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Review

Oncolytic Engineering and Clinical Trials of Herpes Simplex Virus Type 1

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Abstract

Malignant tumors have great harm to human health. Oncolytic engineering of herpes simplex virus 1 (HSV-1) can have the specific targeted effect on malignant tumors with minimal side effects, making it a new hot spot in tumor research. Currently, oncolytic HSV-1 (oHSV-1) is one of the most widely and deeply studied oncolytic viruses. It mainly reduces the side effect of the virus by modifying its viral genes, prevents the oncolytic virus being cleared by the immune system and successfully reaches host cells, and enhances the replication and oncolytic effect of the virus in host cells. Now, clinical and experimental studies are mainly conducted to deliver oHSV-1 into tumors by intra-tumor injection of the viral drugs under the guidance of ultrasound, CT or MRI and other imaging devices. Imaging methods can also be used for oHSV-1 drug delivery detection and accurate diagnosis of solid tumors using oHSV-1. This article reviews and summarizes the basic methods of the engineering of oHSV-1 and its application in clinical trials, as well as some of the problems currently exist.

Keywords: Herpes Simplex Virus Type 1 (HSV-1); Oncolytic Virus (OV); Tumor Treatment; Precision Imaging and Radiotherapy.

Introduction

Tumors originate from transformed cells in tissues or organs that contain heterogeneous cancer cells such as tumor stem cells (1). Malignant tumor is a kind of disease that seriously threatens human life. Traditional treatments for cancer mainly include surgical treatment, radiotherapy, chemotherapy, and drug treatment. These treatments can kill a part of cancer cells, but there are problems such as incomplete treatment, great toxic and side effects, easy to relapse and other problems, and unable to control the recurrence and metastasis of tumors, so it is necessary to find a more specific and effective treatment. Oncolytic virus (OVs) is a naturally-occurring or genetically engineered virus with specific anti-tumor effects of direct oncolysis and activation of innate and adaptive anti-tumor immunity. Oncolytic virus (OVs) therapy is an emerging anti-cancer approach that uses the lytic properties of viral replication to enhance the killing of malignant cells. Oncolytic viruses can be used as a tool to directly induce cancer cell death, and can trigger local and/or systemic immune responses *in vivo* to metastasize cancer cells (2), killing uninfected tumor cells in the distance (3).

Oncolytic virus therapy is a new treatment method. In October 2015, the US FDA officially approved the oncolytic virus drug T-Vec (Talimogene laherparepvec, T-Vec), which is used for unresectable skin, subcutaneous and lymph node lesions recurring after melanoma surgery. In the EU, T-Vec has been approved for unresectable melanoma local treatment of lesions (4). In phase III clinical trials, T-VEC showed improved response rate, as compared to granulocyte-macrophage colony-stimulating factor (GM-CSF), and suppressed the tumor's growth. T-VEC produced CM-CSF, induced the aggregation and maturation of dendritic cells, which processed tumor cell antigens, and then transmitted them to T cells in the lymph nodes, induced the activation of tumor-specific CD8+ T cell, and initiating the specific immune response of the body system. A preliminary clinical report confirmed that T-Vec can transform the immunosuppressed tumor microenvironment (TME) into an immune activated "hot" environment (5). Therefore, T-Vec has a dual mode of action, which can directly cause tumor cell lysis and activate immune-mediated activation of anti-tumor immune response (6).

An ideal oncolytic virus can not only specifically infect tumor cells and replicate in tumor cells, resulting in tumor cell lysis, but also enhance the body's immune response against tumors (7). Many viruses have been transformed into oncolytic viruses (OVs). Oncolytic herpes simplex virus 1 (oHSV-1) is one of the most widely studied and in-depth type of oncolytic viruses. HSV-1 is an enveloped double-stranded DNA virus that contains 85 genes. The researchers modified 45 genes or DNA fragments of its 150Kb genome to inactivate the virus or delete the active part of the virus without affecting its own replication. As an important oncolytic virus, HSV-1 can infect most solid tumors and lyse tumor cells.

1. Characteristics and mechanism of HSV-1

virus

1.1 HSV-1 gene characteristics

An essential feature of OVs is the ability to form lysis cycles of oncolytic viruses in malignant tissues rather than normal tissues. As the first virus genetically modified into OVs, HSV-1 has the following characteristics: (1) It can infect a variety of cells, and the host range is relatively wide, partly because HSV-1 can bind to a variety of receptors, including Cell adhesion molecules, laminin-1 and laminin-2 (for some mutant strains), various heparan sulfate groups, Tumor necrosis factor (TNF) receptor superfamily members 14, and Other media that can infect oncolytic viruses; (2) Short replication cycle and high infection efficiency; (3) The viral genome is large and has been sequenced completely, with large operable space, which allows the insertion of multiple therapeutic factors; (4) High safety, the treatment can be terminated at any time by using antiviral drugs; (5) The virus gene remains free in the host cell and will not be integrated with host gene; (6) After infection, the body can be stimulated to produce CD4 (+) and CD8 (+) T cells, which stimulate the body to produce an immune response. And some studies have shown that CD4(+) T cells play an important role in controlling HSV virus shedding from host cells (8).

