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The Effect of Oncolytic Viruses in Aiding Cancer Immunotherapy

Anushka Singh
Grand Valley State University

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Professor Doug Graham

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Abstract

Oncolytic viruses are known as genetically engineered viruses or ones that can be found in nature, that are used to selectively reproduce in cancer cells and kill them without harming the normal and healthy cells. Oncolytic viruses have been considered an effective form of immunotherapy and offer a new approach for cancer treatment. Only one oncolytic virus has been approved by the Food and Drug Administration (FDA) in the USA, which is T-Vec (talimogene laherparepvec). This is a second-generation oncolytic herpes simplex virus type 1 (HSV-1). Another oncolytic virus has been approved only in China in 2005, which is called Oncorine. It is an E1B-deleted adenovirus, which is used for head and neck cancer and esophagus cancer (Fukuhara, Ino, Todo, 2016). This paper will demonstrate the clinical effectiveness of oncolytic viruses and how they have proven to help with cancer immunotherapy.

I. Introduction

A. Background

Oncolytic viruses have been proven to be effective when it comes to immunotherapy, as they are able to properly induce host antitumor immunity. There are a variety of viruses that have been tested as potential oncolytic viruses such as poxvirus, herpesvirus, picornavirus, etc. Each of these viruses uses multiple cell surface receptors to gain entry. Oncolytic viruses are known to mediate antitumor activity through selective replication and lysis within infected cancer cells and through induction of host antitumor immunity (Kohlhapp and Kaufman, 2016).

B. History

Using viruses as a form of cancer therapy is an old concept and has been around for more than 100 years. In 1912, Italian doctors had discovered a rabies vaccine that was shown to cause cervical cancer regression, which is how the concept of oncolytic virus therapy emerged (Cao, He, Sun, Chen, Wan, Xu, Feng, Li, Chen, and Xiong, 2020). In the 1950's and 1970's, there were a lot more clinical trials conducted that utilized the wild-type viruses for treating tumors, however, the issue was that it was not possible to control the pathogenicity of the virus. It was in the 1980's when oncolytic viruses began to gain more popularity due to the increased advancement in genetic engineering technology, which allowed the genome of the virus to be altered. There was another notable time in 2005 when people were starting to understand that the value of viruses in cancer therapy is in immunotherapy (Gromeier, 2018). Nowadays, viruses are known to effectively mediate immunotherapy.

C. Function of Mechanism

Oncolytic viruses function in a way where they self-replicate so that they can destroy the host in cancer cells. They hijack the cell's protein synthesis and can mediate the production of viral particles. Due to this, the infected host cells lyse, and sub viruses are spread so that they are able to infect other cells. The tumor growth must inhibit the immune system.

These viruses have strong effects on the immune cells entering the tumor tissue, which can change the microenvironment of the tumor. Tumor cells that are infected with the virus express danger signals, for example cytokines, which then

prompt the immune cells outside the tumor to integrate into the tumor and activate non-specific immune cells. A large amount of tumor proteins are released by tumor cells that are lysed by oncolytic viruses, which can be phagocytized by non-specific immune cells. Additionally, tumor-specific antigens are expressed by antigen presenting cells, which can then induce T cells and direct them to attack the uninfected tumor cells (Bai, Hui, Du, Su, 2019).

Viruses contain many different characteristics that can be exploited such as being able to replicate in the host cell, which can allow for self-amplification and make it easier so that every target cell is infected at the time of the first treatment. Another beneficial characteristic is the specificity for a certain type of cell/cell receptor, for example, a neural or epithelial cell. The virus could interact differently with healthy cells as compared to cancerous cells, however, the host response to infections deals with humoral and cell-mediated processes with the host response to malignant cells (Sze, Reid, Rose, 2013).

