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Recent advances in oncolytic virus-based cancer therapy

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ABSTRACT

Administration of oncolytic viruses (OVs) is an emerging anticancer strategy that exploits the lytic nature of viral replication to enhance the killing of malignant cells. OVs can be used as tools to directly induce cancer cell death and to trigger local and/or systemic immune responses to metastatic cancer *in vivo*. The effectiveness of OV therapy was initially highlighted by the clinical use of the genetically modified herpes virus, talimogene laherparepvec, for melanoma therapy. A number of OVs are now being evaluated as potential treatments for cancer in clinical trials. In spite of being engineered to specifically target tumor cells, the safety and off-target effects of OV therapy are a concern. The potential safety concerns of OVs are highlighted by current clinical trial criteria, which exclude individuals harbouring other viral infections and people who are immunocompromised. Despite the potential for adverse effects, clinical trials to date revealed relatively minimal adverse immune-related effects, such as fever. With advances in our understanding of virus replication cycles, several novel OVs have emerged. Reverse genetic systems have facilitated the insertion of anticancer genes into a range of OVs to further enhance their tumor-killing capacity. In this review, we highlight the recent advances in OV therapy for a range of human cancers in *in vitro* and in *in vivo* animal studies. We further discuss the future of OVs as a therapeutic strategy for a range of life-threatening cancers.

1. Introduction

Oncolytic viruses (OVs) infect and kill cancer cells with little to no effect on healthy tissue (Hao et al., 2019; Hassanzadeh et al., 2019; Hietanen et al., 2018; Hirooka et al., 2018; Howells et al., 2017; Hu et al., 2018; Huang et al., 2019; Hutzler et al., 2017; Ilyinskaya et al., 2018; Ismailov et al., 2019; Jacobson et al., 2017; Jenner et al., 2018; Jiang et al., 2018). Reovirus (RV) has the capacity to naturally select interferon pathway-deficient cancer cells, while genomic editing can be utilized to induce cancer cell selectivity in vaccinia virus (VV) and adenovirus (Aitken et al., 2018; Ammour et al., 2018; Badrinath et al., 2018; Binz et al., 2017; Chen et al., 2019; Chon et al., 2019; Deng et al., 2019; Guo et al., 2017; Huang et al., 2019; Hutzler et al., 2017; Kim et al., 2018; Lauer et al., 2018; Le Boeuf et al., 2017; Li et al., 2018). Without genomic editing, RV, VV and adenovirus all have the capacity to destroy cancer cells, however the unedited viruses lack cancer-specific selectivity, meaning that healthy cells may also be affected.

Viruses are categorized into DNA and RNA viruses which are double- or single-stranded. A range of virus families have emerged as potential OVs despite their highly variable replication cycles and differential tissue tropism. Viruses cannot survive without cells and must hijack cellular components to translate their viral proteins, copy their heir viral genomes, and persist, often to the detriment of the host (Fig. 1). Viruses engage cells by binding to cell-surface receptors or through plasma membrane fusion in the case of some enveloped viruses (Fox and Parks, 2018; Kuznetsova et al., 2017; Masemann et al., 2018; Penghui et al., 2019). Some OVs are unique in terms of their innate ability to infect malignant but not healthy tissues, while others can be

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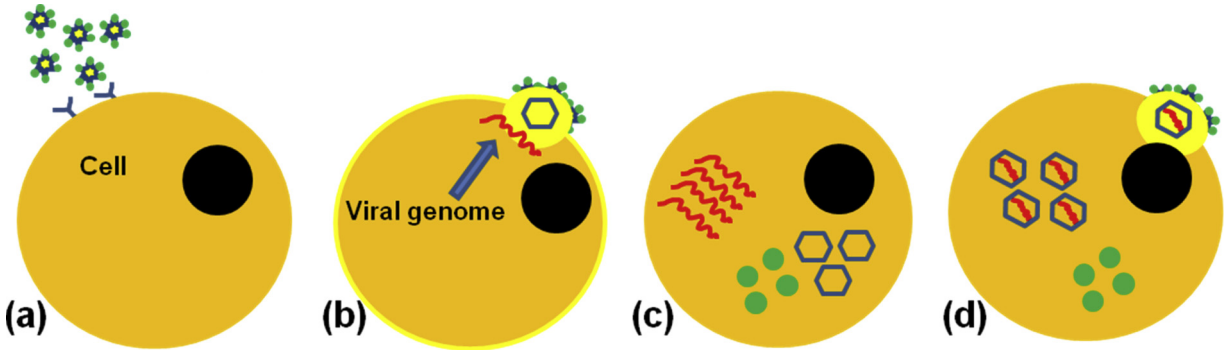

Fig. 1. The four stages of a virus replication cycle: (**a**) Virus-receptor binding, (**b**) virus entry, (**c**) replication/translation, and (**d**) assembly/release.

genetically modified to produce a similar effect (Abdullahi et al., 2018; Abei, 2018; Allan et al., 2018; Altomonte, 2018). An array of intracellular signals mediates tumor selectivity by exploiting innate weaknesses in the cancer cell (Bommareddy et al., 2018; Chen et al., 2019; Chon et al., 2019; Fu et al., 2018; Garofalo et al., 2018; Ghonime et al., 2018).

