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REVIEW ARTICLE

Oncolytic Virus Therapy for the Treatment of Tumor Cells

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ABSTRACT

Oncolytic viral therapy is a new promising strategy against cancer. Oncolytic viruses (OVs) can replicate in cancer cells but not in normal cells, leading to lysis of the tumor mass. Beside this primary effect, OVs can also stimulate the immune system. The effectiveness of OVs has been demonstrated in many preclinical studies and recently in humans, with US Food and Drug Administration approval of the oncolytic herpesvirustalimogenelaherparepvecin advanced melanoma, a major breakthrough for the field. Several oncolytic viruses including canine distemper virus, adenovirus strains, and vaccinia virus strains have been used for canine cancer therapy in preclinical studies. These include pneumonitis, pancreatitis, and colitis, which are relatively infrequent but can limit therapeutic options for some patients. Intratumor injection of oncolytic viruses, in contrast, has a markedly lower rate of serious adverse effects and perhaps greater specificity to target tumor cells. In this review describes that therapeutic effectiveness and safety of the major oncolytic viruses are discussed.

Keywords: Oncolytic virus, cancer, immune system, tumor, Preclinical studies

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1. Introduction

Oncolytic viruses (OVs) comprise a diverse group of biologic agents with potential as cancer therapeutics. Numerous clinical trials are under way or have been completed using this approach. In 2015, in a milestone for the field, talimogenelaherparepvec became the first OV to gain US Food and Drug Administration (FDA) approval in the United States. However, the use of viruses for cancer treatment is not new. Throughout the century, case studies and small trials of various viruses in cancer therapy were reported. These investigations conducted with small numbers of patients used wild-type and of tencrudely prepared viral isolates, and it was not until the 1990s that the eraof genetic engineering of viruses to enhance their oncolytic potential began. The first reported genetically

engineered OV was based on herpessimplexvirustype1 (HSV1). This development was rapidly followed by many studies illustrating the effectiveness of this approach using a diverse range of viruses and tumormodels[1]. The main focus of the field during the early development of OVs was to identify viruses or their engineered variants with tumor-selective replication. However, it has always been appreciated that an immune component is important and may be critical for the therapeutic efficacy of this approach. Indeed, OVs are now broadly considered as immunotherapy agents for which effectiveness in patients depends on activation of host anti tumor immuneresponses[2].

The history of oncolytic virotherapy

Oncolytic virotherapy is the use of a replication-competent virus for the treatment of cancer. There are more than 3,000 species of viruses but not all are suitable as oncolytic agents. The OV must be non-pathogenic, have intrinsic cancer selective killing activity, or can be engineered to express attenuating genes or arming genes. Tumor selectivity could be at the level of receptor-mediated cell entry, intracellular antiviral responses and/or restriction factors that determine how susceptible the infected cell is to support viral gene expression and replication. Historically, there have been anecdotal reports of temporary tumor regression and cancer remission after the patient contracted natural viral infection, including responses of lymphoma after wild type measles virus infection[3].

In the 1950s–1970s, live viruses were deliberately injected into cancer patients and showed promising activity, particularly notable were Egypt 101 West Nile virus (4/34 transient regressions), adenovirus lysates (26/40 showing localized tumor necrosis), and Urabe strain mumps virus [37/90 complete remission or partial responses (PR)]. However, toxicity was also noted in these early studies using viral isolates that were not engineered for tumor selectivity, especially in immune suppressed patients with leukemia or lymphoma whereby 5 of 8 patients experienced severe encephalitis after receiving Egypt 101 isolate of West Nile virus[4].

Mechanism of action of Oncolytic virus

A general mechanistic understanding of OV action is emerging in which therapeutic efficacy is achieved by acombinationofselectivetumorcellkillingandestablishmentof anti-tumor immunity. Immune stimulation is caused by release of cell debris and viral antigens in the tumor micro environment. Tumors electivity in OV therapy is driven by several factors. The first of these is cellular entry a virus-specific, receptor-mediated mechanisms. A specific viral entry receptor is often highly expresse don tumor cells. However, there are also efforts to improve tumors electivity by retargeting OVs to enter cells through tumor-specific receptors. Second, rapid cell division in tumor cells with high metabolic and explicative activity may support increased viral replication compared with normal quiescentcells[5]. In addition, tumor-driver mutations specifically increase the selectivity of virus replication in tumor cells. Third, many tumor cells have efficiencies in antiviral type Iinterferonsignaling, therefore supporting selective virus replication.