From the article *Oncolytic Virotherapy*, Dr. Sze, Dr. Reid, and Dr. Rose feature a diagram that demonstrates the mechanism of how an oncolytic virus attacks a cancerous cell (figure 1). It is shown that an oncolytic virus (black hexagon) attacks the cancerous cell (a). The virus enters the cancer cell with ease due to specificity for a tumor-related cell surface receptor or antigen. After the malignant cell is infected, the cancerous genetic material is propagated and unchecked replication of the oncolytic virus is allowed (b), due to the cell's permissive nature. An infection of the healthy and normal cell (f) is unsuccessful due to the cell's ability to identify and kill any abnormal genetic material. Now,

the infected cell (b) will make viral proteins that are antigenic and can notify the immune system. Additionally, if the virus is genetically equipped, the cell can produce cytokines in order to active the immune system. Since the cancer cell is infected, it becomes swamped by the viral infection and therefore, lyses. This in turn, causes the cancer cell to release new viral particles so that it can infect the neighboring malignant cells (c). The new viral and tumor-related antigens released due to the lysis can be recognized by the immune system and then attacked, which is represented by the lymphocyte (L). Viremia that is due to lysis related activities can cause infection of distant metastases (d), which causes a shift from a locoregional to systemic effect. The immune system is alerted and activated due to the elevation of systemic cytokine levels and activated leukocytes, which enhances the systemic effect. The immune system can also develop memory and therefore, identify tumor antigens which can provide a more durable defense against recurrent diseases.

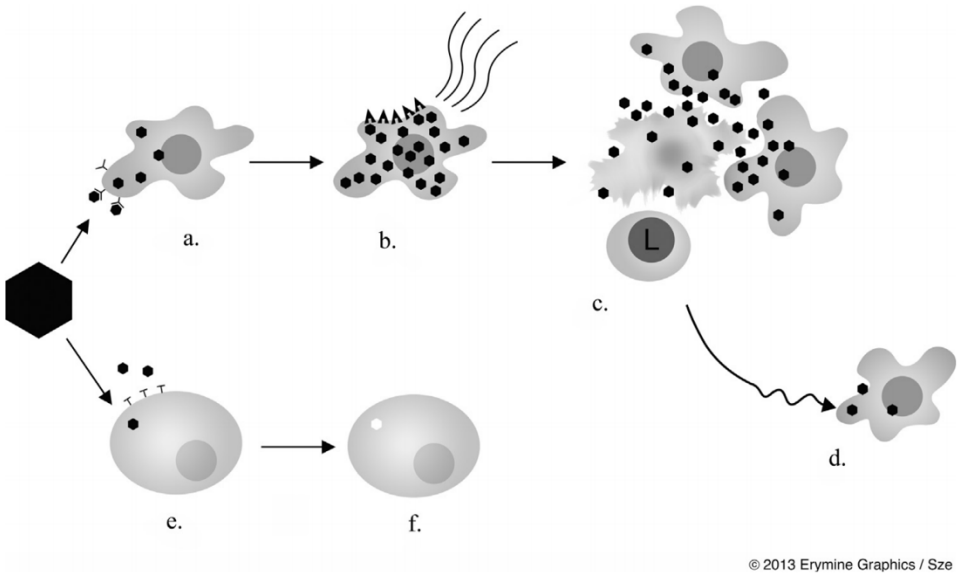

Figure 1: The mechanism of an oncolytic virus attacking a cancer cell

https://www.jvir.org/article/S1051-0443(13)01024-5/pdf

D. Delivery of Oncolytic Virus

There are many ways to administer oncolytic viruses into the body for cancer immunotherapy. There are oral viral vaccines available for viruses such as poliovirus, rabies virus, rotavirus, etc., however, taking the oral route results in immunity being weaker than the parenteral route. The intravenous route is the preferred method, and it is quite convenient. However, even though it is a convenient route, there are disadvantages to this. The intravenous route does not target cancer cells specifically. On top of this drawback, before the virus can even reach the tumor, the antibodies that are made by the pre-existing immunity will neutralize the virus. Therefore, the virus concentration might need to be increased, but that means that it could also increase the inflammatory response, which is not a desired outcome.

Additionally, there are two other routes of radiation intervention: arterial and tumor site administration. The intra-arterial method allows for the virus to be selectively transported to the target cancer cells. Most importantly, this method can avoid antibody neutralization because of limited blood volume and the target organ.

