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Are Oncolytic Viruses a Cure for Cancer? A Look at Reovirus, Adenovirus, and HSV-1 in Cancer Treatment

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Abstract

This paper aims to evaluate the option of utilizing Oncolytic Viruses as a viable treatment in fighting cancer. However, due to the broad nature of the subject, a more limited purview is necessary. With that in mind, the focus will be on a few of the more researched ones: Reovirus, Adenovirus, and HSV-1. In each case, we will examine what makes each of these potential options. This will include an examination of each ones tumor-specificity. Cancer and viral physiology will be discussed as necessary to examine the distinct protein expressions in tumor cells, so that the virus's method of battling the host's cell defense is only effective for cancer cells. In addition, its strength and weaknesses in terms of battling metastasized cancers, overall efficacy, as well as its capability to be used in tandem with other treatments will be discussed. Included in this analysis is the current prognosis of OV as demonstrated in several clinical trials. Finally, we will summarize several current obstacles to OV and some suggested solutions.

Introduction

Cancer is one of the most feared and deadliest diseases that afflict people. Current treatments for cancer surgery, radiotherapy, and chemotherapy have little success in treating metastasized cancers. Scientists continue to search for new potential treatments and cures. One prominent approach is virotherapy, or using viruses to treat cancer. Since the early nineteen hundreds, scientists have noted the correlation between viruses and, at least, the temporary remission of certain cancers. Further understanding of cancer and viruses in the mid-1900's, sparked new interest in the possibility of using virus for cancer treatment. However, those early attempts proved mostly unsuccessful because of the immunogenic nature of viruses. The 1990's ushered in advances in technology, better understandings in the fields of Virology and Cancer biology, and with it renewed interest in Oncolytic Viruses (OV). These viruses are, generally, genetically altered to differentiate between healthy cells and cancer cells, and then as viruses, replicate and lyse cancer cells. It should be noted that most if not all viruses can be altered to have OV-tendencies. However, obviously discussing every type of virus for every type of cancer is not feasible. Instead, a look at the two most researched OV: HSV and Adenovirus-based OV, as well as the naturally occurring Reovirus OV, which practically is easier to study than engineered OV will be the focus. This paper aims to explain the methods of attaining tumor selectivity, current obstacles OV face, and the progress made. In addition, this paper will attempt to project realistic hopes for the future of Oncolytic Viruses, and its impact on cancer treatment.

Cancer and its current prognosis

Cancer is a class of disease in which damaged and physiologically-altered cells replicate uncontrollably. It occurs when the genes regulating replication are altered, usually due to mutation. These mutations either cause hyper-expression of oncogenes, which promote cell growth, or under-expression of tumor-suppressor genes, which limits replication of damaged cells. Currently, the most successful treatment for cancer is surgery; however, its efficacy is limited to instances when the cancer is in a single spot. If the cancer metastasized, through the lymph nodes or bloodstream, surgery's effectiveness is limited. Radiation and chemotherapy are also used to fight cancer. However, the toxicity and side-effects – some serious such as infertility, pain, the possibility of it causing other forms of cancer, and death – and the limitations of these treatments, especially against metastasized cancers, makes further study of cancer necessary.

Virotherapy

Using viruses (virotherapy), as a possible cure for cancer is currently being investigated and has progressed to the level of Phase III clinical trials. Viruses are, obviously, generally regarded as pathogens, although out of the millions of different species only a relatively small number are dangerous to humans. A virus is made up of nucleic acid, either DNA or RNA, a protein coat called a capsid, and sometimes has an envelope. Inherently non-living, viruses must infiltrate and hijack a host cell to replicate. Most viruses lyse the host cell after replication, though some are latent. Scientists think viruses with, little or no pathogenicity to people, are attracted to cancer cells, they can replicate and lyse cancer cells and may be a viable cancer treatment. Additionally, viruses may be used as vectors, — to transport proteins that stimulate host immune response to tumors. These viruses that prefer cancer cells and have little or no toxicity to healthy cells are called OV and achieve this selectivity through different mechanisms.

Criteria for use as an Oncolytic Virus

Viruses need to be able to exhibit certain attributes to be viable oncolytic options. Although a virus doesn't necessarily need all of the forthcoming features, many are needed in general, and some are needed under certain circumstances. Viruses that are pathogenic and infect humans are generally poor choices, since the host's previous exposure to the virus increases the probability that the host has built-up immunity to the virus. The immune system can hamper viral activity and effectiveness. Another concern is safety: viruses are first regarded as a parasitic threat, their capability of hijacking healthy cell metabolism or producing dangerous toxins must be monitored simultaneously with their ability to fight cancer. The ability to kill out-of-control dangerous viruses via antiviral drugs is another aspect of selecting a safe choice. Another

