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RESEARCH ARTICLE

ONCOLYTIC VIROTHERAPY FOR CANCER TREATMENT

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ABSTRACT

Oncolytic virotherapy is a new strategy to reduce tumor burden through selective virus replication in rapidly proliferating cells. The nature of viral delivery, infection, and replication makes oncolytic virotherapy valuable for treating cancer patients, especially those with inoperable tumors. Oncolytic virotherapy is an emerging technology that uses engineer edviruses to treat malignancies. Viruses can be designed with biological specificity to infect cancerous cells preferentially, and to replicate in these cells exclusively. In this review, we describe the basis of oncolytic virotherapy, it's history and the mechanisms by which oncolytic viruses destroy malignant cells and their selection. We also summarize various oncolytic virus and their properties along with oncolytic virotherapy clinical trials and their success rate. We conclude with current challenges and future research in oncolytic virotherapy.

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INTRODUCTION

Virotherapy is an experimental form of cancer treatment using biotechnology to convert viruses into cancer fighting agents by reprogramming viruses to attack cancerous cells, while healthy cells remained relatively undamaged. There are three main branches of virotherapy: anti-cancer oncolytic viruses, viral vectors for gene therapy and viral immunotherapy. Oncolytic Viortherapy is modifying existing viruses to create new oncolytic viruses that are less susceptible to immune suppression while more specifically targeting particular classes of cancer cells. Additionally, these modified oncolytic viruses can be adapted to insert and express cancer suppressing genes and diagnostic proteins. Oncolytic viruses kill cancer cells by selectively targeting tumor cells through engineered mutations that prevent their binding to and replication in normal cells (Visvader and Lindeman, 2012), and/or expressing foreign genes that cause cell death, directly or indirectly (Zeyaullah *et al*., 2012). Many different viruses are used in oncolytic virotherapy. The use of genetically engineered, tumor targeting viruses as oncolytic agents recently has emerged as a promising new area for novel cancer therapies.

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The first viruses to enter the clinic, such as ONYX-015 (an oncolytic adenovirus), demonstrated both the safety and anti-tumor potential of this approach. The past 20 years have witnessed great progress in the development of virus-based cancer therapies with oncolytic viruses belonging to at least ten virus families and many entering the clinical arena. Today, researchers can modify existing viruses to create new oncolytic viruses that are less susceptible to immune suppression while more specifically targeting particular classes of cancer cells.

HISTORY

In early mid 1950s doctors were noticing that cancer patients who suffered a non-related viral infection, or who had been vaccinated recently, showed signs of improvement (Moore, 1949). In the 1940s-50s some of the earliest human clinical trials with oncolytic viruses were started (Huebner *et al*., 1956). Research in this field was limited due to technological limitations. After the 1960's, oncolytic virotherapy was almost entirely abandoned due to the lack of clear and promising results from clinical trials. Now, as genetic engineering has advanced so enormously and rapidly, it has revived interest in oncolytic virotherapy. An increased understanding of virology, as well as experience using viruses in cancer gene therapy, has prompted a new wave of oncolytic virotherapy.

MECHANISM AND SELECTION

There are several different effective mechanisms by which oncolytic viruses destroy malignant cells. The virus itself can destroy tumor cells by replicating. This cycle then can repeat, by infection of adjacent cells and their subsequent destruction by the same mechanism. This feature of viral replication provides continuous amplification of the input dose which continues until stopped by the immune response or a lack of susceptible cells (John *et al*., 2002). The second mechanism, in which some oncolytic viruses synthesize certain proteins during replication that are directly cytotoxic to cancer cells. For example, adenoviruses generate the death protein E3 11.6 kD and the E4ORF4 protein late in the cell cycle; both these proteins are toxic to cell (Tollefson *et al*., 1996 and Shtrichman *et al*., 1998). The third mechanism by which oncolytic viruses act is by initiating specific and nonspecific anti-tumor immune responses. As we know, tumor cells are inherently weakly immunogenic because they express low levels of major histocompatibility complex (MHC) antigens and stimulatory signals such as cytokines which activate a local immune response. Adenoviruses express E1A protein during replication, which mediates killing of tumor cells by increasing their sensitivity to tumor necrosis factor (TNF) (Shtrichman and Kleinberger, 1998). Induction of specific anti-tumor immunity might result in long-term defense against cancer recurrence. Viral peptides are presented on the cell surface with MHC class 1 proteins; this complex is recognized by cytotoxic T lymphocytes, which are attracted to the virally transduced tumor cell. These cytotoxic T lymphocytes then acquire specificity for cancer-specific antigens and kill the cells by a still unknown mechanism (Gooding, 1994).

Viruses are engineered to target specific cell surface receptors or nuclear transcription factors, their use is thereafter limited to tumors that express the relevant target, but so far there has been a preference for clinical translation of oncolytic viruses with broader host-range spectra. Safety considerations must drive the choice of a virus for a given indication. Different viruses have differing toxicities, and genetic manipulation may lead to unexpected toxicities. Important factors to be considered in the safety analysis of oncolytic viruses include natural and engineered virus tropism, virus mutability and capacity for evolution and transmissibility, immunomodulatory, antiapoptotic, and cytotoxic gene products, prevalence of population-based antiviral immunity, and the availability of drugs or antisera to eliminate unwanted or persistent infections.

