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Review of The Basis for Oncolytic Virotherapy and Development of the Genetically Modified Tumor-Specific Viruses

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Abstract

As a hard-to-treat complicated condition, cancer was treated through the surgical removal techniques before the early twentieth century. Thereafter, a combination of surgical removal and chemotherapy, radiotherapy, and immunotherapy served this purpose. In addition, virotherapy was born of the advances in molecular biology and genetics. Improved tumorspecificity, targeted delivery, and increased efficiency have been the fruits of the genetic modifications of oncolytic viruses, which have resulted in the development of new weapons against cancer, especially for patients with cancerous inoperable tumors. This paper presents a review of the basis for oncolytic virotherapy and development of the genetically modified tumor-specific viruses. A discussion on the contribution of oncolytic virotherapy to the treatment of cancer, clinical trials and the success of rate of these trials is also presented. The conclusion section addresses the safety concerns articulated through the previous trials and the current and future challenges to oncolyticvirotherapy.

Keywords: Cancer; Oncolytic Viruses; Cancer Therapy

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Introduction

Cancer (excluding skin cancer) has incidence and mortality rates of 10,055.6 per 100,000 people and 6,208.7 per 100,000 people, respectively [1]. It is a complex difficult-to-cure disease. Moreover, significant advances in cancer therapy (including surgery, radiotherapy, chemotherapy and immunotherapy) were made in the early 1900s. None of these treatments covered all tumors at all stages. Tumors could neither be removed surgically nor treated at all times by dint of the high-energy radiation beams or intravenous poisoning. Even the combination of these proved to be ineffective.

History and Fundamentals of Virotherapy

Our understanding of the genetic basis for human diseases has improved significantly in the past decade. However, cancer genetics, which explains the complexity of human malignancies through the explosion of genomic sequences and molecular profiling data, has been affected most profoundly. This complication often interferes with the therapeutic regimes. Hence, it is reasonable to conclude that improvements in the current success rate rely on the sophisticated therapeutic methods that invade cancer cells in multiple targeted ways. The Oncolytic Viruses (OVs), which have the intrinsic ability to selectively replicate in and kill cancer cells, have been used to treat primary and metastatic cancers, staging a tremendous potential for revolutionizing the management of what has become a human disaster. A number of viruses are being developed around the world for this purpose [2]. Viruses were not accidentally used to treat cancer. Rather, observations revealed that, sometimes, cancer patients, who were also

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suffering from an infectious comorbidity experienced brief periods of clinical remission. For instance, as regards leukemia, it was found out that infection with the influenza virus occasionally had beneficial effects [3-4]. In addition, despite the lack of reports on the complete treatment of leukemia with infectious comorbidities, treatments based on causative agents were expected to comprise the alternative to the ordinary treatments for leukemia [3].

The first clinical trials involved the transmittance of body fluids containing viral particles to other cancer patients and observation of the results without knowledge of their biological behavior. Viruses were destroyed and eliminated by the immune system, hence the cessation of the growth of malignant cells. Many efforts were made in the 1950s and 1960s to develop viruses with greater tumor specificity [5]. Murine Sarcoma 180 was completely destroyed when treated with oncolytic viruses, which was a prominent a landmark in the history of virotherapy [6]. A new wave of oncolytic virotherapy has been triggered by the deeper insight into virology and the experience of using viruses in gene therapy. In recent years, a promising treatment for cancer involves the use of genetically engineered tumor-specific viruses that function as oncolytic agents. ONYX-015 (an oncolytic adenovirus) was the first oncolytic virus that proved the safety and the antitumoral potential of this approach [5].

