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Recent Advances of Oncolytic Virus in Esophageal Cancer Therapy

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Abstract: *Esophageal cancer (EC) is a common digestive tract tumor with high invasiveness and poor prognosis. According to global statistics in 2020, EC ranks 7th in incidence and 6th in mortality. Traditional treatment options include surgery, radiotherapy, and chemotherapy, but often produce adverse reactions, drug resistance, and poor prognosis. In recent years, tumor immunology has rapidly developed, and biological immune therapy has become a new treatment method. Oncolytic viruses (OV) have shown good therapeutic effects in the treatment of EC in recent years. Recombinant adenoviruses OBP-301 (telomelysin) and H101 are widely studied OVs in EC treatment. With the rapid development of tumor immunotherapy, OV therapy has become a research hotspot in the treatment of EC. This review article summarizes the mechanism of action of OVs and their research progress in the treatment of EC.*

Keywords: *Esophageal cancer; Immunotherapy; Oncolytic virus; Review*

1. Introduction

Esophageal cancer (EC) is a common digestive tract tumor with high invasiveness and poor prognosis. According to global statistics in 2020, the incidence and mortality rates of esophageal cancer ranked 7th and 6th, respectively [1]. The incidence and mortality rates of esophageal cancer have remained high over the past 35 years [2]. Currently, the traditional treatment options for esophageal cancer include surgical treatment, radiotherapy, and chemotherapy. For early-stage esophageal cancer, surgical resection or ablation surgery can be used for treatment. However, since early symptoms of esophageal cancer are often not obvious, patients may miss the best time for surgical treatment when they seek medical attention. Therefore, traditional comprehensive treatments such as radiotherapy and chemotherapy are often used in clinical practice to treat esophageal cancer. However, traditional treatments not only have significant adverse reactions and can easily develop drug resistance, but also result in unsatisfactory prognosis, with a 5-year net survival rate of only 30.3% [3]. Therefore, it is particularly important to find more effective treatment methods for esophageal cancer.

In recent years, tumor biology and tumor immunology have made rapid progress, and biological immunotherapy for tumors has become a new treatment method. This treatment method uses the patient's own immune system to activate the patient's anti-tumor immunity, prevent immune escape and metastasis of the tumor, and achieve the goal of treating or controlling tumor spread. As a new development in treatment methods, immunotherapy includes immunomodulatory drugs, adoptive immunotherapy, oncolytic viruses, and tumor vaccines [4, 5].

Oncolytic viruses (OVs) usually include DNA and RNA viruses. DNA viruses include adenovirus, vaccinia virus, herpes simplex virus, and parvovirus; RNA viruses include reovirus, coxsackievirus, poliovirus, measles virus, Newcastle disease virus, and vesicular stomatitis virus, among others. Adenovirus OBP-301 (telomelysin) and H101, which have undergone genetic recombination, are currently widely studied OVs in the treatment of esophageal cancer (EC). With the rapid development of tumor immunotherapy in recent years, oncolytic virus therapy for EC has shown promising results and has become one of the research hotspots in the treatment of esophageal cancer. This article reviews the mechanism of action of oncolytic viruses and their research progress in the treatment of esophageal cancer.

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2. Mechanism of oncolytic virus therapy

2.1. Selective replication and direct killing

The Normal cells have multiple signaling pathways that can detect and clear viruses. However, in tumor cells, interferon (IFN) pathway signaling and protein kinase R (PKR) activity are often abnormal, allowing oncolytic viruses (OVs) to enter and selectively replicate within cancer cells [6]. Therefore, OVs can target and infect tumor cells, and in most cases, they can also manipulate various abnormal signaling factors within the cells to prevent apoptosis. This provides the virus with more time to replicate. Once the tumor cells are specifically lysed, the oncolytic virus can release a large number of viral particles to infect surrounding tumor cells [7]. However, once all the surrounding tumor cells are lysed, the virus is restricted to replicating in the tumor site due to its own defects and the immune clearance of the body, while healthy tissues are not harmed [8].

