Recent advances in Adeno-based Oncolytic Viral therapy

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ABSTRACT:

Adeno based oncolytic viral therapy is an emerging mechanism to treat cancer having rare side effects as compared to the previous treating methods. This process approach directly to the cancer cells without harming healthy cells. The signals and acceptors for specific targeting is engineered in the adenovirus to cross all the barriers of host immune response and create neo-viruses which further do the cancer cell destruction. This review will provide a brief elaboration on the recently approved naturally and engineered oncolytic viruses and summarise the modifications occurred in them and the results of clinical trials.

Keywords: Cancer, DNA viruses, Adenovirus, targeted therapy, auto immune response, oncolysis, drug development, oncolysis.

1. INTRODUCTION:

Cancer is a major cause of death globally. While therapies for the treatments for the disease have dramatically, traditional chemotherapy or radiotherapy, not to mention a myriad of treatment-related side effects still have minimum side effects against many types of cancer. This condition suggests a need for novel therapeutic methods, and the use of viruses is one such approach. For more than a century the potential of viruses to kill cancer cells has been recognized. [1, 2] They accomplish this through a variety of pathways, including direct lysis, apoptosis, toxic protein expressions, autophagy and shut-down of protein synthesis, as well as the activation of anti-tumoral immunity[3]

For cancer therapy, viral infecting focused on infecting a limited number of target cells with a replicating virus, which would replicate, amplify and spread to adjacent cells, destroying the tumor by a lytic mechanism called Oncolysis.[1]

An active host immune response against the viruses that rapidly eliminates the virus has been seen as a significant obstacle to the effectiveness of successful cancer viro-therapy. Indeed, several studies have shown that suppressing the immune system has increased the efficacy of Oncolytic Adenovirus (OAds). There has, however, been accumulating evidence that the virus-induced immune activation can generate innate and adaptive immune responses that are critical to mediating the antitumor responses. [4]

2. Mechanism Of Oncolysis:

Two primary mechanisms including direct lysis and activation of host itself immune system itself to activate cancer cell, are involved in cancer removal by OVs.

2.1 Direct lysis:

With direct Oncolysis, as a direct result of replication or infection the virus causes lysis or apoptosis of a host cell. The immune system stimulates the antiviral pathway such as Type1 interferon which inhibits the OVs replication, when entering a normal or healthy cell. The lytic cycle is recapitulated by replication in Cancerous cell as the viral particles are released and neighbouring cells are infected. The viral load continues to increase through this method until IFN's immune response is attenuated by an interaction between released antigen and TLRs or depletion of susceptible host cells.

2.2 Induction of an immune response:

Tumor cells can be destroyed by induction of tumor specific immune response. Infected tumor cells are highly immunogenic; TLR pathway and release of tumor-derived antigens stimulates the immune response occurs by and are captured by antigen-presenting cells (APCs) such as Dendritic cells (DCs) and macrophages. As shown in the figured the cell lytic activity of cancer cell is accompanied by replication of OVs and release of neo-oncolytic viruses, TAAs, DAMPs and PAMPs. The releases of new OVs infect other cancer cells and destroy cancer cells that are nearby absolutely. In addition, a systemic immune response could theoretically trigger a response to distant lesions that are not injected. The potential for tumor-specific immune response activation by oncolytic has led to the engineering and clinical testing of oncolytic viruses designed to boost this response. [5]

