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Review Article

A Promising Modality of Oncolytic Virotherapy for Cancer Treatment

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Abstract

Tumors are complex entities that continue to challenge modern medicine to develop more effective cancer therapies. Oncolytic virotherapy is a relatively new and thriving field of therapy targeted towards curing cancer by using the infamous viruses to selectively infect and kill tumor cells. Better resistance and specificity to tumor cells as well as their multiple mechanisms of cytotoxicity compared to contemporary means of 9oncotherapy present oncolytic virotherapy as a fascinating and viable field of scientific inquisition in the persistence battle with cancer. Even though it is state of the art in cancer therapy, virotherapy has some fall shorts. This include activation of the immune system to oncolytic viruses, inability to remove all metastatic cells, demands of combination therapy for real efficacy and, lack of cell culture and animal tumor models that accurately reflect the characteristics of cancerous tissues in human patients. To overcome these constraints, detailed understanding about manipulation of: the viral genetic makeup, biology of abnormally growing tumor cells and the complex system of the host's natural immune response mechanisms for their tumor selectivity and mechanisms of action is necessary.

INTRODUCTION

Despite the fact that cancer therapies have significantly improved, traditional cancer treatments which include radiotherapy, chemotherapy, and surgery up to date have limited effects against many forms of cancer, without mentioning a plethora of unpleasant treatment related side effects. This situation shows the need for novel and more refined treatment strategies that can selectively kill tumor cells without harming normal cells and one such approach is oncolytic virotherapy [1].

Oncolytic virotherapy is a promising new treatment approach which is based on selective replication of viruses in cancer cells and their subsequent spread within a tumor without causing damage to normal tissue [2]. It is a unique class of cancer therapeutics with different mechanisms of action that involves using nature's own agents to fight back malignant cells [3]. Based on their preferential replication in tumor cells, viruses from nine families have progressed to clinical trials of oncolysis: DNA viruses include *Adenoviridae*, *Herpesviridae*, *Parvoviridae*, and *Poxviridae* and RNA viruses *Paramyxoviridae*, *Picornaviridae*, *Reoviridae*, *Retroviridae*, and *Rhabdoviridae* [4]. These viruses have shown encouraging safety results but their efficacy as a single agent is limited, showing that they are not potent enough as monotherapies to render complete tumor regressions or to induce sustained clinical responses [5].

Despite this, several major advances have been made to improve the selectivity and efficacy of oncolytic viruses. Thereforethe intent of this review is to compile literatures on the potentials of oncolytic viruses as cancer therapy and limitation associated with Virotherapy.

ONCOLYTIC VIROTHERAPY FOR TREATMENT OF CANCER

Oncolytic viruses represent an emerging class of cancer therapeutics that are naturally occurringor engineered viruses having the potential to specifically infect and replicate in tumor cells while leaving healthy cells unharmed [6]. In addition to their direct oncolytic activity, OVs also induce immune responses to themselves and to the infected tumor cells [3].

Typically, viruses implemented in oncolytic viral therapy fall into two broad categories. The first categories are wild type animal viruses that are cytotoxic to human cancer cells and preferentially replicate in cancer cells but do not typically infect normal cells often due to elevated sensitivity to innate antiviral signaling or dependence on oncogenic signaling pathways. These include autonomous *parvoviruses, myxoma virus* (MYXV*; poxvirus*), *Newcastle disease virus* (NDV*; paramyxovirus)*, *reovirus*, and *Seneca valley virus* (SVV*; picornavirus*). The second category are viruses that have been attenuated by serial passage in culture, or that are genetically manipulated for use as vaccine vectors, including *measles virus* (MV; *paramyxovirus*), *poliovirus* (PV; *picornavirus*), and *vaccinia virus* (VV; *poxvirus*), and/or those human viruses in which important genes that are not required for virus replication in tumor cells have been genetically engineered with mutations/ deletions. These include *Adenovirus* (Ad), *herpes simplex virus* (HSV), VV, and *vesicular stomatitis virus* (VSV; *rhabdovirus*) [2]. Many of the distinguishing characteristics of cancer, which include resisting apoptosis, limitless replication potential, insensitivity to growth inhibition, genome instability,

DNA damage stress, and avoiding immune destruction, provide an appropriate and necessary environment for OVs [7].