2.2. Induction of anti-tumor immune response

After infecting tumor cells, oncolytic viruses (OVs) typically induce systemic innate and tumor-specific adaptive immune responses. First, during the process of oncolytic virus replication, antiviral pathways are activated, inducing the expression of type I interferon (IFN) and cytokines. At the same time, type I IFN and DAMPs can directly activate natural killer (NK) cells, achieving an anti-tumor effect.

When tumor cells infected by oncolytic viruses die, they release tumor-associated antigens (TAA). TAA promotes adaptive immune responses, thereby mediating tumor regression. In addition, dying tumor cells also release pathogen-associated molecular patterns (PAMPS), other cell damage-related molecular pattern signals (DAMP), and cytokines (such as type I IFN, tumor necrosis factor-α, IFNγ, and interleukin-12). These can enhance the activation of antigen-presenting cells, thereby activating antigen-specific CD4 and CD8 T cell responses and inflammatory response signal transduction [9, 10].

2.3. Countering tumor-mediated immune escape

Tumor cells have multiple mechanisms of immune escape in the body. For example, they can express immune inhibitory surface receptors on the surface of tumor cells and within the tumor microenvironment, preventing immune cells from exerting their cytotoxic effects. Tumor cells also secrete cytokines (such as IL-10, transforming growth factor-β (TGFβ), and indoleamine-2,3-dioxygenase (IDO)), which inhibit the recruitment of tumor-associated macrophages [11]. Oncolytic viruses can modify this suppressive microenvironment by changing the cytokine environment and various mechanisms of immune cell types in the tumor microenvironment.

At the same time, tumor cells killed by oncolytic viruses release previously hidden antigens, which can be absorbed by local antigen-presenting cells (APCs). If new antigen-specific cytotoxic T cells are produced against these antigens, they can kill tumor cells that have not been infected by the virus in circulation, thus countering some of the immune escape mechanisms [12].

2.4. Direct Disruption of Tumor Blood Vessels

Tumor growth often accompanies the formation of new blood vessels, which provide abundant nutrients and oxygen to promote tumor growth. Not only can tumor blood vessel endothelial cells and stromal cells be directly destroyed, leading to the collapse of tumor blood vessels, but also specific replication within blood vessels can occur, which can further disrupt tumor blood vessels by promoting the generation of angiogenesis inhibitors such as endothelial inhibitors and vasoinhibins[11].

3. Preclinical Study of Oncolytic Viruses in Esophageal Cancer

3.1. Adenovirus

Adenovirus (Ad) is a double-stranded DNA virus with a icosahedral capsid ranging in size from 70 to 90 nm. Due to its large genome, it can incorporate long DNA sequences, allowing for various engineering modifications. OBP-301 (telomelysin) is a attenuated type 5 adenovirus that contains a human telomerase reverse transcriptase promoter to regulate virus replication. In a phase I dose-escalation study of OBP-301 combined with radiotherapy, the objective response rate was 7.83% after

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intratumoral injection of OBP-301 combined with radiotherapy. The clinical complete response (CR) rate was 3.60% in the first stage and 0.8% in stages II/III[13]. H101 is a recombinant human type 5 adenovirus (Ad5), and the first oncolytic adenovirus approved by the Chinese FDA. It differs from wild-type Ads because the E1B55 kDs gene and E3 region of H101 are deleted[14, 15]. This oncolytic virus can selectively enter tumor cells and replicate within them, leading to cancer cell lysis with minimal damage to surrounding normal cells. In addition, anotherstudy found that radioresistance may be caused by cancer stem cells (CSCs). As CSCs require telomerase for proliferation, telomerase-specific oncolytic adenovirus vectors carrying apoptotic tumor necrosis factor-related apoptosis-inducing ligand and E1A genes (Ad/TRAIL-E1) may preferentially target CSCs, thus enhancing the anti-tumor ability of OV.