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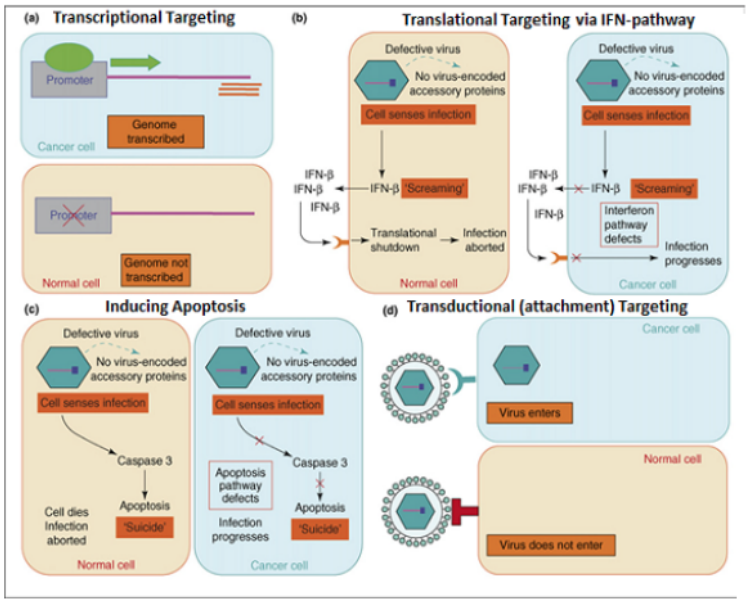
drugs is another aspect of selecting a safe choice. Another safety concern is the possibility that the virus may mutate into a dangerous virus. To limit this, viruses that cannot enter the host cell's nucleus or that cannot undergo recombination with host genes are recommended. Viruses with certain characteristics are better suited to fight cancer than others. Viruses with rapid life cycles that replicate, lyse, and spread to other cancer cells quickly are more suited as OV than slower viruses. Another critical feature for OV is its requirement to be tumor-selective rather than targeting both healthy and tumor cells indiscriminately. Often, the Oncolytic virus by itself is not powerful enough to wipe out the cancer. Its effectiveness may be increased when used together with conventional treatments – radiation and chemotherapy. In a similar way, OV can be combined with genes that also fight cancer, using the virus as both vector and oncolytic agent. Therefore, the ability to easily manipulate the viral genome to insert these genes, as in the case of adenoviruses, is an important feature. Finally, to counter metastasized cancers, the ability to deliver it intravenously is critical to efficiently spread the OV. (Kelly & Russell, 2007)

Methods of Tumor Selectivity and Tumor Cell Death

Oncolytic viruses achieve tumor-selectivity in four distinct ways: targeting transcription, targeting attachment, IFN-signaling, and cell apoptosis (Figure 1). Some viruses can be altered with a tissue-specific-promoter in their genome to regulate genes essential for viral replication. Thus, only in tumor cells is the factor that is required for replication available. An example of this method is Adenovirus 7870, engineered so that its E1B is under the control of prostate cancer-specific promoter (Small et al, 2006). A second method is by targeting viral attachment. To understand this, some knowledge of tumor physiology is needed. As stated earlier, cancer cells are mutated cells that are out of control. As such, they often result in distinct proteins that are either overexpressed or mutated. Viruses can be engineered to bind to the proteins, thereby becoming tumor-selective. Coxsackie A21, from the picornovirus family, utilizes this method by binding to intercellular adhesion molecule-1 (ICAM-1) and decay accelerating factor (DAF) which are overexpressed in cancer cells (Shafren et al, 2011). Third, many cancer cells have defective IFN-pathways. Viruses can be altered so that their defense to block IFN-pathways is removed, leaving them extremely vulnerable in normal cells to interferon. However, tumorous cells with defective pathways are unable to carry out the pathway and, therefore allow viral replication. Examples of this method are demonstrated by the wild-type Reovirus and the ICP-34.5-null HSV-1-based OncoVEX GM-CSF, which will be explained in detail later. Finally, the last method involved apoptosis – programmed cell death. In response to infection, host cells carry out apoptosis as a virus-limiting mechanism, facilitated by tumor suppressor protein, p53. Tumor cells commonly lack expressed p53 genes because it also carries out cell death in response to uncontrollable growth. These p53-null cells are unable to effect cell death when infected , allowing viral replication. Adenovirus Onyx-15 uses this technique through deletion of its E1B gene, though as explained later this is not a precise explanation. Once inside the tumor cell, virus brings about cell death by normal viral replication and lysis. Additionally, viruses may induce apoptosis, enabling the increase of viral progeny. Moreover, viruses attract the host's immune system; in turn, an activated immune system eliminates cancer cells, through natural killer and other cells.

Figure 1: Methods of Tumor-Selectivity Source: Russel & Peng 2007



Reovirus

There are several viruses that are naturally oncotropic, possessing an affinity for tumor cells. One such species is the Reovirus, a virus that structurally has no envelope and contains double stranded RNA. Short for Respiratory Enteric Orphan virus, it usually infects the respiratory system and intestines. The reovirus also has several factors that make it a viable option as an OV. First, it's very common. Additionally, it has minimal pathogenicity to adults, and does not typically cause symptoms. Reovirus's oncotropic nature is linked to its replication mechanism through the overexpressed EGFR\RAS-pathway.

Reovirus: Ras-pathway Selectivity?

There are two prevalent theories for reovirus replication. (Strong et al, 1998) The first possibility is that reovirus binds to EGFRs, or Epidermal

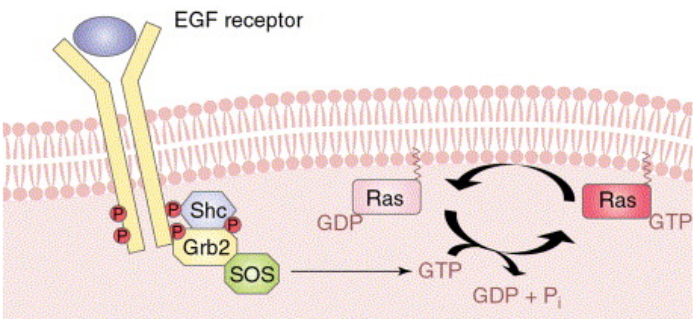


Figure 2: Ligand-Mediated activation of EFG receptor, stimulates Ras-Pathway by phosphorylation. The pathway regulates activation of membrane effectors. Source: Norman et al., 2005

growth factor receptors, which in turn, activates tyrosine kinase, triggering a chain of cell signaling leading to the subsequent steps of the infection process. Alternatively, reovirus may take advantage of a signal transduction pathway previously activated by EGFR in the host cell. The latter possibility implies a correlation, albeit indirect, between reovirus replication and EGFR stimulation. Thus, having established a connection between the two, the tumor-specifity can be explained. In the case of healthy host cells, virus replication phosphorylates double stranded RNA-activated protein kinase (Bischoff & Samuel, 1989). This leads to intermolecular transphorylation (Thomis & Samuel, 1993), activating the protein kinase. This in turn phosphorylates the alpha subunit of eIF-2 which inhibits viral translation (Panniers & Henshaw, 1983). However, in tumerous cells, PKR phosphorylation is inhibited by an overactive Ras-pathway –common oncogenes prevalent in about half of all cancers (Strong et al, 1998)—allowing viral RNA translation to occur (Figure 3). An obvious defiecency, then, in utilization of Reoviruses as OV is its dependence of cancers with compromised Ras pathways.

