

Oncolytic Virotherapy in Solid Tumors

Subjects: **Immunology**

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Oncolytic virotherapy (OVT) is a promising approach in cancer immunotherapy. Oncolytic viruses (OVs) could be applied in cancer immunotherapy without in-depth knowledge of tumor antigens.

oncolytic virus

tumor microenvironment

antitumor immune response

delivery

genetic modification

1. Introduction

The first hints of the possible anticancer effects of viruses occurred during the early 20th century, with evidence of tumor regression in patients with simultaneous viral infections [1]. Such reports persisted until the 1950s, when the primary clinical studies on the tumor-killing ability of viruses that form the cornerstone of today's achievements were carried-out [2]. Since then, various preclinical and clinical studies have attempted to optimize the viruses for increasing specificity, efficiency, and reducing adverse events (AEs), which led to the introduction of oncolytic virotherapy (OVT) as emerging immunotherapy of cancers [3]. Oncolytic virus (OVs) or cancer-killing viruses are defined as natural or genetically modified viruses that are able to selectively proliferate in tumor cells without damaging normal cells [4]. This natural tropism of some viruses to tumors is due to an increase in some receptors (such as CD54) on the surfaces of tumor cells or defects of tumor cells to induce innate immunity against viruses [5]. So far, various DNA and RNA OVs have been used to treat cancer [6]. The majority of DNA viruses are double-stranded, while RNA viruses are predominantly single-stranded. The advantages of double-stranded DNA viruses are their large genomes which enable them to carry large eukaryotic transgenes and high fidelity DNA polymerase, maintaining the virus genome integrity during replication [7]. Regarding their relatively small size, RNA viruses cannot encode large transgenes. However, they are better candidates in the delivery system due to less induction of immune responses [8]. Several RNA viruses and DNA viruses, including reovirus (RV), Seneca Valley virus (SVV), poliovirus (PoV), parvovirus (PV), vaccinia virus (VACV), and herpes simplex virus (HSV) have the ability to cross the blood-brain barrier (BBB) enabling their use in brain tumors [9][10][11][12][13][14]. OVT started with wild-type viruses such as Newcastle disease virus (NDV), myxoma virus (MYXV), SVV, PV, coxsackievirus (CV), and RV [3]. However, genetic modification was a revolutionary achievement in the OVT providing greater specificity and efficacy against tumors with higher safety for healthy cells [15]. Genetically modified OVs (GMOVs) mainly include PoV, measles virus (MeV), adenovirus (AdV), VACV, HSV, and vesicular stomatitis virus (VSV) [3]. The first GMOV was HSV-1, introduced in 1991 [16]. So far, three OV-based drugs have been approved for cancer treatment, the first of which was an unmodified ECHO-7 virus called Rigavirus which was approved in 2004 in Latvia under the brand name Rigvir for melanoma [17]. However, the approval was withdrawn in 2019 due to its low efficacy. The two

other approved OV is GM-OV include Oncorine (H101 adenovirus), which obtained approval for head and neck cancer in China in 2005 [3], and T-VEC or Imlygic (HSV-1), which was approved in 2015 in the United States and Europe for non-surgical melanoma [18]. The efficacy of OV on many cancers, such as melanoma, glioblastoma, triple-negative breast cancer (TNBC), head and neck cancers, and colorectal cancers has been elucidated [19][20][21][22][23], and a large number of clinical trials are currently evaluating the wild-type and GM-OVs efficiency and safety in various cancers which are listed in Table 1. Along with the therapeutic approaches, GM-OVs expressing reporter genes can be applied in the diagnosis of various cancers by positron emission tomography or single-photon emission computed tomography [24].

Table 1. Oncolytic viruses that reached the clinical phase.

Oncolytic Virus	Modification	Combination Therapy	Cancer Type (Clinical Trial Phase)	Ref.
HSV-1	Virulence gene ICP34.5 and ICP47 are deleted and human GM-CSF gene is inserted	ICIs (anti-PD1, anti-CTLA4)	Melanoma (I, II), Sarcoma (I, II)	[25] [26] [27]
		-	Breast cancer (I), Head and neck cancer (I, I/II), Gastrointestinal cancers (I), Melanoma (I, II, III)	[28] [29] [30] [31] [32]
	Virulence gene ICP34.5 is deleted	-	Oral SCC (I), Pediatric extracranial cancers (I)	[33] [34]
		Chemotherapy	Chemo-resistant metastatic colon cancer (I, I/II)	[35] [36]
	Virulence gene ICP34.5 is deleted and ICP6 gene is inactivated	Radiotherapy	Glioblastoma (I)	[37]
	Naturally mutated	-	Pancreatic cancer (I)	[38]
NDV	Autologous tumor lysate and IL-2 is added	-	Stage III of Melanoma (I)	[39]
	Naturally attenuated	-	Advanced solid tumors (I)	[40]
	One-cycle replicating cytopathogenic NDV	-	Glioblastoma (I/II)	[41]
CVA21	-	ICIs (anti-PD1)	NSCLC (Ib), Bladder cancer (Ib)	[42]
		-	Bladder cancer (II), Advanced melanoma (II)	[43] [44]

