Oncolytic Viruses: A Viable Treatment Option for Treating Cancers

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ABSTRACT

Cancer is a disease that is based on the same principles that split species apart over time: evolution. Cancer cells have mutations in them that do not control cell proliferation, and the causes for cancer can come from different places; they could be hereditary or could be from environmental causes like toxic carcinogens. Either way, it is known that cancer is a problem that has been plaguing many species and is a main topic of study in humans. In these studies, new ideas for treatments have developed and even brought to the medical field as treatments, and one such treatment is the use of viruses in aiding to target and destroy cancer cells; these viruses are otherwise known as oncolytic viruses. The goal of this research paper is to evaluate a treatment option that aims to spare patients with cancer diagnoses from having healthy cells affected by the treatment option, something that is not currently offered in current cancer treatment options. This paper will research characteristics oncolytic viruses take advantage of and the mechanisms of these viruses used to target cancer cells. The paper will also investigate treatments that have been approved for treating specific cancers, and whether oncolytic viruses can serve as a viable treatment option to treat cancer soon based on current research done thus far.

Introduction

Current cancer treatments, such as chemotherapy and radiation therapy, help to destroy cancer cells but come at the expense of the health of the patient; such treatments often destroy both cancer tissue and normal tissue. Oncolytic Viruses (OVs) are viruses that are intended to target and destroy cancer cells without causing significant harm to healthy cells. OVs are intended to target these cancer cells, selectively enter cancer cells and induce cancer cell death by targeting certain surface proteins or receptors and taking advantage of the weakened defense systems that cancer cells have. These OVs are most often created by taking an existing platform (existing virus; take for instance, an adenovirus) and genetically modifying its genetic information to target characteristics only expressed or overexpressed by cancer cells. Although some OVs are naturally occurring (such as reoviruses), most often they are created in a lab. Traditional viruses target a wider array of cells, which includes both tumor and healthy cells. Traditional viruses aim to replicate using a cell’s machinery and spread to other cells in order to repeat the process. These viruses often find themselves battling against cells that have better defense mechanisms and antiviral proteins to help fight off these viruses. These infected cells can also undergo programmed apoptosis in order to prevent viral replication. In the end, these viruses often cause more harm than they do good or do not help fight against existing cancer cells. Many recent developments in OV research have been more focused on the immunological aspect of using OVs as a cancer therapy. Essentially, this means that researchers are looking into more ways to induce immune responses against cancer cells. According to Mary Cook and Aman Chauhan, researchers looking at the efficacy of T-Vec (the only FDA-approved oncolytic virus) for treating melanoma, stated that OVs, namely T-Vec, can alter the tumor environment and create a significant improvement in immune response to cancer cells. Currently, there are a few OVs that are undergoing further investigation in clinical trials; all of which are OVs that are currently in phase II and III trials, or impending certification from the FDA. The research here shows that there is significant evidence that OVs can be used as a viable therapy. The application of OVs could present itself with advantages not given by other forms of cancer treatment or
therapies, and its application could also lead to disadvantages or show limitations in its use. The research paper attempts to conclude whether Oncolytic Viruses are viable options to treat cancer using current research and information.

