

Oncolytic Virotherapy and The Immune System

Asya Yılmaz

Tarsus American College, Murathan Dist. 1202/8 St. No. 8 Evka-1, Buca, İzmir, 35400, Turkey; asyayilmaz424@gmail.com
Mentor: Mr. Eric Trujillo

ABSTRACT: In order to awaken the innate and adaptive immune systems in response to malignant tumor growth, activation of effector cells like T- and B-cells through pro-inflammatory cytokine release prompted by apoptosis is vital in oncolytic virotherapy. As cancerous cells commonly exhibit abnormal behavior that escapes the radar of the immune system, the discovery of oncolytic virotherapy was essential to establishing an effective anti-tumor response. With certain combinations of immunotherapies, digging at the root of cancer, which is the uncontrolled division of abnormal cells, becomes possible, provoking a forcefully enacted treatment inside the host that uses both the immune system and external therapeutic agents in the fight against cancer. Such treatments as the combination of immune checkpoint inhibitors or macrophage-mediated responses and oncolytic virotherapy enable a higher chance of improvement in the prognosis.

KEYWORDS: Biomedical and Health Sciences; Immunotherapy; Oncolytic Virus; Inflammatory Response; Macrophage-mediated Response.

■ Introduction

From the beginning of the 20th century, oncolytic virotherapy attracted attention as naturally acquired virus infections seemed to cause the shrinkage of the tumors, possibly leading to complete disappearance. Chance encounters of tumors with viral infections starting from 1904 led researchers to conduct more comprehensive research on the possible usages of virotherapy on cancer.¹ In fact, the first commercialized oncolytic virus (OV), Oncorine (H101), was approved in 2005 by the Chinese State Food and Drug Administration (SFDA) for head and neck cancer.² Later, in 2015, the U.S. Food and Drug Administration (FDA) approved the T-VEC virus for melanoma.³

As OVs presented dual promise in cancer therapy, they were received with much interest. Apart from their oncolysis ability, a process in which OVs force the cancerous cells to burst due to continuous virus replication, the possible usage of combination therapies alongside oncolytic virotherapy made them a worthwhile investment in the fight against cancer. As the main target with oncolytic virotherapy is the positive response from the immune system, multiple ways to achieve this result have been orchestrated, mainly enhanced by their tendency to work well with other immunotherapies and their high immunogenicity. Therefore, the need for a brief but inclusive work to attract attention to this promising field was realized. All in all, this research treatise considers the body's immune surveillance system and the possible methods to trigger the adaptive and innate immune systems into recognizing and eliminating tumors through using OVs alongside other complementary therapies.

■ Discussion

As early as 1909, Paul Ehrlich had laid the understanding of the importance of immune surveillance against tumors. He hypothesized that the host's defense prevented cells from

evolving into tumors, but his hypothesis could not be proven due to the lack of equipment and understanding during his time.⁴ Experiments done with transplantation models later proved the theory of immune surveillance, as tumors were rejected in syngeneic hosts as opposed to normal tissues, hinting at the presence of tumor-specific antigens.⁴

OVs are indeed favorable in cancer treatment due to their various possible usages, from direct oncolysis to their effects in combination with other immunotherapies to elicit an immune response from the host. When cell lysis is initiated due to continuous virus replication inside the tumors, tumor-associated antigens (TAAs) are released, thereby triggering the immune system. Simultaneously, phagocytosis clearance of the apoptotic cells leads to triggering anti-inflammatory signaling pathways by apoptotic cell surface molecules via phagocyte receptors, also boosting the host autoimmunity.⁵

The combination of OVs with the dynamic characteristics of the host immune system remains a critical but, to some extent, unpredictable area. Findings on the issue of immune system effects on the injected OVs and the loss or gain of efficacy depend on various variables, from the genetic modification of the OVs to signaling pathway activation of the host. Interestingly, the advantage of OVs is apparently not reduced with the triggered anti-viral immune response as opposed to the results of prior research; instead, as long as there exists a balance between the triggered anti-viral response and the operation of OVs, for example, by deleting viral genes, activation of stronger anti-tumor response is possible.⁶

Targeting Tumor Vasculature with Oncolytic Viruses:

Tumor neovasculature is vital for the continuous feeding of the tumors; hence, targeting tumor vasculature by OVs in hopes of starving the tumor has gained attention in recent years. On the one hand, the collapse of the tumor vasculature was reported to lead to tumor hypoxia, nutrient restriction,

and pro-inflammatory cytokine release, showing promise in the field.⁷ On the other hand, the said vasculature is essential in transporting cancer therapeutics and various effector cells, leading researchers to aim for the normalization of tumor vasculature to maximize the anti-tumor activity of leukocytes and blood-borne therapeutic drugs. Although studies to finalize the debate of shutting down versus normalizing tumor vasculature is yet to produce a definitive answer, certain studies using OV's to disrupt the established tumor vasculature bear the potential of achieving a favorable prognosis. One such study by Breitbach *et al.* involved intravenous administration of the vesicular stomatitis virus (VSV), causing the tumor vasculature to be destroyed while the normal vasculature remained intact.⁸ Continuous VSV replication was followed by an inflammatory response, including neutrophil-dependent forming of micro-clots, enabling Breitbach and colleagues to observe blood clots in tumor vasculature in the following 24 hours upon intravenous administration.⁸ As such, it was proposed that OV's not only caused the lysis of the cell but also directly infected the tumor vasculature, demonstrating the factors VSV anti-tumor activity depended on, which were infection of tumor vasculature and intravascular coagulation, all the while underlining the importance of the route of delivery through which the VSV first came in contact with the endothelial cells, explaining its propensity to cause vascular collapse.

For further demonstration, Figure 1 (B) represents the formation of clots and initiation of vascular collapse after infection of the endothelium of the tumor vasculature by OV's and recruitment of neutrophils. In contrast, (A) represents oncolysis, and (C) represents the role of VEGF in the regulation of angiogenesis and tumor growth, yielding oncolytic effects.⁹

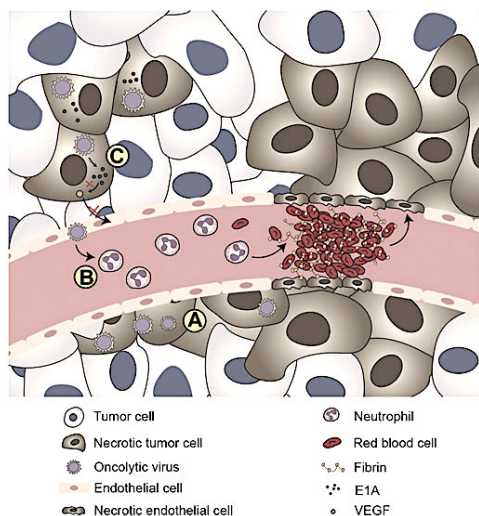


Figure 1: Demonstration of vascular collapse.

Chronic and Acute Inflammatory Reactions:

Inflammation is the host's response to healing the afflicted tissue. This requires the activation and directed migration of leukocytes (neutrophils, monocytes, and eosinophils) to the sites of damage.¹⁰ Inflammation is viewed as a major component of innate immunity, triggered by pathogen-associated molecular patterns (PAMPs) or damage-associated

molecular patterns (DAMPs), mainly recognized by pattern-recognition receptors (PRRs). Upon activation, the release of inflammatory chemokines and cytokines is mediated, triggering adaptive immune system components like T- and B-lymphocytes, intensifying the initial inflammatory response.¹¹

The observations of German doctor Rudolf Virchow in the 1860s hinted at a possible connection between inflammation and cancer. However, only in recent years, tumor-associated inflammation was accepted as a hallmark of cancer.¹² Inflammation followed by cancer was observed to make up about 15% - 20% of cancer deaths, while recent observations of tumor-elicited inflammations were found to be a potential target for cancer therapy.^{11,13} Although inflammation is a natural response by the host immune system to eliminate pathogens, different types of inflammation were seen to have contradictory effects on the development and progression of cancer. While tumorigenic pathogens force the host immunity into persistent infection following chronic inflammation, associated with a negative prognosis, acute inflammation is followed by the stimulation of dendritic cell maturation and antigen presentation, resulting in anti-cancer responses and the alerting of the immune system.^{11,12} The sensitivity of certain cancers, such as bladder carcinoma, to acute inflammation or the boundaries of the initiation of inflammation types are still understudied. However, it bears much potential for cancer therapy when possibly used alongside highly immunogenic OV treatment, for the possibility of subverting host immunity through anti-tumor responses and alerting the immune system through acute inflammation.

