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Lung cancer and oncolytic virotherapy——enemy's enemy

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ABSTRACT

Lung cancer is one of the malignant tumors that seriously threaten human health worldwide, while the covid-19 virus has become people's nightmare after the coronavirus pandemic. There are too many similarities between cancer cells and viruses, one of the most significant is that both of them are our enemies. The strategy to take the advantage of the virus to beat cancer cells is called Oncolytic virotherapy. When immunotherapy represented by immune checkpoint inhibitors has made remarkable breakthroughs in the clinical practice of lung cancer, the induction of antitumor immunity from immune cells gradually becomes a rapidly developing and promising strategy of cancer therapy. Oncolytic virotherapy is based on the same mechanisms that selectively kill tumor cells and induce systemic anti-tumor immunity, but still has a long way to go before it becomes a standard treatment for lung cancer. This article provides a comprehensive review of the latest progress in oncolytic virotherapy for lung cancer, including the specific mechanism of oncolytic virus therapy and the main types of oncolytic viruses, and the combination of oncolytic virotherapy and existing standard treatments. It aims to provide new insights and ideas on oncolytic virotherapy for lung cancer.

Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality, a small number of patients with advanced lung cancer have achieved unprecedented clinical effects from immunotherapy represented by immune checkpoint inhibitors(ICIs) [1]. Oncolytic virotherapy (OV) is another type of cancer immunotherapy with broad anticancer activity [2]. The concept of using the oncolytic virus to treat cancer has now been demonstrated in several recent clinical trials, and a real therapy for melanoma received FDA approval [3]. A systematic review and meta-analyses evaluate the efficacy and safety of OV in lung cancer and showed that the objective response rate was significantly higher in patients receiving oncolytic adenovirus H101 monotherapy or combination with chemotherapy than in patients only receiving chemotherapy [4]. OV has broad research prospects in the field of lung cancer.

How does OV work in lung cancer?

OV is increasingly important in cancer therapy because they combine direct oncolysis with stimulation of antitumor immunity (Fig. 1). Oncolytic viruses are designed to preferentially infect and replicate in tumors, which not only promotes immunogenic cell death but also increases the number of immune mediators entering the tumor microenvironment that disrupt intratumoral immunosuppression and induce systemic antitumor immunity of the host [5,6]. Enadenotucirev (previously known as ColoAd1), a tumor-selective chimeric adenovirus, was detected in resectable non-small cell lung cancer(NSCLC) to stimulate local high antitumor immune response such as the infiltration of CD8+ T cell [7]. Furthermore, using oncolytic adenovirus or vaccinia virus-infected reprogrammed somatic-derived tumor cell vaccine (VIReST) regimen to vaccinate high-risk populations can prevent tumor progression and initiate long-term anti-tumor immune response monitoring, which can be used in the treatment and prevention of lung cancer [8]. Besides, computers could identify optimal vaccine candidates for subunits of an oncogenic virus that causes lung cancer, and these epitopes have great therapeutic potential as vaccines against lung cancer [9]. More and more breakthroughs have been made in preclinical and clinical trials of OV for lung cancer, as shown in Tables 1 and 2

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Design and delivery of oncolytic viruses

Tumor-associated stroma limits the efficacy of oncolytic viruses by forming barriers that prevent efficient virus penetration and spread, and more critically, their viral therapeutic efficacy is strongly hindered by limited viral spread and negative immune regulation in the tumor microenvironment [27]. One of the limitations of intravascular delivery of oncolytic viruses is that systemic administration will be hindered by antiviral immunity. Some studies have obtained adenoviral vector Ad5-3M by targeting functional sites in the viral capsid. Delivering oncolytic virus to mice with lung cancer not only observed that the virus replicated in tumor cells inhibited tumor growth, but also resisted antiviral immunity [28]. To enhance antitumor activity, Blood Outgrowth Endothelial Cells (BOEC) can be used to deliver the interferon-β-expressing oncolytic vesicular stomatitis virus VSV-IFNβ vector in a preclinical model of NSCLC, with VSV - IFNβ-infected human BOECs showed excellent antitumor activity and mouse survival in immunodeficient A549 xenograft model mice and infected BOECs killed NSCLC cells in vitro and protected VSV-IFNβ from antibodies [29]. Coincidentally, microfluidic encapsulation of oncolytic adenovirus demonstrated excellent in vivo antitumor activity against A549 lung tumor-bearing mice through a combination of inhibiting proliferation, and amplifying oncolysis, and potentially immunomodulating [30]. Additional studies have shown that systemic delivery of oncolytic adenovirus and paclitaxel encapsulated in extracellular vesicle (EV) preparations significantly increased transduction rates and infectious titers in vitro, while effectively inhibiting the growth of human lung cancer in animal xenograft models [31]. At the same time, the virus itself can also be used as a carrier for other treatments. The use of viral vectors and cationic carriers combined with various aerosol delivery technologies can develop new specific carriers for lung cancer treatment [32].