Cancer Cells

Before understanding how oncolytic viruses can be effective for use in cancer treatments, it is important to understand what makes cancer cells different from healthy cells; these differences make up many of the reasons why the mechanisms behind oncolytic viruses are effective. Essentially, cancer cells are variations of healthy cells with damaged DNA, the genetic material of the cancer cells, which makes cancer a genetic disease. Damage of DNA in cancer cells can damage oncogenes (genes that encourage cancer proliferation or growth) or tumor suppressor genes (genes that suppress cancer proliferation). Certain factors do increase the chance of damaging healthy cell DNA and turning a healthy cell into a cancer cell. According to the National Cancer Institute (2002), cancer can be from UV radiation, various chemicals, viruses, smoking, heredity, and from mistakes from cell divisions, only 10% of cancers emerging due to pre-existing genetic factors. Although cancer cells have damaged DNA, which causes them to make proteins that end up hurting the cell’s overall health, cancer cells can hide themselves from the immune system and trick the immune system into identifying cancer cells as healthy cells. Although cancer cells are genetically different from healthy cells, they still contain transmembrane proteins (proteins that lie on the surface of a cell, ready to be ‘scanned’ by macrophages) that healthy cells have. Despite the similar variety of transmembrane proteins, differences in cancer cells’ genetic makeup either upregulates or downregulates the presence of some transmembrane proteins. One important transmembrane protein is PD-L1. PD-L1 (short for Programmed Death Ligand 1) is a transmembrane protein that is responsible for maintaining immune homeostasis (by identifying and not attacking healthy cells). Using PD-L1, as well as other surface receptors like CD47 and CD42, some cancers and tumors are unable to be identified by the immune system and are often left alone by the immune system. Tumors are then able to replicate to create a bigger tumor microenvironment, undergo angiogenesis (new blood vessels to deliver oxygen and nutrients to the tumor microenvironment), and finally metastasize without any interference from the immune system. This lack of tumor growth is harmful to its surrounding cells and will be fatal without any intervention. Another important receptor to look at is the EGFR, otherwise known as the Epidermal Growth Factor Receptor. This receptor is responsible for helping control cell proliferation. Defects in the EGFR or overexpression of it can predictably lead to uncontrolled cell proliferation. Uncontrolled tumor growth, along with eventual metastasis after angiogenesis, leads to interference and impairment of nerves, organs, or blood vessels that is needed to support life. By growing into other areas that are occupied by functional, healthy cells, tumors can block blood supply and starve healthy cells, leading to impairment of ability that those cells specialize in. As cancer cells continue to grow and metastasize, symptoms worsen, and the likelihood of fatality increases.

Surface Receptors and Signaling pathways that can be targeted in Cancer cells

Surface Receptors and Proteins

Given the fact that cancer cells hold genetic information that has been damaged, it is apparent that cancer cells have specific differences that oncolytic viruses (OVs) should be able to exploit. One such difference is the expression of surface receptors and proteins. As mentioned before, OVs are either evolved or engineered to bind to certain surface proteins and receptors that are overexpressed or only expressed in cancer cells. The following sections go over the most common cell receptors that cancer cells express and thus targeted by OVs in order to gain access to the cell and continue their viral mechanisms.
PD-L1

Noted in the previous section, a common surface protein overexpressed is the Programmed Death-Ligand 1 (PD-L1). According to Cagle and Allen, “Programmed death ligand-1 is a regulatory molecule… which has an immunoregulatory function by dampening the immune response when bound to one of its complementary ligands… The likely physiologic role of [PD-L1] is to prevent excessive tissue destruction during inflammatory states” (Programmed Death 1 Ligand 1 - an Overview | ScienceDirect Topics, n.d.). Essentially, the ligand serves as a tool that can be used by cells to identify themselves as harmless to the immune system, thus stopping immune responses for cells that are identified as ‘healthy and harmless. As explained by Cagle and Allen, tumors and cancer cells can also express PD-L1 on the cell surface. Like healthy cells that use PD-L1 in order to identify themselves as healthy cells, tumors/cancer cells can also express PD-L1 in order to avoid an immune response against them. Although the same surface protein is used by cancerous and noncancerous cells, the frequency at which the surface receptor is being expressed is different. As reported by Yu et al., “Overexpression of high-aggregate PD-L1 in tumors leads to poor prognosis in cancer patients” (Yu et al., 2016). This entails that in most cases, a higher expression of the PD-L1 protein leads to higher chances of tumors and cancers going unnoticed by T-Cells of the immune system. However, at least according to Wang et al., this positive correlation between PD-L1 expression and poor prognosis is not definitive in all cancer cases, including colorectal cancer. Besides this, higher expression levels of PD-L1 are associated with poorer prognosis in cases including lung cancer, gastric cancer, colorectal cancer, esophageal cancer, and pancreatic cancer. In summary, PD-L1 and its associated PD-1 pathway is a “significant mechanism of immune suppression within tumor microenvironment” and its overexpression is a key part of preventing cytolysis from T-cells. The use of PD-L1 in oncolytic virotherapy is still to be further studied upon as it is not a protein that can directly attach upon any understood viral particles, but it stands that further study of the frequent overexpression of PD-L1 in cancer cells and possibly establish new pathways that can serve as another pathway/mechanism for OVs in the future.