Li et al.[16]found in in vivo and in vitro studies of esophageal cancer models that oncolytic adenovirus-mediated dual knockdown of survivin and octamer-binding transcription factor 4 (OCT4) has a synergistic anti-tumor effect and the reversal of EMT is considered one of the important mechanisms for achieving therapeutic effects. Tumor necrosis factor (TNF) is the most potent bioactive factor discovered to date. In addition to directly killing or inhibiting tumor cells, TNF also mediates the cytotoxic effects of monocytes and macrophages. However, its short half-life and severe side effects limit its application. Jiang et al.[17]constructed a recombinant adenovirus SG502-TNF that can specifically target tumor cells and stably express TNF, which has significant killing effects on TE-1 cells in vivo and in vitro. This finding demonstrates the potential clinical application of adenovirus SG502. Furthermore, a study found that p21 (WAF1) plays a role in mediatingoncolytic virus replication and has potential significance for adenovirus therapy for cancer[18].

3.2. Herpes Simplex Virus

Herpes simplex virus is a virus with a linear double-strandedDNA genome that provides a variety of possibilities for modifying oncolytic viruses. These modifications can not only enhance the virus's oncolytic ability but also reduce the incidence of adverse reactions [19].

OH2 is an engineered oncolytic herpes simplex virus type 2 that selectively amplifies tumor cells and expresses granulocyte-macrophage colony-stimulating factor to enhance the anti-tumor immune response. In a multicenter phase I/II trial, the safety, tolerability, and anti-tumor activity of OH2 as a monotherapy or in combination with HX008 (an anti-programmed cell death protein 1 antibody) were studied in patients with advanced solid tumors. The duration of response for two responders receiving monotherapy with OH2 was 2.1+ and 38.2+ months, respectively, while for two responders in the combination treatment cohort, the duration of response was 56.2+ and 18.45+ months, respectively. The experiment found that monotherapy with OH2 could induce changes in the tumor microenvironment, with a significant increase in CD3 and CD8 cell density and programmed death ligand 1 expression in patient biopsies after treatment compared to baseline[20].

3.3. Newcastle Disease Virus

Newcastle disease virus (NDV) is an enveloped paramyxovirus with a single-stranded negative-sense RNA genome. Due to its effective replication in cancer cells, specific killing of cancer cells, and limited toxicity to normal cells, this virus has been used to treat cancer patients [21, 22]. Multiple studies have shown that NDV can induce apoptosis in various cancer cells by activating the mitochondrial apoptotic pathway (intrinsic pathway) and the death receptor pathway (extrinsic pathway)[23-25].

In a study, researchers constructed a novel dual-specific anti-tumor oncolytic adenovirus named Ad-hTERT-E1a-HN by inserting the HN gene of NDV and the hTERT promoter into the RAPAd.I adenovirus vector, and compared it with a control recombinant adenovirus. The results showed that Ad-hTERT-E1a-HN specifically replicated in human EC-109 tumor cells, selectively restricted their growth, and had no adverse effects on L02 cells. In addition, in vivo anti-tumor experiments demonstrated that Ad-hTERT-E1a-HN significantly inhibited tumor growth, especially by intratumoral injection[26].

3.4. Vesicular Stomatitis Virus

Vesicular stomatitis virus (VSV) is a member of the family Rhabdoviridae, which is a non-segmented negative-sense RNA virus that encodes five viral proteins (N, P, M, G, and L) [27]. In a study, the potential anti-tumor effects of wild-type VSV (wt) and the M51R mutant matrix protein (mMP) on apoptosis, necroptosis, necrosis, and autophagy in esophageal squamous cell carcinoma (SCC) (S-30) cells were investigated. The results showed that VSV exerted oncolytic activity through different cell death

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pathways, especially the autophagy pathway, in KYSE-30 tumor cells, indicating that M51R-mMP may be used to enhance oncolytic efficacy[28].

4. The Efficacy and Safety of Oncolytic Virus Therapy for Esophageal Cancer

4.1. Combination Therapy

Although multiple studies have shown promising results of OV therapy in combination with anti-tumor drugs, the efficacy of OV as a monotherapy for cancer treatment is still not satisfactory. Therefore, combination therapy strategies are necessary. Studies have shown that OV in combination with other therapies can improve therapeutic efficacy[29, 30].