A second major limitation of the therapeutic efficacy of oncolytic viruses is antagonism by limited diffusion within solid tumors. AdUV was isolated by repeated treatment of viral particles of the oncolytic adenovirus wild-type Ad5 dl309 with C-type UV irradiation, which was shown to lyse cancer cells more efficiently [33]. Moreover, the function of oncolytic viruses is dependent on the immune response in the tumor microenvironment, and the combination therapy of interleukin 10 (IL-10) and oncolytic adenovirus Ad-hTERT in the treatment of lung cancer enhanced the antitumor efficacy [34]. Systemic administration of the IL-12-expressing NV1042 virus also performs more effectively in treating metastatic lung tumors than its non-cytokine parent, NV1023 [35]. The use of secreted or membrane-bound IL-23 vaccinia virus induces antitumor effects in a variety of tumor models [36].

Effective immunotherapy requires simultaneous targeting of cancer cells and immunosuppressive stromal cells, and poor tumor targeting of oncolytic adenoviruses after systemic administration is considered the third major limitation of viral therapy for disseminated cancer. To enhance the targeted ability of oncolytic viruses, some research finds that tumor-infiltrating T cells can be more efficiently activated and redirected by oncolytic adenoviruses equipped with bispecific T cell engager (BiTE) antibodies, and arming oncolytic adenoviruses with BiTEs could overcome “targeted limitation” of OV [37]. An engineered oncolytic group B adenovirus encoding with BiTEs could target both tumor cells and immunosuppressive stromal cells. This BiTE binds fibroblast activation protein (FAP) on cancer-associated fibroblasts (CAFs) and CD3ε on T cells, resulting in efficient T cell activation and fibroblast death [38]. As FAP is highly overexpressed in CAFs, oncolytic adenovirus OAd-FBiTE armed with FAP-targeting bispecific T cells can retarget infiltrating lymphocytes to CAFs, enhancing viral spread and T cell-mediated cytotoxicity targeting of tumor stroma [39]. Another oncolytic herpesvirus expressing PD-L1 BiTE, which produces a pro-inflammatory response and eliminates cells that promote tumor progression, also prevents systemic toxicity [40].

Oncolytic virus combined with standard treatment of lung cancer

In a meta-analysis of the efficacy and safety of oncolytic virus combination therapy, combination therapy improved objective response rates in lung cancer patients compared with conventional therapy alone [41]. OV is a particularly attractive option for preventing postoperative local recurrence and distant metastasis, and improving postoperative survival in lung cancer patients, they can directly target residual tumor deposits and beneficially modulate the postoperatively suppressed systemic immune environment [42]. Meanwhile, radiotherapy has shown excellent immunoediting activity in NSCLC, and combining OV with it provides an optimal strategy for lung cancer treatment [43]. The