Epidermal Growth Factor Receptor (EGFR)

One of the more well-known oncogenic receptors that are commonly altered in cancer cells is the Epidermal Growth Factor Receptor, otherwise known as the EGFR. According to Thomas and Weihua, “EGFR is… commonly expressed/overexpressed membranous oncogenic protein in cancer” and given that it is frequently expressed in cancers, it stands that “EGFR remains an ideal therapeutic target for cancers” (Thomas et al., 2019). This surface receptor is responsible for inducing cell proliferation when the cell is in the presence of EGF, otherwise known as Epidermal Growth Factor ligands. When these ligands combine with EGFR, the receptor then signals for growth into the cell. However, when a mutation occurs in genes that encode for the EGFR receptor are mutated (mutations in the short arm of chromosome 7), overexpression of the EGFR starts to occur. With more receptors on the cell, the uncontrolled cell proliferation of oncogenesis starts to occur. This overexpression of the EGFR serves as the foundation of some cancers; this means that some OVs can target EGFR in hopes of selectively targeting cancer cells.

2.1.2.0 Aberrant Signaling pathways.

Although the main difference that OVs tend to take advantage of is the difference in expression levels of certain receptors, it is important to understand that this is not the only oncogenic characteristic that these viruses can take advantage of; aberrant signaling pathways that exist in cancer cells also contribute to the replication of OVs when these viruses infect cancerous cells. The following sections go over the most common types of aberrant signaling pathways that exist in cancer cells, which allow for the replication of OVs.
Defective p53 pathway

Mutations in cancer cells often occur to dysregulate or defect the function of tumor suppressor genes. One such gene includes the p53 pathway. The p53 tumor suppressor gene is responsible for regulation of the cell’s progress through the cell cycle and cell proliferation, and when damaged, could lead to uncontrolled cell proliferation, otherwise known as cancer. The p53 pathway can be inactivated in multiple ways; according to Creative Biolabs, “the p53 tumor suppressor pathway is inactivated… through direct mutation of p53 or the loss of upstream regulators such as p14ARF or downstream p53 effectors such as Bax” (Mechanisms of Oncolytic Virus Targeting Tumor Cells - Creative Biolabs, n.d.). The mutations or loss of these regulators essentially mean that these cells do not undergo abortive apoptosis when infected with viral particles. Due to this lack of abortive apoptosis, cancer cells can serve as a medium in which OVs can replicate in while being benign to normal cells, given that the viral particles are genetically modified or naturally do not encode proteins that degrade the p53 gene in normal cells.

Defective PRK and IFN signaling pathways.

One other difference that can be exploited by OVs are the Interferon (IFN) and the Protein Kinase R (PKR) pathways in cancer cells. Usually when a healthy cell becomes infected with viral particles, it triggers the production of interferons, a signaling molecule that signals for an increasing antiviral defense. When these IFNs are produced, they bind to specific receptors on surrounding cells called interferon receptors (IFN-Rs). The binding of IFNs to IFN-Rs leads to the activation of PKRs. These PKRs are then responsible for taking dsRNA (double stranded RNA) from viral particles and ultimately results in the synthesis of proteins in the cell that can effectively prevent the virus from effectively replicating. In cancer cells, however, these signaling pathways are often weakened. One common instance, according to Creative Biolabs, is the activation of the RAS signaling pathway. When the RAS signaling pathway is activated in cancer cells, the autophosphorylation of PKR, a key step in the PKR signaling pathway that ultimately leads to proteins that make up antiviral defenses, is inhibited. Due to inhibitions in the IFN and PRK signaling pathways, OVs can take advantage of weakened antiviral defenses to replicate, while being genetically engineered or naturally not strong enough to take control over a healthy cell’s machinery in order to support viral replication.