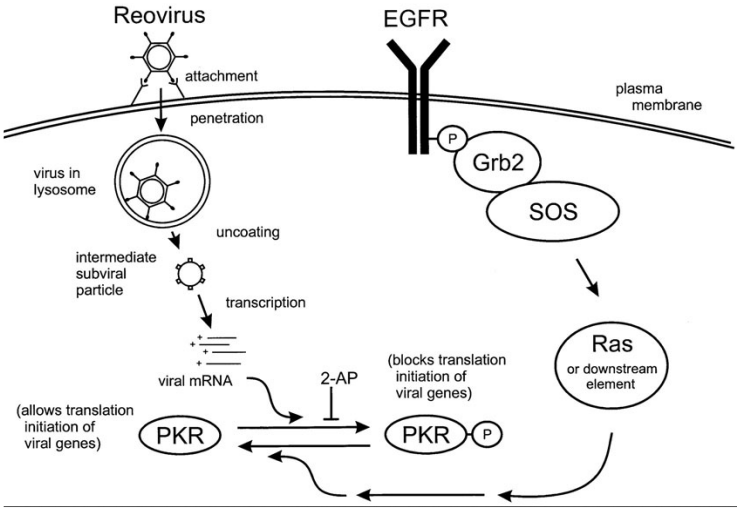


Figure 3: The molecular basis of reovirus oncolysis: usurpation of the host cell Ras signaling pathway. For both untransformed (reovirus-resistant) and EGFR-, Sos- or Ras-transformed (reovirus-susceptible) cells, virus binding, internalization, uncoating and early transcription of viral genes all proceed normally. In the case of untransformed cells, secondary structures on the early viral transcripts inevitably trigger the phosphorylation of PKR, thereby activating it, leading to the phosphorylation of the translation initiation factor eI F-2α, hence the inhibition of viral gene translation. In the case of EGFR-, Sos- or Ras transformed cells, the PKR phosphorylation step is prevented or reversed by Ras or one of its downstream elements, thereby allowing viral gene translation to ensue. The action of Ras (or a downstream element) in promoting viral gene translation (and hence reovirus infection) in the untransformed cells can be mimicked by deletion of the Pkr gene or by blocking PKR phosphorylation with 2-aminopurine (2-AP). (Source: J. Strong et al, 1998)

Clinical Trial for OV Reolysin

Reolysin, the commercial Reo-OV owned by Oncolytics Biotech Inc., has undergone several trials. The reovirus has been studied for a variety of cancers: melanoma, pancreatic, non-small cell lung, ovarian, colorectal, and head and neck cancers. In human non-small cell lung cancer (NSCLC), Reovirus type 3 Dearing strain was tested in vitro when combined with the chemical paclitaxel. ReoT3D, alone, demonstrated lytic activity in 7 of 9 NSCLC cell lines examined. The combination of ReoT3D and paclitaxel showed increased poly (ADP-ribose) polymerase (PARP) cleavage and caspase activity relative to just the Reovirus alone, indicating a higher rate of apoptosis (Shizuko et al,2009). Similarly, in June 2012, the NCIC began a Phase II trial of intravenous Reolysin for patients with advanced or metastatic breast cancer. The aim of the study is to evaluate the difference between paclitaxel and the combination of paclitaxel and Resolysin. Approximately 50 patients will be in each arm of the trial (Clinicaltrials.gov).

Adenovirus

The Adenovirus is a popular candidate and therefore is one of the most well- researched OV. Structurally, it is a DS-DNA, which makes it easily susceptible to genetic manipulation.. The most famous adeno-OV is the China-approved H101, the only currently approved OV, adenovirus for head and neck cancer (Garber, 2006).

Mechanism for Tumor Selectivity

The H101, and the similar Onyx-15, gain their selectivity by deletion of the E1B gene – the gene which produces proteins to delay host-cell lysis. In healthy cells, the E1B-defecient virus's replication is blocked by the host's cell tumor suppressor protein p53. However, cancer cells lacking p53 would be unable halt viral replication and host cancer-cell lysis. Although this strategy is clever, it was proven incorrect by first the virus's targeting of healthy p53-containing cells. Moreover, wild-type E1B Onyx-15 viruses have had as much success in some trials as the genetically manipulated E1B-deficeint. Nevertheless, although the exact mechanism for selectivity is unknown, the H101 in Phase III trials, "reported a 79% response rate for H101 plus chemotherapy, compared with a 40% for chemotherapy alone." (Garber, 2006) On the other hand, the Phase III trial, admittedly, failed to study patient survival rate, so the ultimate effectiveness is unknown. Additionally, its complementary success with chemotherapy, instead of its stand-alone efficacy, as well as the inability to deliver the OV intravenously limits the potential of fighting metastasized cancer. Thus, the success of the OV is only moderate.