OV therapy was first demonstrated in the 1990s, when a recombinant, live-attenuated, thymidine kinase (TK)-negative herpes simplex virus (HSV-1) displayed tumor cell killing capacity (Lee et al., 2019; Perez et al., 2018). TK is a key enzyme in the pyrimidine salvage pathway. To-date, Talimogene Laherparepvec (the genetically modified HSV herein termed T-VEC), is the only FDA approved OV licenced for the treatment of non-resectable melanoma (Andtbacka et al., 2015; Appleton et al., 2015; Greig, 2016; Harrington et al., 2015; Johnson et al., 2015; Kim, 2015; Kohlhapp and Kaufman, 2016; Kohlhapp et al., 2015; Lee et al., 2019; Perez et al., 2018). This study was rapidly followed by numerous subsequent studies highlighting the effectiveness of OVs in a range of tumor models (Table 1). The main focus of OV development is the identification of viruses and recombinant variants that selectively replicate in tumor-cells (Ilyinskaya et al., 2018; Jiang et al., 2018; Jung et al., 2018; Kim et al., 2018). It is widely accepted that for an OV to be successful it must specifically replicate in tumor cells, be stable *in vivo*, and not undergo chromosomal integration, ultimately preventing the initiation of virus-induced disease (Kalyanasundram et al., 2018). OVs including HSV-1, RV, and VV also induce tumor-specific adaptive immune responses in host cells, leading to indirect malignant cell death (Badrinath et al., 2018; Chen et al., 2019; Chon et al., 2019; Deng et al., 2019; Ghonime et al., 2018; Le Boeuf et al., 2017).

Other OVs induce endoplasmic reticulum (ER) stress resulting in immune cell lysis and the release of molecular patterns that attract cancer targeting immune cells (Fig. 2) (Chon et al., 2019; Ghonime et al., 2018; Lal et al., 2018; Oseledchyk et al., 2018; Saha et al., 2018; Wang et al., 2019; Yin et al., 2017). To effectively trigger the immune response necessary for the removal of tumor cells, it is necessary to not only trigger an immune response but also to recruit immune cells. A number of OVs have been designed to express immunostimulatory transgenes, such as interleukins (IL). These viruses include Tanapoxvirus (TANV) expressing IL2, VV expressing IL24 and HSV-1 expressing IL12 (Alessandrini et al., 2019; Lv et al., 2016; Patel et al., 2016; Zhang et al., 2018). Other immunostimulatory transgenes have also been incorporated in OV treatments, such as modified adenovirus expressing OX-40 (Jiang et al., 2017). Through the expression of these immunostimulatory transgenes, an immune response is triggered and immune cells, including T cells such as $CD8^+$ T and $CD4^+$ T, macrophages and natural killer cells, selectively target tumor cells as a result of intratumoral injection. Where OVs have not been modified to express immunostimulatory transgenes, some therapeutic strategies utilize OVs in combination with immunotherapy agents, such as anti-cytotoxic F cell antigen 4 or programmed cell death 1 antibodies (Chesney et al., 2017; Ribas et al., 2017).

The emergence of OVs as a promising therapeutic strategy in oncology is therefore clear. In this context, this review summarizes recent progress in this area and describes the ongoing *in vitro* and clinical trials that support the promise of viral oncotherapy.

2. Recent advances in OV-based therapy for various cancers

2.1. Melanoma virotherapy

Melanoma treatment highlights the benefits of engineered OVs including the FDA approved talimogene laherparepvec (T-VEC) (Cavalcante et al., 2018), a modified herpes simplex virus type 1, which selectively targets tumors (Liu et al., 2003). As a standalone therapy, Andtbacka et al. demonstrated that T-VEC elicited a favourable response in patients with unresected advanced stage melanoma. Patients treated with the OV were found to have an improved objective response to treatment, and were shown to have longer overall survival (Andtbacka et al., 2015).

