

Oncolytic adenovirus: A tool for reversing the tumor microenvironment and promoting cancer treatment (Review)

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Received November 13, 2020; Accepted February 11, 2021

DOI: 10.3892/or.2021.8000

Abstract. Immunogene therapy can enhance the antitumor immune effect by introducing genes encoding co-stimulation molecules, cytokines, chemokines and tumor-associated antigens into treatment cells or human cells through genetic engineering techniques. Oncolytic viruses can specifically target tumor cells and replicate indefinitely until they kill tumor cells. If combined with immunogene therapy, oncolytic viruses can play a more powerful antitumor role. The high pressure, hypoxia and acidity in the tumor microenvironment (TME) provide suitable conditions for tumor cells to survive. To maximize the potency of oncolytic viruses, various methods are being developed to promote the reversal of the TME, thereby maximizing transmission of replication and immunogenicity. The aim of the present review was to discuss the basic mechanisms underlying the effects of oncolytic adenoviruses on the TME, and suggest how to combine the modification of the adenovirus with the TME to further combat malignant tumors.

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1. Introduction

Solid tumors are a major cause of mortality in humans (1). Due to the advanced proliferative, invasive and migratory abilities of tumor cells, the prognosis for patients with cancer is extremely poor (2). Effective tumor therapy is disrupted immunosuppression of immune cells in the tumor microenvironment (TME) and tumor specificity of stromal cells (3). For example, chemotherapy, while killing tumor cells, stimulates other cells in the TME to release signals that promote tumor growth, ultimately resulting in treatment tolerance (4). Drug development with specific targeting of tumor cells and the TME will be a promising approach to tumor therapy. Thus, several studies have focused on the transformation of oncolytic adenoviruses (5,6), which can specifically target tumor cells and retain the efficacy of the drug at the tumor site. Gene therapy is a novel approach to cancer treatment (7), which aimed to target any aspect of tumor occurrence (8). Thus, in terms of genetic modification, several strategies have been adopted to overcome obstacles and reverse the TME.

2. Oncolytic adenovirus

An adenovirus is a non-enveloped double-stranded DNA virus with a symmetrical icosahedral structure (9). The genome is ~36 kb in length and can encode >40 gene products (10). These gene products are divided into three subtypes based on their transcription start time, including early, middle and late stages (11). Early gene products are predominantly responsible for coding gene regulation, including the E region, while late gene products are predominantly responsible for coding structural proteins, including the L region (12,13). Among adenovirus subtypes, adenovirus serotype 3 (Ad.3) and adenovirus serotype 5 (Ad.5) are the most commonly studied subtypes, and Ad.5 is the most commonly used subtype (14). Following infection, the oncolytic adenovirus initially recognizes specific receptors on the

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Key words: oncolytic adenovirus, tumor microenvironment, gene therapy, immune checkpoints

surface of tumor cells and triggers their internalization (15). Subsequently, it enters tumor cells, viral genomes migrate to the nucleus through microtubules, and early viral proteins in the E1 region immediately begin to be transcribed (16). The protein binds to Rb to release the transcription factor, E2F, which also activates the cell cycle, allowing oncolytic adenovirus-infected cells to enter the S phase (6,17). Concurrently, the E1A protein maintains p53 stability and inhibits tumor growth by relying on the p53 pathway (18). The release of E2F also triggers the coordinated activation of viral genes, which results in the production of new virions, the lysis of infected cells and the spread of viral offspring (19). The oncolytic adenovirus continuously replicates in tumor cells, eventually lysing tumor cells and infecting other tumor cells via the same mechanism of action (20-23). Due to the large loading capacity of the oncolytic adenovirus vector, therapeutic genes are commonly inserted into the adenovirus vector (24,25). Due to the continuous replication and accumulation of adenoviruses in tumor cells, therapeutic genes are expressed and thus spread, playing a synergistic antitumor role (26).