Mechanism of Antitumoral Efficacy of Oncolytic Viruses

Oncolytic viruses use various mechanisms to destroy cancer cells. Replication is one of these mechanisms. The initial infection of only a few tumor cells prompts a chain reaction, resulting in the destruction of the surrounding tumor cells. Subsequently, the replication of the virus selected for the tumor cells stops and the normal tissue is spared as soon as the virus reaches the surrounding normal tissue and infects it. The input dose is by virtue of viral replication amplified continuously until stopped by the immune response or by a lack of susceptible cells [6]. Besides, some oncolytic viruses synthesize certain proteins that are directly cytotoxic to the tumor cells during their replication. Specific and nonspecific antitumoral immune responses are also provoked as a result. Given that tumor cells concurrently express low levels of the histocompatibility complex (MHC) antigens and make signals (such as cytokines activating local immune responses), they have poor inherent immunogenic characteristics. Protein E1A, which mediates the eradication of tumor cells by increasing their sensitivity to the tumor neurosis factor (TNF), is expressed by adenoviruses express during replication [7]. Viral peptides are marked on the cell surface with MHC class 1 proteins; this complex is recognized by cytotoxic T lymphocytes (CTLs) that are attracted by the virally transduced tumor cells. These cells improve the specificity of tumor-specific antigens, resulting in the demise of cells through an unknown mechanism [6].

Four mechanisms through which oncolytic viruses can lyse the tumor cells enhance the sensitivity of tumor cells to chemotherapy and radiation therapy. An example is the adenoviral E1A gene product. This powerful chemosensitizer is present in cells by functional p53. It makes these cells susceptible to DNA damage from chemotherapy and radiation by inducing high levels of p53 in them. Normal, non-transformed cells remain unaffected. In the absence of functional p53, this gene product sensitizes tumor cells to chemotherapeutic agents through an unknown mechanism [8].

The expression of therapeutic transgenes inserted into the viral genome comprises the last mechanism through which oncolytic viruses mediate antineoplastic activity. These therapeutic viruses offer a specific advantage over the replication-incompetent viruses that have been employed in the vast majority of gene therapy applications until now. As the virus replicates, the inserted gene expression is simultaneously amplified to exert an amplified antitumor effect. Some researchers have also inserted prodrug-converting enzymes, such as viral thymidinekinase and bacterial cytosine deaminase (CD), into the replication conditional adenoviruses to enhance tumor cell lysis [6,8]. To augment the antitumor immune response of the tumor cells, other researchers have introduced various immunostimulatory genes such as interleukins-4 (IL-4) and -12 (IL-12) into oncolytic herpes viruses [6].

Development of Oncolytic Viruses

Although chemotherapy and radio-therapy are the pillars of advanced cancer treatment, they suffer limitations such as tumor cells that develop resistance to these agents. Therefore, they have a relatively low narrow therapeutic index. Moreover, increased dose or hybrid therapies designed to overcome this resistance or increase tumor cell lysis are slightly toxic to normal tissues. However, as viral replication proceeds preferentially in tumor cells, oncolytic viral therapy increases the therapeutic index between tumor cells and normal cells. The major challenge to the administration of oncolytic viral therapy for cancer patients is the immune system of the host. The genetically engineered tumor-targeting quick viruses form a promising new approach to cancer therapy [9]. The techniques for modification of viruses and enhancement of their clinical utility are listed hereunder.

Selection Criteria

Firstly, the selected virus must suit storage and production at high titres. A double-stranded DNA

genome is advantageous, because it has greater stability during storage, diminishing the odds of hazardous mutations. The most suitable viruses are viruses like adenoviruses and herpes simplex viruses, which have been used and studied viruses most commonly.

Generating Tumor Selectivity

Transductional and nontransductional targeting accounts for the tumor-specificity and selectivity of the oncolytic viruses.