Methods of Improving Adeno-OV

Adenovirus Combined with siRNA Gene Regulation

siRNA – small interfering RNA – is a small double-stranded RNA consisting of aproximately 20 base pairs. Biologically, its most significant function is its involvement in gene regulation. More specifically, for our discussion, is the importance of its role in RNA interference by shutting off a gene. siRNA is phosphorylated to separate into single strands. One RNA strand becomes part of the (RISC) RNA-induced silencing complex. There it guides the endonuclease (which breaks nucleotide backbone) Argonaute to cleave mRNA. siRNA was considered

(and still is potentially) a promising way to cure cancer by inhibiting translation of oncogenic proteins caused by mutated genes in tumor cells. However, it has faced several obstacles in its utilization. Problems included incidental activation of the innate immune system (WBC) and interferon induction. Also, off-targeting may occur if the siRNA can bind to different genes other than those intended. The possibility of joining OV and also using the adenovirus as a vector for RNA delivery has been altered to target tumors mitigates the potential of off-targeting occurring and also lessens the risk of RNA activating the innate immune system (Choi et al, 2012). Mortalin, a protein which is overexpressed in cancer cells and plays a role in inhibiting tumor suppressor protein p53, is one gene that can be targeted by shRNA -small hairpin RNA. In an experiment, the Ad-ΔB7-shMot was injected into breast cancer tumors caused by overexpressed mortalin which were xenografted into mice. The adeno-OV demonstrated enhanced apoptosis, substantiating interest in this method (Yoo et al, 2010). Another strategic use of siRNA is to target VEGF, vascular endothelial growth factor, a signal protein that stimulates angiogenesis. Specifically, U6 promoter (RNA Polymerase III promoter) was used to control shRNA expression. This adenovirus, designated Ad- ΔB7-shVEGF, in mice, demonstrated increased anti-tumor activity and increased duration time when compared to just OV alone. It also justified the theory that the adenovirus with VEGF-targeting shRNA has an anti-angiogenesis affect by the reduction in tumor vessels. Additionally, the combination of the two worked better than Ad- ΔE1-shVEGF, the viral vector (without replication capabilities), demonstrating that the combination works better than each alone (Yoo et al, 2007).

Oncolytic Adenovirus Armed with Suicide genes

Scientists are able to engineer oncolytic adenoviruses to add a transgene. This bolsters Adeno-OV efficacy by killing both the infected cell and neighboring tumor cells. Prodrug activating- genes, also called suicide genes, is a separate possibility in treating cancer. However, it may be possible to combine the two in order to enhance treatment. The HSV thymidine kinase gene, when combined with the prodrug gancyclovir is the most prominent suicide gene. Procedurally, HSV-tk phosphorylates gancylovir, which is further phosphorylated by other kinases into gancyclovir triphosphate. This activated form is toxic to both viral and cellular DNA synthesis and can spread to other tumor cells through gap junctions. Several experiments with divergent results question the effectiveness of this technique. In an experiment in mouse models for Retinoblastoma (Xunda et al, 2009), Colon Cancer (Wildner et al, 1999), Hepatic cancer (Zheng et al, 2009) and in malignant gliomas (Nanda et al, 2001) (figure 4) it was found that the HSV-tk adeno-OV showed promise. On the other hand, improvement was not found in treatment combined with GCV of peritoneal carcinomatosis which metastasized from colon cancer (Wildner and Morris, 2000). Furthermore, in several Cancer cell lines, mesothelioma, lung cancer, and cervical carcinoma and an intraperitoneal tumor model, HSV-th adeno-viruses and GSV didn't reduce tumor size. The effectiveness of this approach may be limited because the toxicity towards viral replication may stop further spreading of OV and outgain its cancer toxicity (Lambright et al. (2001). Moreover, Aghi et al, (1999) proposed the theory that in some tumors, the number of gap junctions can be low, hindering secondary effects of the toxic molecule and shifting the scale towards inhibiting viral growth. However, both the number of studies and the currency of some of the studies in favor should indicate that perhaps the experiments that reported no gain had technical problems such as the duration of the experiment or the viral dosage. Another altered OV is the AdFGR-adenovirus, which utilizes a double-suicide transgene. The adenovirus lacks its E1B-55kD and contains the cytosine deaminase thymidine kinase fusion and the HSV-tk gene. Chemically, cytosine deaminase converts 5-flourocytosine into 5-flourouracil, a molecule enzymatically converted into pyrimidine antimetabolites which are anti-tumoral (Duarte et al., 2012). Further, when combined with intravenously supplied glancyclovir, 5-flourocytosine, and radiation therapy boosts potency. In Phase I clinical trials for patients with prostate cancer, this regimen led to greater delay of tumor growth and an 80% complete response to treatment, in patients with either newly diagnosed intermediate or high-risk prostate cancer (Rogulski et al, 2000). In a different experiment, Zhang and Huang (2006) found that the double suicide gene wasn't harmful to human epithelial and fibroblast cells and also increased potency with respect to lung cancer cell lines.

HSV OV: A Case Study of OncoVEX GM-CSF

Another class of well-researched OV is the HSV1-based viruses. The most famous example is called OncoVEX GM-CSF. Previous examples of OV have demonstrated that the vast majority work best in conjunction with conventional treatments. However, OncoVEX is an exception – and an optimistic outlier – of what OV may be able to do. HSV has double stranded DNA, an icosahedral protein capsid, and a lipid bilayer envelope. The HSV is an excellent candidate for study because it is easily manipulated genetically. Additionally, it has a versatile ability to infect many types of cells and a rapid replication cycle which increases the rate of cellular lysis.

