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Polymeric oncolytic adenovirus for cancer gene therapy

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ABSTRACT

Oncolytic adenovirus (Ad) vectors present a promising modality to treat cancer. Many clinical trials have been done with either naked oncolytic Ad or combination with chemotherapies. However, the systemic injection of oncolytic Ad in clinical applications is restricted due to significant liver toxicity and immunogenicity. To overcome these issues, Ad has been engineered physically or chemically with numerous polymers for shielding the Ad surface, accomplishing extended blood circulation time and reduced immunogenicity as well as hepatotoxicity. In this review, we describe and classify the characteristics of polymer modified oncolytic Ad following each strategy for cancer treatment. Furthermore, this review concludes with the highlights of various polymer-coated Ads and their prospects, and directions for future research.

1. Introduction

Cancer is responsible for about 25% of all deaths in the US, the second most common cause of death in the US, exceeded only by heart disease, and is a major public health problem in many parts of the world. Cancer is one of the most serious diseases and increasing at an alarming rate [1]. Invasive surgical operation and chemotherapy have been used to treat the cancer in the clinic. In spite of the advance in conventional cancer treatment, the overall survival rate of cancer patients is significantly low with unwanted adverse side effects. Thus new strategies are needed to provide better treatment for cancer. Moreover, the Agency for Healthcare research and Quality estimates that the direct medical costs (total of all health care costs) for cancer in the US in 2013 were $91 billion. As a result of these converging influences, we are at a crucial juncture where novel and advanced therapeutic approaches against cancer are solely needed.

Adenoidal-pharyngeal-conjunctival virus, now named as an adenovirus (Ad) was first discovered by Wallace Rowe and his colleagues in 1953. Following cytopathogenic effects of Ad in tissue culture, the Ad was used in a clinical trial for the treatment of cervical cancer in 1956. After the first clinical gene therapy in 1989, the number of gene therapy clinical trials using an Ad vector worldwide has reached 496 in 2015 — ranking the first place (22.5% of all cases including viral & non-viral vectors) (http://www.wiley.co.uk/genmed/clinical/). Ad vector itself has many outstanding advantages, like an efficient nuclear entry mechanism and high gene transduction efficiency. However, the efficacy and duration of transgene expression with replication-incompetent Ad are limited. Here, cancer-specific replicating Ad (oncolytic Ad) is emerging as a promising new modality for cancer treatment. Oncolytic Ad has the improved efficacy over replication-incompetent Ad and the enhanced expression of therapeutic gene with diminished potential side effects caused by undesired expression of therapeutic gene in normal tissue (Fig. 1).

During two decades, the oncolytic virus has been evolved to generate advanced therapeutic efficacy (Table 1). Most clinical and preclinical studies have focused on oncolytic virus modifications, providing improvements on tumor transduction, tumor targeting, cancer-specific replication, intratumoral dissemination, and modulation of antiviral and antitumor immune responses as well as arming with transgenes [2]. Especially, armed oncolytic virus and hybrid engineering of oncolytic virus promise an emerging approach in cancer treatment. The virotherapy using oncolytic Ad has been widely used in clinical applications due to the high titers that can be achieved, ability to insert larger size of therapeutic genes, and high transduction efficiency in dividing and non-dividing cells. Importantly, when oncolytic Ad replicates, they do not integrate their genome into host, therefore oncolytic Ad does not induce mutagenesis related with oncogene. These unique features give oncolytic Ad potency as gene carrier and increase safety than other oncolytic viruses such as oncolytic retro-, lenti-, and adeno-associated virus [3,4].

For the therapy in cancer patients, no oncolytic virus is currently licensed by the US Food and Drug Administration and the European

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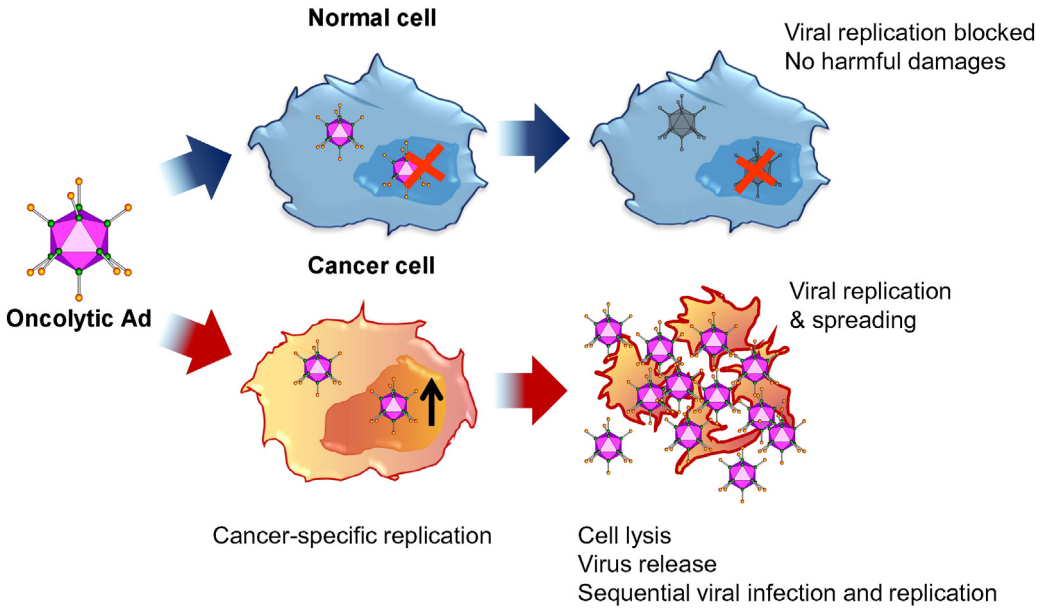

Fig. 1. Schematic diagram of the cancer cell-specific killing of oncolytic adenovirus (Ad). Oncolytic Ad can replicate and destroy cancer cells by cancer-specific oncolysis while sparing normal cells.