ADVANTAGES OF USING ONCOLYTIC VIRUSES FOR CANCER TREATMENT

OVs have many features that make them advantageous and distinct from current therapeutic modalities. These are a low probability for the generation of resistance, as OVs often target multiple oncogenic pathways and use multiple means for cytotoxicity, their replication in a tumor selective fashion and relatively non-pathogenicity. The other advantages is virus dose in the tumor rises with time because of in vitro virus amplification, unlike classical drug pharmacokinetics that decrease with time and lastly safety features can be built in, such as drug and immune sensitivity [3].

Oncolytic viruses can enable scientists to overcome one of the biggest challenges in treating cancer that is to specifically target cancerous site without harming the surrounding normal cells. If problems associated with effectiveness of the drug and the host immune responses are well addressed, oncolytic viruses will serve as powerful tools to fight cancer [2].

CRITERIA FOR SELECTION OF ONCOLYTIC VIRUSES

Even though, viral oncotherapy has incredible potential for disease treatment, yet for successful application, in addition to their preference to replicate in tumor cells, the viral agents need to meet stringent criteria for safety and efficacy [8]. The first thing that need due thought for selecting viruses for oncotherapy is safety, to plan a safe oncolytic viral selection, certain criteria ought to be given due consideration. These incorporate tumor specificity, odds of regaining pathogenicity, plausibility of transmission to healthy individual, undesired side effects and pre-existing immunity [9].

The second main factors that need to be considered in choosing oncolytic viruses are efficacy. The efficacy of OVs helps to achieve the other major goal of viral therapy that is complete regression of cancer cells. Efficacy can be further enhanced by developing strategies for efficient delivery of viruses and overcoming the host antiviral immune reaction. Approaches to prevent antiviral response include serotype switching, which is administration of different viral serotypes during treatment cycle [10] and modification of amino groups with the aid of mixing viral particles with polymers so that antibody cannot recognize the virus particle (polymer coating) and use of cellular vehicles [11].

MECHANISMS OF ACTION OF ONCOLYTIC VIRUSES

There are many mechanisms by which OVs result in cell death of infected cancer cells, including direct lysis, initiation of apoptosis, pyroptosis (caspase-1-dependent cell death), autophagic cell death, and necrosis, which is often dependent on the virus type, the cancer cell type or a combination of both. Antitumor effects of oncolytic viruse has generally two considerable components, the first one is direct lysis of both virally infected and non-infected neoplastic cells and the second one being initiation of the systemic immune response to virally-induced cell destruction within the tumor [12].

Molecules like cytokines, tumor-associated antigens, and other danger signals, including damage-associated molecular pattern molecule and pathogen-associated molecular pattern molecules are released during OV-mediated cell death. The host immune response to these molecules with local release of cytotoxic perforins and granzymes that can destroy nearby non-virally infected tumor cells, and this is known as “immune-associated” bystander effect [13].

Tumor associated antigen, which can include mutated proteins, fusion proteins, and tissue- and/or cancer-specific overexpressed proteins, function as weak antigens and they are released following direct oncolysis of virus-infected tumor cells [14]. Virally mediated cell death of cancer cells activateand prime the host immune system against Tumor associated antigen. These results in antitumor effects by cytotoxic CD8+ T cell at distant tumor sites that were not locally treated with the virus when the host immune system is activated and primed against tumor associated antigen [15]. DAMPs, including adenosine triphosphate, calreticulin, heat shock proteins, and high mobility group box 1 protein as well as OV-specific PAMPs are also released due to virally-mediated cell death by necrosis and autophagy [13]. In addition to what has been said, natural killer (NK) cells response against tumor cells could also be stimulated directly by type I IFNs and DAMPs, showing one instance of how post OV treatment also involves the innate immune system in the antitumor response [17].