3. TME of solid tumors

The TME is the internal environment for the growth of tumors, which includes tumor cells (27,28), stromal cells (tumor-associated vascular endothelial cells and tumor-associated fibroblasts), immune cells [T lymphocytes and B lymphocytes, tumor-associated macrophages (TAMs), dendritic cells (DCs) and natural killer (NK) cells], the extracellular matrix (ECM) and signaling molecules such as IL-4 and IL-10 (29-31). The ECM includes various proteins, glycoproteins, proteoglycans and other biochemical substances, which regulate vascular endothelial cells and fibroblasts, and promote tumor growth and cell migration (32) (Fig. 1). In the TME, tumor blood vessels are constantly supplying oxygen and nutrients to support tumor growth (28,32-34). When the tumor is exposed to hypoxic conditions locally, tumor blood vessels receive signal stimulation and generate branches from existing blood vessels (35,36). However, the structure of these tumor vessels differs from that of normal vessels, with absence of basement membranes, uneven diameter and size of the tubes, and short circuit of arteries and veins, resulting in tumor interstitial hypertension (37,38). Under hypoxic conditions, tumor cells undergo glycolysis and produce more lactic acid, which lowers the pH of the TME (39). Proton transport channels exist in all parts of tumor tissues, which transfer the metabolized H⁺ out of tumor tissues and maintain the pH in the TME (40-42). However, pH reduction in normal tissues results in necrosis, which is more conducive to tumor metastasis and growth (43). Among the myeloid progenitors cells located in the TME, myeloid-derived suppressor cells (MDSCs), mast cells and most TAMs play key roles in promoting tumor development (44). MDSCs are immunosuppressive precursors of DCs, macrophages and granulocytes (35,45). MDSCs maintain a normal tissue dynamic balance in response to a variety of systemic infections and injuries (33). Several animal models have demonstrated that MDSCs can promote tumor angiogenesis and disrupt the main mechanisms of immune surveillance by interfering with antigen presentation, T-cell activation and NK cell killing of DCs (46,47). It has also been reported that

most cells are recruited into the tumor, where they release factors that promote endothelial cell proliferation to promote tumor angiogenesis (48-50). Increasing evidence suggests that microenvironment-mediated external stimulation plays a key role in tumor cell survival and drug resistance (28,51). The complexity of the TME makes it difficult for the traditional oncolytic virus to reverse the conditions set by the TME while targeting tumor cells (27,52). The traditional oncolytic virus can only inhibit the growth of tumor cells to a certain extent.

Owing to the constant improvement of genetic engineering techniques, it is getting easier to develop oncolytic adenovirus constructs with required properties. Preclinical trials involve wild-type and recombinant oncolytic adenovirus (Table I), aimed to reverse the TME while suppressing tumor cells (6,53) (Fig. 2). Several oncolytic adenoviruses are currently undergoing clinical trials as antitumor agents, and notably some progress has been made in reversing the TME (Table II). An ongoing clinical trial is testing RGD (Delta-24-rgd), a genetically modified oncolytic adenovirus, as an agent against glioma. The first results obtained in the phase I trials indicate that 20% of patients showed durable responses and CD8⁺ T cells infiltrated the tumor in large quantities (54). TILT-123 in preclinical studies altered the cytokine balance in the TME towards Th1 and resulted in a significant increase of the survival rate in severe combined immunodeficiency (SCID) mice with human tumors (55,56). The currently ongoing phase I trial is recruiting patients with solid tumors to evaluate the safety.

4. Adenovirus modification combined with immune cells in the TME

DCs. DCs are derived from the bone marrow and play a key role in inducing and maintaining antitumor immunity (57,58). Infiltration of mature DCs into the tumor can enhance immune activation and increase the recruitment of antitumor immune effector cells and pathways (58,59). However, in the TME, the antigen-presenting function of DCs may be lost or inefficient (60). Tumor cells can inhibit the function of DCs or change the TME by recruiting immunosuppressive DCs (61). CD40 is a member of the tumor necrosis factor receptor family and is expressed in DCs, which is a target for infiltrating T cells (62). CD40L is instantaneously expressed in T cells, which activates the maturation of DCs and triggers the immune response. Adenovirus delivery of CD40L induces DC activation, thereby inducing a Th1 immune response (63). The oncolytic virus restricts CD40L expression in cancer cells, thus decreasing systemic exposure and weakening the systemic immune response (64,65). Currently, there are already two phase I/II clinical trials involving LOAd703 that are recruiting patients. One of the studies is recruiting patients with pancreatic cancer to evaluate whether it supports the current treatment standards for pancreatic cancer and whether it can improve the survival rate of patients. Another study recruited patients with malignant melanoma and monitored their tumor response, immune response, virus shedding and survival rate. One of the major virulence factors of bacteria was *Helicobacter pylori* neutrophil-activating protein (HP-NAP), which is a TLR-2 agonist capable of chemotaxis of neutrophils, and monocytes and stimulates them to produce reactive oxygen species (66,67). HP-NAP also induced