Transductional Targeting

Transductional targeting refers to the modifications in the specificity of viral coat protein and the resulting increase in entry into target cells. It also reduces entry to non-target cells. Although this approach is entirely viable with other viruses, it has been mostly limited to adenoviruses. serotype 5 (Ad5) is the most commonly used group of adenoviruses. The bond between serotype 5 (Ad5) and the host cells is forged by the interactions among the cellular coxsackievirus, adenovirus receptor (CAR), and the knob domain of the adenovirus coat protein. Adenovirus infection is contingent upon these receptors, which indicate that CAR-negative cells could be made adenovirus-sensitive as a result of transfection with CAR cDNA [9]. Viralinternalization also depends on an Arginine-Glycine-Asparagine (RGD) motif at the base of the adenovirus coat protein that binds to integrins, causing endocytosis. Research results have been also indicative of the contribution of CAR to cell adhesion, and possibly tumor suppression. Although expressed widely in epithelial cells, CAR expression in tumors is extremely variable, leading to resistance to Ad5 infection. Ad5 is retargeted from CAR to another receptor, which is ubiquitously expressed on tumor cells, through one of the following mechanisms [6,9].

Adapter Molecules

The administration of specific adapter molecules with the selected virus helps redirect viral coat protein tropism, which refers to fusion proteins made of an antibody raised against the knob domain of the adenovirus coat protein, fused to a natural ligand for a cell-surface receptor. There is evidence of the increase in viral transduction due to the presence of adapter molecules. Adapter molecules increase system complexities, yet its effect on the virus stability is unknown [10].

Coat-Protein Modification

Genetic modifications to the fiber knob domain of the viral coat protein are carried out to alter its specificity.

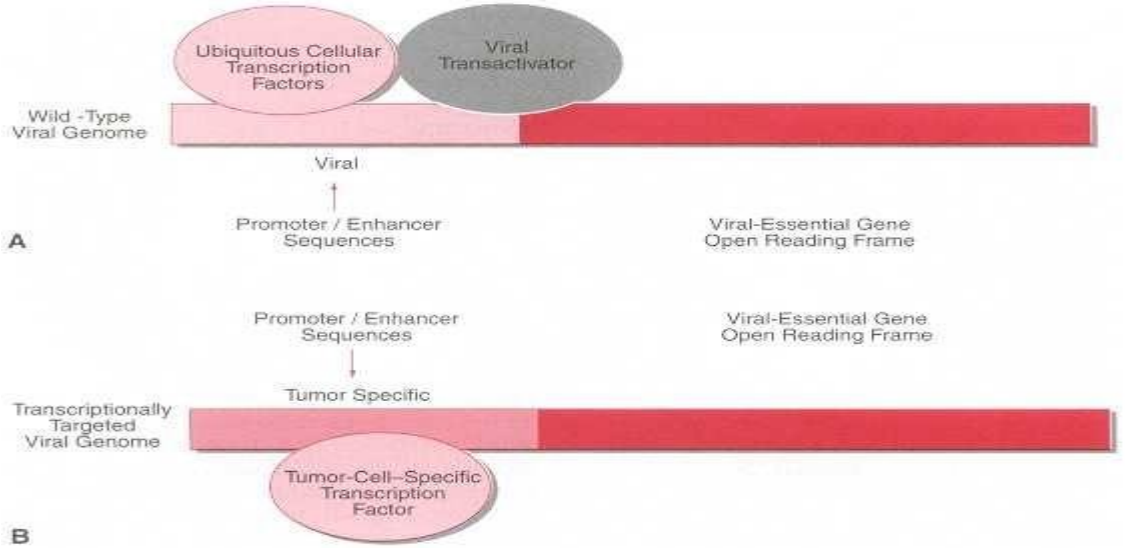
The introduction of short peptides to the C-terminal end of the coat protein successfully modifies viral tropism. It is, however, impossible to add larger peptides to the C-terminus because it reduces adenovirus integrity possibly due to an effect on fiber trimerisation. The HI-loop structure of the fiber protein can tolerate peptide insertions of up to 100 residues without any negative effects on adenovirus integrity [10]. The introduction of RGD motif to the HI loop of the fiber knob protein shifts specificity toward integrins, while Oncolytic virus 4 is frequently overexpressed in Oesophageal Adenocarcinoma. These viruses proved to be effective and selective therapeutic agents for Oesophageal Adenocarcinoma in combination with a form of non-transductional targeting [11].