The use of T-VEC in combination with immunotherapy in patients with advanced melanoma has been found to be an effective therapeutic strategy, particularly in patients resistant to immunotherapy alone (Chesney et al., 2017; Ribas et al., 2017). The combination of OV with immunotherapy enables the body to activate an immune response at the tumor, by injecting OVs directly into the tumor. By attracting tumor specific immune cells, the infected tumor cells can then be directed to the immunotherapeutic agent for destruction (Chesney et al., 2017; Ribas et al., 2017). In work undertaken by Chesney et al., T-VEC was directly injected into the tumor and used in combination with the anti-cytotoxic T-cell antigen 4 Ipilimumab. This therapeutic approach was shown to be well tolerated by patients and their overall response to treatment was found to improve (Chesney et al., 2017). In a similar study involving advanced melanoma patients by Ribas et al., T-VEC was again administered by intratumoral injection, this time in conjunction with the systemic injection of the programmed cell death-1 antibody pembrolizumab. Like other T-VEC therapeutic approaches, this combination was well-tolerated. Analysis of patient outcomes revealed that this combination therapy promoted increased infiltration by immune cells such as $CD8^+$T. This response was also observed in some previously pembrolizumab-resistant patients. Additionally, both objective and complete responses were improved in the advanced melanoma patients given this treatment (Ribas et al., 2017).

Other OVs used in combination with known antitumor interventions have recently been investigated. Though vesicular stomatitis virus (VSV) is a potent OV, its associated neurotoxicity and rapid induction of neutralizing antibodies prevent its systemic application (Dold et al., 2016). Kimpel et al. demonstrated that these limitations could potentially be surmounted by generating VSV-GP through the substitution of VSV glycoprotein G with the lymphocytic choriomeningitis virus (LCMV) glycoprotein GP. They demonstrated that primary human

Table 1
Table representing a number of the different classes of oncolytic viruses being investigated as potential therapeutic strategies for a wide array of cancers. Table contents adapted from active, anticipatory and completed clinical trials *via* www.clinicaltrials.gov.

Class	Virus Name	Cancer Types	Therapeutic Approach	Clinical Trial Stage
Adenovirus	LOAd703	Pancreatic cancer	Combination	I/II
	DG007	Bladder cancer	OV only	II
	DNX-2440	Glioblastoma	OV only	I
	CAdVEC	Head and neck squamous cell carcinoma	OV only	I
		Salivary gland, bladder, lung, breast, gastric, esophageal and colorectal cancers		
		Pancreatic adenocarcinoma		
	ColoAd1 (enadenotucirev)	Resectable colon, non small cell lung and bladder cancers	OV only	I/II
		Resectable renal cell carcinoma		
		Solid tumor		
		Meatstatic colorectal and bladder cancers		
		Ovarian cancer		
Adenovirus/Herpes Simplex Virus	ADV/HSV-tk	Metastatic non small cell lung cancer	Combination	II
		Metastatic triple negative breast cancer		
Herpes Simplex Virus Type 1	TBI-1401(HF10)	Solid tumor	OV only	I/II
		Pancreatic Cancer	Combination	
		Melanomas		
	G207	Glioma	Combination	I/II
		Astrocytoma		
		Glioblastoma		
	rQNestin34.5v.2	Gliomas	Combination	I
		Astrocytomas		
		Oligoendrogliomas		
		Glioblastoma		
		Brain cancer		
Herpes Simplex Virus Type 2	OH2	Solid tumor	Combination	I
		Gastrointestinal cancer		
Intratumoral	ASP9801	Metastatic cancer	OV only	I
Measles Virus	MV-CEA and MV-NIS	Ovarian cancer	Combination	I
		Primary peritoneal cavity cancer		
Reovirus	Palcreorep (wild type reovirus)	Recurrent plasma cell myeloma	Combination	I
Vaccina Virus	Pexa-Vec	Various colorectal cancers	Combination	I/II/III
		Solid tumors		
		Hepatocellular carcinoma		
		Metastatic tumor		
		Advanced tumor		
	TG6002	Glioblastoma	Combination	I/II
		Brain cancer		
	GL-ONC1	Advanced cancer	OV only	I
		Solid organ cancers		
	T-VEC	Skin cancers	OV only	II

melanoma cultures infected with VSV-GP were efficiently killed. VSV-GP also prolonged survival in mouse melanoma models (Kimpel et al., 2018). However, a drawback of the virotherapy was the lack of cancer remission, which questions the clinical efficacy of this approach. Li et al. investigated the oncolytic adenovirus H101 in combination with G protein subunit alpha q (GNAQ) silencing approaches (Li et al., 2019). GNAQ is a known driver of melanoma and has been frequently targeted in uveal melanoma (UM) treatment. The combined silencing of GNAQ and H101 inhibited UM cell proliferation, and enhanced apoptotic induction, mediated *via* MEK1/2 inhibition and enhanced YAP phosphorylation (Kuryk et al., 2019). This highlighted the potential of H101 to enhance other established antitumor strategies.