LIMITATIONS OF ONCOLYTIC VIRUSES AS CANCER THERAPY

Figure 1 Several viruses have been shown to possess oncolytic abilities but as with almost any new therapeutic strategy, there are several challenges in the field of oncolytic virotherapy that need to be addressed. Getting viruses to the site of the tumor has been difficult to understand since most experiments require injecting high viral titers directly into the tumor site. The efficacy of eliminating metastasized cancer by using oncolytic therapy may be very low since all cancerous cells must be removed to prevent relapses. Systemic delivery of oncolytic viruses via IV injection is difficult because of viral tropism and activation of the immune system upon viremia [18].

The process of immunogenic cell death induced by OV infection, that enables to effectively activate the host immune system against cancer cells, can also be harmful to continual replication of Oncolytic viruses. Antibodies secreted against viral PAMPs and/or cytotoxic T cells that recognize viral PAMPs can destroy OVs as a result of the systemic antitumor response [17].

In addition to oncolytic viruses, the optimal treatment regimen in most cases probably includes a combination of radiation, chemo- or immunotherapy. However, while apparently effective, the combination of two or more treatment modalities in one host may introduce additional variables into an already complex equation, possibly with threatening consequences.One prominent concern is the use of replication-competent viruses in patients with compromised immunity e.g. after radiation therapy.

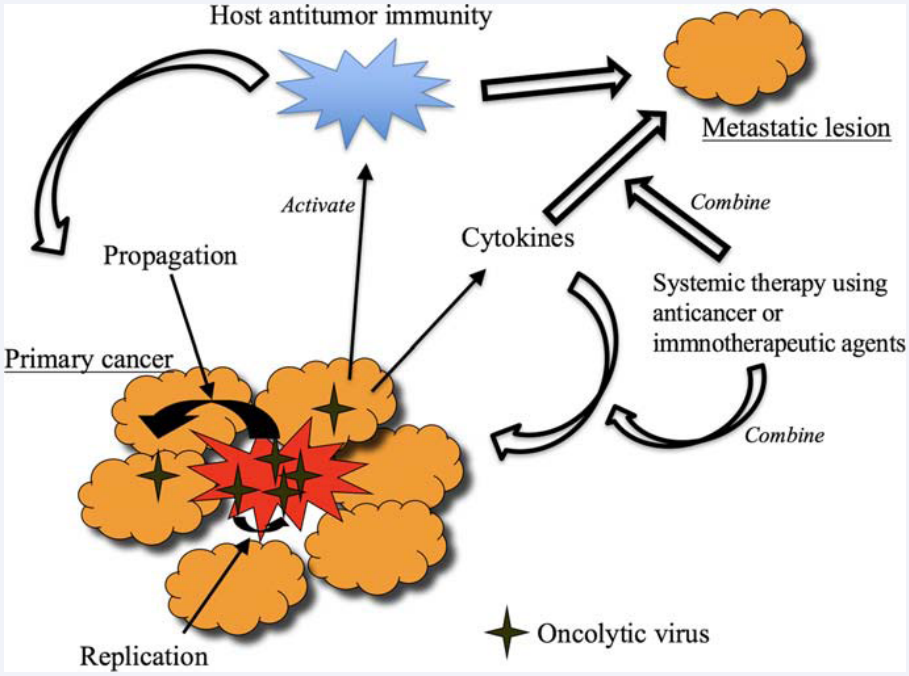

Figure 1 Mechanisms of action of oncolytic virus therapy. Local replicationof oncolytic virus induces specific antitumor immunity in thecourse of its oncolytic activities that act on remote lesions. A combinationwith immune checkpoint inhibitors or chemotherapy mayenhance the efficacy of oncolytic virus therapy, becauseinduction of T cell response alone is not sufficient for sustained antitumor effect [17].