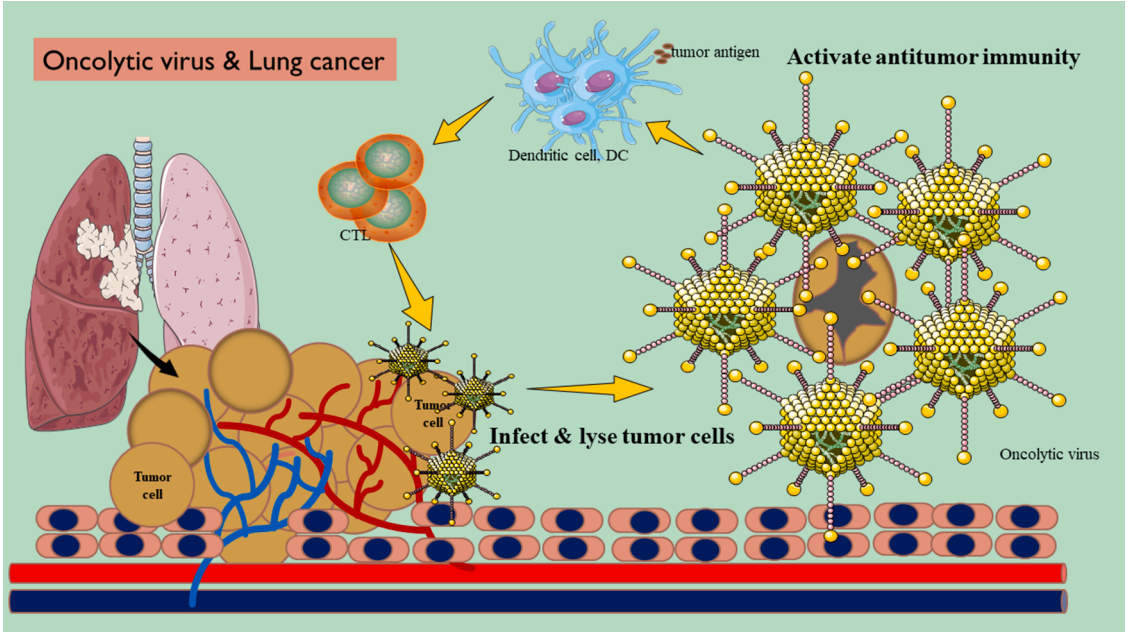

Fig. 1. OV is an important direction for lung cancer immunotherapy as it eliminates cancer cells through direct oncolysis and indirect activation of the body’s antitumor immunity.

Table 1
Preclinical exploration on the specific mechanisms of OV in lung cancer treatment

Oncolytic virus	Mechanism	Ref
Newcastle Disease Virus (NDV)	Selectively kills malignant cells	[10]
	NDV is a potent inducer of immunogenic cell death (ICD).	[11]
rNDV-GFP	rNDV-GFP maintains tumor-selective replication properties and induces tumor cell apoptosis.	[12]
NDV-FMW	NDV-FMW triggers caspase-dependent apoptosis in lung cancer spheroids and promotes autophagic degradation in lung cancer spheroids by inhibiting the AKT/mTOR pathway	[13]
NDV-HUJ	Virus-selective oncolysis is dependent on apoptosis and is associated with higher levels of viral transcription, translation, and progeny virus formation.	[14]
Coxsackievirus B3 (CVB3)	CVB3 is a potent oncolytic virus for KRAS-mutant lung adenocarcinoma-targeted therapy.	[15]
microRNA-modified CVB3 (miR-CVB3)	miR-CVB3 retains the ability to infect and lyse KRAS-mutant lung adenocarcinoma and TP53/RB1-mutant SCLC cells	[16], [17]
EHV-1	Animal virus EHV-1 replicates efficiently in a human adenocarcinoma cell line (A549)	[18]
Oncopox-trail	The TRAIL protein mainly induces apoptosis and inhibits necrosis, and the oncolytic poxviruses carrying the trail gene have better cytotoxicity	[19]
CF33-GFP	Infiltration of tumors by CD8+ T cells	[20]
Bovine Herpesvirus 1 (BoHV-1)	BoHV-1 infection of tumors reduces their protein levels of histone deacetylase (HDAC) by inducing DNA damage	[21]
Low pathogenic oncolytic influenza virus IAV	IAV infection of Raf-BxB mice leads to reversal of immunosuppressed tumor-associated lung macrophage function to an M1-like pro-inflammatory active phenotype	[22]
Measles virus (MV) vaccine strains	MV oncolysis is associated with in vivo activation of caspase-3	[23]
Oncolytic myxoma virus (MYXV)	Tumor-specific viral replication, induction of tumor necrosis, and growth inhibition-associated cytotoxic immune cell infiltration	[24]
Oncolytic adenovirus H101	Very potent cytotoxicity, G2/M phase arrest, and cell lysis and inhibition of tumor growth,	[25]
Recombinant oncolytic adenovirus Ad-apoptin	Ad-apoptin targets AMPK and inhibits glycolysis, migration, and invasion of lung cancer cells through the AMPK/mTOR signaling pathway	[26]