Method of Tumor-Selectivity

OncoVEX GM-CSF has both the deletion of its ICP 34.5 and ICP47 genes which engenders tumor-selectivity. ICP34.5 codes for a protein that is thought to prevent the host cell's attempt to block translation by activating PKR (Smith et al, 2006); ICP47 blocks the translocation of the TAP-dependent peptides, leaving the MHC I in the ER, and ensuring that CD8 cytotoxic T cells are unable to recognize the infected cell(Galocha et al, 1997). The OV, in addition to the ICP34.5 and ICP47 gene deletions, is also inserted with the gene that makes the protein granulocyte macrophage-colony stimulating factor. GM-CSF is a cytokine usually secreted by white blood cells to stimulate other WBC to grow and move to the infection site. In this case, the OV would provide a secondary anti-cancer benefit by bringing WBC to fight the cancer cells. (Liu et al, 2003)

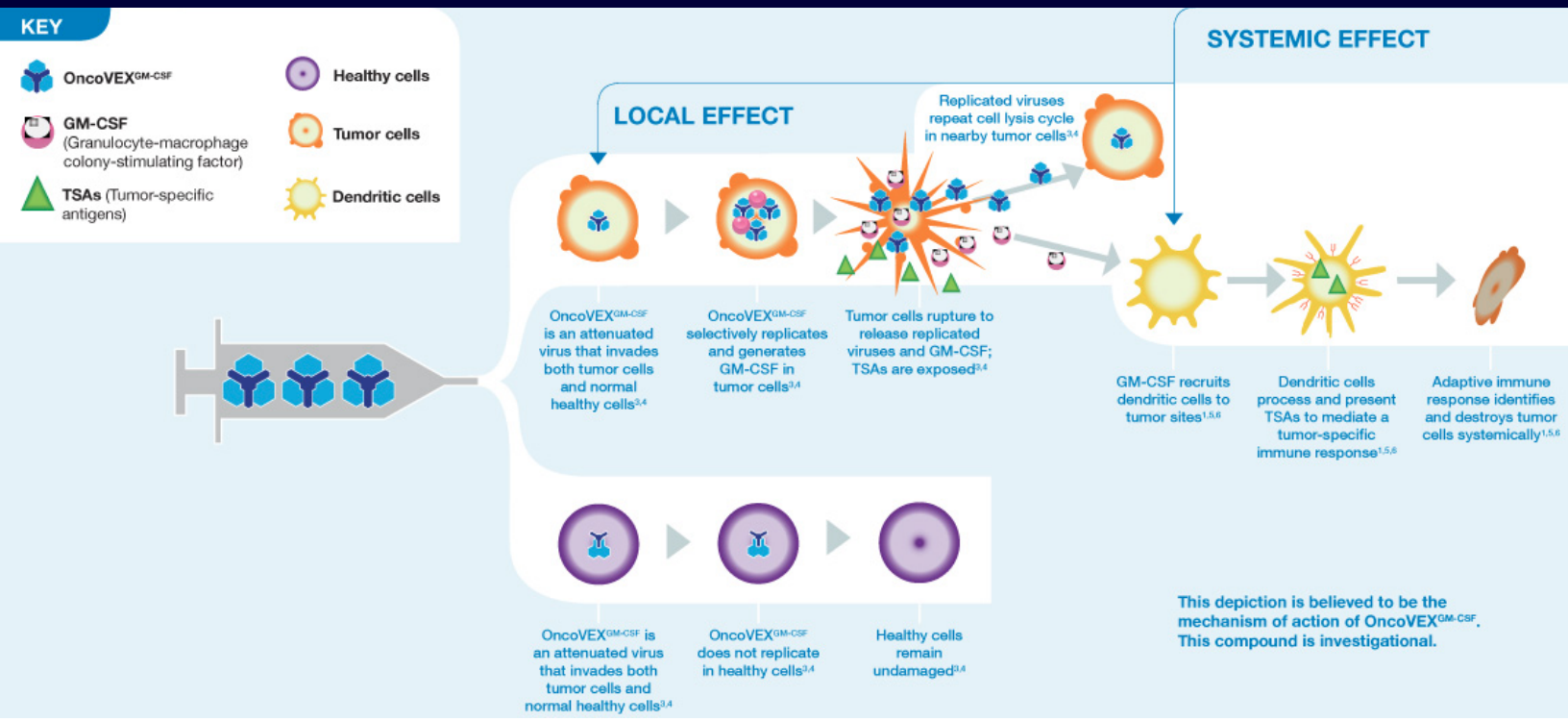


Figure 4: Source: www.amgenoncology-international.com

Clinical Trial for OncoVEX GM-CSF for Late-Stage, Stage III or IV Melanoma

Stage IV Melanoma, does not currently have many viable treatment options. Currently, the most effective treatment is high-dose of IL-2 with a survival rate of approximately 15-20%, with only a small number of patients with long-term benefits. The toxicity of IL-2 coupled with its mediocre benefit makes this treatment problematic. To test OncoVEX GM-CSF in a Phase II clinical trial for late stage melanoma, patients with unresectable, malignant late Stage III or IV melanoma were treated with 106 plaque forming units/ml of up to 4ml, depending on their exact stages of melanoma. Then, after 3 weeks, the regimen changed to 108 PFU/ml for two more weeks. In all, 50 patients were enrolled in the trial, and they received an average of 6 injections. The OV did cause flu-like symptoms. However, there was a 28% response rate, including 8 complete responses – 16% -- and 5 partial responses. Twelve out of the 13 of these had these responses sustained for 7-31 months; Overall 2-year survival rate was 52% (26/50) (Senzer et al, 2009). Additionally, several of these patients who participated in the trial had tumor samples evaluated for immunological activity. An increase of MART-1-specific lymphocytes in the tumor environment, in both injected and untreated tumors in addition to the diminished number of regulatory T cells and myeloid-derived-suppressor cells indicates increased anti-tumor immunity. Based on these results, a Phase III clinical trial is underway, initiated in late 2009, in a similar structure to the Phase II, except on a larger scale, with more patients and a more precise aim to see exactly how effective OncoVEX GM-CSF can be against late-stage melanoma (Cancerresearch UK, 2009).