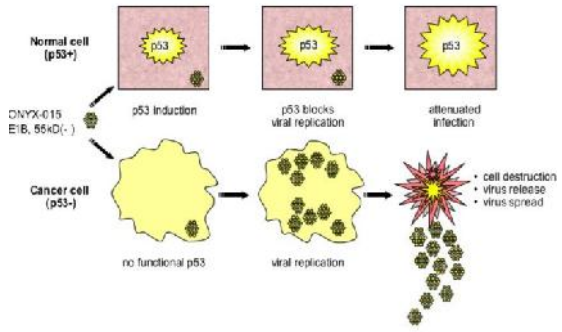

Fig 1: Mechanism of action of Oncolytic virus

Criteria for Selecting Oncolytic viruses against Tumors

- Pathogenesis of the oncolytic virus (biological behavior of the virus)
- Tumor type
- Tropism of the virus in relation to location of the tumor
- Presence of viral receptor in the target tumor cells.

Oncolytic Viruses

Literally, Onco- refers to cancer while Lytic- refers to killing v Oncolytic viruses (OVs) are viruses that have the ability to specifically infect and lyse cancer cells, while leaving normal cells uninfected[7]. Examples are;

- Adenovirus
- Measles virus
- Vaccinia virus
- Vesicular stomatitis virus (VSV)
- Reovirus
- Marabiala virus
- Coxsackie virus
- Newcastle disease virus (NDV)

Measles virus is a negative strand RNA paramyxovirus which is highly fusogenic and induces extensive cytopathic effects of syncytial formation. Intercellular fusion (F) increases bystander killing of tumor cells, and induces immunogenic danger signals which can elicit host mediated cellular antitumor activity. Recombinant Edmonston strain measles virus encoding the sodium iodide symporter (MVNIS) or soluble carcinoembryonic antigen (MV-CEA) are in Phase I/II clinical testing in patients with relapsed or recurrent cancers including multiple myeloma, ovarian cancer, glioma, breast cancer and mesothelioma. Intratumoral injections of Edmonston-Zagreb vaccine strain was also tested in 5 patients with cutaneous T cell lymphoma. Overall, no drug related dose limiting toxicities were observed in the trials even with high intravenous dosing, and in one study, MV-NIS induced complete remission of disseminated multiple myeloma after one systemic administration of 1011 infectious virus. Immunological analysis of peripheral blood T cells in ovarian cancer patients who received MV-NIS showed induction of tumor antigen specific cytotoxic T cells after measles virus therapy. A unique feature of MV-NIS is that it permits serial monitoring of the pharmacokinetics of viral replication in the infected tumors through noninvasive

SPECT or PET imaging, enabling validation of virus delivery and infection of tumor metastases[9]. Other MV engineering strategies include retargeting the H attachment glycoprotein (G) to obtain highly tumor selective viruses, encoding the wild type P accessory protein to enhance viral spread by antagonizing the host cellular antiviral immunity, potency enhancing cytotoxic genes to pair with a prodrug for chemo virotherapy, radiotracer enhancing transgene for imaging and radiosensitization (radio virotherapy), and immune modulatory transgenes such as anti-CTLA-4 and PDL-1 antibodies.

2. Vaccina virus

Vaccinia is a complex double-stranded DNA virus, brickshaped particles with a size of approximately 300 x 240 x 120 nm. Infectious vaccinia virus particles have a lipoprotein envelope surrounding a complex core of linear doublestranded DNA (191 636 bp, encodes for ~250 genes). Vaccinia encodes all the proteins it needs for its replication in its genome, some of which have immune evading properties allowing the virus to establish infection. Vaccinia virus enters the cell via fusion of viral and cellular membranes, which is mediated by entry-fusion complex. No specific receptor to facilitate entry of the virus into the cell has yet been discovered[10]. After the entry, viral particles are uncoated, and transcription of early genes by the viral RNA polymerase starts followed by the expression of intermediate and late genes.

Vesicular Stomatitis Virus:

Vesicular stomatitis virus selectivity is dependent on deficient interferon signaling. An engineered VSV variant over expressing interferon β is currently in a clinical trial for liver cancer. It isthought that interferon β may act synergistically with VSV by protecting normal cells frominfection and causing tumor cell–specific destruction and antitumor immune responses[11].

Reo virus:

Reovirus, is a segmented dsRNA consisting of 10 to12 segments, each generally encoding one protein. The virus has been broadly tested in oncolytic virotherapy of human cancers over the past decade. While its expansion in phase II and III clinical trials for treatment of human cancer patients, it has been hardly studied as a oncolytic agent in pet animals. Recently, in vitro study demonstrated for the first time that canine mast cell tumors (MCT) were highly susceptible to reovirus infectio. Furthermore, a single intratumoral injection of reovirus significantly regressed canine mast cell tumor xenografts. However, reovirus also infected normal canine mast cells raising safety concerns[12].