Non-Transductional Targeting

It refers to the process of altering the genome of the virus so that it can only replicate in the tumor cells. There are two ways of attaining this goal: transcription targeting, where genes essential for viral replication are placed under the control of a tumor-specific promoter; and attenuation, which involves the deletion of the viral genome that results in the elimination of such functions that are necessary for replication and cytolytic effects of that particular virus and are dispensable in cancer cells, making the oncolytic viruses tumor specific [6].

Transcriptional Targeting

In this method, a tumor-specific promoter takes over the essential viral gene. In addition, the gene is only expressed in cell types where all the transcription factors required for the promoter function are present. A suitable promoter should be active in the tumor but inactive in the majority of the normal tissue, particularly in the liver because it is exposed to blood born viruses the most. To treat a range of cancers different promoters have been identified and studied. Cyclooxygenase-2 enzyme (Cox-2) expression is a suitable tumor-specific promoter. It is elevated in a range of cancers and has low liver expression. Moreover, Cox-2 is a potential tumor-specific promoter and a candidate for other cancer types, including ovarian cancer. Another suitable tumor-specific promoter is prostate-specific antigen (PSA), whose expression is greatly elevated in prostate cancer. CN706 is a CRAd with a PSA tumor-specific promoter driving the expression of the adenoviral E1A gene required for viral replication (See figure A and B) [12].



Attenuation

Similar alterations are observed in the cell signaling pathways of the cancer cells and virus-infected cells, especially those that govern progression through the cell cycle. A viral gene serving to alter a pathway is dispensable in cells where the pathway is defective. However, this does not apply to cells with active pathways. Attenuation involves deleting viral genes, or gene regions, with the aim of eliminating viral functions that are expendable in tumor cell rather than normal cells. The host cell must be induced into S-phase by viral proteins interfering with cell cycle proteins to set the scene for adenovirus replication. The adenoviral E1A gene is responsible for inactivation of several proteins, including Retinoblastoma, and allowing entry into S-phase. The adenovirus E1B55kDa gene cooperates with another adenoviral product, E4ORF6, to inactivate p53 and prevent apoptosis. For example, inAd5- Δ24E3, there are 24 base pair deletions in the retinoblastoma-binding domain of the E1A protein. As a result, it fails to silence retinoblastoma and induce S-phase in host cells. To wit, *Ad5-Δ24E3* is only able to replicate in the proliferating cells such as tumor cells. Moreover, the herpes simplex virus genome contains the enzymes thymidine kinase and ribonucleotide reductase, whose cellular forms account for the production of dNTP's that is required for DNA synthesis and is only expressed in Oncolytic virus 5 during the G1 and S phases of the cell cycle. Herpes simplex virus replication in quiescent cells is made possible by these enzymes allow. Hence, the herpes simplex virus will only be able to replicate in proliferating cells, such as cancer cells if they are inactivated by mutation. A LacZ insertion in *G207* herpes simplex virus mutant inactivates ribonucleotide reductase [6,9].

The HSV-1 viral mutant d120 is deleted from the viral essential gene α4 and does not replicate upon infecting cells. By placing the α4 gene under the transcriptional control of the albumin enhancer/promoter elements and limiting viral replication to albumin expressing cells the transcriptionally targeted HSV-1 G92A was created. Regardless of the albumin expression, wild-type HSV-1 replicated efficiently in the cells, whereas virus G92A replicated more efficiently in the albumin expressing cell lines compared to the nonalbumin-expressing cell lines. In a similar vein, the calponin promoter has also been utilized to control expression of HSV-1 α4. Calponin mRNA is overexpressed in soft-tissue/bone tumors, serving as a means of targeting such tumors with replication-conditional viruses.