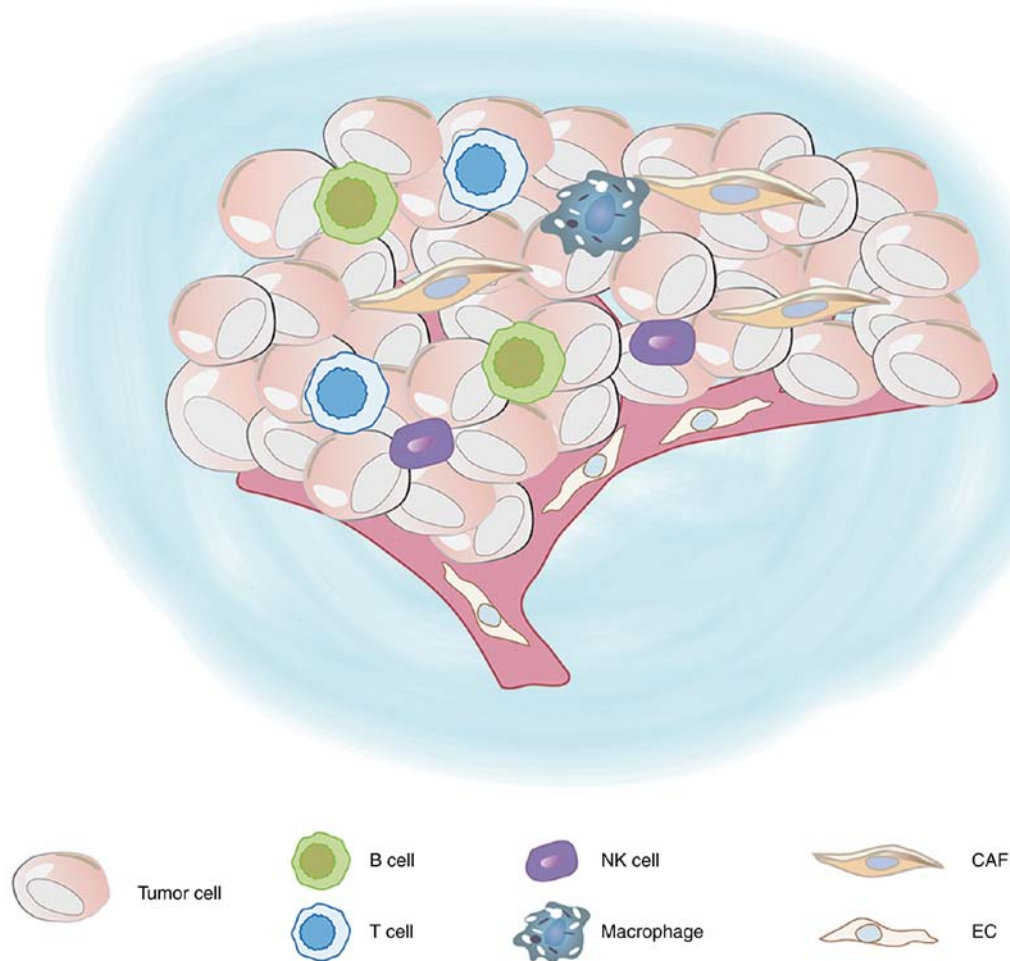


Figure 1. Schematic diagram of the tumor microenvironment.

Th1-polarized immune responses by stimulating the secretion of interleukin (IL)-12 and IL-23 and other pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α and IL-8 (68). Ag-presenting-HP-NAP-activated DCs effectively amplified Ag specific T cells, an important characteristic of mature DCs (69). HP-NAP-activated DCs resulted in Th1 cytokine secretion, with high IL-12 expression, relatively low IL-10 secretion and migrated to CCL19 (69).