Several Obstacles to OV and Possible Methods of Overcoming Them

Antibody Neutralization and Complement Activation of OV

Because of the pathogenic nature of viruses, people have developed immune responses to them. In the case of OV, antibodies which neutralize OV are an obstacle to its success. The vaccinia virus, named after its use as a smallpox vaccine, has made human immune systems resistant to the Vaccinia OV. Another example is in the case of Reovirus OV. Since reoviruses are very common, many people have been exposed to them, which has caused a built-up immunity towards it. Over time, researchers have come up with a number of methods to overcome antibodies. One way is to deliver serotypes or chimera virus, a similar virus but with enough variants that it would not attract the antigen-specific antibodies (Zhang et al, 2011). Another strategy is what is termed the "Trojan horse." Similar to what occurred in the mythical story of Troy, cells – for instance, dendrocytes – are extracted from host, are ex vivo injected with OV, and reinserted into the host, effectively disguising viruses in host cells (Yotnda et al, 2004). The complement system is related to antibody neutralization, by helping antibodies and phagocytes clear pathogens from the host organism. The vaccinia virus naturally secretes a virulence factor, vaccinia complement control protein, which binds to complement molecules C3b and C4b (Girgis et al, 2008). Also, it reduces the number of CD4 and CD8 cells by the infection site, raising the possibility of using the regulatory protein to inhibit complement system (Pushpakumar et al, 2011); in our case in combination with OV. In the case of Adeno-OV, in vivo pre-clinical studies indicate that complement system activity can be reduced by the addition of the masking agent polyethylene glycol, which limits protein-protein interaction

(Tian et al, 2009). Second, Adeno-OV may be able to induce the Protectin protein which inhibits complement binding.

Antiviral Cytokines and Physical Barriers

Cytokines play an important role in host immune defense against viruses. IFNs 1, 2, and 3 promote apoptosis in host cells infected by virus, stopping viral replication, and antiviral cellular resistance in uninfected cells. Although an important positive feature in host versus virus in the case of pathogenic viruses, in the case of OV the Interferon systems are a problem hindering the spread of the virus. To overcome this obstacle, the previously mentioned Trojan horse strategy is implemented. In this case, Adeno-OV is injected into mesenchymal stem cells, which hide the OV and suppress activated T-cells (Ahmed et al, 2010). Another strategy is via pretreatment with histone deacetylase inhibitors which block the protein that expresses cytokine related DNA . Treating glioma with an HSV-based OV, Otsuki et al. (2008) employed valproic acid before injecting the OV. It reduced host ability to activate IFN-stimulated genes, and therefore increased potency. Another hindrance is that the liver and spleen absorb many viruses, removing them from the bloodstream. Kupffer cells – macrophages located in the sinusoids of the liver- absorb the vast majority of Adenovirus-type-5. Several strategies have been proposed to counter this issue. The anticoagulant warfarin depletes the number of Kupffer cells, thereby preventing Liver uptake of subsequent Adeno-OV. A second possibility raised by Zhang et al. (2011) involves blood coagulation factor X. The protein factor X cleaves prothrombin, activating it into thrombin. This factor is involved in liver uptake because it binds to the hexon protein of the virus (coat protein in Adenovirus); therefore, a hexon-chimeric Adenovirus, or an altered adeno-OV which only weakly binds to factor X has demonstratively less liver uptake.

Conclusion

The use of viruses as an anti-tumor agent is a complex topic. Oncolytic viruses are effective against cancer as demonstrated in clinical trials performed with OncoVEX GM-CSF, Adenovirus-based Onyx-15, and Reolysin, as well as other viruses. Based on these studies, the utilization of oncolytic viruses in combination with chemo and radiation therapy as conventional treatment is a promising possibility for the near future. However, there is little evidence that oncolytic viruses will play a large role in cancer treatment by supplanting current treatments. Second generation viruses such as increasing oncolytic potency by arming it with anti-tumor genes, and other methods, and third generation may improve viral effectiveness, but it is unrealistic to anticipate such techniques transforming OV as a reliable, independent cure for cancer.

References

Aghi, M., Chou, T. C., Suling, K., Breakefield, X. O., & Chiocca, E. A. (1999). Multimodal Cancer Treatment Mediated by a Replicating Oncolytic Virus That Delivers the Oxazaphosphorine/Rat Cytochrome P450 2B1 and Ganciclovir/Herpes Simplex Virus Thymidine Kinase Gene Therapies. Cancer Research, 59(16), 3861-5. Retrieved from http://cancerres.aacrjournals.org/content/59/16/3861.full.

Ahmed, Atique U., Cleo E. Rolle, Matthew A. Tyler, Yu Han, Sadhak Sengupta, Derek A. Wainwright, Irina V. Balyasnikova, Ilya V. Ulasov, and Maciej S. Lesniak. "Bone Marrow Mesenchymal Stem Cells Loaded With an Oncolytic Adenovirus Suppress the Anti-adenoviral Immune Response in the Cotton Rat Model." Molecular Therapy18.10 (2010): 1846-856. Print.

Biovex (2011, January 27). Mechanism for the dual-action cancer therapy. Developing oncolytic virus therapies The next wave views from Oncos Therapeutics. Retrieved from http://oncolyticvirus.wordpress.com/

Bischoff, J. R., & Samuel, C. E. (1989). Mechanism of interferon action. Activation of the human P1/eIF-2 alpha protein kinase by individual reovirus s-class mRNAs: s1 mRNA is a potent activator relative to s4 mRNA.. Virology, 172(1), 106-115. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2475969.