Table 2
Clinical Trials of Lung Cancer-Associated Oncolytic Viruses

Registration Number	Title	Interventions	phase
NCT02053220	Mechanism of Action Trial of ColoAd1 (MOA)	Colo-Ad1	Phase 1
NCT05076760	Study of MEM-288 Oncolytic Virus in Solid Tumors Including Non-Small Cell Lung Cancer (NSCLC)	MEM-288 Intratumoral Injection	Phase 1
NCT02879760	Oncolytic MG1-MAGEA3 With Ad-MAGEA3 Vaccine in Combination With Pembrolizumab for Non-Small Cell Lung Cancer Patients	Ad-MAGEA3 MG1-MAGEA3	Phase 1/ Phase 2
NCT04725331	A Clinical Trial Assessing BT-001 Alone and in Combination With Pembrolizumab in Metastatic or Advanced Solid Tumors	BT-001	Phase 1/ Phase 2
NCT00861627	Phase 2 Study of REOLYSIN® in Combination With Paclitaxel and Carboplatin for Non-Small Cell Lung Cancer With KRAS or EGFR Activation	REOLYSIN®	Phase 2
NCT03004183	SBRT and Oncolytic Virus Therapy Before Pembrolizumab for Metastatic TNBC and NSCLC (STOMP)	ADV/HSV-tk	Phase 2
NCT03740256	Binary Oncolytic Adenovirus in Combination With HER2-Specific Autologous CAR VST, Advanced HER2 Positive Solid Tumors (VISTA)	CAdVEC	Phase 1
NCT05180851	Safety and Efficacy of Recombinant Oncolytic Adenovirus L-IFN Injection in Relapsed/Refractory Solid Tumors Clinical Study (YSCH-01)	Recombinant L-IFN adenovirus injection	Early Phase 1
NCT05205421	A Study of Oncolytic Virus Injection (RT-01) in Patients With Advanced Solid Tumors	Oncolytic Virus Injection (RT-01)	Phase 1
NCT04301011	Study of TBio-6517 Given Alone or in Combination With Pembrolizumab in Solid Tumors (RAPTOR)	TBio-6517;	Phase 1/ Phase 2
NCT00625456	Safety Study of Recombinant Vaccinia Virus to Treat Refractory Solid Tumors	Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (JX-594)	Phase 1
NCT00314925	Safety Study of Seneca Valley Virus in Patients With Solid Tumors With Neuroendocrine Features	Seneca Valley Virus	Phase 1
NCT01721018	Intrapleural Administration of HSV1716 to Treat Patients With Malignant Pleural Mesothelioma. (1716-12)	HSV1716 Intra-pleural delivery	Phase 1/ Phase 2
NCT01503177	Intrapleural Measles Virus Therapy in Patients With Malignant Pleural Mesothelioma	oncolytic measles virus encoding thyroidal sodium iodide symporter	Phase 1

combination of radiation therapy and the oncolytic virus can increase the antitumor effect and selectively kill human NSCLC cells [44].

Even more striking is that the combination of chemotherapeutic drugs and oncolytic viruses showed stronger cytotoxicity and oncolytic effects, as shown in Table 3.

Oncolytic virus combined with lung cancer immunotherapy strategy

By interfering with cancer-mediated immunosuppression, ICIs have been approved as a standard treatment for a variety of malignancies, including NSCLC [53]. However, most patients do not respond well to ICI-based immunotherapy, and OV is one of many promising immunomodulatory therapies that could improve the efficacy of the immune microenvironment by modifying the tumor, promoting T cell infiltration within the tumor, and can improve the response rate of ICIs, thereby improving anti-PD-1 immunotherapy [54,55]. Viruses are well-known immunosensitizers that cause tumor cell lysis and promote immune-mediated tumor cell recognition and destruction [56]. For example, the oncolytic adenovirus Delta-24-RGDOX expressing the immune co-stimulatory factor OX40 ligand (OX40L) combined with tumor-targeted ICIs exhibits excellent tumor-specific lymphocyte activation and tumor-associated antigen specificity proliferation of CD8+ T cells, thereby activating antitumor immunity [57]. Infection with low pathogenicity influenza virus (IAV) combined with ICI resulted in increased levels of M1-polarized alveolar macrophages and increased lung infiltration by cytotoxic T lymphocytes in NSCLC, suggesting that IAV has synergistic antitumor efficacy against ICI-resistant lung cancer and Immunomodulatory efficacy [58]. Another triple therapy combining oVV with PD-1 or TIM-3 blockade was proved to be more effective in refractory lung cancer [59]. Combining oncolytic viruses with tumor-targeted ICIs is a competitive strategy for the treatment of lung cancer.