1.2 The specific process of HSV-1 infecting host cells

HSV-1 adheres to the surface of the host cell membrane, mainly through the glycoproteins (g) B and C on the surface to bind to the heparan sulfate proteoglycan on the surface of the host cell ,which changes the structure of adhesin-1, causes gH/gL to bind with gB, further initiates the fusion of virus envelope and host cell membrane, and releases virus particles into the cytoplasm of host cells. gD must interact with receptors and gH/gL to promote virus entry into cells(9).PCR technology is used to detect the gene replication of the virus, or the expression level of the capsid protein of the virus to detect the total amount of virus entering the cell, so as to understand the sensitivity of the cell to the virus. At the same time, it plays a role in killing tumor cells and eliminating viral infections early through humoral (such as the combination of antibodies and complement) and cellular immune mechanisms, so virus particles entering the cell are likely to be degraded by lysosomes and undegraded along microducts into the nucleus. Once the genome of the virus enters the nucleus, even in the incubation period, the replication of the virus will cause damage to the host cell.

1.3 oHSV-1 delivery route

As oHSV-1 is a new treatment method, its administration and treatment requirements are different from current treatment methods (10). oHSV-1 can be delivered into tumors through various routes, and the main limitation of oncolytic virus treatment is how to accurately deliver the virus to the target cells. For most ongoing or completed clinical trials, the main approach is to inject the oncolytic virus directly into the tumor. The obvious advantage of intratumoral injection is that OV can reach very high concentrations in the tumor. Intratumor injection under the guidance of ultrasound, CT or

MRI imaging equipment can make the operation more accurate and convenient to a certain extent.

oHSV-1 can also enter various systems throughout the body through arteriovenous injection or intraperitoneal infusion. This type of injection allows the virus to enter both carcinoma in situ and metastatic tumors that are obvious or undiagnosed .Each step of this process can cause physiological and immune barriers to virus transmission, and only a small part of the virus can enter tumor cells.

1.4 Mechanism of oHSV-1 specific infection of tumor cells

One of the ways to improve virus specificity is to genetically modify tumors so that oncolytic viruses can only replicate specifically in tumor cells, but not to infect normal and post-meiosis cells. The mechanism is shown in step (a) and (b) of Figure 1.

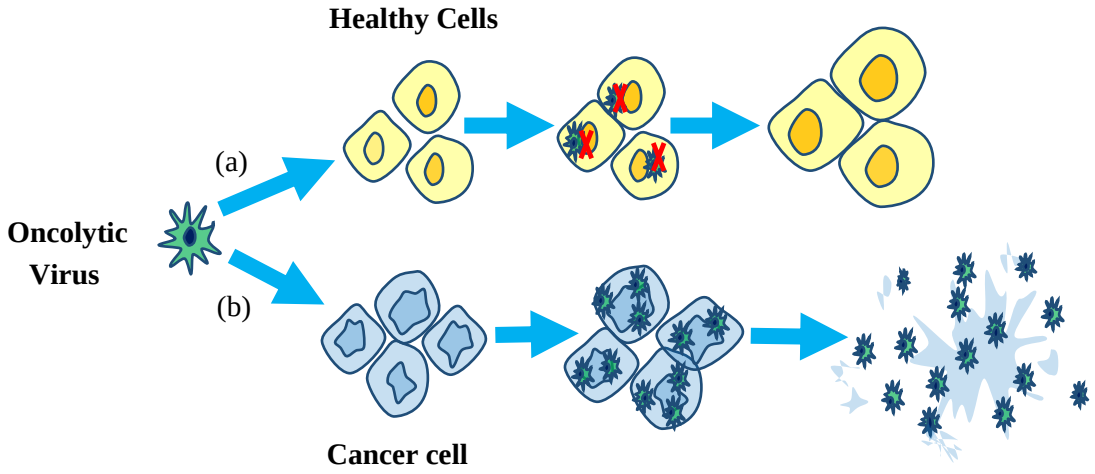

Figure 1. Infection and killing of tumor cells by an oncolytic virus

(a) An oncolytic virus cannot replicate in normal, healthy cells

(b) An oncolytic virus targets cancer cells, multiplying within the cells before destroying them, and virus replication leads to cell lysis(direct effect) and the release of progeny virions, resulting in virus spread throughout the tumor, causing the body's immune response.