Figure 1. Differences Between Cancer Cells and Healthy Cells. The diagram above shows the physical and mechanical differences between cancer cells and healthy cells. These differences are important because these differences are what allow OVs to target and destroy cancer cells while keeping healthy cells majorly unharmed. Information needed to create figure from the University of Washington. Created with BioRender.com
Figure 2. Difference in Surface Protein and Surface Receptor Expression. The diagram above shows the expression level differences of surface protein PD-L1 and surface receptor EGFR. As shown above, oncogene expression levels for cancer cells express a much higher frequency of both the PD-L1 protein and the EGFR receptor. Information needed to create figure from Thomas et al. and Yu et al. Created with Biorender.com

Mechanisms of Oncolytic Viruses

Like many other viruses, OVs can enter a person’s body and undergo viral replication and spread to other cells in the body. However, in order to ensure that these viruses can enter the body without any resistance, live OVs are entered by intramuscular injection. As OVs enter the bloodstream, the viral particles float through the body in search of cancer cells. OVs are modified to target certain surface proteins that are overexpressed in cancer cells and exploit defected/aberrant signaling pathways in cancer cells. One such protein that OVs target is the previously mentioned EGFR. The EGFR (Epidermal Growth Factor Receptor) is a transmembrane receptor that is responsible for regulating key aspects of cellular growth. When the compatible OV attaches to the cancer cell via the EGFR, the virus particle, depending on the platform that the OV is based on, can be sent through multiple different processes, and the outcome will differ greatly depending on what type of cell that is infected. One common process is the entering of viral particles into the cell. In this pathway, when the viral particle enters through endocytosis, the capsid, or the shell that holds the viral genetic information, is broken down. The subsequent mechanisms that transpire will differ depending on the type of cell that is infected.

When an oncolytic cell successfully enters a healthy cell, the cell can attack viral particles to prevent the viral particles from replication, or the cell would undergo induced apoptosis in order to also prevent viral particles from replication. This process undergoes a different process in cancer cells, however. When an OV successfully enters a cancerous cell, the cell, preexisting with damaged DNA and machinery due to aberrant/defected signaling pathways, is unable to properly identify/fight against the presence of a viral particle. As a result, these viruses can undergo viral replication without much resistance. After the viral particles enter the cell via endocytosis, the genetic information is then taken out of the capsid. This genetic information is then taken to the nucleus and enters the nucleolus. The nucleus and the embedded nucleolus are both parts of the cell that are places where delicate DNA and the “manual” for cellular replication takes place. In the same way that our cells use DNA as the instructions for cellular replication, viral particles also take use of cellular machinery in order to replicate other viral particles. As genetic information enters the nucleus, viral RNA is then replicated by viral RNA polymerase. By replicating the RNA, the RNA polymerase in turn makes a set of instructions that can be used to replicate and produce more viral particles. These instructions are called the mRNA, a single strand that encodes the same genetic information that the mRNA came with. The mRNA then leaves the nucleus in search for a ribosome, or structures that are the sites of protein synthesis in the cell. After finding
a ribosome, the mRNA begins to be read in a process called translation. In this process, subunits of the ribosome start to match the base pairing on the mRNA being read, attracting tRNA molecules. As the mRNA is read, tRNA is attached to each respective base pairing. Once the tRNA is attached, amino acids (subunits of proteins that give proteins their function) that are attached to the tRNA start to create a chain of amino acids. As this chain of amino acids starts to get bigger, the overall protein, or the viral particle in this case, continues to finish. This process (starting with RNA polymerase replicating viral RNA into mRNA and finishing with a new viral particle being replicated) continues to repeat itself.

As replication continues in these cells, the viral particles start to grow in number. Eventually, these viral particles then increase the internal pressure of the cell, thus resulting in cell lysis. When cell lysis does occur, cancer cell proteins called tumor antigens are released, along with the new viral particles that caused cell lysis in the first place. These new viral particles then spread to other areas of the body through the bloodstream in search of more tumor cells. Meanwhile, tumor antigens that are released by tumor cell lysis alerts the immune system of the presence of tumor cells, in which the immune system starts creating antibodies that can be used to flag cancer cells in the immune system and later be destroyed by the immune system. The immune system, now being activated by tumor antigens from lysed cancer cells, can recognize metastatic lesions, otherwise known as cancer cells, that have traveled through the bloodstream and into other areas of the body. The ‘arming’ of the immune system gives the person in question undergoing the immunotherapy a better chance for a good/better prognosis than before the introduction of OVs.