ONCOLYTIC VIRUS

Oncolytic viruses belong to various families. They undergo different engineered modifications, which are designed to enhance tumor selectivity, improve intratumoral replication, modify immune responses, enhance vascular delivery, and express antitumorigenic genes that function independently of virus replication. The following are the three best studyied oncolytic viruses. Adenovirus, it's a non enveloped, non integrated, double stranded DNA virus that has been extensively studied for its oncolytic potential. It has a wide host-cell range and large genomic capacity, but it show Coxsackie adenovirus receptor (CAR) variability in human cancers and expression on normal cells, preexisting antiviral immunity, hepatic adsorption, toxicity. Vaccinia virus, it has wide host-cell range, large genomic capacity and established vaccine potential but it face difficulties with systemic delivery. Herpes Simplex Virus, it has wide host-cell range, large genomic capacity, neurotropism, ability to evade preexisting antiviral immunity and available antiviral drugs but it show hepatic adsorption (Toda *et al*., 1999). Other viruses in clinical trials include Coxsackie virus (CVA21), measles virus (Edmonston), parvovirus, poliovirus (Sabin), retrovirus.

CLINICAL TRIALS

The earliest human clinical trials with oncolytic viruses were started in the 1940s-50s(4). Oncolytic virotherapy has some success, even at this early stage. Now herpes virus and adenovirus are being evaluated in ongoing clinical trials for intractable cancers (Deanna Cross and James K. Burmester, 2004). The most famous adenoviral therapy is ONYX-015 viral therapy. ONYX-015 is a manipulated adenovirus that lacks the viral E1B protein (Rudin *et al*., 2003). Without this protein, the virus is incapable of replicating in cells with a functioning p53 pathway. In most tumors, this pathway is deficient due to mutations, thus allowing ONYX-015 to replicate and lyse the cancer cells (Bischoff *et al*., 1996). In squamous cell carcinoma of the head and neck, ONYX-015 has been used in phase I and II trials, resulting in tumor regression which correlated to the p53 status of the cancer. Tumors with an inactive p53 pathway had a better response (Nemunaitis *et al*., 2000). ONYX-015, combined with chemotherapy in phase II, produced an even better tumor response, leading to phase III trials (Lamont *et al*., 2000). NV1020, a derivative originally used for vaccine projects, has various mutations, including a deletion in the thymidine kinase region and a deletion across the long and short components of the genome, as well as an insertion of thymidine kinase gene under the control of the α4 promoter (Cozzi *et al*., 2001).

NV1020 is in phase I and phase II clinical trials for the treatment of colorectal cancer metastases to the liver. G207 is mutated so that it has attenuated neurovirulence and incapable of replicating in nondividing cells. G207 is being tested in treatment of malignant glioma in a phase I clinical trial (Cassel *et al*., 1983). Vaccinia-GM-CSF virus with insertion of GM-CSF and lac Z genes into viral TK locus is researched for treating Melanoma , this study is currently under phase I and phase II clinical trials (Miyatake *et al*., 1999). CV707 and CV787 with ADV 5 strain are being researched for organ confined and metastatic Prostate cancer (Papanastassiou *et al*., 2002 and MacKie *et al*., 2001). Various factors in oncolytic virotherapy must be considered during the planning of clinical trial, such as tumor type, the presence of viral receptors in the targeted tissue, the genetic disturbances of cancer, previous exposure to vector related viruses, concurrent viral infection, and the patient's immune status.

CHALLENGES

The fact that oncolytic virotherapy has not yet entered the mainstream of medicine reflects numerous technical and biological challenges. As true for any drugs and agent systemic

delivery is subject to non specific and non target binding, such as in the blood components ,vessel walls, lungs, and heart between the site of delivery and the targeted tumors. Viruses that are extremely specific are yet to be created so that intravenous delivery can be possible by avoiding these drawbacks. Combination therapy with drugs, radiation, monoclonal antibodies, small molecule inhibitors, and/or other oncolytic viruses can have increased efficacy. For example, viruses can sensitize cells to radiation, and radiation can enhance viral infection, replication, and gene expression, resulting in greater tumor cell death (Touchefeu *et al*., 2011). It would be better for the patient if one or more combinations of oncolytic virus therapy, radiotherapy, targeted chemotherapy, antisense therapy and antibody therapy could be delivered as single entity. In addition, when combined with cytotoxic gene expression, oncolytic virotherapy can affect not only rapidly dividing cells, but those in the surrounding tissue, making the microenvironment less favorable for cancer growth (Deanna Cross and James K. Burmester, 2004). These are the key targets that are needed to be achieved, but first of all, we must ensure that oncolytic virotherapy is easy to use, effective and economically viable.

Future research

In the era of modern biotechnology and with better understanding of cancer biology and virology, it has become feasible to engineer the oncolytic viruses to increase their tumour selectivity and enhance their oncolytic activity. Intravenous delivery is probably the most convenient and inexpensive route. A great deal of research is targeted at increasing tumor delivery and decreasing toxicity of intravenously administered oncolytic viruses. Monoclonal antibodies and small-molecule inhibitors can complement oncolytic virotherapy by altering regulatory pathways, increasing viral replication, and enhancing the induction of apoptosis (Nguyen *et al*., 2009). While numerous engineering modifications have already been done, these viruses have yielded limited results in terms of clinical efficacy, strategies are being researched to improve virus delivery, tumor specificity and penetration, reduce virus clearance, and increase the tumor-directed immune response.

Conclusion

Oncolytic virotherapy is a complex but promising emerging field within oncology. Many clinical trials around the world have had good results with high success rates using oncolytic virotherapy, and many more clinical trials are in progress with new viral vectors for the treatment of intractable cancers. Significant active research is being done to improve the accessibility, safety and efficacy of oncolytic virotherapy. Oncolytic virotherapy suffer a slow growth since it's begning due to technological limitation. Recent advances in molecular biology, and other large-scale genome modification tools have made is possible to construct heavily engineered oncolytic vectors and therefore it might prove to be ultimate cure for cancer.

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