Marabillia virus:

Canine distemper virus (CDV) is an enveloped, negativesense single stranded RNA virus of the family Paramyxoviridae, closely related to human measles and rinderpest virus, that infects different cell types, including epithelial, mesenchymal, neuroendocrine and hematopoietic cells of various organs and tissues. It is a close relative of measles virus (MV). CDV is able to infect canine lymphoid cell lines, histiocytic sarcoma cell lines, such as DH82 cells. Moreover, CDV induced an increase of apoptotic cells in neoplastic lymphocytes in vitro. Historically, children with Hodgkin's disease were observed to experience regression after concurrent MV infection. These explanations stimulated the consideration of attenuated MV for the treatment of human lymphoma and, consequently, measles virus has revealed promising anti-tumor activity against a variety of malignant tumors in both preclinical and clinical studies[13]. Because of its similarity to MV, this finding underscore the possible relevance of CDV as an oncolytic agent and the formulation of the hypothesis that CDV represents a suitable candidate for a virus based therapy of tumors in dogs. CDV binds to the cellular receptor, the signaling lymphocyte activation molecule (SLAM or CD150), which is over-expressed on malignant canine B and T lymphocytes. Attenuated CDV was able to infect canine lymphoma cells in cell culture via binding to CD150 and to induce apoptosis in these cells.

Coxsackie virus:

Coxsackie virus is an enterovirus belonging to the Picornaviridæ family of nonenveloped viruses containing a linear, positive sense, single-stranded RNA genome. Because RNA viruses replicate in the host cytosol without a DNA phase, insertional mutagenesis is not possible. Coxsackie viruses are divided into two subgroups, A and B, based on pathogenicity in mice. At least 23 serotypes of group A and six serotypes of group B have been described. Coxsackie viruses are considered to be a minor human pathogen. Young children, aged five years and under, are more susceptible to coxsackie virus A disease, often produced by serotype A16. Infection of individuals occurs mainly via entry through exposed areas, such as the skin and mucosal surfaces (i.e., hands, feet, mouth, throat, and eyes). However, in most cases, infection is asymptomatic or elicits only mild disease associated with "common cold-like" symptoms. Various non-engineered strains of coxsackie virus from both groups are currently being tested as single oncolytic therapeutics or in combination with conventional chemotherapy drugs[14].

Newcastle disease virus (NDV)

NDV is an avian paramyxovirus and has been tested as an oncolytic or oncolysate cancer vaccine, for more than 50 years. NDV strains, MTH-68/H (veterinary vaccine strain), HUJ, a no virulentlento genic strain, and PV701, have been tested clinically. In the United States, PV701 has been given intravenously to 113 patients with advanced cancers in 3 Phase 1 trials. In a trial of 79 patients, a CR was observed for 1 patient, and a PR in 1 patient. It was also shown that higher doses of PV701 can be better tolerated with less infusion reactions if the patients first received a 5-10-fold lower dose for desensitization. Clinical development of a mesogenic strain (intermediate virulence) of NDV as an oncolytic agent for cancer therapy has been hampered by its select agent status due to its pathogenicity in avian species. As such, a recombinant NDV based on the mesogenic NDV73T strain with compromised infection of avian cells but not mammalian cells and encoding GM-CSF (Medimmune, MEDI5395) was generated and is in preclinical testing.

Clinical therapies of oncovirus

Immunomodulatory mechanisms of oncoviral therapy:

It is similar to other immunotherapies oncolytic viruses have a multimodal mechanism of action with both direct

and indirect toxic effects on tumor cells such as autolysis, immune cell honing, destruction of vascular supply and potentiation of other adjunctive anti-cancer therapies[15].

Vaccine mechanism of oncoviral therapy:

The concept of tumor vaccination has existed for some time; however, the mechanistic considerations of how to effectively prime and activate the immune system against tumor cells have not translated into major clinical success. The underlying physiology of this process consists of immune conditioning and generation of memory T-cell responses by exposing antigens that are expressed robustly and specifically in the target tissue. The use of viruses to deliver antigens is beneficial as the encoded genetic material is well conserved during infection and subsequent translation. In particular, a multifaceted response to tumor antigens released following necrosis and apoptosis results from exposure to PAMPs, danger associated molecular patterns (DAMPs: such as heat shock proteins, uric acid, calreticulin, HMGB-1), and cytokines (such as IFN 1, interleukin 12, and TNF α).