The pitfall of the aforesaid transcription-targeted techniques is the need for creating individualized viruses per tumor type. Besides, tumors can vary in their expression of specific transcription factors depending on the tissue type, limiting the benefits of such viruses for broad tissue types. An adenovirus that targets tumor endothelial cells was constructed to tackle these challenges. Targeting the tumor vasculature confers two benefits: genetic stability and a common process involving multiple solid tumors. The process of angiogenesis by endothelial cells involves the upregulation of multiple endothelial cell receptor complexes such as VEGF and tumor growth factor (TGF)-β. The adenovirus preferentially replicates in dividing endothelial cells compared to tumor cells by giving the transcriptional control of the adenoviral E1A and E1B genes to the Flk-1 (VEGFR-2) and endoglin (CD105/TGF-β receptor component) promoter/enhancer sequences [12].

Therapeutic Gene Delivery with Replication-Competent Viruses

Therapeutic Genes have also been employed with replication-selective tumor viruses. The delivery of immunomodulatory genes, prodrug-converting enzymes (suicide gene therapy), and cytotoxic genes comprise these strategies. Replication-

competent HSV-1 has been created to express the immunostimulatory IL-12 gene and the prodrug-converting enzyme cytosine deaminase gene. Replicating adenoviruses have also been created. These adenoviruses express the cytotoxic TNF-α gene and the genes encoding the prodrug-converting enzymes cytosine deaminase and thymidine kinase. However, the delivery of a cytotoxic gene with a replication-competent virus seems counterintuitive, while these approaches seem to amplify the therapeutic effect of antitumor therapy. By delivering the therapeutic gene, tumor cell destruction might be enhanced by eliciting a bystander effect, which results in the death of the neighboring infection-free tumor cells [9,12].

Combination of Chemotherapy/Radiotherapy with Replication-Competent Viruses

Researchers have made attempts to assess the utility of combining standard anticancer agents with replication-competent viruses. By increasing the replication potential of the viruses radiation ionization reinforces the therapeutic potential of both replication-competent adenovirus and HSV-1. It has also been reported that a variety of chemotherapeutic agents increase the efficacy of replication-conditional adenovirus and HSV-1. In this treatment paradigm, the results from a Phase II clinical trial conducted on patients with recurrent head and neck cancer treated by a combination of E1B-deleted adenovirus (ONYX-015) with 5-FU and cisplatin are more appealing. According to the preliminary results, chemotherapy manages to magnify the therapeutic effect of replication-conditional adenovirus [9]. The genesis of the genetically engineered viruses that selectively replicate in tumor cells based on the knowledge of cell and viral molecular biology was illustrated above. The other replication-competent viruses under study include Newcastle disease virus and parvoviruses.

Several clinical trials have also been launched to determine the therapeutic efficacy of the current generation of the replication-conditional viruses. Meanwhile, more fundamental science studies on tumors and viral biology are paving the way for the creation of more potent oncolytic viruses with reinforced safeguards to specifically target the tumors. The existing studies have mainly focused on the benefits of the replication-conditional viruses for regional therapy (i.e., direct tumor inoculation). Nevertheless, the ongoing studies suggest that these viruses function as systemic therapeutic agents that target metastases. To serve this purpose, the virus must survive the systemic circulation and then focus on the malignant cells. To have a successful entry and have their gene expression driven by tumor-cell-specific transcription factors such viruses could bind selectively to tumor-cell-specific receptors [6].

The Clinical Trials of the Oncolytic Viruses and Their Success Rate

Oncolyticvirotherapy has been somewhat successful even at this initial stage. Herpes virus, adenovirus and many others are being evaluated in the ongoing clinical trials for intractable cancers [13]. Adenoviral therapy is the first viral therapy employed to treat cancer. It was used in combination with virus ONYX-015. This virus (ONYX-015) is a manipulated adenovirus without the viral E1B protein [16]. As mentioned, the virus will not replicate in cells with a functioning p53pathway without the aid of this protein. In most tumors, mutation leaves this pathway defective or non-functional, allowing ONYX-015 to replicate and lyse the cancer cells [13]. In squamous cell carcinoma of the head and neck, ONYX-015has been used in phase I and II trials, resulting in tumor regression correlated to the p53 status of the cancer. Tumors with an inactive p53 pathway displayed a better response. When ONYX-015 was used in combination with chemotherapy in phase II it yielded better tumor response and lead to phase III trials [14].

