very immunosuppressive and inhibits the immune system from successfully responding to cancer. Oncolytic viruses release pathogen associated pattern molecules when they lyse tumor cells. These PAMPs stimulate the immune system which converts the tumor from an immunosuppressive environment to an immunologically inflamed environment. This conversion, also known as turning a “cold” tumor to a “hot” tumor, is associated with improved patient outcomes. Furthermore, tumors rely on tumor associated blood vessels and endothelial cells within the TME to receive nutrients for tumor proliferation or else they starve. OVs have the ability to target endothelial cells which decreases blood perfusion within the tumor. This decrease in perfusion is correlated with tumor necrosis. These oncolytic virus facilitated effects in the TME should be further studied as a way to better understand the course of OV infection, so treatments can be modified to most effectively treat tumors.

Not without challenges, OVs show great potential as a therapy for cancer whether on their own or in combination with another therapy. Between all of the wild type OVs mentioned, only one phase III has been completed. More phase III trials and research must be conducted to advance these wild type OVs as oncolytic agents. From 2000-2020, 97 clinical trials have been published on oncolytic viruses with many more planned for the future [73]- demonstrating the potency of the OV field. Future studies will

undoubtedly try to address the challenges of wild type OVs discussed and bring them to the forefront of cancer treatment.

Executive Summary:

Introduction
- Oncolytic Virus (OV) were first proposed in 1904
- Modified herpes simplex virus was first approved in 2015
- OVs preferentially replicate in cancer cells and do not replicate in human cells
- Tumor microenvironment inhibits immune response to cancer
- Wild Type OVs H-1 Parvovirus (H-1 PV), Measles Virus (MV) , Newcastle Disease Virus (NDV), and Reovirus focused on in review which have limited genomic engineering

Categories of Wild Type OVs
- MV: single stranded RNA genome, uses SLAM receptor, favorable clinical trial results (phase I)
- Reovirus: double stranded RNA genome, unidentified cell receptor, limited clinical success as monotherapy
- H-1 PV: single stranded DNA genome, expressed oncotoxic protein NS1, safe with promising efficacy in phase I trials
- NDV: single stranded RNA genome, takes advantage of damaged IFN response in tumor cells, prolonged progression free survival in clinical trials

Challenges for Wild Type OVs
- Tumor specific tropism is not perfect and is not fully understood, noncancer cells can be infected by OV and some tumor cells are resistant
- Efficacy in clinical trials has been limited and needs to be improved
- Adverse events while limited pose a safety issue to OV therapy

Oncolytic Viruses' Effects on the Tumor Microenvironment
- Tumor microenvironment (TME) prevents immune response with immunosuppressive molecules and physical barriers
- OVs can convert the tumor microenvironment to become immune inflamed
- OV have target shown to target endothelial cells which can starve the tumor

Combination Therapies
- Immune checkpoint inhibitors synergize with OVs because both therapies boost immune response toward cancer, this combination is safe and shows promise in efficacy
- Chemotherapy in combination with OVs can improve efficacy and reduce chemotherapy side effects

Conclusion and Future Perspective
- Further research is essential for the progression of wild type OVs
- OVs demonstrate potential as therapy for cancer

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