**Figure 3.** Healthy Cell When Infected with Oncolytic Virus. Due to genetically modified genes that were changed in the lab, OVs present no harm to healthy cells since these virus particles are not designed to target cells characteristic of healthy cells. In the case that a healthy cell is infected by an OV, the cell can destroy viral particles and progeny without major harm to the cell. Information needed to create figure from Creative Biolabs. Created with BioRender.com
Advantages and Limitations of Oncolytic Virus Therapy

Advantages of using Oncolytic Viral Therapy

Oncolytic Viruses, despite being a relatively new type of cancer therapy, present some advantages over other types of cancer treatments. One of the many advantages is the nature in which the viruses work, also known as the mechanisms of OVs. As explained in the previous section, OVs work to selectively target cancer cells instead of healthy cells. This leaves the person undergoing Oncolytic Viral treatment to experience less symptoms than would be seen with other forms of cancer treatment such as chemotherapy and radiation therapy. Due to the lesser extent of which healthy cells are destroyed, oncolytic virus therapy can lead to lessen fatigue, hair loss, anemia, and nausea among other side effects that would be seen with chemotherapy. Lessened side effects can lead to a less stressful treatment period during therapy.

Another benefit that oncolytic virus therapy provides is the mechanisms in which OVs work; more specifically, it is the mechanism that allows for the direct lysis and targeting of cancerous cells. This mechanism is responsible for keeping healthy cells unharmed while making sure that cancer cells are destroyed. By keeping these healthy cells unharmed, the person in question taking OVs will experience less symptoms while keeping their immune system unharmed.

Limitations of Using Oncolytic Viral Therapy

Despite the advantages that OVs provide the patient, there are outcomes and side effects that can become problematic for the progress of the therapy. One such disadvantage is the possibility of mutating cancer cells. Like the frequency of surface receptor/protein expression and the defects in signaling pathways, cancer cells are also more likely to be...
subjected to random mutations. According to the University of Washington, “tumor tissue had random mutation rates up to 100 times higher than normal tissue from the same patient… it means that cancer cells in a tumor will have mutations that protect them from therapeutics” (University of Washington, 2007). What this essentially means for Oncolytic Viral treatment is that there is a likelihood where the effectiveness of the therapy will be reduced due to evolving characteristics of cancer cells. In other words, the cancer may start to adapt to avoid OVs. This can be avoided through frequent biomarker testing in order to ensure that the specific virus being administered is effective in treating cancer.

Mutations in these characteristics also bring about another possible issue: errors in transcription and translation of the OV’s genetic information. In one instance according to Champagne et al., “despite protein quality control mechanisms, amino acid shortage… induces aberrant proteins by ribosomal shifting” (Champagne et al., 2021); in other words, cancer cells have a higher chance to cause errors in translating mRNA genetic material, as well as other types of genetic materials that hold the instructions to make functional proteins. In the case where the genetic information of an OV is not translated properly, the virus could show characteristics that are not desired, and make the new viral progeny ineffective to achieve its oncolytic effects.

Another part of this immunotherapy to be weary of will be the reduction in overall lysis by the OVs. According to the mechanisms in which OVs act, the immune system becomes aware of the tumor by presence of tumor antigens in the bloodstream and new viral progeny. Due to newfound identification of OVs in the body, the immune system will start to attack the oncolytic virus along with remaining cancer cells. Though this usually will mean that overall progress of the treatment continues, the rate at which cancer cells are targeted will decrease.

Figure 5. Changes Caused to Oncolytic Virus Progeny after Replicating through Faulty Cancer Cell Replication Machinery. This diagram displays the steps in which a virus with the correct viral genetic information can be altered by errors in translation during replication to make new viral particles. This thereby increases the possibility that these viral particles behave differently. Information needed to create figure from Creative Biolabs. Created with BioRender.com
Figure 6. Average Mutation Rates in Cell Types. The figure above shows a graph that compares average mutation rates between normal cells and cancer cells from the same patient. The graph shows that cancer cells can present more obstacles in terms of targeting cancer cells and replicating within cancer cells. Information needed to create figure from Thomas et al. Created with BioRender.com

Oncolytic Viruses in Clinical Trials and in Use for Treatment

Despite being a relatively new therapy, multiple Oncolytic Viruses are at least in the clinical trial phase or beyond and are being tested in order to see their viability for treating their respective type of cancer. The sections below go over viruses that are currently used in clinical settings.