In recent studies by Ammour et al., the oncolytic potential of the attenuated mumps virus (MV) vaccine strain Leningrad-3 (L-3) was evaluated in a panel of human metastatic melanoma cell lines (Ammour et al., 2018). These cells were permissive to MV infection, following which MV replication induced melanoma cell death. These apoptotic effects were dependent on cytokine expression, particularly type I interferons. This study highlighted how the attenuated form of a disease-causing human pathogen holds therapeutic potential as an OV agent for human melanoma (Ammour et al., 2018).

Tanapoxvirus (TANV) is a virus which has not been as widely studied, primarily due to inability to cause severe disease in humans (Conrad et al., 2015; Seibert et al., 2013; Suryawanashi et al., 2017; Zhang and Essani, 2017; Zhang et al., 2018, 2017). From a molecular perspective, TANV is a large DNA virus that primarily infects skin cells. Zhang et al. developed a recombinant TANV expressing mouse Interleukin-2 (IL-2) through replacement of the viral TK with the mIL-2 transgene and assessed the antitumor potency of this chimeric virus in melanoma tumors (Zhang et al., 2018). IL-2 was engineered as it can activate T cells, natural killer (NK) cells, and macrophages. The study showed that mIL-2-TANV increased the antitumor activity and improved cancer regression (Zhang et al., 2018). Histopathological studies revealed extensive cancer cell death and increased tumor accumulation of mononuclear cells (Zhang et al., 2018). This exciting study highlighted how modified TANV is a potential therapeutic for human melanomas, in which IL-2 expression can enhance its therapeutic efficacy.

2.2. Lung cancer virotherapy

Lung cancer (LCa) is a leading global cause of cancer-related deaths (Bucknell et al., 2018). Newcastle disease virus (NDV) was previously found to cause autophagic cell death in cancer cells, but was only recently shown to be oncolytic to lung cancer (LCa) (Jiang et al., 2018; Kalyanasundram et al., 2018; Raghunath et al., 2017; Rush et al., 2018; Ye et al., 2018; Yurchenko et al., 2018). Ye and colleagues found that NDV enhances the accumulation of calreticulin, a phagocytic signal, on the cell surface of LCa cells and can induce the cellular release of HMGB1 and HSP70. These findings had translational significance since the infection of LCa xenograft models with NDV significantly inhibited