Macrophages. TAMs are divided into specific M1-like macrophage subsets and specific M2-like macrophage subsets, and M1-like macrophage subsets are activated by the classical pathway and exert notable antitumor effects (70,71). In the TME, specific M2-like macrophage subsets are the most common, and their cytokines IL-6, TNF, IL-1 and IL-23 promote tumor growth and metastasis and silence T-cell function (72,73). Selective removal of specific M2-like macrophage subsets has become a research hotspot. Granulocyte-macrophage colony-stimulating factor (GM-CSF) can affect macrophages, promote their rapid differentiation to mature macrophages, prolong the life of mature macrophages, and enhance their cellular immune function (74). By inserting GM-CSF into the Ad5 vector, ONCS-102 induced notable antitumor immunity (75). ONCS-102 is currently being assessed in two phase I clinical trials in advanced peritoneal malignancies and malignant pleural mesothelioma. Ad-CD-GMCSF is an adenovirus

carrying cytomegalovirus promoter cytosine deaminase (CD) and GM-CSF (75). Adenovirus vectors expressing CD and GM-CSF are well tolerated in refractory tumors (5). CD47 is a cell surface transmembrane protein present in normal tissues (76). It is highly expressed in malignant tumor cells and binds to signaling regulatory protein- α (SIRP α) expressed on macrophages to inhibit macrophage phagocytosis, resulting in immune escape. SIRP α -FC fusion protein inserted into the oncolytic adenovirus vector blocks the binding of CD47 to macrophages, leading to a large increase in macrophage infiltration in tumor tissues, thus enhancing the antitumor effect (77). MMAD-IL13 loaded with IL13 demonstrated enhanced antitumor effects by inducing apoptosis in the TME *in vivo*, and decreased the percentage of specific M2-like macrophages (78). Scott *et al* (79) constructed a set of bivalent and trivalent T-cell adapters (BiTEs/TriTEs), which can specifically recognize CD3 ϵ on T cells and the folate receptor or CD206 on specific M2-like macrophages. T-cell adapters were used to specifically direct the cytotoxicity of endogenous T cells to M2-like macrophages and deplete M2-like macrophages in tumor tissues. There was a significant increase in specific M1-like macrophage fraction among surviving macrophages, indicating a reversal of macrophage type in the TME (79).

NKs. NK cells have a notable antitumor effect in the initial stages of tumors, which can eliminate tumor cells (30). However, at the

Table I. Partial oncolytic adenovirus trials to reverse the tumor microenvironment.

Oncolytic adenovirus	Gene modification	Target cells in TME	Target tumor cells	(Refs.)
Ad3-hTERT-CMV-hCD40L	CD40L	DCs	A549	(64)
LOAd703	CD40L	DCs	A549	(65)
Ad5 [i/ppt-sNAP]	HP-NAP	DCs	LNCaP	(69)
ONCOS-102	GM-CSF	Macrophages, CD8 ⁺ T cells	AB12	(75)
Ad-CD-GMCSF	GM-CSF	Macrophages, CD8 ⁺ T cells	Colon cancer cell line	(5)
SG635-SF	A signal regulatory protein- α (SIRP α)-IgG1 Fc fusion gene	Macrophages	SK-OV3, HO8910	(77)
MMAD-IL-13	IL-13	Macrophages	Cal-27, SCC-4, Tca8113	(78)
EnAd	BiTEs/TriTEs	Macrophages	DLD-1	(79)
Ad-CCL21-IL21	CCL21	DCs	PC-3M, THP-1, HeLa, Caco-2	(82)
Ad-CCL21-IL21	IL-21	NK cells	PC-3M, THP-1, HeLa, Caco-2	(82)
Ad-E2F/IL15	IL-15	NK cells, CD8 ⁺ T cells	U87MG, BGC823, SW620, HCT116	(84)
ICO15K-FBiTE	FBiTE	CAFs, T cells	HT1080, A549	(53)
AdCEAp-miR126/34a	miR-126, miR-34a	Vascular endothelial cells	Pancreatic adenocarcinoma	(96)
VEGF-CRAAd	VEGF	Vascular endothelial cells	NCI-H28, NCI-H226, NCI-H20, NCI-H2452, MSTO-211H	(97)
SKL002	CTLA4	T cells	HepG2, A549, Lovo, HeLa, HCT116, SW780	(106)
Ad5-PC	PD-1	CD8 ⁺ T cells	HCC-LM3, H22, Hepa1-6, A549, B16-F10, LLC1	(105)