Deleting the ICP34.5 gene improves the ability of the virus to specifically target tumor cells. Deleting the ICP47 gene enhances the oncolytic effect of the virus by inhibiting antigen presentation within the host cell. At the same time to insert foreign genes, not only will not affect the activity of the virus, but also can enhance the oncolytic effect of the virus, such as a new HSV-1 strain RH018A isolated from a patient with herpes, by deleting the strains encode genes ICP34.5 and ICP47 and insert the gene encoding the fusion protein GALV-GPR, and developed a new virus strain that can enhance the ability to directly kill tumors in vivo, which is used in oncolytic therapy (11). For example, MH1004 is HSV-1 inserted with the tumor suppressor gene P53 based on the deletion of the IR recombinant virus MH1001. In tumor cells, the P53 gene is

expressed, and its ability to replicate and inhibit tumor cell proliferation was enhanced in the mouse melanoma model neuromas, and the dose used in later treatment was also lower (12).When OVs infect tumor cells, the inherent defense mechanism of the host cell may hinder the replication of the virus and prevent the virus spreading between tumor cells. Experiments have shown that histone deacetylase 6 inhibitor (HDAC6i) enhance the replication and oncolytic effect of viruses in host cells through pharmacological or genetic methods (13).

2. Some progress of oHSV-1 in tumor treatment

The study found that the combination of proteasome inhibitor bortezomib and oHSV-1 for the treatment of tumors can not only cause the death of tumor cells, but also enhance the activity of NK cells，to enhance the effect of treating tumors. We also observed that treatment of tumor cells with bortezomib before oHSV infection resulted in a RIPK1-dependent necroptotic cell death, leading to JNK-dependent reactive oxygen species (ROS) production (14). Due to the great heterogeneity of tumor cells, the early detection of tumors has been not ideal. Using telomerase-specific and tumor-specific OHSV-1 to target telomere reverse-transcriptase positive cancer cells and make them express green fluorescent protein, cancer cells in N0M0, N+M0~M1 can be detected. In the experiment, the cancer cells of lung cancer, colon cancer, liver cancer, stomach cancer, pancreatic cancer and glioma were detected. Among 21 lung non-small cell cancer samples, 81% of the cancer cells showed a reduction in the relevance of treatment (15).

The most significant advances in immunotherapy of tumors are through targeting the cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1)/PD-1 ligand (PD-L1) pathways Clinical development of immune checkpoint inhibitors (16). With the clinical efficacy of oncolytic immunotherapy, it has been proven that it can further enhance the combination with immune checkpoint inhibitors and can synergize with other existing immunotherapy to improve the oncolytic effect. Experiments show that the combined use of EGFR-CAR NK-92 cells and oHSV-1 shows a more effective oncolytic effect in the mouse breast cancer brain metastasis tumor model, and the mice in the experimental group have a longer survival time than the mice in the control group (17), UV light inactivated HSV-1 (UV -HSV-1) Partially through Toll-like receptor (TLR) 2/Protein kinase (K) C/nuclear factor (NF)-κB can not only effectively promote the dose-dependent CD19 expression, IFN -γ production and natural killer cell (NK) cell movement and degranulation, and synergistic IL-15 and IL-12 can promote NK cell activation and anti-leukemia effect, prolong human acute myeloid leukemia (AML) survival time of model mice (18). T-Vec combination can effectively block Cytotoxic T cell Antigen-4(CTLA-4)'S monoclonal antibody ipilimumab (trade name Yervoy) is used to treat advanced melanoma. Compared with ipilimumab alone, the objective efficiency is significantly improved. These data indicate that this combination has stronger anti-tumor activity than

ipilimumab and there are no additional safety issues (19).

3. Advances in the use of OHSV-1 in tumor precise imaging and radiotherapy

It is reported that oncolytic viruses have attracted more and more attention in imaging precision imaging and radiotherapy of solid tumors. Oncolytic viruses can also express genes that can be visualized and oncolytic, enabling noninvasive real-time molecular imaging and targeted radionuclide therapy in vivo. Nuclear medicine equipment such as scintillation scanners, gamma cameras, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can detect picomolar to millisecond Moore's radioactive tracer. Through the combination of nuclear medicine equipment and traditional medical imaging technology Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) (PET/CT, SPECT/CT and PET/MRI), it can greatly Improve the tissue resolution of PET and SPECT. Oncolytic viruses express reporter genes and probes in tumor cells，these reporter genes and probes can bring together radionuclides so that exogenous equipment can detect these radionuclides. Through continuous improvement in instrumentation, development of new reporter genes and probes, molecular imaging will become an indispensable tool for biomedical research. Various reporter genes and probes for nuclear medicine imaging have been developed，many of which have already been utilized with several strains of oncolytic viruses (20-21). The human sodium–iodine symporter gene (hNIS) is one of the most mature nuclear medicine report genes reported so far. Studies have shown that hNIS can be cloned into measles virus, vesicular stomatitis virus, and adenovirus for use in animal model tumor imaging, virus replication, and biodistribution studies (22).