T-Vec

Currently, there is only one OV that is approved by the Food and Drug Administration (FDA) for treating cancer; more specifically for subsets of melanoma. That virus is known as the Talimogene Laherparepvec virus, otherwise known as the T-Vec virus. The T-Vec virus is a genetically modified herpes simplex virus engineered to treat melanoma. T-Vec can also be used to treat advanced melanoma as well, both by itself and in combination with other types of immunotherapies. T-Vec is a modified Herpes Simplex Virus “with the insertion of the granulocyte monocyte colony-stimulating factor (GM-CSF) gene and deletion of infected cell protein 34.5 and ICP47 genes” (Zhang et al., 2023). The T-Vec virus is currently being administered to patients who have metastatic melanoma. According to Zhang et al., few patients did complain of slight feverish symptoms and slight edema at the site of injection, but these symptoms usually lasted less than 24 hours. It is also to be noted that the toxicity profile of T-Vec is mild and tolerable. T-Vec as an immunotherapy is limited in its scope of when it can be effective. However, it does appear that T-Vec can be an effective treatment for treating melanoma, even without being supplemented by other immunotherapies.

G47-Delta

G47-Delta is an oncolytic virus that, until very recently, was in clinical trials; the virus, based off the same herpes simplex virus that the T-Vec was based off, was approved for use in Japan. The G47-Delta virus is engineered to treat glioblastomas (aggressive cancer that forms in the brain and neck). The most adverse effects of the virus, according
to Todo et al., are fever, headaches, and vomiting. The toxicity of the virus shows to be mild and tolerable, making for an effective treatment option for those with glioblastomas.

**Limitations**

All the research sourced for this article was done in very specific environments, and other factors can be involved in the targeting of cancer cells. For instance, it is a possibility that research done to find expression rates for aberrant surface receptors/proteins and signaling pathways are not consistent from cancer cell to cancer cell, making it more difficult for OVs to selectively target/harm only cancer cells. It is also a possibility that the mutation rates of cancer cells, relative to human cells, is not accurate due to possible lack of ample time given to find accurate mutation rates of cancer cells. Due to the specific and controlled environments that these cancer cells were held in, mutation rates of cancer cells in this research may not be representative of mutation rates of cancer cells that are targeting in patients. The relatively new introduction of OVs like T-Vec and G47-Delta possibly does not show the entire extent that OVs can have on human health long term.

**Conclusion**

In the search for a therapy that could lead to a better outcome, scientists have been looking for therapies that can provide better solutions than the main types of cancer treatments we use today, such as chemotherapy, radiation therapy, and surgery. More specifically, scientists look for therapies that will cause the least amount of adverse side effects. One such therapy that scientists have found is a type of immunotherapy called Oncolytic Virus (OV) therapy; the use of OVs in order to help target and destroy cancer cells directly while helping the immune system identify and destroy cancer cells as well. It is shown that the application of oncolytic viruses could present itself with advantages not given by other forms of cancer treatment or therapies, and its application could also show limitations in its use. Findings in current literature and research conclude that OVs can find certain types of cancer cells throughout the body; they are able to find cancer cells that are both benign and malignant, given that they have the correct information to do so. This last part is important to understand as well. As cancer cells mutate, their ability to stay the same and have the specific characteristics that OVs use to target cancer cells decrease, limiting their ability to target cancer cells. The immune system will also start to attack the virus along with tumors, decreasing an OV’s ability to directly reach and lyse cells. Despite the limitations, OVs have been developed for use and are being used as therapies to treat specific types of cancers. With further research, we can find more ways to target cancer cells by continuing to understand more about the cancer environment in which cancer cells exist. Based on this research thus far, it is apparent that oncolytic viruses do serve as a viable option for treating cancer for only specific types of cancers. Although OVs are limited, their potential to treat benign and metastatic cancer make them an intriguing option to delve further into with new research. With new development that occurs with oncolytic virus immunotherapies, OVs can be found and engineered to be used to treat a broader spectrum of cancers. Hopefully, research in Oncolytic Virus therapy can lead to a treatment that can at least be considered a cure for cancer.

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