Medicines Agency yet (http://www.fda.gov/Drugs, http://ema.europa.eu). In the preclinical and clinical level, Ad is the most extensively investigated oncolytic virus [39–41]. Especially, the Chinese State Food and Drug Administration approved a recombinant Ad encoding human tumor suppressor gene p53 (rAd-p53, Gendicine) in 2003 and a recombinant oncolytic Ad (H101, Oncorine®) for combination treatment with chemotherapy in refractory head and neck cancer patients.

Here, we summarized the recent clinical trials of oncolytic Ad therapy (Table 2). Most phase I clinical trials of oncolytic Ad demonstrated mild, manageable, and transient vector-related toxicities, which is crucial factor for moving on to next phase clinical trials. Moreover, advanced clinical trials of oncolytic Ad have proved clinical responses in tumors that are resistant to chemotherapy or radiotherapy and have distant metastasis [42]. Early clinical trial of oncolytic Ad was evaluated with the administration of oncolytic Ad-alone. In localized prostate cancer phase I clinical trials, CG7870, expressing E1A under control of the rat probasin promoter and E1B under control of the prostate-specific antigen (PSA) promoter–enhancer, and the E3 region genes observed no partial or complete PSA responses [43,44]. Also the intravesical instillation of CG0070 is being studied as a standalone therapy in bladder cancer patients who failed BCG-based immunotherapy [45]. Recently, combined oncolytic Ad and chemotherapy could convey stronger anti-tumor effects by providing synergistic mode of actions by oncolysis and chemotherapeutic mechanism, potentially attenuating cancer cell resistance to virotherapy or chemotherapy [37,38]. GM-CSF coding capsid chimeric Ad, CGTG-102 moves on to the phase I for advanced solid tumors, alone or in combination with cyclophosphamide chemotherapy [40,46]. In a phase III clinical trial, Ad5/3-D24-GMCSF showed efficacy in melanoma patients refractory to other forms of therapy [47]. Ad-OC-TK/VAL is the first *in vivo* Ad gene therapy used to treat bone metastasis in prostate cancer patients, suggesting potential benefit of combined treatment with docetaxel-based chemotherapy for hormone-refractory metastatic prostate cancer [48,49]. About 50% of all human cancers and over 90% of patients with small cell lung cancer have altered p53 tumor suppressor gene function. Also, dendritic cells are the most potent antigen presenting cells, then most effective in inducing a primary anti-p53 cytotoxic T lymphocytes response. 78.6% of Ad.p53-DC (INGN-225) patients showed positive immune response, followed by better clinical response to second-line chemotherapy and a trend towards improved survival [50]. Ad with 2 cytotoxic gene systems of cytosine deaminase (CD)/5-fluorocytosine (5-FC) and herpes simplex virus thymidine kinase (HSV-1 TK)/valganciclovir (vGCV) has treated the prostate cancer patients, which makes malignant cells sensitive to specific pharmacological agents (cytotoxic gene therapy) and improves the effectiveness of radiation therapy by radiosensitization [51]. This multimodal biological approach to improve the effectiveness of radiation therapy reported a clinically meaningful reduction in positive biopsy results at 2 years in men with intermediate-risk prostate cancer [51]. DNX-2401 (Ad-Δ24) and ICOVIR® (Ad-Δ24-RGD), engineered to replicate only in cells with altered retinoblastoma 1 signaling pathway are being studied in patients with advanced melanoma or other solid tumors as a standalone therapy as well as in patients with recurrent glioblastoma, combined with interferon Gamma or Temozolomide [19,45,52]. VCN-01, Ad expressing human sperm adhesion molecule 1 (SPAM1, PH20 hyaluronidase) is being tested in patients with advanced pancreatic cancer or other solid tumors [45]. See Tables 3 and 4.

Table 1
Advances in oncolytic virotherapy.

Conventional genetic engineering	
Transduction	
Modification of surface proteins with tumor specific markers	[5]
Modification of viral envelope proteins	[6]
Transcription; tumor-specific promoter/enhancer	[7–10]
Engineering of Armed OV	
Integration with sequences coding for enzyme, protein, short-hairpin RNAs	[11]
tumor suppressor or suicide genes	[12,13]
Co-stimulatory molecule; CD ligand	[14]
ECM-degrading genes	[15–18]
Immunostimulatory cytokines; interleukin, GM-CSF	[19–21]
Inhibitor of angiogenesis	[22,23]
Increase susceptibility of infected cells to chemo and radiotherapy	[24]
miRNA, siRNA	[25,26]
Hybrid engineering	
Tumor-associated antigen (Oncolytic vaccine)	[27,28]
Cell vehicle	
Tumor-infiltrating cells; macrophages, myeloid-derived suppressor cells	[29,30]
MSC	[31,32]
Cytokine gene modified cell	[33]
T cell based	[34]
Co-administration of chemotherapeutics	[35–38]

ECM; Extracellular matrix, GM-CSF; Granulocyte macrophage colony-stimulating factor, MSC; Mesenchymal stem cell.

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