On the other hand, significant obstacles towards the application of safe and efficacious viral therapies have become apparent. These frequently relate to the lack of cell culture and animal tumor models that accurately reflect the characteristics of cancerous tissues in human patients. Viral agents administered IV can be particularly effective against metastatic cancers, which are especially difficult to treat conventionally. However, blood-borne viruses can be deactivated by antibodies and cleared from the blood stream quickly e.g. by Kupffer cells; extremely active phagocytic cells in the liver, which are responsible for adenovirus clearance. Avoidance of the immune system until the tumor is destroyed could be the biggest obstacle to the success of oncolytic virus therapy [18].

Recent discoveries in cancer immunotherapy have shown that induction of T cell response alone is not sufficient for sustained antitumor effect, combination of OVs with T cell checkpoint inhibitors is possibly the most promising suppression of T cell inhibitory mechanisms by inhibiting T cell checkpoint factors, such as CTLA4 and programed death (PD-1) can be useful in light of the immunosuppressive nature of advanced tumors [19]

CURRENT STATUS OF CLINICAL TRIALS

The first oncolytic virus launched for clinical use was another E1B gene-deleted adenovirus termed H101 (Oncorine). Based on the results of a phase III clinical trial in patients with squamous cell cancers of the head and neck or esophagus, H101 was approved by the Chinese FDA in 2006, but was not approved in Western countries [20,21]

T-Vec (talimogene laherparepvec), a second-generation oncolytic herpes simplex virus type 1 (HSV-1) armed with GM-CSF, was recently approved as the first oncolytic virus drug in the USA and Europe. The phase III trial proved that local intralesional injections with T-Vec in advanced malignant melanoma patients can not only suppress the growth of injected tumors but also act systemically and prolong overall survival [22] based on the promising results of a phase III clinical trial [23] This virus, given the brand name Imlygic, was subsequently approved in Europe and Australia in 2016.

Many types of oncolytic viruses have undergone preclinical studies for the treatment of urological cancers, as well as other malignancies, and some have already been tested in clinical trials [24-26]. For example, a phase I trial of the third-generation oncolytic HSV-1, G47D, in patients with prostate cancer was started in 2013 and completed in 2016.

Other oncolytic viruses that are closing in on drug approval in North America and Europe include vaccinia virus JX-594 (pexastimogene devacirepvec) for hepatocellular carcinoma, GM-CSFexpressing adenovirus CG0070 for bladder cancer, and Reolysin (pelareorep), a wild-type variant of reovirus, for head and neck cancer. In Japan, a phase II clinical trial of G47Δ, a third-generation oncolytic HSV-1, is ongoing in glioblastoma patients [27].

CONCLUSION AND RECOMMENDATIONS

Viruses are rapidly emerging as a promising new modality in the fight against cancer. The use of OVs in the treatment of neoplasms following their wide diversity and successful use in preclinical studies has become an increasingly encouraging area of investigation. The primary advantage of oncolytic viral therapy has been the ability to selectively target tumor cells with minimal

damage and toxicity to the surrounding normal tissue. The safety profiles of these viruses coupled with their ability to amplify their dose through replication at the target site, and then spread within the tumor to lyse neoplastic cells and decrease the tumor burden turn them into unique anticancer therapeutics. OVs therefore have much to offer as anticancer agents. A large number and variety of OVs might become available to clinical oncologists, to be used as single agents or in combined regimens with drugs and radiation for maximum effect.

- To overcome potential or identified deficiencies of the virotherapy in the clinical setting, more advancing genetic engineering (taming) of oncolytic viruses are the best option.
- Further investigation is necessary for better understanding the mechanisms of action of oncolytic viruses and tumor microenvironment to achieve wide therapeutic index and maximum efficacy.

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