II. Literary Review

A. Positive Studies

There have been many types of cancers that have been targeted in clinical trials when it comes to using oncolytic viruses. The most common tumors were melanoma and GI cancers. There were 30 clinical trials for melanoma, which accounted for 1000 patients. Meanwhile, there were 76 trials targeting patients with GI cancer (Macedo, Miller, Haq, Kaufman, 2020). Figure 2 below shows the different types of cancers that have been targeted in oncolytic virus clinical trials. Some other common cancer types are head and neck cancer, breast and gynecological cancers, genitourinary cancers, and sarcomas.

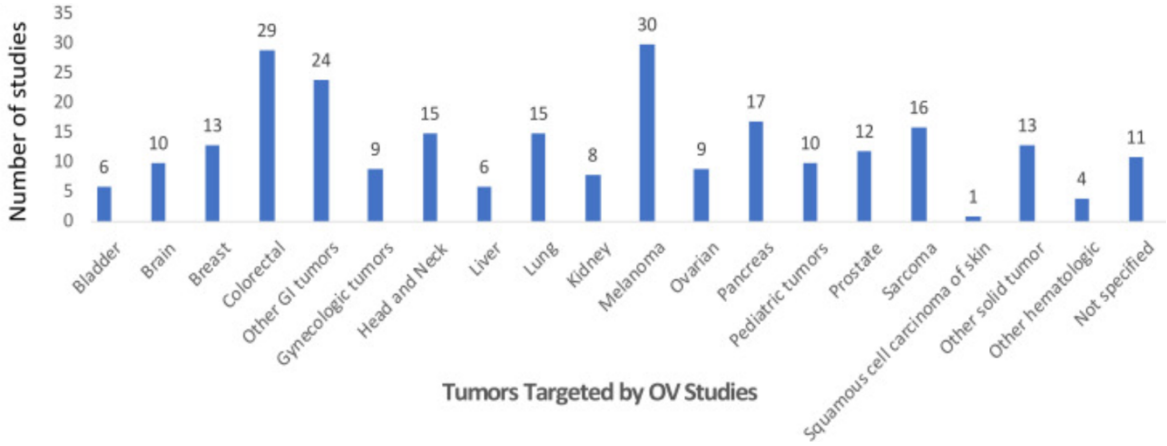

Figure 2: Cancer types targeted in oncolytic virus clinical trials

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7552841/

There have been many studies that have demonstrated positive results when it comes to oncolytic viruses in cancer therapy. In the journal *Recent Advances of Oncolytic Virus in Cancer Therapy (Mondal, Guo, He, Zhou, 2020),* there were multiple trials performed regarding the use of T-VEC. A phase I trial of T-VEC was conducted which included 30 patients that were all affected with various types of cancers, 9 of whom had refractory metastatic melanoma. Melanoma is cancer that begins in the melanocytes, and it is classified as metastatic melanoma when it spreads from the skin to other body parts. The T-VEC injection was administered intratumorally, which led to remission in two patients, and they had no adverse effects. This led to a phase II clinical trial that had stage III or IV melanoma. Out of the 50 patients that were treated with T-VEC intratumorally, 8 patients had accomplished a complete response, whereas 5 had a partial response. This led to a phase III clinical trial, where there were 436 patients with stage IIIb, IIIc, and IV unresectable melanoma. They were also treated with T-VEC and it was compared with the recombinant GM-CSF (granulocyte-macrophage colony-stimulating factor). For the 436 patients that were treated, the double response rate was much higher for those treated with T-VEC as compared to GM-CSF. Overall, T-VEC showed profound efficacy and there were not any adverse side effects except for fatigue, chills, and pyrexia. The success of these trials, especially the third phase, played a huge role in the FDA approval of T-VEC.