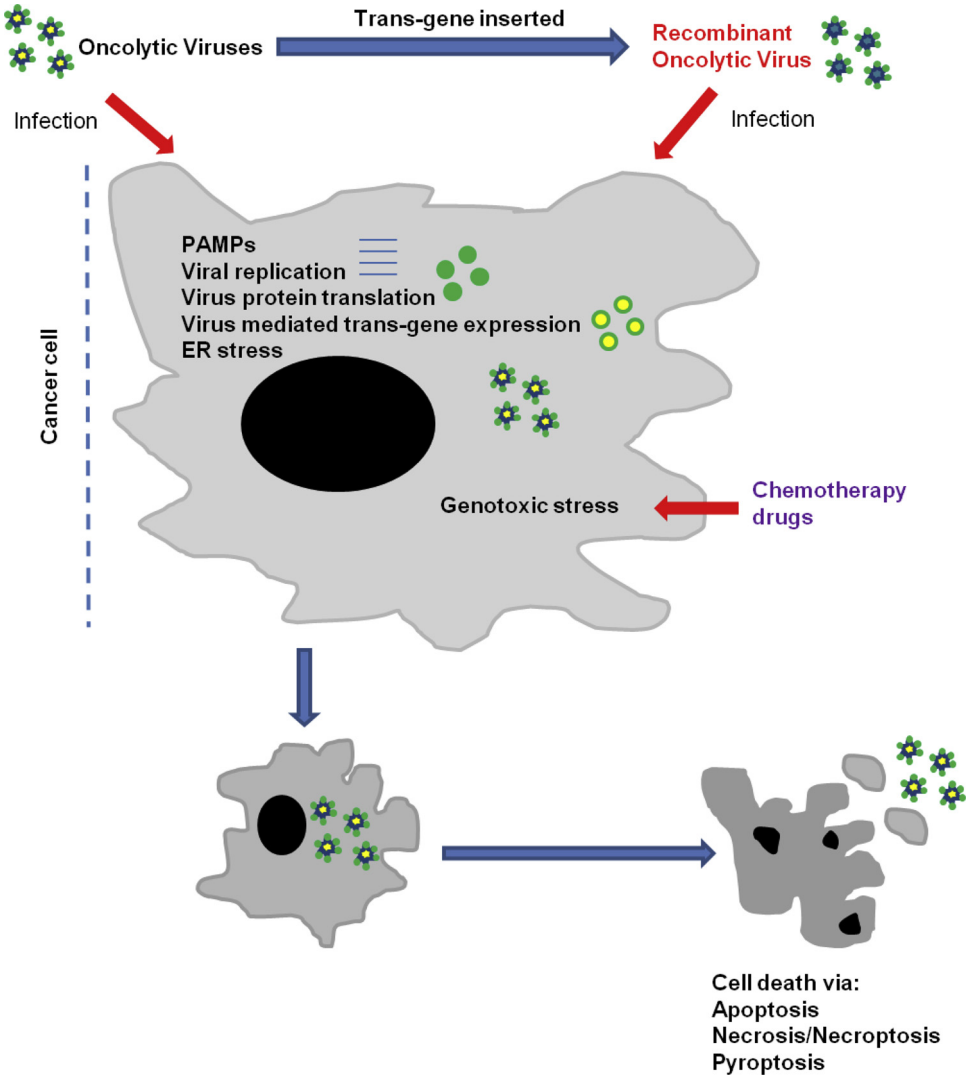

Fig. 2. Oncolytic activity of natural and recombinant oncolytic viruses.

tumor growth (Ye et al., 2018).

Non-small cell lung cancer (NSCLC) is a common LCa that represents a specific clinical challenge due to its high resistance to radiation and chemotherapy. The activation of Ras/Raf/MEK/ERK signalling is a hallmark of NSCLC tumors (Park et al., 2019; Rizzo et al., 2019; Wiesweg et al., 2018). However, this also enhances susceptibility to specific virus infections to which aberrant Ras signalling is pro-viral. In this regard, Masemann et al. recently demonstrated that influenza A virus (IAV) readily infects and replicates in NSCLC cells (Masemann et al., 2018). In transgenic NSCLC models, low-pathogenic IAV caused oncolysis, eliminating the majority of the tumor mass. IAV mediated these effects through its ability to restore and redirect immune cell functions within the NSCLC tumor microenvironment (Masemann et al., 2018). As a result of this study, the potential benefits of IAV infection combined with known anti-NSCLC agents to LCa warrant further investigation as a therapeutic strategy.

Combination of chemotherapy drugs with OVs has been found to enhance cytotoxic responses and oncolysis. Garofalo et al. assessed the delivery of oncolytic adenoviruses with paclitaxel (Pax) encapsulated in extracellular vesicles (EVs). The formulation was shown to reduce tumor growth in mouse xenograft models of human LCa (Garofalo et al., 2018). Transcriptional analysis of the treatment group demonstrated that a limited overlap of differentially expressed genes (DEGs) between Pax and adenovirus monotherapy existed. This suggested that synergistic genetic reprograming is triggered by the EVs and may be responsible for the observed tumor killing effects (Garofalo et al., 2018).

In vitro data shows promise for VSV as a treatment for LCa, however, resistance to VSV infection can occur in tumor cells through the type I interferon (IFN) response. In a novel approach, Patel et al. combined the JAK/STAT chemotherapeutic agent, ruxolitinib (Rux), with VSV-IFNβ to enhance its replicative ability in LCa cells (Patel et al., 2019). When the combination treatment was assayed for tumor cytotoxicity, Rux-VSV enhanced tumor killing. Experiments performed in drug-resistant NSCLC mouse models found that Rux treatment prevented NSCLC cells from enhancing PDL-1 levels in response to VSV, thus enhancing virus replication in tumor cells. The combination of Rux and VSV-IFNβ improved the survival of NSCLC mice with no immune infiltration into the tumor. This supports the clinical efficacy of the Rux-VSV-IFNβ for LCa treatment regimens.

VV is known to rapidly disseminate throughout the circulatory system. Lv et al. constructed a tumor-targeting VV carrying IL-24 that was inserted at the site of the viral-TK. The modified VV efficiently infected and destroyed LCa cells increasing caspase-activation and decreasing STAT3 expression. *In vivo*, VV was shown to express high levels of IL-24 in tumors, inhibit STAT3 activity, and induce tumor cell apoptosis, highlighting its potential for human LCa treatment (Lv et al., 2016).

From a strictly clinical perspective, Alberts and colleagues described positive treatment outcomes in a LCa patient receiving Rigvir virotherapy. Rigvir is a non-pathogenic ECHO-7 virus widely known for its ability to prolong early-stage melanoma patient survival, in the absence of virus induced side-effects (Hietanen et al., 2018; Ismailov et al., 2019; Proboka et al., 2018; Tilgase et al., 2018a, b). The patient had presented with small cell lung cancer stage IIIA, which was stabilized by Rigvir therapy (Alberts et al., 2016). This highlighted the potential of virotherapy with Rigvir for small cell lung cancer, but clinical trials in a large cohort of patients are now required to corroborate the potential of this therapeutic approach.