Oncolytic Virus	Modification	Combination Therapy	Cancer Type (Clinical Trial Phase)	Ref.
RV	-	-	Advanced solid tumors (I), Recurrent glioma (I), Extracranial solid tumors (I), Melanoma (II), Pancreatic adenocarcinoma (II)	[45] [46] [47] [48] [49]
		Chemotherapy	Advanced solid tumors (I), Ovarian cancer (IIb), Peritoneal cancer (IIb), Melanoma (II), Metastatic breast cancer (II), Advanced head and neck cancer (I/II) Pancreatic adenocarcinoma (II)	[50] [51] [52] [53] [54]
		Radiotherapy	Advanced solid tumors (I)	[55]
PoV	Recombinant oral PoV Sabin-1: the internal ribosome entry site (IRES) is replaced with the IRES from human rhinovirus-2: nonpathogenic	-	Recurrent glioblastoma (I)	[56]
AdV	AdV3 fiber knob is inserted into the backbone of AdV5, A 24-base pair in the E1 gene is deleted: CRAd GM-CSF gene is inserted	-	Ovarian Cancer (I), Gynecologic malignancies (I), Advanced solid tumors (I)	[57] [58] [59]
		Chemotherapy	Chemo-resistant advanced solid tumors (I)	[57]
	RGD motif is inserted into the AdV5 fiber knob: Integrin targeted instead of CAR dependence GM-CSF gene is inserted	-	Chemo-resistant advanced solid tumors (I)	[60]
	Prostate-specific antigen (PSA)-selective	Radiotherapy	Metastatic prostate cancer (I)	[61]
	Conditionally replicating GM-CSF expressing AdV	-	Bladder Cancer (I, II), Head and neck cancers (I)	[62] [63]
	Human telomerase reverse transcriptase (hTERT) is inserted: tumor selective replication	-	Advanced solid tumors (I)	[64]
	E1B-deleted AdV: selective replication in P53-deficient cells	Chemotherapy	Advanced solid tumors (I), Malignant glioma (I), Recurrent head and neck cancer (I, II), Gastrointestinal cancers	[65] [66]

Oncolytic Virus	Modification	Combination Therapy	Cancer Type (Clinical Trial Phase)	Ref.
			(II), Colorectal cancer (II), Advanced sarcoma (I/II),	[67] [68]
	Chimeric AdV: Ad11p/Ad3, AdV5- cytosine deaminase/HSV-1 thymidine kinase: suicide gene for safety	-	RCC (I), NSCLC (I), Colorectal cancer (I), Urothelial cancer (I), Prostate cancer (I, II), Glioma (II)	[69] [70] [71] [72]
VACV	GM-CSF gene is inserted Thymidine kinase gene is deleted	Chemotherapy	Metastatic melanoma (I), HCC (I, II), Colorectal cancer (I), Ewing sarcoma (I), neuroblastoma (I),	[73] [74] [75] [76]
	FCU1 transgene is inserted: metabolize 5-FC to 5-FU-monophosphate	Chemotherapy	Chemo-resistant liver tumors (I)	[77]
	Thymidine kinase gene and hemagglutinin gene and F14.5 gene are deleted Luciferase gene, beta-galactosidase, and beta-glucuronidase are inserted	Chemotherapy and radiotherapy	Head and neck cancer (I), Colorectal cancer (I) Advanced solid tumors (I)	[78] [79] [80]
MeV	Genetically modified to express carcinoembryonic antigen	-	Ovarian cancer (I)	[81]
SVV	-	-	Neuroblastoma (I), rhabdomyosarcoma (I), Neuroendocrine malignancies (I)	[82] [83]
Poxvirus	Genetically modified expressing costimulatory and adhesion molecules such as B7-1, LFA-3, ICAM-1	-	Colorectal cancer (I), Melanoma (I)	[84]
PV	-	-	Glioblastoma (I/II)	[85]

OVs can kill the tumor cells in the following main ways: 1. OVs infect and replicate specifically in tumor cells leading to direct lysis of tumor cells. Malignant cells have defects in antiviral responses allowing OVs to replicate and lyse malignant cells [7]; 2. OVs can induce different types of immunogenic cell death (ICD), including necrosis, necroptosis, immunologic apoptosis, pyroptosis, and autophagy. Tumor cell death or lysis causes the release of tumor-associated antigens (TAA) and neoantigens (TAN) and damage-associated molecular patterns (DAMPs), which increase inflammation and improve the efficacy of immunotherapy [25,26]; 3. OVs, especially GMOVs, can enhance tumor antigen presentation and prime the immune response in the tumor microenvironment (TME) by induction of antiviral responses, inflammation, cytokine production, and expression of costimulatory molecules [86]

[87]; 4. The infection of vascular endothelial cells (vECs) by OV destroys tumor vasculature, resulting in tumor necrosis and the infiltration of immune cells into the TME [88].