As mentioned earlier, oncorine is the first oncolytic adenovirus that was approved by the China Food and Drug Administration Department (CFDA), which was combined with chemotherapy in order to treat nasopharyngeal carcinoma in

2005. There had been a phase III clinical trial that included patients with head and neck squamous cell carcinoma and esophageal cell carcinoma. It was injected intratumorally and H101 was combined with cisplatin and 5-fluorouracil (PF) or adriamycin and 5-fluorouracil (AF) was compared with PF or AF treatment alone (Mondal, Guo, He, Zhou, 2020). The safety and efficacy of this H101 injection was observed in the trial. It served as a huge milestone as it was quite successful, and it was launched in the market. After it was launched, there were additional clinical trials that tested for oncorine regarding the four types of cancers. It turned out to be successful for treating malignant plural effusion, which had a 38% complete recovery (Mondal, Guo, He, Zhou, 2020).

There have also been studies proving how oncolytic viruses can help potentiating prostate cancer immunotherapy. The microenvironment for prostate cancer has plenty of immunosuppressive strategies that don't allow the development of antitumor immune responses. For example, lymphocytes (natural killer cells and CD4+/CD8+) stay in an anergic state, therefore, they have the ability to express inhibitory immune checkpoints. Some of these include programmed cell death and cytotoxic T lymphocyte antigens. Antigen-presenting cells (macrophages and dendritic cells) have little to no expression of major histocompatibility complex (MHC) molecules. Additionally, the tumor expresses inhibitory immune checkpoint receptors such as programmed cell death ligand 1 and V-type immunoglobulin domain-containing suppressor of T cell activation, and harbors immunosuppressive cells, myeloid derived suppressor cells, cytokines, metabolic products, and prostaglandins (Lee and Gujar, 2018). This microenvironment immunosuppression

inhibits the antitumor action of the immune cells. The role of oncolytic viruses kicks in when they trigger an antiviral immune response, where type I interferons and pro-inflammatory cytokines are released. This allows for immune cells to do their job and enter the tumor microenvironment. When oncolytic viruses kill the cancer cells, it causes the release of unavailable tumor antigens, which are processed by antigen-presenting cells. Tumor-specific T cell immunity is then stimulated.

In addition to oncolytic viruses, other drugs can be used in combination with them so that it can have a greater effect on the success of immunotherapy. Out of the 97 clinical trials reporting oncolytic viruses from 2000 to 2020, 61 trials were conducted with oncolytic virus monotherapy, while 36 reported that oncolytic viruses were given in combination with at least one other treatment (Macedo, Miller, Haq, Kaufman, 2020). The most common drugs were cytotoxic chemotherapy agents and chemotherapy prodrugs. Other treatments used in combination with oncolytic viruses included radiation therapy, immunotherapy, and targeted therapy. The most common chemotherapy agents used were paclitaxel and carboplatin which were often used together. Additionally, some studies used cyclophosphamide which was used as preconditioning chemotherapy to help enhance antitumor immune responses.

One of the most important combination therapies include CAR-T therapy with oncolytic viruses. CAR-T (chimeric antigen receptor T) cell therapy has an in vitro design, modification, and amplification of T cells that are taken from patients' blood to allow them to identify the surface antigens on tumor cells by the transduced CAR structure on the surface of the T cell. After amplification has occurred, the CAR-T cells are injected intravenously into the patient. Park et al performed a study that

involved therapeutic combination using oncolytic viruses and CAR-T therapy. They used an oncolytic chimeric orthopoxvirus that carries CD19t (OV19t) to make CD19t at the cell surface.

B. Negative Studies

While there has been plenty of research supporting the use of oncolytic viruses for cancer immunotherapy, there are also some limitations to this approach. It is sometimes difficult to select the best route of administration for the oncolytic virus. Usually, oncolytic viruses are ideal for direct IT injection, however, this can limit the number and location of tumors that can be directly treated (Macedo, Miller, Haq, Kaufman, 2020). Intravenous delivery can infect metastatic lesions that are in multiple locations, however, administration of oncolytic viruses into the circulation is limited by dilution in peripheral blood and clearance by antibodies that already exist, as well as serum proteins. Therefore, choosing which route to take for administration can be difficult and have limitations. For example, when it comes to T-Vec, since HSV-1 spreads from cell to cell, oncolytic HSV-1 is the most effective when it is administered intralesionally and it may not work as well intravenously. However, it has been proven in clinal trials in melanoma patients that local intralesional injections with oncolytic HSV-1 can act on remote lesions via induction of systemic antitumor immunity (Fukuhara, Ino, Todo, 2016).