2.3. Pancreatic cancer virotherapy

Pancreatic cancer (PCa) is a fatal malignancy, which displays resistance to many chemotherapy agents. Despite advances in other cancer fields, the prognosis of PCa remains poor, with a 5-year survival rate of only 7%, highlighting the need for improved anti-PCa therapeutic strategies (Binz et al., 2017; Chen et al., 2019; Felt et al., 2017; Hirooka et al., 2018; Wu et al., 2017). Recent studies have shown that the addition of OVs to chemotherapy can overcome PCa resistance. Binz et al. investigated the cytotoxic effects of oncolytic VV in combination with Pax plus gemcitabine (Gem) in human PCa cell lines *in vitro* (Binz et al., 2017). In two of the four cell lines assessed, the combination regimen enhanced tumor cell apoptosis when compared to monotherapies. Interestingly, in the tumor cell lines that were not responsive, a lack of viral replication was observed. These findings demonstrate that high levels of virus-replication are essential to produce enhanced and long-lasting antitumor immunity.

Smac is a mitochondrial derived activator of caspase, which has been identified in PCa tumors to enhance chemosensitivity. On this basis, Chen et al. assessed oncolytic VV-mediated Smac gene transfer in PCa tissue. VV-Smac caused high levels of cytotoxicity, potentiated apoptosis, and produced synergistic effects with Gem both *in vitro* and *in vivo* whether used alone or in combination with Gem. This demonstrated the potential of VV-Smac as a therapeutic candidate for PCa, particularly when administered together with chemotherapeutic agents (Chen et al., 2019). Using a similar approache, Wu et al. constructed a VV harbouring ING-4 to explore its therapeutic efficacy in combination with Gem. VV-ING4 significantly increased ING4 expression, and enhanced PCa cell cytotoxicity through apoptotic induction and G2/M cell cycle arrest. Addition of Gem to the VV-ING4 therapy synergistically enhanced the killing effects both *in vitro* and *in vivo*, highlighting the potential of this approach as a PCa therapeutic strategy (Wu et al., 2017).

The use of VSV to induce PCa cell death has been extensively studied. It is well established that some pancreatic ductal adenocarcinoma (PDAC) cell lines display resistance to VSV infection, primarily through JAK1/2 signalling. JAK inhibitors including Rux stimulate VSV replication and oncolysis in resistant cell lines (Binz et al., 2017; Chen et al., 2019; Felt et al., 2017; Hirooka et al., 2018). Felt et al. further explored the response of PDAC cells to VSV tropism by assessing VSV attachment to PDAC and its potential contribution to resistance (Felt et al., 2017). They found that VSV attachment to HPAF-II cells, the PDAC cell line with the highest resistance, was the weakest and that these cells displayed the lowest levels of low-density lipoprotein receptor (LDLR) expression. LDLR is a known VSV attachment receptor. Statin treatment of HPAF-II cells enhanced LDLR expression but failed to improve VSV attachment or LDL uptake. Attachment of VSV to HPAF-II cells was significantly improved by treating HPAF-II cells with Polybrene and DEAE-dextran which overcame the resistance to VSV. This 3-way combination approach would now benefit from assessment *in vivo* to determine its potential in the treatment of OV therapy resistant PDAC tumors.

From a clinical perspective, the safety and anti-PCa tumor activity of HSV-1-HF-10 was assessed in phase I dose-escalation trials, in combination with erlotinib and Gem (Hirooka et al., 2018). The trials were single arm, open-label Phase I trials in which HSV-1-HF-10 was injected every 2 weeks. The study included 9 patients, of which 5 had Grade III myelosuppression, and 2 developed serious adverse events, none of which were attributed to HSV-1-HF-10 treatment. This trial demonstrated that direct HSV-1-HF-10 injection with erlotinib and Gem was safe and warrants further investigation as an anti-PCa therapy.