Macrophage-mediated Responses to Oncolytic Virotherapy:

Tumor-associated macrophages (TAMs) are an important part of the tumor microenvironment (TME). Depending on their activation, they may either have positive or negative effects on tumorigenesis.¹⁴ Due to their dual nature, they are promising partners with oncolytic virotherapy to act as an intermediary between the TME and cytotoxic lymphocytes of the innate immune system, such as natural killer (NK) cells; or T lymphocytes and B lymphocytes of the adaptive immune system, to eliminate tumors.

When macrophages elicit enhancing antitumor responses, adaptive and innate immune system cells will be alerted, ultimately causing the elimination of cancerous cells. On the other hand, since TAMs may cause the suppression of the immune system in TME, it is important to combine both therapies in a balance to restrain the immunosuppressive, tumor-supportive properties of macrophages. Macrophages are highly plastic cells, and depending on the environment, they can undergo drastic changes that can either affect tumorigenesis negatively or positively. Such duality has been separated as classically activated macrophages that elicit a positive response, also known as the M1 subtype, and alternatively activated macrophages that elicit a negative response, known as the M2 subtype. However, it has recently come to attention that such distinct separation was only sometimes possible due to the multiple activation states of the macrophages.^{14,15} Since OV's work as strong immunological stimuli,

they can be used to convert the phenotype functions of macrophages accordingly.¹⁶

The most abundant molecule in the TME is macrophages; therefore, they are an essential target in cancer therapy, mainly used in two ways. The first method is to reduce the TAM populace in the TME either through its depletion or the restriction of monocyte recruitment that gives rise to TAMs. The second is by re-modifying macrophages through converting M2-like TAMs into M1 phenotypes or giving rise to macrophage-mediated anticancer responses such as phagocytosis.¹⁴ As explained above, specific functions of macrophages can be altered by OV as they are highly plastic, making OV the ideal partner to therapies including macrophages, though their connection is still understudied.

Combined Therapy of Immune Checkpoint Inhibitors and Oncolytic Viruses:

Immuno-oncology (IO) is a specific cancer treatment area that targets the host immune system to fight against cancer. In particular, the oppression of the immunosuppression ability of cancer by antibodies (Ab) that target immune checkpoint molecules caused positive results in the field.¹⁷ Therefore, the first immune checkpoint inhibitor (ICI), ipilimumab, was approved by US FDA for the treatment of advanced melanoma in 2011.¹⁷

Since apoptosis caused by OV is followed by the release of immune-stimulatory molecules such as PAMPS, TAAs, and DAMPS, the immunosuppression ability of tumors is canceled.¹⁷ In fact, there is strong evidence suggesting that the unresponsive, cold tumors may be converted into responsive hot tumors by OV, thus showcasing their compatibility with IO drugs. Certain studies on their combination yielded the result of elevated pro-inflammatory cytokine release, prompting the activation of NK cells and T-cells inside of the tumors, changing the state of the TME into that of a hot tumor.¹⁷

However, in clinical trials, OV were seen to lose the advantageous tumor specificity they possessed when administrated over a period of time, caused by the loss of essential signaling pathways due to mutation, especially in heterogeneous tumor populations.¹⁷ Therefore, first-generation OV like Rigvir and ONYX-015 as monotherapies yielded ineffective results, further highlighting the importance of combination therapies.¹⁷ As IO drugs also stimulate the host immune system, their combination with OV produces elevated results, possibly marking one of the most efficient combination therapies.

Risks of Oncolytic Virotherapy:

Although oncolytic virotherapy bears much potential, it is vitally important to be mindful of their adverse effects and to study the possible ways to decrease the incompatibility between the injected OV and the host, recognizing the importance of continuous experiments on the viruses. Below is Table 1, showing various types of OV that are being clinically tested.