Today, ONYX-015 is being evaluated as a preventive treatment for precancerous oral tissue. Similar to in precancerous cells, the p53 pathway-inactivating mutations will allow ONYX-015 to destroy and eradicate the precancerous cells before tumor development [15].

Another adenovirus is virus CV706, whereby the prostate-specific antigen (PSA) gene promoter-enhancer element is inserted upstream of E1A gene. This virus replicates specifically in tissues with high PSA expressions [15]. This viral vector is being studied after definitive radiotherapy in a phase I/II dose-escalation trial of intra-prostatic injection in patients with non-metastatic recurrent prostate carcinoma. Results have unveiled the significant antitumoral properties of this treatment (Table 1).

The tumor specificity of these viruses is secured by gene manipulations. For instance, NV1020 has various mutations, including a deletion in the thymidine kinase region and a deletion across the long and short components of the genome. It also involves the insertion of thymidine kinase gene under the control of the α4 promoter [6]. Due to the G207 mutations, it has attenuated neurovirulence, leading to its inability to replicate in non-replicating cells [6]. These viruses employ different cell targeting mechanisms. While the thymidine kinase that is expressed from the viral genes sensitizes cells to the ganciclovir, the lytic portion of the cell cycle kills cells directly. They have proved to the successful in the experiments on animal models and *in vitro* experiments in treating a wide range of solid cancers. G207 is being tested for the treatment of malignant glioma in a phase I clinical trial. NV1020 is also in phase I and phase II clinical trials for the treatment of colorectalcancer metastases in the liver. This virus has been evaluated for the treatment of glioblastoma [16].

Table 1. Partial list of oncolytic viruses in clinical trials, *Adapted from* Viral Oncolysis. John T, Mullen, Kenneth K, Tanabe, The Oncologist 2002; 7:106-119.

Name	Strain	Genetic alterations	Diease	Phase
ONYX-015	Adv 2/5 chimera	E1B-55 kD detection	Head and neck cancer	II-III
			Ovarian cancer	I
			Primary and secondary liver tumors	I-II
			Pancreatic cancer	I
CV706	Adv 5	Regulation of EIA under the PSA promotor, E3 detection	Prostate cancer (organ-confined)	I-II
CV787	Adv 5	Regulation of EIA under the rat probasin promotor and EIB under the human PSA promotor, wild-type E3	Prostate cancer (organ-confined and metastatic)	I-II
G207	HSV-1	*lac* Z insertion into ICP6 gene; detection of both copies of $\gamma_1$34.5 gene	Malignant glioma	I-II
NV 1020	HSV-1/HSV-2	700 bp tk detection + 15 kb detection across the joint region, which contains an exogenous copy of tk gene under control of HSV-1 α4 promotor and a 5.2 kb fragment of HSV-2 DNA	Colorectal carcinoma liver metastases	I
Vaccinia-GM-CSF	Vaccinia	Insertion of GM-CSF and *lac* Z genes into viral *TK* locus	Melanoma	I-II
PV701	NDV	Naturally attenuated	Advanced solid cancers	I

OncoVEXGM-CSF is a 2nd generation oncolytic *herpes simplex* type 1 virus that encods human GM-CSF. OncoVEXGM-CSF represents an improvement in the previous vaccines and virus-based therapies for the treatment of cancer. This is because it has been genetically reprogrammed to attack cancer cells only. The antitumor response in the near and distance regions is improved through the insertion of the human GM-CSF gene into the viral genome. Moreover, the expression of GM-CSF in the local tumor environment serves the following biological functions:

a) Induces local inflammation
b) Enhances dendritic cell activity
c) Produces antiangiogenic effect
d) Increases HLA class II expression

Without causing any significant additional toxicity OncoVEXGM-CSF was easily added to a standard chemoradiation regimen along with each cycle of cisplatin [16].