2.4. Glioblastoma

Glioblastoma is one the most common and aggressive forms of brain tumor. While anti-cancer therapeutics have continued to progress for other cancer forms, treatment options for glioblastoma remain limited. With prognosis remaining at only 10% survival after more than 5 years, the search for more effective therapeutic strategies is crucial. OVs have shown promise for the treatment of glioblastomas (Martikainen and Essand, 2019). Among these treatments, various OVs and treatment combinations have been tested. Using the modified adenovirus DNX-2440 (also known as Delta-24-RGDOX), Jiang et al. engaged the concept of combining OV and immunotherapy. The group generated DNX-2440 to express the immune stimulator OX-40 ligand, thus enabling the virus to specifically enhance activation of T-cells that would facilitate tumor recognition (Jiang et al., 2017). The group tested DNX-2440 in mouse models of glioblastoma and found that DNX-2440 was able to recruit immune cells such as $CD8^+$ T cells, induce autophagy and immunogenic cell death. However, with DNX-2440 treatment alone, efficacy was limited in some animals due to upregulation of programmed death ligand 1 (PD-L1) expression, which resulted in immune suppression. To overcome this, Jiang et al. administered intratumoral injections of DNX-2440 and a PD-L1 antibody. This combination was shown to overcome immune suppression and improve survival in mouse models. DNX-2440 is now in phase 1 clinical trials.

Another modern approach to utilize OVs in the treatment of glioblastoma is the retargeting of viruses. In pre-clinical work undertaken by Alessandrini et al., the Herpes simplex virus type 1 (HSV-1), was retargeted to erbB-2 and armed with IL12 (virus name: R-115). Using mouse models of glioblastoma, the group demonstrated that R-115 was fully virulent in target cells and could specifically target tumor cells. By administering an intratumoral injection of R-115, overall survival was improved and complete removal of the tumor was observed in 30% of animals (Alessandrini et al., 2019). The incorporation of IL12 in modified oncolytic HSV-1 OV approaches has been utilized previously with relative success. By incorporating IL12, the immune response is triggered, facilitating the specific targeting of tumor cells. M032 is also undergoing clinical trials as a therapeutic strategy for treating glioblastoma (Patel et al., 2016). Unlike previous modified HSV-1 s and current clinical trials incorporating OV HSV-1 s, the concept of using a fully virulent HSV-1 is relatively new and undergoing further preclinical investigations (Alessandrini et al., 2019).

Other modified HSV-1 s have also shown potential in combination with more traditional cancer treatments, for treating glioblastoma. In a phase 1 clinical trial conducted by Markert et al., the modified HSV-1 G207 was used in combination with radiation therapy. By giving an intratumoral injection of G207 prior to administering a single dose of radiation, most patients in the trial were found to have stable disease or showed a partial response (Markert et al., 2014). Further support for the potential of G207 for the treatment of glioblastoma was provided in a 2015 case study (Whisenhunt et al., 2015). In this case, the patient had been treated with limited success using traditional cancer therapeutics. However, following treatment with G207 in combination with low dose chemotherapy, the patient survived for 7.5 years, 6 of which were disease-free (Whisenhunt et al., 2015).

Vaccina viruses have also shown potential in the treatment of glioblastoma. In work carried out by Foloppe et al., vaccina virus was modified to express the suicide gene *FCU1* as well as targeted deletion of the *J2R* and *IL4* genes. Known as TG6002, this modified oncolytic

vaccina virus was designed with the intention of selectively and safely targeting tumor cells (Foloppe et al., 2019). What this group found was that TG6002 could induce tumor selective viral replication and sustain therapeutic levels for an extended period as well as having antitumor effects (Foloppe et al., 2019). This OV is now in phase 1 and 2 clinical trials.

2.5. Other important human cancers

Prostate cancer (PrCa) is the second most prevalent cancer in Western males. For the treatment of PrCa, many OV-based therapeutic strategies are emerging. One such strategy was demonstrated by Hao et al. who inserted mK5 (mutational kringle5 of human plasminogen) into a DD3-promoted (differential display code 3) oncolytic adenovirus and assessed its effects on PrCa cells. MK5 is known for its ability to inhibit tumor angiogenesis and cell proliferation, while DD3 is a PrCa promoter which transcriptionally enhances viral replication. The recombinant virus elicited strong antitumor effects, and further *in vivo* studies are now required to confirm the oncolytic potential of this virotherapy (Hao et al., 2019). In another study, Raghunath et al. produced a recombinant NDV against PrCa stem/tumor initiating cells that showed oncolytic therapeutic efficacy in mouse models (Raghunath et al., 2017).

In other cancer studies, Cheng et al. engineered an oncolytic HSV-1 to deliver the antitumor protein phosphatase 1 regulatory subunit 15A (MyD116) to breast cancer (BCa) cell lines. This approach demonstrated enhanced virus replication and oncolytic activity in both MCF-7 and MDA-MB-231 cells, highlighting the therapeutic potential of this recombinant (Cheng et al., 2018). In another interesting approach, Lal and colleagues developed a recombinant measles virus (MV) harbouring the pro-apoptotic BNiP3 gene and explored its ability to induce apoptosis in BCa cells *in vitro*. The combination of this virotherapy with Pax or other chemotherapeutic agents was found to further enhance its tumor killing ability, effectively highlighting this triple therapy as a potential anti-BCa strategy (Lal and Rajala, 2018).