Cancer Research UK : A trial of OncoVEX GM-CSF for melanoma that cannot be removed : CancerHelp UK. (n.d.). Cancer Research UK: the UK's leading cancer charity : Cancer Research UK. Retrieved from http://www.cancerresearchuk.org/cancer-help

/trials/trial-oncovex-gmcsf-melanoma-cannot-be-removed

Choi, J. W., Lee, J. S., Kim, S. W., & Yun, C. O. (2012). Evolution of Oncolytic adenovirus for cancer treatment. Advanced Drug Delivery Reviews, 64(8), 720-729. Retrieved from http://dx.doi.org.lb-proxy8.touro.edu/10.1016/j.addr.2011.12.011.

ClinicalTrials.gov. (2012, July 31A Study of Reolysin For Patients With Advanced/Metastatic Breast Cancer - Full Text View -). Home - ClinicalTrials.gov. Retrieved December 27, 2012, from http://clinicaltrials.gov/show/NCT01656538

Duarte, S., Carle, G., Faneca, H., Pedroso de Lima, M. C., & Carle, V. P. (2012). Suicide gene therapy in cancer: Where do we stand now? Cancer Letters, 324(2), 160-170. Retrieved from http://dx.doi.org.lb-proxy8.touro.edu/10.1016/j.canlet.2012.05.023,.

Galocha, Begoña, Ann Hill, Barbara C. Barnett, Aiden Dolan, Alejandra Raimondi, Richard F. Cook, Joseph Brunner, Duncan J. McGeoch, and Hidde L. Ploegh. "The Active Site of ICP47, a Herpes Simplex Virus–encoded Inhibitor of the Major Histocompatibility Complex (MHC)-encoded Peptide Transporter Associated with Antigen Processing (TAP), Maps to the NH2-terminal 35 Residues." J Exp Med.185.9 (1997): 1565-572. NCBI. Web.

Garber, K. (2006). China Approves World's First Oncolytic Virus Therapy For Cancer Treatment. Journal of the National Cancer Institute (JNCI), 98(5), 298-300. doi:10.1093/jnci/djj111.

Girgis, N. M., Dehaven, B. C., Fan, X., Viner, K. M., Shamim, M., & Isaacs, S. N. (2008). Cell surface expression of the vaccinia virus complement control protein is mediated by interaction with the viral A56 protein and protects infected cells from complement attack.Journal of Virology, 82(9), 4205-4214.

Kelly, E., & Russell, S. J. (2007). History of Oncolytic Viruses: Genesis to Genetic Engineering. Molecular Therapy, 15(4), 651-659. doi:10.1038/sj.mt.6300108.

Lambright, E. S., Amin, K., Wiewrodt, R., Force, S. D., Lanuti, M., Propert, K. J,. Litzky, L., Kaiser, L. R., Albelda, S. M. (2001). Inclusion of the herpes simplex thymidine kinase gene in a replicating adenovirus does not augment antitumor efficacy. Gene Therapy, 8(12), 946-953. Retrieved from http://www.nature.com/gt/journal/v8/n12/full/3301489a.html.

Liu, B L., M. Robinson, Z-Q Han, R. H. Branston, C. English, P. Reay, Y. McGrath, S. K. Thomas, M. Thornton, P. Bullock, C. A. Love, and R. S. Coffin. "ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties." Gene Therapy10 (2003): 292–303. Print.

Nanda, D., Havenga, M., Vogels, R., Avezaat, C. J., Bout, A., & Smith, P. S. (2001). Experimental Therapeutics: Treatment of Malignant Gliomas with a Replicating Adenoviral Vector Expressing Herpes Simplex Virus-Thymidine Kinase. Cancer Research, 61, 8743-8750. Retrieved from http://cancerres.aacrjournals.org/content/61/24/8743.full.

Norman, K. L., & Lee, P. (2005). Not all viruses are bad guys: the case for reovirus in cancer therapy. Drug Discovery Today, 10(12), 847-855. Retrieved from http://dx.doi.org.lb-proxy8.touro.edu/10.1016/S1359-6446(05)03483-5,.

Otsuki, Akihiro, Ankita Patel, Kazue Kasai, Masataka Suzuki, Kazuhiko Kurozumi, E. Antonio Chiocca, and Yoshinaga Saeki. "Histone Deacetylase Inhibitors Augment Antitumor Efficacy of Herpes-based Oncolytic Viruses." Molecular Therapy 16.9 (2008): 1546-555. Print.

Panniers, R., and EC Henshaw. "A GDP/GTP Exchange Factor Essential for Eukaryotic Initiation Factor 2 Cycling in Ehrlich Ascites Tumor Cells and Its Regulation by Eukaryotic Initiation Factor 2 Phosphorylation." J. Biol. Chem. 258.13 (1983): 7928-934. Print.

Pushpakumar, S. B., Perez-Abadia, G., Soni, C., Wan, R., Todnem, N., Patibandla, P. K., Fensterer, T., Zhang, Q., Barker, J. H., & Maldonado, C. Enhancing complement control on endothelial barrier reduces renal post-ischemia dysfunction. Journal of Surgical Research, 170(2): e263-e270. (2011).

Rogulski, K. R., Wing, M. S., Paielli, D. L., Gilbert, J. D., Kim, J. H., & Freytag, S. O. (2000). Double suicide gene therapy augments the antitumor activity of a replication-competent lytic adenovirus through enhanced cytotoxicity and radiosensitization. Human Gene Therapy,11(1), 67-76.

Russel, S. J., & Peng, K. W. (2007). Viruses as anticancer drugs. Trends in Pharmacological Sciences, 28(7), 326-333.