Accordingly, a considerable part of OVT effects on tumors is achieved by changing the TME from an immunosuppressive to the immunostimulatory microenvironment and affecting the tumor vasculature and matrix. Moreover, the success of OVT in solid tumors largely depends on the OV access to the tumor.

2. Oncolytic Virus Effects on TME

The long-term effects of immunotherapy in solid tumors are mostly unsatisfactory, partly due to the immunosuppressive condition of TME and low infiltration of immune cells. TME consists of tumor cells, tumor-associated fibroblasts (TAF), vEC, mesenchymal cells, myeloid-derived suppressor cells (MDSCs), and tumor-infiltrating leukocytes (TILs), such as T cells, B cells, dendritic cells (DCs), natural killer (NK) cells, macrophages, and neutrophils [89]. The presence of exhausted cytotoxic T lymphocytes (CTLs), helper T-cells (THs), and NK cells, as well as a large number of regulatory T-cells (Tregs), tolerogenic DCs, MDSC, and M2-macrophages, induce immunosuppressive milieu in the TME through inhibitory ligands and secretion of inhibitory cytokines such as interleukin (IL)-10, tumor growth factor (TGF)- β , IL-35, and IL-27 [90]. OVs can change the paradigm in the TME and convert cold tumors to hot ones by various mechanisms.

2.1. OV-Mediated Lysis of Tumor

Direct oncolysis activity of OVs is the first stimulus of the immune response in the TME [91]. Overexpression of surface receptors such as CD46, CD54, CD155, CD55, and integrins enhances OVs' preferable entry to tumor cells [92][93][94][95][96]. In normal cells, viral components known as pathogen-associated molecular patterns (PAMPs) are sensed by pattern recognition receptors (PRRs) and induce the production of interferon (IFN)-I through the Janus kinase signal transducer and activator of transcription (JAK-STAT) and Nuclear Factor (NF)- κ B signaling pathways. IFN-I activates the protein kinase RNA-activated (PKR) signaling pathway leading to protein synthesis blockade and viral clearance [97]. Tumor cells have defects in antiviral pathways such as IFN-I, PKR, and JAK-STAT, resulting in the survival and proliferation of OVs, specifically in tumor cells [98][99][100]. Lysis of OV-infected cells releases a very diverse TAAs that prime immune cells to induce a local and systemic vaccination against the released TAAs [91]. While many cancer immunotherapies depend on identifying and targeting TAAs (one or several limited TAAs), OVT can vaccinate patients against the entire TAA and TAN treasure of cancer through a phenomenon called antigen/epitope spreading. Hence, OVT could be considered a kind of personalized immunotherapy. Interestingly enough, recent studies have reported the increase of TAA- and TAN-specific T cells in the blood of patients with melanoma and ovarian cancer treated with OVs, suggesting that the in situ OV injection might enhance the systemic antitumor response [101][102][103]. This finding raises hopes for the anti-metastatic effects of OVT. TANs are assumed to be derived from high mutational burden of tumor cells [104][105]. These immunogenic TANs are capable of eliciting tumor-specific immune responses and serve as ideal targets in immunotherapy [104][105][106]. However, TAN-specific T cells are not activated enough in cancer patients due to the poor presentation of TANs, lack of costimulatory signals, and abundance of inhibitory immune checkpoints in the

TME [106]. OV, especially armed OV, have been shown to activate the TANS-specific T cells by increasing the access of APCs to the TANS (epitope spreading), enhancing the TANS processing and presentation by APCs, and providing costimulatory signals [106][107][108]. Accordingly, Wang et al. demonstrated that VACV armed with PD-L1 inhibitor and GM-CSF enhanced TANS presentation and activated systemic T cell responses against dominant and subdominant (cryptic) neoantigens [106], so OVT could potentiate the antitumor immune responses by activating the TANS-specific T cells.