TME, tumor microenvironment; DCs, dendritic cells; NK, natural killer; CAFs, cancer-associated fibroblasts.

advanced tumor stage, NK cells gradually lose their antitumor ability and become dysfunctional (80). IL-21 is involved in NK cell differentiation (81), and the oncolytic adenovirus equipped with IL-21 exerts an obvious inhibitory effect on the proliferation of tumor cells (82). Similarly, NK cells can be activated by IL-15 (83), and oncolytic adenovirus (Ad-E2F/IL15), which expresses IL-15, can lyse tumor cells and coordinate with immune cells to enhance the antitumor response (84).

5. Adenovirus modification combined with stromal cells in the TME

Cancer-associated fibroblasts (CAFs). CAFs are a major component of the tumor stroma, which regulate the TME and influence the behavior of tumor cells, and play crucial roles in the occurrence, development, invasion and metastasis of tumors (85,86). Fibroblasts in the TME secrete growth factors such as hepatocyte growth factor, fibroblast growth factor and CXCL12 (87), which promote the growth and survival of malignant cells, and act as chemokines to induce the migration of other cells into the TME (88,89). Concurrently, CAFs form a barrier in tumors and prevent the effective penetration and transmission of oncolytic virus, thus limiting its efficacy (90,91). By modifying oncolytic adenovirus, the effects of tumor cells and CAFs will be inhibited at the same time (92). Fibroblast activation protein- α (FAP) is highly expressed in CAFs. The FAP single-chain antibody is

linked to an anti-human CD3 single-chain variable region (scFv) and loaded into oncolytic adenovirus. FAP scFv, while specifically recognizing and targeting CAFs, activates T cells and enhances T-cell-mediated cytotoxic effects on tumor-associated fibroblasts, thus weakening the cell barrier caused by CAFs and enhancing oncolytic activity (24,53).

Vascular endothelial cells. Blood vessels play a vital role in the development of tumors, providing nutrition and metastasis channels for tumor cells (93). The phenotype of vascular endothelial cells changes in the TME. Tumor cells secrete vascular endothelial growth factor (VEGF) and other endothelial growth factors to promote the generation of tumor neovascularization (94). Given that the downstream target gene of microRNA (miRNA/miR)-126 is VEGF (95), miR-126 is loaded into the oncolytic adenovirus, namely ADCEAP-miR126/34A, which decreases the generation of tumor blood vessels (96). Concurrently, the VEGF promoter is inserted into the adenovirus vector, targeting the tumor vascular endothelial cells via the same mechanism of action enhancing the oncolysis of adenovirus (97). IL-24 is a tumor suppressor molecule with broad-spectrum antitumor activity (98). It inhibits the growth of tumor cells by inhibiting tumor angiogenesis (99). A previous study has demonstrated that while expressing IL24, CRAAd-IL24 significantly increased the release of virus particles and enhanced their antitumor effect (6).