Consequent to this, vigorous antigen presenting cell maturation occurs which then cascades to CD4+ and CD8+ T-cell activation[16]. CD4+ and CD8+ T-cell responses can mediate global anti-tumor effects at distant loci and direct tumor cell killing. Immune conditioning has been explored as in the case of Newcastle DiseaseVirus transfection in IFN-depleted lung tumor cells which can modulate genetic transcription of IFN β. Additional studies in animal models and early human trials have shown that oncolytic viruses can produce antibody mediated, complement dependent, and tumor-cell specific cytotoxicity. The consequences of this include triggering of autophagy or apoptosis, recruitment of lymphocytes and phagocytic cells, and direct toxic injury from inflammatory cytokines. This has previously been described as creating an "immune storm" within a tumor to augment antigen recognition that can lead to lesion debunking and facilitate adjuvant therapies. Moreover, this can theoretically be further harnessed and tailored to target tumors by genetic manipulation. Consequently the use of an oncolytic virus can be used as an effective tumor vaccine[17].

Oncolytic viruses as adjuvant therapy

Another avenue by which oncolytic viruses can impact oncologic care is by functioning as a therapeutic adjuvant. Concomitant administration with other therapies may have two primary mechanisms: augmenting other immune therapeutics and overcoming primary resistance patterns.The enhancement of other immunotherapies is potentially mediated by the creation of a pro-inflammatory milieu able to upregulate the targets for additional interventions such as co-regulatory checkpoint blockade. Consistent with this notion, CTLA-4 and PD-L1 are known to be increased at and mediate peripheral immune tolerance upon inflammation or tissue damage. Adjuvant administration of oncolytic viruses upregulate the expression of pro-inflammatory cytokines such as IFNγ which would in turn increase JAK 1/2 signaling and antigen expression to augment tumor response to checkpoint blockade[18]. This has been shown to be clinically beneficial in initial trials where an adjunctive oncolytic virus with CTLA-4 or PD-1 inhibition was superior to either monotherapy. Furthermore, early phase clinical trial suggest oncolytic viruses in conjunction with PD-1 inhibition can mold the tumor cell niche to be more susceptible to other non-immune anticancer treatments. Patients showing tumor response when treated with these agents display typically higher tumor-infiltrating lymphocyte counts (independent of baseline level) as well as upregulation of PD-L1 and IFNγ.

3. Systemic effects of oncoviral therapy

An intriguing finding in the study of oncolytic viruses has been the effects on distant metastases in patients with locally inoculated lesions, a phenomenon commonly known as "abscopal" effect. The range of oncolytic viral transfection is unquestionably limited to a locoregional distribution as has been demonstrated in multiple animal and human models where metastatic lesions have been sampled and proven to be absent of viral DNA or RNA. However, the impact of oncolytic viruses has been found to extend to loci devoid of virus causing regression or delayed tumor growth. It is unclear how this effect occurs and whether it ismediated directly by an unidentified and yet unmeasured viral product, by crossed-antigenic reaction or as a consequence of global immune conditioning/ stimulation. Although recruitment of tumor infiltrating lymphocytes to distant uninjected metastatic sites after oncoviral injection has been consistently documented, the characteristics of the immune response differ from that of the primary site. One animal study illustrated the infiltration of CD8+ and CD 4+ T-cells at the remote lesions in an IFN I dependent manner though regulatory T-cells were absent despite being noted at the site of inoculation. **Current approaches to delivery of oncolytic viruses**

One of the greatest challenges for effective oncoviral therapy has been sufficient drug delivery. There is exceptionally poor bioavailability of systemically administered oncolytic viruses. Moreover, even in the case of intravenous delivery the host immune system rapidly sequesters and degrades the attenuated virus through the reticuloendothelial system lead by red pulp macrophages in the spleen and Kupffer cells of the liver. Viral particles are opsonized by antibodies, complement, and other factors to enhance endothelial cell and macrophage binding and phagocytosis. Of note, there are no reports of poor dose tolerance to oncoviral therapy or reverted virulence by the inactivated particulates.

Balancing the degree of local immunosuppression provides a complex challenge in oncoviral therapy[19]. On one end immunosuppression can increase intratumoral distribution of the therapy. Conversely, augmentation of the host immune system will enhance targeting of transfected tumor cells but the intratumoral viral spread will be pruned. Consequently and to date, the only route by which oncoviral therapies have been delivered in sufficient quantity to be clinically efficacious is via loco-regional or direct inoculation[20].

4. Conclusion

The substantial prevalence and death associated with cancers continue to challenge modern medicine to develop more reliable therapies. One of the greatest hopeful novels cancer therapies is oncolytic virotherapy. This process is based on the capability of OVs to infect and lyse tumor cells and to initiate tumor-specific immunity. Oncolytic viruses including human and canine adenoviruses, canine distemper virus (CDV), reovirus and vaccinia virus strains have been tested with substantial results in preclinical studies. The evolution of oncologic therapies has led to increasingly targeted and nuanced regimens that seek to impose maximal impact on malignant cells, while simultaneously sparing collateral non-tumor tissues and minimizing adverse effects. This is most prominent in the rapid development within the realm of immunotherapy where the preponderance of efforts to date has utilized systemic agents.

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