Despite this drawback, there is another major concern when it comes to oncolytic virus therapy. Researchers are concerned than the efficacy might be reduced due to the circulating antibodies. For viruses that cause viremia, they are

more likely to be vulnerable to neutralizing antibodies. Because of this, the antitumor effect of intravenous administration could be limited to patients who have had treatment done before.

III. Discussion

A. Opinion

In my opinion, taking advantage of the mechanism of oncolytic viruses for cancer immunotherapy is a beneficial and promising concept that has lots of potential in the future. This mechanism allows innate and adaptive immune responses to be generated, which can help produce an immune response against tumor antigens and therefore, an immunological memory. While there can be hurdles for oncolytic viruses, I believe with more extensive research, this can be a strategic method to help fight cancer.

B. Future Direction for Research

As established, oncolytic viruses have proven to be beneficial in treating cancer, however, there is still lot of room for improvement and future research needed for this to be successful to the full extent. So far, there have been many pre-clinical animal models, however, we are not quite sure how the anti-viral responses can vary in humans. New research needs to be done to create viruses that can correctly stimulate the immune system in hopes of achieving the desired response, while at the same time, trying to avoid aberrant inflammation which could be harmful for patients. Additionally, it has been proven in studies that the true potential of oncolytic viruses is achieved when used in combination with classical treatments and newer therapies. Therefore, future research should be

conducted so that the oncolytic viruses can be as safe as possible and allowing them to function properly in synergy with other compounds so that we can achieve the full potential.

Regarding future research for treating prostate cancer with oncolytic viruses, there will be a need of global and integrated consideration of immunology and more clinical progression. Not only does there need to be more research about the local tumor microenvironment, but there needs to be an emphasis on metastatic sites due to the reason that prostate cancer can metastasize to bones. Next, there needs to a better understanding of prostate cancer stem cells due to immunosuppression and the implications of oncolytic virus treatments. Immunosuppression related to prostate cancer is critical because a lot of immunotherapies focus on correcting an impaired antitumor immunity, and also because the immunosuppressive entities originating from local and metastatic locations can affect the functionalities of immune mediators (Lee and Gujar, 2018).

Something different to research for would be changing T cell response with a cytokine-expressing oncolytic virus. There are different types of T cell populations that can targeted by viral therapy such as T regular and T effector cells. T regular cells have been studied quite a lot regarding oncolytic viral therapy. They are responsible for creating an immune-suppressing environment. For example, HSV expresses IL-12 which was used in a glioma model by Cheema et al. in 2013. It was concluded that the virus decreased the T regular cells and

increases chances of survival. Due to this success, there should be research in this area in the future.

Additionally, cytotoxic T lymphocytes (CTLs) improve the antitumor immune environment, and with the increase in CTLs in the tumor microenvironment, there is improved patient survival. Oncolytic viruses can help recruit more CTLs into the tumor microenvironment, therefore, more research into cytokine-expressing viruses used to enhance CTL recruitment and activation can result in a promising future (Pearl, Markert, Cassady, Ghonime, 2019).

There are other oncolytic viruses such as the reovirus which is naturally occurring, and it has been gaining more attention recently. Reovirus oncolysis happens by the apoptosis mechanism along with autophagy. In HCV-associated hepatocellular carcinoma, reovirus has helped with inducing a pro-inflammatory response which suppresses the replication of HCV in host cells. More research in other kinds of oncolytic viruses will help with cancer immunotherapy.

IV. Conclusion

Oncolytic virus therapy has shown to have a positive effect in cancer immunotherapy, and its role in presenting antitumor effects is highly important. The efficacy of oncolytic virus therapy is predicted to improve in the future, in addition to immunotherapy. This is the beginning of a new era of cancer treatment, where patients can choose to go for oncolytic virus therapy. With more research in oncolytic viruses, there can be a promising future in cancer immunotherapy.

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