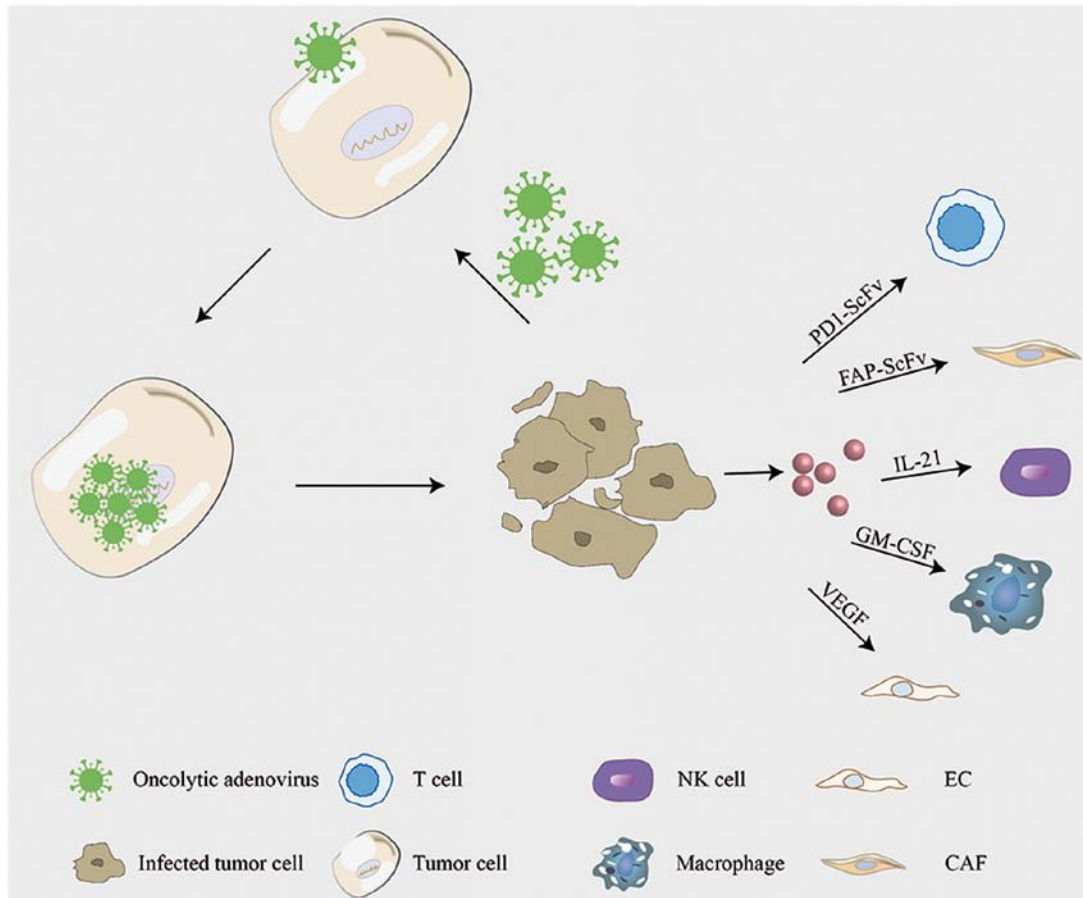


Figure 2. Oncolytic adenovirus mechanism of action. When the oncolytic adenovirus specifically infects tumor cells, it releases new virus particles and transmits them to other tumor cells. It also delivers cytokines, growth factors, fusion proteins and other substances that act on other corresponding cells in the tumor microenvironment.

6. Adenovirus modification combined with immune checkpoints in the TME

Checkpoint molecules are regulatory molecules that play an inhibitory role in the immune system and are critical to maintain tolerance, prevent an autoimmune response and minimize tissue damage by controlling the timing and intensity of the immune response (100,101). The expression of immunological checkpoint molecules on immune cells suppresses the immune cell function as the host fails to produce an effective antitumor immune response. There are numerous receptors on tumorigenic immune escape T cells, including co-stimulatory signal receptors that can stimulate T-cell proliferation, and co-inhibitory signal receptors that can inhibit T-cell proliferation (102). Immune checkpoint molecules are predominantly inhibitory molecules, in which the immune checkpoint on T cells suppresses the immune function of T cells, causing tumor escape (103). However, the clinical benefits of monotherapy with immune checkpoint inhibitors, such as anti-programmed death-1 antibody, are limited to small populations (104). Zhang *et al* (105) designed an adenovirus (Ad5-PC) to express a soluble fusion protein (programmed cell death protein 1/CD137L), which significantly increased the number of T lymphocytes in the TME and effectively improved the survival rate of tumor-bearing mice (105). After loading anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody into the adenovirus vector, tumor cells were infected.

CTLA-4 antibody was significantly expressed in tumor cells and its antitumor activity was significantly enhanced (106). Ad5/3- Δ 24aCTLA4 can express CTLA-4 human intact monoclonal antibody, and in the normal donors and patients with advanced solid tumors in the peripheral blood mononuclear cells that were tested (107). Ad5/3- Δ 24aCTLA4 significantly enhanced the immune response and activated the pro-apoptotic effect of T cells (107).