Compared with traditional MRI, magnetic resonance molecular imaging (MRMI) uses contrast agents and molecular probes, which have high imaging specificity and sensitivity, and can be used to study the functions of cell molecules under normal and pathological conditions in vivo. Oncolytic viruses express reporter genes and probes in tumor cells. Due to Oncolytic viruses had higher tumor selectivity, molecular imaging of oncolytic viral may provide a more sensitive and specific diagnostic technique to detect tumor origin and, more importantly, presence of metastases (21). In the early stages of cancer development, biochemical changes in cell metabolism occur before detectable tumor masses form. Current molecular imaging technology targets molecular dynamics research and uses molecular tracers to detect tumor lesions. It has high sensitivity and specificity, and provides necessary information for prognosis and treatment (23).Therefore, oncolytic viruses have important application prospects in the clinical application of imaging imaging and radiotherapy of solid tumors. Current research has shown that oncolytic viruses can be used not only for the treatment of tumors, but also for tumor imaging through different molecular imaging techniques, and the combination of oncolytic virological treatment and radiotherapy may produce better

anti-tumor effects.

4. Some improvement strategies of oHSV-1

The loss of tumor-specific T cells in the tumor microenvironment seems to be an important feature related to innate and acquired resistance to checkpoint blockade. Therefore, new strategies are needed to induce anti-tumor immune responses, to synergize anti-pd -1/L1 therapy, to reverse the immune-deficient tumor microenvironment, and to reconstruct tumor-to-system anti-pd -1/L1 treatment sensitivity. Compared with normal tissues, oncolytic viruses preferentially replicate in tumors and promote immunogenic cell death and induce host anti-tumor immunity (24). Moreover, even the genotype and phenotype of the same type of tumor are still different. Initial research showed that oHSV-1 ability to target the most harmful tumor cell subsets (25). Even though HSV-1 can target many types of tumor cells, not all tumor cells have a microenvironment suitable for virus replication. One way to promote viral infection of tumor cells is to redirect different receptors of virus-infected tumor cells. This receptor is highly expressed in tumor cells but low in normal cells. The microenvironment of tumors can cause many obstacles for effective virus infection. In areas of highly differentiated tumor extracellular matrix and tissue necrosis, both will slow down OHSV spread.

5. OHSVs in clinical trials

After more than ten years of development, the HSV-1 oncolytic virus has entered a variety of clinical trials. The classic ICP34.5 mutant oncolytic virus HSV1716 deletes a gene of 759 bp including double copies of ICP34.5. Applying HSV1716 to childhood cancer patients, adverse events caused by the virus include low fever, chills and mild cytopenia, which were well tolerated (26).In the preclinical trial of HSV1716 treatment of hepatocellular carcinoma, intratumoral injection significantly reduced the hepatocellular carcinoma of the nude mouse model, and the virus can effectively replicate in the tumor cells, showing a good oncolytic effect and improving the patient's Long-term survival rate.

Based on the first generation of ICP34.5 mutant oncolytic virus, oncolytic virus G207 deleted the double copies of the ICP34.5 gene and inserted the galactosidase gene of Escherichia coli at the position of the RR gene to making the virus highly sensitive to ganciclovir or acyclovir treatment. G207 is also a promising drug for the treatment of central nervous system tumors. The first phase of pediatric trials of continuous infusion of G207 through intratumoral catheters for the treatment of recurrent or progressive malignant brain tumors is ongoing. In addition to the therapeutic effect of G207 on the nervous system, studies have shown that it can treat meningioma, breast cancer, ovarian cancer, squamous cell carcinoma of the head and neck skin, prostate cancer, bladder cancer, urinary tract tumors, renal cell carcinoma, and pancreatic cancer. And colon cancer metastatic liver cancer has a therapeutic effect.

G47Δ is a derivative of G207, which deletes

the ICP47 gene on the basis of G207, thereby enhancing the antigen presentation of major histocompatibility complex 1 (HC-1), and at the same time deleting ICP6 and GICP in the G207 gene, the promoter region of Us11, which makes the IEα47 promoter can control the Us11 gene.