Reovirus (respiratory enteric orphan virus) is a double-stranded RNA virus linked to mild upper respiratory infections or enteritis. The activation of transcription factors (NFκB), MAP kinase pathways, and cell-cycle arrest, and apoptosis are the outcomes of infection with. Besides, since it is a double-stranded RNA virus, the replication of the viral genome activates double-stranded RNA-activated protein kinase (PKR). Activated PKR phosphorylates the translation initiation factor, eIF-2α, resulting in the cessation of protein synthesis. The actions of PKR need to be stopped or inhibited for the viral replication. This goal can be achieved by activating mutations in the Ras signalling pathway by transfecting genes encoding proteins that activate the Ras pathway, i.e., EGFR, v-erbB oncogene, or SOS. Ras activation induces an inhibitor of PKR [16].

Ras-activating mutations unfold in 30% of human tumors. Reovirus replication is expected to be possible in tumors with such mutations. This hypothesis is supported by the initial results from tumor models. Tumors with activated Ras (i.e. gliomas, colorectal, and ovarian cancers) are sensitive to reovirus infection. Reovirus oncolytic therapy is appealing due to its natural safety profile and lack of disease pathologies associated with wild-type reovirus infection [12,17].

Vesicular stomatitis virus (VSV), as a rhabdovirus, consists of 5 genes encoded by a negative sense single-stranded RNA genome. In nature, it infects insects as well as livestock, causing relatively localized and non-fatal illness. Infection with this virus leads to death of the malignant cells because VSV undergoes a rapid cytolytic replication cycle and results in roughly a 1000-fold amplification of this virus within 24h. Hence, VSV is properly suits therapeutic uses. Several researchers have also indicated that systemically-administered VSV can be delivered to a tumor site, where it replicates and induces disease regression, often leading to durable cures. Attenuation of the virus by engineering a Met-51 deletion from the matrix protein virtually frees normal tissues from all infections without affecting replication in tumor cells. Finally, recent findings have mirrored the potential of this virus for curing brain tumors [18-20].

Table 2. Oncolytic viruses along with their advantages and disadvantages for cancer therapy, *Adapted from* Viral Oncolysis. John T, Mullen, Kenneth K, Tanabe, The Oncologist 2002; 7:106-119.

Vector (size)	Advantages	Disadvantages	Inser size
Adenovirus (36 kb)	Infects dividing and nondividing cells Efficient gene transfer Nontoxic to host cells High viral titers possible Antigenicity generates immune response	Antigenicity generates immune response Small insert capacity	7.5 kb
HSV-1 (152 kb)	Infects dividing and nondividing cells Potential for prolonged gene expression Large transgene capacity High viral titers possible Sensitive to acyclovir/ganciclovir Antigenicity generates immune response	Possibility of herpes encvephalitis Antigenicity generated immune response	40-50 kb
Vaccinia virus (187 kb)	Transient gene expression Efficient gene transfer and expression Large transgene capacity Antigenicity generates immune response Infects most mammalian cell types	Antigenicity generates immune response Safety cocerns in immunosuppressed patients	25 kb
Reovirus (RNA)	Mild pathogenicity Unable to infect normal cells Antigenicity generates immune response	Infects only cells with an activated *ras* pathway	?
NDV (RNA)	Not pathogenic in humans Does not establish a permanent infection in host High potency	Mechanism of selective tumor cell lysis unclear Transgene insertion reduces viral replication	?

Conclusion

Viruses are capable of targeting and destroying cancer cells in human cancer patients. Cancer gene therapy is a growing field maturing very rapidly. Oncolytic viruses will indubitably be a part of the future cancer therapies. Attempts are made by researchers to overcome the challenges to viral therapy. Moreover, a number of viruses are being processed and modified to produce viruses with improved safety and efficacy by virtue of the advances in genetic engineering and biotechnology. Different types of cancer are also being explored in various ongoing clinical trials. The results from most of these clinical trials, which employ oncolytic virotherapy, have been satisfactory with high success rates, and many more clinical trials are under way with new viral vectors for the treatment of untreatable cancers.

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