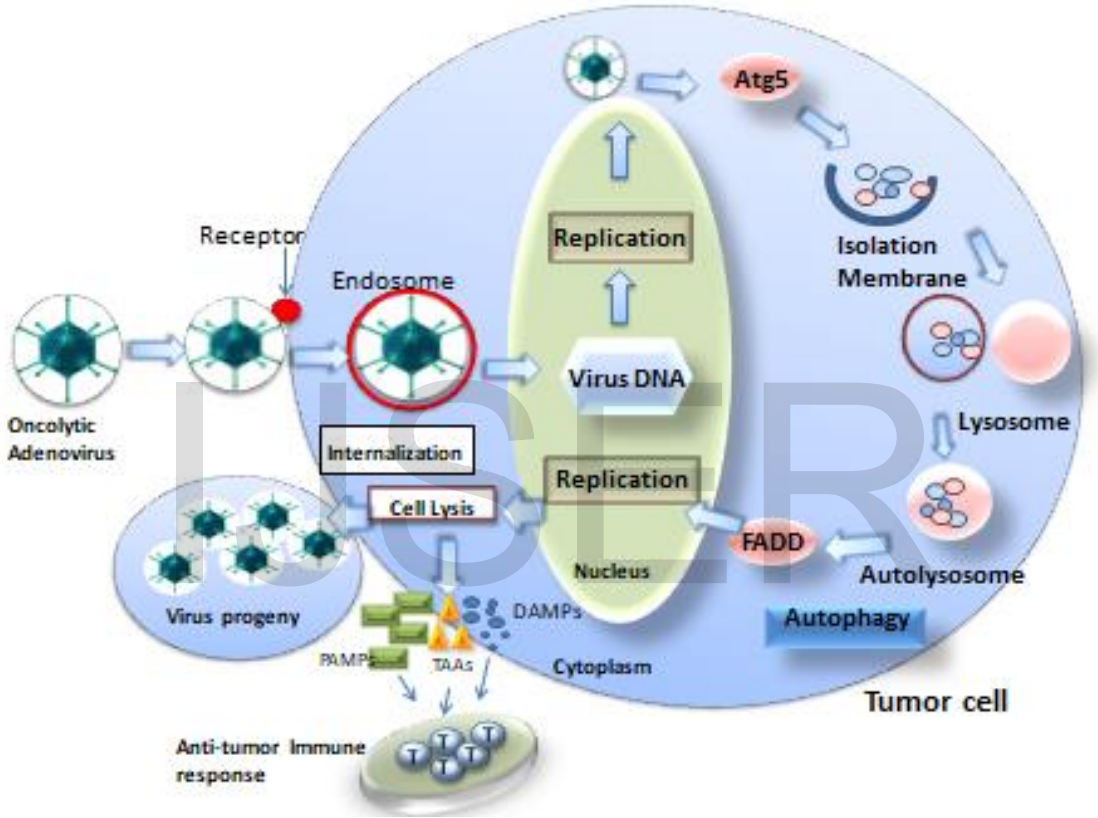

Figure 1: Oncolytic viral mechanism inside cell.

3. Why Adenovirus As Oncolytic Viral Therapy:

Adenoviruses (Ads) generally and widely used in Oncolytic Viral therapy are around 90nm-non enveloped icosahedral linear Double stranded DNA virus widely and frequently used in oncolytic virotherapy. [6] As a result of rapid viral replication Oncolytic adenovirus has emerged as a new antitumor strategy for inducing the lytic death of tumor cells. Ads vectors have broad capacity for transgene (up to 36kb). [7]Human Ad serotype 5 (Had5) is widely studied and used as a gene and targeted therapy. Ads capsid's structural proteins including hexon, penton, fibre, pIX play major role in communicating with cancer surface receptors and promoting entering in to targeted cell.[8] The lack of integration, however, improves protection because it is unlikely that the host cell will be at the risk for mutagenesis. As therapeutic agent, Ad5 serotype is widely used as it is capable of infecting and promoting surface attachment and host cell internalization through cellular coxsackievirus and adenovirus receptor (CAR) and αv integrin. In cancer cell CARs and αv integrin are overexpressed

specifically, so the off targeting effect of Ad-based treatment in noncancerous cell should not increase.

Naturally Occurring Oncolytic Viruses:

Towing to the lack of means to monitor viral pathogenicity at the time, the concept of using naturally occurring viruses for the treatment of cancer was almost abandoned after intensive attempts during the 1960s and 1970s. However, along with the emerging growth of the genetically modified viruses the concept was revived and newly created naturally occurring viruses are usually in those humans that are not pathogenic.

Representative clinical trial of OVs as cancer therapy

Table 1*:* Shows naturally occurring viruses based drugs and their outcomes

Drug Name	Modification	Phase	Cancer type; route; no. of patient	Outcome	Reference
ParvOryx01	Wild type	I and II	Glioblastoma multiform; firstly, intratumoral and peritumoral and, secondly; intravenous and intratumoral; 18	No or few symptoms, tumor resection needed.	[9]
Reolysin	Reolysin, wild type	II	Prostate, malignant glioma, metastatic colorectal, multiple myeloma and solid cancers, metastatic melanoma; intravenous; 73	Ultimately activate the immune checkpoints towards antitumor reaction[10]	[11]

[12]

Genetically Engineered Oncolytic Viruses:

Designing and modifying the viral genome to construct a non-pathogenic virus has become the traditional approach for oncolytic virus development with the development of modern techniques of genetic engineering and growing knowledge about the roles and structures of viral genes. For this technique DNA viruses are used typically. Such as:

Table 2: Shows genetically engineered oncolytic viral drugs and their outcomes

Drug	Modification	Phase	Cancer type; route; no. of patient	Outcome	Reference
T-Vec	Modified JS-1 strain of HSV, deletion of *RL1*, encoding ICP34.5, and *US12*, encoding ICP47, insertion of *US11* and *GM-CSF*	III	Breast, Head/neck Gastrointestinal, and Malignant melanoma; Direct injection;436	Showed efficient treatment of Advanced melanoma	[13]
Seprehvir (HSV1716)	Deletion of gene encoding ICP34.5, maintain expression of thymidine kinase	I and II	Mesothelioma, Refractive solid tumor; Intravenous; 12	No dose limiting toxicities (DLT), viral shedding was noted in any patient. Tumor shrinkage occurs.	[14, 15]
JX-594	Single knockout of TK genes, insertion of hGM-CSF which promotes myeloid and dendritic cell mutation.	II	Liver cancer; Direct intratumoral injection; 30	Intravenous stability for delivery, Strong cytotoxicity, Stimulating anti-tumor activity and extensive safety experience as a live	[16]

				vaccine.	
CG0070	Deletion of E2F-1 promoter, insertion of GM-CF gene	II	Non muscles invasive bladder cancer(NMIBC); Intravesical; 67	23% CR results, 44% complete response rate, Induce antitumoral activity.	[17, 18]
G47Δ	Deletion of nonessential *α47* gene,	II	Glioma, Breast cancer, Prostate cancer, Hepatocellular Carcinoma, Colorectal cancer, Malignant Mesothelioma, Olfactory Neuroblastoma ; Intratumoral injection; Model animal	Efficiency to enhance the regulation of the replication capability via CD8+Tcell-dependent which further inhibit the tumor growth.	[19, 20]

Barriers in Mechanism of Oncolytic Virotherapy:

The effectiveness of OVs that requires a number of obstacles can be diminished:

Barriers limiting OVs Delivery:

Adequate amount of drug through intravenous injection must be able to deliver at tumor site without being captured and destroyed by pre-existing immunity to virus. OVs in combination with Histone deacetylase (HDAC) inhibitor is the promising approach to deliver drug with great efficacy.[21] HDAC inhibitor induces cell death of cancer by inhibiting angiogenesis.

Barriers affecting intratumoral virus infection and spread:

Productive infection and multiplication of oncolytic virus in tumor cells is necessary to complete the OVs therapy. But the main hindrance in the procedure is the host immune response that occurs with the start of OVs multiplication simultaneously. The IFN molecules mostly attack the virions through many mechanisms including autocrine and paracrine route of signal transformation. Tumors that have growth rate higher than the transmission rate of OVs during the whole process may escape from destruction and have chance to regrow in future. [22]

4. Future Directions:

Oncolytic virotherapy has changed its focus to suppression through virus-mediated immune response from direct oncolysis by the virus. Host immunity can effectively clear the virus During virotherapy, which is essential for the protection of cancer patients, but anti-tumor immunity is preferably acquired before the adenovirus is cleared.[23] The microenvironment of the tumor immunosuppressive could give a window of opportunity, for viral propagation. To make tumor-associated antigens more accessible to the immune system afterwards, strategies should therefore be created. While targeting T cells with immune checkpoint inhibitor antagonist antibodies avoid some of the toxicity produced by cytokines, the effect of expressing immune virus co-stimulators on the surface of tumor cell should be more confined to the tumor cells. A safer solution may also be techniques that target the immune inhibitors.

5. Conclusion:

Cancer immunotherapy is most comprehensive method of treatment for cancer. In patients, CAR T cells and checkpoint blockade antibodies have shown impressive long lasting complete response, but patients still do not respond to treatment or rapidly relapse after treatment. [24] We now have a giant tool box for accessing combination therapeutics to evaluate the best choices to improve the immune system after decades of mapping the tumor microenvironment, designing novel immunostimulatory strategies and discoveries means to hamper immunosuppressive cells. The area of oncolytic virotherapy is expanding and, in combination with chemotherapy or other

therapeutic modalities, viruses continue to hold promise as successful therapy. Adeno-based targeted therapy and novel viral species are also emerging and worth pursuing to as continue work is being done to strengthen the currently available oncolytic viruses and FDA approval for engineering advancement.

In contrast to small molecular drugs, Viruses have unique and special properties. Besides carrying anti-tumoral therapeutic genes, they can replicate and spread. However, the human body has evolved ways to resolve infection over the course of evolution and this has put a major obstacle to the full therapeutic effectiveness of oncolytic viruses. Recent developments in our understanding of tumor biology and virology have helped solve some of these hurdles, and numerous groups have successfully targeted characteristics ranging from virus transmission to host immune response alteration. This joint effort is expected to eventually pave the way for the creation of successful and safe cancer therapy.

6. Conflicts Of Interest:

The authors declare no conflict of interest.

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