Shafren, D., Davies, B., Chan, E., Yuan, M., Green, E., Stewart, J., Dr. G. Au. (2011). Viralytics - Home. Retrieved from http://www.viralytics.com/media/presentations/2011-06-23%20Oncolytic%20Activity%20of%20Coxsackievirus%20A21%20%28CAVATAK%29%20in%20Human%20Pancreatic%20Cancer%20WGICC.pdf

Shashkova, E. V., Doronin, K., Senac, J. S., & Barry, M. A. (2008). Macrophage depletion combined with anticoagulant therapy increases therapeutic window of systemic treatment with oncolytic adenovirus. Cancer Research, 68(14), 5896-5904.

Shizuko, S., Mussio, J. K., Yang, Q., Nagashima, K., Parchment, R. E., Coffey, M. C., . . . Shoemaker, R. H. (2009). Synergistic antitumor activity of oncolytic reovirus and chemotherapeutic agents in non-small cell lung cancer cells. Molecular Cancer, 8(47). doi:10.1186/1476-4598-8-47.

Small, E., M. Carducci, J. Burke, R. Rodriguez, L. Fong, L. Vanummersen, D. Yu, J. Aimi, D. Ando, and P. Working. "A Phase I Trial of Intravenous CG7870, a Replication-Selective, Prostate-Specific Antigen–Targeted Oncolytic Adenovirus, for the Treatment of Hormone-Refractory, Metastatic Prostate Cancer." Molecular Therapy14.1 (2006): 107-17. Print.

Smith, K. D., J. J. Mezhir, K. Bickenbach, J. Veerapong, J. Charron, M. C. Posner, B. Roizman, and R. R. Weichselbaum. "Activated MEK Suppresses Activation of PKR and Enables Efficient Replication and In Vivo Oncolysis by 134.5 Mutants of Herpes Simplex Virus 1." Journal of Virology 80.3 (2006): 1110-120. Print.

Strong, J. E., Coffey, M. C., Tang, D., Sabinin, P., & Lee, P. (1998). The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. The EMBO Journal,17(12), 3351-3362. doi:10.1093/emboj/17.12.3351.

Thomis, D.C., and C.E. Samuel. "Mechanism of Interferon Action - Evidence for Intermolecular Autophosphorylation and Autoactivaton of the Interferon-Induced, RNA-Dependent Protein-Kinase PKR." JOURNAL OF VIROLOGY 67.12 (DEC 1993): 7695-700. Web.

Tian, J., Xu, Z., Smith, J. S., Hofherr, S. E., Berry, M. A., & Brynes, A. P. (2009). Adenovirus activates complement by distinctly different mechanisms in vitro and in vivo: indirect complement activation by virions in vivo. Journal of Virology, 83(11), 5648-5658.

Wildner, Oliver, R. M. Blaese, and J. C. Morris. "Therapy of Colon Cancer with Oncolytic Adenovirus Is Enhanced by the Addition of Herpes Simplex Virus-thymidine Kinase."Cancer Res. 59.410 (1999): n. pag. Web.

Wildner, O., & Morris, J. C. (2000). The Role of the E1B 55 kDa Gene Product in Oncolytic Adenoviral Vectors Expressing Herpes Simplex Virus-tk: Assessment of Antitumor Efficacy and Toxicity. Cancer Research, 60. Retrieved from http://cancerres.aacrjournals.org/content/60/15/4167.full.

Ji, Xunda, Jufeng Zhang, Lin Cheng, Fang Wei, Huiming Li, Xinjian Liu, Xiafang Chen, Chuanyuan Li, Yufei Wang, and Qian Huang. "Oncolytic Adenovirus Delivering Herpes Simplex Virus Thymidine Kinase Suicide Gene Reduces the Growth of Human Retinoblastoma in an in Vivo Mouse Model." Experimental Eye Research 89.2 (2009): 193-99. Print.

Yoo, J. Y., Ryu, J., Gao, R., Yaguchi, T., Kaul, S. C., Wadhwa, R., & Yun, C. O. (2010). Tumor suppression by apoptotic and anti-angiogenic effects of mortalin-targeting adeno-oncolytic virus.. The Journal of Gene Medicine, 12(7), 585-595. Retrieved from DOI: 10.1002/jgm.1471.

Yoo, J. Y., Kim, J. H., Kwon, Y. G., Kim, E. C., Kim, N. K., Choi, H. J., & Yun, C. O. (2007). VEGF-specific Short Hairpin RNA–expressing Oncolytic Adenovirus Elicits Potent Inhibition of Angiogenesis and Tumor Growth . Molecular Therapy, 15, 295-302. doi:10.1038/sj.mt.6300023 .

Yotnda, P., Savoldo, B., Charlet-Berguerand, N., Rooney, C., & Brenner, M. (2004). Targeted delivery of adenoviral vectors by cytotoxic T cells. Blood, 104(8), 2272-2280.

Zhang, J. F., & Huang, C. (2006). Combined Oncolytic Adenovirus with Double Suicide Gene in Killing Lung Cancer. Molecular Therapy, 13. doi:10.1016/j.ymthe.2006.08.933.

Zhang, Z., Kimmel, J., Hu, Z., & Seth, P. (2011). Systemic delivery of a novel liver-detargeted oncolytic adenovirus causes reduced liver toxicity but maintains the antitumor response in a breast cancer bone metastasis model. Human Gene Therapy, 22(9), 1137-42.

Zheng, F. Q., Xu, Y., Yang, R. J., Wu, B., Tan, X. H., Qin, Y. D., & Zhang, Q. W. (2009). Combination effect of oncolytic adenovirus therapy and herpes simplex virus thymidine kinase/ganciclovir in hepatic carcinoma animal models. Acta Pharmacologica Sinica,30(5), 617-27. Retrieved from http://search.proquest.com.lb-proxy8.touro.edu/docview/213027610.