Another direction is to directly arm oncolytic viruses with ICIs

A novel recombinant oncolytic virus VV, VV-α-TIGIT, encoding a fully monoclonal antibody against T cell immunoglobulin and ITIM domain (TIGIT) significantly increased T cell recruitment and activation in the tumor microenvironment [60]. Another engineered oncolytic vaccinia virus, VV-scFv-TIGIT, encoding a single-chain variable fragment (scFv) targeting T-cell immunoglobulin and ITIM domain, induces

Table 3
Study of oncolytic virus therapy combined with standard chemotherapy for lung cancer

Oncolytic virus	Synergistic antitumor effect	Ref
MYXV	Oncolytic myxoma virus (MYXV) combined with low-dose cisplatin enhances the treatment effect of lung cancer.	[24]
P/V-CPI-5	P/V-CPI-5 infection sensitizes airway cancer cells to DNA damaging agents, and combination with chemotherapeutic agents has enhanced the killing of airway cancer cells	[45]
TG4010	TG4010 in combination with standard chemotherapy in advanced NSCLC is feasible and well-tolerated.	[46]
	TG4010 enhances chemotherapy efficacy in advanced NSCLC	[47]
	TG4010 plus chemotherapy can improve progression-free survival.	[48]
Pelareorep (reolysin)	Reolysin in combination with paclitaxel and carboplatin was well tolerated, and reovirus was beneficial to chemotherapy.	[49]
Oncolytic Adenoviruses (OAds)	Oncolytic adenovirus combined with temozolomide synergistically enhances lung cancer cell death and significantly inhibits the growth	[50]
GLV-1h68	cyclophosphamide and GLV-1h68 have synergistic antitumor effects on PC14PE6-RFP lung adenocarcinoma xenografts	[51]
OBP-301 (Telomelysin)	the combination of OBP-301 and gemcitabine have therapeutic synergism in human lung tumor xenografts	[52]

potent antitumor immunity [61]. Oncolytic viruses expressing antibodies against immune checkpoint domains successfully combine the advantages of OV with an intratumoral expression of ICIs to enhance antitumor efficacy.

Apart from the combination with ICIs, the combination of OV with other therapies has gradually attracted people's attention. The immunosuppressive tumor microenvironment(TME) is a huge obstacle to the success of adoptive cell therapy in solid tumors. Oncolytic immunotherapy with engineered adenovirus destroys the TME by infecting tumor cells as well as the surrounding stroma to improve tumor-directed chimeric antigen receptor (CAR)-T cell function [62]. Another study shows that PM21-NK cells could kill P/V virus-infected lung cancer cells more efficiently [63]. In terms of anti-angiogenic therapy, studies have used a herpes simplex virus 1 mutant (HSV-Endo) expressing endostatin in a mouse model of lung cancer. Tumor burden was significantly reduced in the orthotopic flank model, along with reduced microvessel density [64]. Measles attenuated Edmonston strain (MV-Edm) combined with NF-κB signaling pathway inhibitor pS1145 enhanced its oncolytic effect and promoted apoptosis in human lung cancer cells A549 and H1299 [65]. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-armed oncolytic adenovirus ZD55-TRAIL exhibits enhanced cytotoxicity and induces apoptosis in A549 spheres via the mitochondrial pathway, suggesting that the gene-armed oncolytic adenovirus is a potential therapeutic method for lung cancer [66]. Exploring the combination of standard treatment for lung cancer and OV is of increasing concern.

Conclusion

Until today, it becomes an irrefutable truth that we cannot eliminate all tumor cells as we can't do that to coronavirus, how to live with them is the wisest choice. OV is one of the attractive modern experimental techniques for the treatment of human cancers, showing a remarkable antitumor effect on malignant tumors. But so far, only one OV has been approved by the FDA—T-Vec, a modified form of herpes simplex virus type 1 (HSV-1) [67], Therefore, it deserves our unremitting efforts to continue to develop novel oncolytic viruses, deepen basic research on the specific mechanisms of immune modulation that enhance oncolytic virus replication and improve tumor-killing rates, and develop oncolytic combination therapies that can synergize with other existing standard treatments for lung cancer. More importantly, developing a vaccination system to prevent tumor progression and initiate long-term anti-tumor immune monitoring is of great significance for the treatment and prevention of lung cancer.

Author contribution

Dr. Zhang Li and Dr. Zhang Feiyue do equal contributions to the manuscript and are tied as the co-first author.

Dr. Haifeng Liang is the corresponding author of the manuscript.

Professor Li Gaofeng provided us with important advice and confidence in this revision, and our team unanimously agreed to include him as the second author of the article.

Declaration of Competing Interest

No conflict of interests exists in the submission of this manuscript, and the manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and is not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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