7. Outlook

Recently, the transformation technology of oncolytic adenoviruses has significantly progressed. However, increasing evidence suggest concerns about the tumor-promoting effect of the TME. Thus, the transformation of oncolytic viruses into TME has become a research hot spot; however, the *in vitro* simulation of the TME does not accurately reflect the human microenvironment. Cytokines and growth factors were added to the cell culture, either co-cultured with tumor cells and other cells, or with three-dimensional scaffoldings to simulate the TME. However, due to the complexity of the TME, it remains difficult to completely simulate the human TME completely *in vitro*. Currently, xenotransplantation of immunodeficient mice is the most commonly used animal experimental method for studying human tumors. Briefly, human tumor cells are inserted into mice; however, this fails

Table II. Clinical trials of oncolytic adenoviruses affecting the tumor microenvironment (Jan. 2021, ClinicalTrials.gov).

Trial number	Oncolytic adenovirus	Study title	Target	Phase
NCT01582516	Delta-24-rgd	Safety Study of Replication-competent Adenovirus (Delta-24-rgd) in Patients With Recurrent Glioblastoma	Recurrent glioblastoma	I, II
NCT04695327	TILT-123	TNF α and IL-2 Coding Oncolytic Adenovirus TILT-123 Monotherapy (TUNIMO)	Solid tumor	I
NCT04217473	TILT-123	TNF α and Interleukin 2 Coding Oncolytic Adenovirus TILT-123 During TIL Treatment of Advanced Melanoma (TUNINTIL)	Advanced melanoma	I
NCT02705196	LOAd703	LOAd703 Oncolytic Virus Therapy for Pancreatic Cancer	Pancreatic cancer	I, II
NCT04123470	LOAd703	A Phase I/II Trial Investigating LOAd703 in Combination With Atezolizumab in Malignant Melanoma	Malignant melanoma	I, II
NCT03514836	ONCOS-102	A Phase I/II, Safety Clinical Trial of DCVAC/PCa and ONCOS-102 in Men With Metastatic Castration-resistant Prostate Cancer	Prostate cancer	I, II
NCT02963831	ONCOS-102	A Phase 1/2 Study to Investigate the Safety, Biologic and Anti-tumor Activity of ONCOS-102 in Combination With Durvalumab in Subjects With Advanced Peritoneal Malignancies	Advanced peritoneal malignancies	I, II
NCT04053283	NG-641	First in Human Study With NG-641, an Oncolytic Transgene Expressing Adenoviral Vector	Metastatic or advanced epithelial tumours	I
NCT03852511	NG-350A	First in Human Study of NG-350A (an Oncolytic Adenoviral Vector Which Expresses an Anti-CD40 Antibody) (FORTITUDE)	Metastatic or advanced epithelial cancer	I
NCT04097002	ORCA-010	First in Man Clinical Study to Evaluate Safety and Tolerability of an Oncolytic Adenovirus in Prostate Cancer Patients.	Prostate cancer	I, II

to fully reflect the human TME. Several factors affect the oncolytic effect of an oncolytic virus. The strong immune response and severe cytokine storm when the virus first enters the host may be fatal. Subsequent challenges arise at later stages during elimination of oncolytic virus by the immune system of the host. It is hypothesized that the selection of oncolytic viruses will be the focus of future research, and it will be individualized, with the intent that the oncolytic virus most suitable for each patient can be selected, based on the characteristics of the tumor cells and the TME.

Acknowledgements

Not applicable.

Funding

This review was funded by Programs for the National Natural Scientific Foundation of China (grant no. 81430035), the Major National Science and Technology Projects-Major New Drug Creation (grant no. 2019ZX09301-132), the Changjiang

Scholars and Innovative Research Team in University (grant no. IRT_15R13), and the Guangxi Science and Technology Base and Talent Special Project (grant no. AD17129003).

Availability of data and materials

Not applicable.

Authors' contributions

XW and YZ conceived the subject of the review. LZ designed the review. XW wrote the manuscript, performed the literature research as well as interpreted the relevant literature, and prepared the figures. LZ analyzed the review critically for important intellectual content. XW and LZ edited and revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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