Tumor vascular shutdown is a known effect of OV delivery; while some consider this to be an antitumor mechanism, this effect can pose problems such as reduced tumor perfusion and enhanced tumor hypoxia. To overcome this problem, Matuszewska et al. used thrombospondin-1 type-I repeats (3TSR) to normalize the tumor vasculature prior to administration of NDV to mouse models of advanced-stage epithelial ovarian cancer (EOC) (Matuszewska et al., 2019). EOC is a challenging treatment option for clinicians due to its high interpatient and intratumoral heterogeneity. Mice treated with this combination therapy showed a significant reduction in primary tumor mass, confirming that vascular normalization enhances NDV activity. This NDV treatment may be applicable for other cancer types. In other approaches to EOC treatment, Tong et al. assessed the efficacy of a newly identified oncolytic virus, the Maraba virus (MRBV), in heterogeneous *in vitro* tumor models (Tong et al., 2017). Different levels of oncolytic activity were observed mainly due to the variable permissiveness of EOC cells to MRBV. The study identified the LDLR as a mediator of MRBV infection, which may be important when considering the susceptibility of EOC cells to this virotherapy.

Colorectal carcinoma (CRC) remains a major cause of cancer-related mortality for which liver metastasis is the most prominent cause of death. To date, no effective therapeutic approach for CRC liver metastasis has been developed. To identify new treatment possibilities, Zhang et al. evaluated the effects of oncolytic herpes simplex virus type 2 (oHSV2) (Zhang et al., 2019). *In vitro,* the virus inhibited the growth of CT-26 cells and liver metastasis was reduced in xenograft tumor mouse models. Thus, oHSV2 is a promising therapeutic strategy for the inhibition of CRC cell metastasis to the liver. In clinical CRC studies, Tilgase et al. reported the case of a stage IV CRC patient who had received bevacizumab, FOLFOX-4, surgery, and Rigvir (Tilgase et al., 2018a). Patient outcomes included pathological remission for this advanced cancer, demonstrating the need for larger scale studies to confirm clinical efficacy.

Of the various forms of liver cancer, hepatocellular carcinoma (HCC) is the most common. When diagnosed early, HCC can be treated *via* surgical resection, while other cases of localized, small HCC tumors can be treated *via* percutaneous ablation (Forner et al., 2012). However, HCC is unresectable and/or chemoresistant for many, making the development of other therapeutic strategies essential. Pexastimogene devacirepvec (Pexa-Vec) is an oncolytic virus derived from the vaccina virus and has shown considerable promise for the treatment of HCC, specifically unresectable HCC. In a phase II clinical trial by Heo et al., treatment of advanced HCC patients with Pexa-Vec was found to be well-tolerated and improved overall survival (Heo et al., 2013). However, in a more recent clinical trial by Moehler et al., Pexa-Vec was administered to HCC patients who had not been responsive to treatment with the tyrosine kinase inhibitor sorafenib. This clinical trial found that while Pexa-Vec treatment was well-tolerated and produced a T-cell response, overall survival did not improve (Moehler et al., 2019). Taken together, these clinical trials signify the potential of Pexa-Vac in the treatment of some forms of advanced HCC. The promise of Pexa-Vec for HCC treatment has led to phase III clinical trials (Abou-Alfa et al., 2016).

3. Conclusions and future perspectives

The identification of tumor-selective virus-mediated cell death has led to the emergence of oncolytic viruses as an alternative therapeutic approach for cancer treatments. Many studies now demonstrate the tumor killing ability of an array of human and animal virus infections. To date, the range of oncolytic viruses is large and variable, including transient single stranded RNA viruses such as IAV and NDV, to larger more persistent DNA viruses including TANV. While the replication cycles of these viruses drastically differ, their common functionality in cancer treatment lies in: (1) their ability to selectively induce apoptosis in cancer cells; (2) their ability to boost immune defences against tumor tissue; and (3) their synergistic anticancer activity with known chemotherapeutic agents. These effects have been highlighted in the recent *in vitro* and *in vivo* animal studies highlighted in this review. However, it is now clear that the transition in a clinical human setting requires significant improvement. From a safety perspective, the potential side effects caused by the injection of live viruses and the reversion of non-disease causing virus strains to a more pathogenic phenotype remain an issue. In addition, direct tumor targeting is not always achievable due to harsh tumor microenvironments. This review has highlighted the continuing discovery of oncolytic viruses and their cytotoxic tumor killing potential. Translation of these findings to human disease represents the next challenge to oncolytic virus anticancer therapy.

Declaration of Competing Interest

None.

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