NV1020 removes the 700pb thymine site gene in the HSV-1 genome, inactivates the ICP24 gene, and deletes a single copy of the ICP34.5 gene plus a 15kb long segment UL and a short segment US junction Gene, thereby removing UL56. At the same time, a 3.4 kb double copy of UL5/6 was inserted into the viral gene to induce the ICP4 promoter to start the expression of the thymine gene. In clinical trials, NV1002 was injected into the body through hepatic artery injection, and at the same time assisted with conventional chemotherapy, patients who received each injection of NV1002 had a brief mild toxic fever reaction, and the virus-related toxic reaction of grade 3/4 was limited to the transient lymphocytosis of the two patients, and no quantity-related clinical adverse reactions were observed (2).

6. Problems and prospects of oncolytic viruses

At present, the oncolytic virus therapy is mainly administered by intra-tumoral injection, which maximizes the restriction of oncolytic virus in tumor cells and at the same time maintains a certain concentration of oncolytic virus in tumor cells. However, this method of administration can only be administered under the guidance of some imaging equipment for some tumors of the nervous system or internal organs, and for some diffuse metastatic cancer lesions or small cancer metastatic lesions that are not visible to the naked eye, treatment still has many inconveniences and cannot be used to the maximum. Moreover, many oncolytic viruses are tested in animal experiments in nude mice, and the safety in human body needs further experiments study.

At present, the anti-tumor effects of several HSV-1 oncolytic viruses have been evaluated clinically and good results have been achieved. After intratumoral injection of oncolytic virus, it only replicates in tumor cells and causes lysis of tumor cells, without causing damage to normal cells or tissues, especially in the nervous system. In addition, both radiochemotherapy and prodrugs have been shown to have a synergistic effect with HSV-1. However, their safety against viral replication and mutation still needs to be evaluated clinically. Studying the toxicity of combination therapy to normal cells and tissues is necessary in the next step of HSV-1 in clinical trials.

Due to its unique advantages, HSV-1 is transformed into oncolytic virus, which can specifically recognize tumor cells without destroying normal cells, and can stimulate the body to produce an anti-tumor immune response, which has a very broad application prospect in the field of tumor therapy. With more in-depth research on oncolytic viruses, the existing problems will be solved, and oncolytic viruses will also become one of the main methods to treat tumors in the future.

Table 1. Oncolytic HSV-1 in clinical trials

Virus	Genetic modification	Trial phase	Tumor Type	Administration Mode	Side effect	Combination therapy
G207	LacZ(+) ICP6(+)	I	Glioma	Intra-tumor	Flu-like symptoms	Radiotherapy
	ICP34.5(-)	II	Glioma	Intra-tumor	Flu-like symptoms	no
R1716	ICP34.5(-)	I	Solid tumors of non-central nervous system	Intra-tumor	Gastrointestinal disorders	no
		I	Glioma	Intra-tumor		no
		I	Oral squamous cell carcinoma	Intra-tumor		no
		I	Melanoma	Intra-tumor		no
NV1020	UL24(-) UL55(-)	I	Colorectal cancer	vein		no
	UL56(-) ICP34.5(-)	I / II	Colorectal cancer liver metastasis	Hepatic vein infusion		no
HF10	Highly attenuated	I	Solid tumor	Intra-tumor	Flu-like symptoms	no
		I	Pancreatic cancer	Intra-tumor		no
		I	Breast cancer	Intra-tumor		no
		I	Oral squamous cell carcinoma	Intra-tumor		no
		I	Melanoma	Intra-tumor		Yervoy
Oncovex (T CASE)	ICP47(-)	III	Melanoma	Intra-tumor		no
	ICP34.5(-)	II	Melanoma	Intra-tumor	Flu-like symptoms, pain, fatigue, breathing difficult, autoimmune vitiligo	no
	GM-CSF(+)	I / II	Oral squamous cell carcinoma	Intra-tumor		Chemotherapy
		I	Melanoma	Intra-tumor		Yervoy
OricnX010	ICP34.5(-)	I	Solid tumor	Intra-tumor		no

Declarations

1) ***Consent to publication***
We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2) ***Ethical approval and consent to participants***
Not applicable.
3) ***Disclosure of conflict of interests***
We declare that no conflict of interest exists.
4) ***Funding***
None
5) ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article.
6) ***Authors' Contributions***
Authors contributed to this paper with the design (RRD), literature search (RRD), drafting (RRD), revision (RRD and WX), editing (RRD and WX) and final approval (RRD).
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None
8) ***Authors' biography***
None

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