2.2. Induction of Immunologic Cell Death

Apart from the direct lysis of cancer cells, OV can induce various ICDs in virus-infected cells through induction of endoplasmic reticulum (ER) stress [109]. Infection of tumor cells with AdV, CV-B3, MeV, VACV, HSV, and H1-PV has been shown to induce ICD and autophagy in cancer cells [110][111]. ICD is characterized by the expression and release of DAMPs such as ATP, uric acid, heat shock proteins, ecto-calreticulin, and HMGB1, as well as extracellular proinflammatory cytokines [112]. Extracellular ATP acts as a danger signal which attracts and activates DCs [113]. HMGB1 and calreticulin can activate DCs via toll-like receptor (TLR)-4 signaling [114]. In addition, calreticulin neutralizes CD47 receptors on the tumor cell surface, and thereby, increases the tumor cell engulfment by macrophages [115]. OV-mediated ICD, along with other ICD-inducing methods such as chemotherapy and radiotherapy, break immune tolerance against the tumor and increase lymphocyte and neutrophil infiltration, leading to antitumor response and more survival in preclinical models [110].

2.3. Stimulation of Antitumor Immune Response

Besides the release of DAMPs, cancer cell death also causes the release of viral PAMPs in the TME. These PAMPs mainly include DNA, ssRNA, dsRNA, proteins, and capsid contents that activate innate immune cells through stimulating PRRs such as retinoic acid-inducible gene (RIG)-1, cyclic GMP-AMP synthase (cGAS), and stimulator of interferon genes (STING) [112]. DCs, as a bridge between the innate and adaptive immune systems, play a critical role in generating the antitumor response. DCs elicit a specific response against TAA-expressing tumor cells by engulfing OV-infected cells and cross-presentation of TAAs to CD8+ T and CD4+ T cells [116]. On the other hand, the OV-derived PAMPs cause maturation of myeloid and plasmacytoid DCs, leading to the production of proinflammatory cytokines such as IFN- α , IFN- γ , IL-12, IL-1 β , IL-6, IL-8, and tumor necrosis factor (TNF)- α [89][117][118]. These functional DCs, mainly CD103+ and BATF3+, prime CD8+ T cells against tumors [119]. Innate immune signaling, such as the cGAS-STING pathway, plays a pivotal role in the recruitment of lymphocytes to the TME through the expression of CXCL9 and CXCL10 [120]. Parallel to DCs, innate lymphoid cells (ILCs) also respond to the released PAMPs leading to higher inflammation and antitumor responses [18]. As an example, arenavirus-infected melanoma cells produce a high level of CCL5, leading to recruitment of NK cells and melanoma regression [121]. Interestingly, in situ antitumor responses following OVT are mainly mediated by IFN-I, whereas OVT-mediated systemic antitumor responses appear to be mediated by IFN-II excreted from TILs [122]. In general, the innate immune response to OV increases lymphocyte infiltration, antigen presentation, and activation of the antitumor adaptive immune response through an IFN-mediated mechanism [18]. T cell activation requires at least three consecutive signals (peptide-MHC, CD28-B7, and stimulatory cytokines), all of which are defected in

TME to escape adaptive immune responses. OV, as potent immunogens, induce all three signals needed to activate T cells [18]. OVT increases the expression of B7-1/2 and CD40 on the surface of DCs and induces the expression of MHC-peptide on the surface of tumor cells leading to optimal activation of T cells [123]. Conversion of the TME phenotype from immunologically inert to immunologically active status can augment the effectiveness of the immunotherapeutic modalities.

2.4. Effect of OV on Tumor Vasculature

Some OVs, such as HSVs and VACVs, can target tumor stromal cells, such as TAFs, vECs, and pericytes, thereby destroy the tumor's complex structure [86]. TGF- β secreted by tumor cells makes TAFs susceptible to OV infection [124]. OVs also reduce the fibrosis in the TME. VSV has been shown to infect hepatic stellate cells (HSCs), leading to tumor fibrosis reduction [125]. OVs affect the tumors vasculature by replicating in the tumor vECs. Vascular endothelial growth factor (VEGF) secreted from tumor vECs suppresses the antiviral response and allows the replication of OVs in endothelial cells through ERK1/2 and STAT3 pathways [126]. Following infection and replication, the OVs reduce VEGF production from the infected cell resulting in angiogenesis prevention in the tumor. OVs' antiangiogenic properties further limit tumor growth by decreasing the oxygen and nutrition supplies [6]. VACV is shown to replicate in the tumor vEC and cause vascular destruction and ischemia [88]. Neutrophil infiltration into the TME seems essential for OVT-mediated ischemia through the induction of thrombosis in small tumor vessels [88]. It has been shown that the administration of JX-594 in hepatocellular carcinoma destroyed tumor vasculature without affecting patients' normal vessels [89]. Thus, targeting of stromal cells by OVs increases the infiltration of immune cells into the TME, and converts immuno-deserted or immune-excluded tumors (with low TILs) into immune-infiltrated tumors [18]. OVT-mediated changes in the TME, including lymphocyte infiltration into the tumor, enhancement of TAAs/TANs presentation, and heating the TME can improve other immunotherapies such as adoptive cell therapy (ACT) and immune checkpoint inhibitors (ICIs) [89].

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