Combining OV with radiation and chemotherapy can produce a synergistic effect. OBP-301 can sensitize human cancer cells to ionizing radiation by inhibiting DNA repair, and radiation can enhance OBP-301 infection mediated by coxsackievirus and adenovirus receptors. The combination of both can significantly improve therapeutic efficacy[31]. In another study, the ability of histone deacetylase inhibitor (HDACI) trichostatin A (TSA) to enhance the oncolytic activity of H101 was evaluated. The results showed that HDACI TSA effectively and selectively enhanced H101 viral particle replication in ESCC both in vitro and in vivo[32].

Simultaneously, combining two different OV can also produce a synergistic effect. A study on the combination therapy of adenovirus and vaccinia virus showed that repeated injection of the same virus can promote anti-viral rather than anti-tumor immunity, and tumors may establish innate anti-viral defenses to limit oncolytic virus replication.The results showed that in two anti-viral animal models, alternating injection of two oncolytic viruses with different immune profiles (adenovirus and vaccinia virus) induced a significant delay in anti-viral immune and innate cell responses[33].

4.2. Adjusting Delivery Methods

Currently, the conventional delivery methods for oncolytic viruses (OVs) mainly include intratumoral injection and intravenous injection (IV). Ideally, IV administration is the most desirable delivery method because it has the potential to reach both primary and metastatic tumors. However, the presence of specific antibodies against common viruses in human serum can quickly kill the virus, making intratumoral injection the main route of administration in OV therapy.

In one study, various engineered therapeutic cells (ThCs) were created, loaded into micro-porous gelatin methacryloyl (GelMA) hydrogel (CellDex) capsules, and cultured in vitro before transplantation to the surgical debulking solid tumor. Experimental studies have shown that both allogeneic and autologous ThCs, such as stem cells (SCs), macrophages, NK cells, and T cells, can proliferate within CellDex capsules and migrate out of the gel in vitro and in vivo. Additionally, tumor cell-specific therapeutic proteins and oncolytic viruses released from CellDex capsules can be retained and prolong their anti-tumor effects[34].

Another study investigated the use of nanoparticles (NPs). One of the main problems with various OV carriers for cancer treatment clinical trials is their elimination by the reticuloendothelial system during systemic delivery. Therefore, the use of nanoparticles canimprove the delivery efficiency of drugs. To further enhance the efficiency of nanoparticles in drug delivery, various chemical modifications can be applied to the surface of nanoparticles. The complex strategy of using OV enclosed in nanoparticles has resulted in successful clinical outcomes in the treatment of various cancers[35].

4.3. Altering the Tumor Microenvironment

Malignant tumors not only consist of a heterogeneous population of tumor cells but also involve resident and infiltrating non-transformed cells, secreted factors, and extracellular matrix (ECM) proteins, which together form the tumor microenvironment (TME). This immunosuppressive microenvironment presents a significant challenge for OV therapy. Therefore, altering the TME can change the tumor's immunosuppressive state and enhance the efficacy of OV therapy.

Using OV that specifically expresses pro-inflammatory cytokines such as TNF and GM-CSF can promote tumor cell lysis and improve the anti-tumor effect[17]. In addition, arming OV with cytokines that enhance immune responses, such as IL-12 and IL-18, is also a common therapeutic strategy[36]. When tumor cells are lysed by OV, a large number of tumor-associated antigens (TAA), pathogen-associated

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molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) are released, which can induce an inflammatory immune response and convert the immunosuppressive TME into an inflammatory reaction TME. This process can reawaken anti-tumor immune responses, induce immunogenic cell death, and trigger a strong anti-tumor immune response[37].

5. Conclusion and Outlook

As a new development in the field of tumor immunotherapy, OV therapy has revealed some mechanisms forkilling EC cells in previous research. Although some clinical trials have achieved promising results, most studies still focus on preclinical experimental mechanisms. As a method of tumor therapy, OV has shown unique advantages. Due to the limitations of single-agent OV therapy, combination strategies with traditional radiotherapy, chemotherapy, or other immunotherapy have been favored for the treatment of solid EC, and have achieved better efficacy in clinical trials. Multiple clinical studies have shown that OV can bring clinical benefits to EC patients in different stages of progression, even those with metastatic or inoperable tumors. With the development of genetic engineering and molecular biology technology, an increasing number of genetically recombined OV have been developed. The challenges of OV therapy in clinical treatment include how to improve OV delivery and reduce adverse reactions.

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