In OV usage, two main factors are important to consider. Firstly, potent anticancer immunotherapy may result in autoimmune diseases and very well implicate healthy cells, so their dosage and compatibility with the type of cancer should

be arduously studied before they are approved. Secondly, they are highly immunogenic, meaning they are likely to elicit an immune response from the host.¹⁸ While the latter can be balanced and turned into a favorable end result through the combination of various immunotherapies, the former yields complications due to the difficulty of researching virus-cancer compatibility and the unpredictable patterns of adverse reactions the host may produce. Therefore, creating non-pathogenic viruses through modification of the viral genome in oncolytic virotherapy has aroused much interest due to their capacity to offer a safer prognosis by aiming to weaken virus pathogenicity, reducing side effects, increasing target selectivity, and inserting exogenous therapeutic genes into the virus genome to increase its expression in the tumor, consequently improving treatment through modified OV.^{19,20}

Table 1: Oncolytic viruses in the trial.

Virus	Name	Phase	Tumor	Combination	Reference
Adenovirus	ONYX-015 Oncorine (H101) Ad5-CD/Tkrep ONCOS-102	III I/II Pilot I/II III I I	SCCHN Pancreatic Cancer Advanced Cancers Advanced Sarcoma SCCHN or esophageal cancer Prostate cancer Solid tumors	Cisplatin Gemcitabine Irinotecan + 5-FU or IL-2 Mitomycin-C, doxorubicin, cisplatin 5-fluorouracil + cisplatin or adriamycin 5-fluorocytosine, valganciclovir, radiation Cyclophosphamide	Khuri et al. ²¹ Hecht et al. ²² Nemunaitis et al. ²³ Galanis et al. ²⁴ Xia et al. ²⁵ Freytag et al. ²⁶ Ranki et al. ²⁷
Herpes Simplex Virus	Talimogene laherparepvec G207	I/II Ib I	SSCHN Melanoma Glioma	Radiation, cisplatin ipilimumab (CTLA-4 inhibitor) Radiation	Harrington et al. ²⁸ Puzanov et al. ²⁹ Markert et al. ³⁰
Reovirus	RT3D	I/II	Advanced cancers	Carboplatin/paclitaxel	Karapangiotou et al. ³¹
Vaccinia	GL-ONC1 JK-594 (Pexa- Vec)	I I/IIa	Head and neck carcinoma Colorectal cancer	Cisplatin, radiation Irinotecan	NCT01584264 ³² NCT01394539 ³³

Delivery Routes of OV and Possible Adverse Effects:

Two main routes of OV injection are direct intratumoral delivery and intravenous delivery, with either of them posing different advantages and disadvantages. Intratumoral delivery is the commonly used method of OV delivery, encompassing the direct injection of OV into tumor masses. While the dose and spread of the OV can be better controlled when delivered intratumorally, this delivery method is unsuitable for deep and organ-specific tumors. On the other hand, intravenous delivery encompasses the injection of the OV directly into the vein, enabling the virus to spread more efficiently, especially for organ-specific tumors. During a phase I clinical trial, it was also seen that intravenous delivery of oncolytic virus HSV G207 to children with progressive or recurrent malignant supratentorial brain tumors yielded positive results, confirming the ability of the OV to breach the blood-brain barrier to reach brain tumor tissues.^{19,34}

However, despite the positive results observed in various trials, it is worth noting that intravenous delivery requires highly selective target tissues since increasing the concentration of the virus will not lead to better selectivity or wider spreading of the virus but instead will lead to toxicity, resulting in questionable biosafety of OV therapy.¹⁹ As some treatments require a

specific route of delivery due to the tumor environment, it is important to research OV_s *in vivo* and *in vitro* on a deeper level to observe the cancer-specific behaviors of each treatment type.

Decreasing the Risk of Oncolytic Viruses:

According to Li *et al.*, there are mainly three ways of improving OV safety: selecting non-pathogenic viruses, modifying the pathogenicity rate of the viruses, and recombination of various viruses.¹⁹ For the issue of selecting viruses that are non-pathogenic, the parvovirus is an example that is harmless to humans due to their natural hosts being rats. Since this kind of approach depends on the overexpression of cytokines from sites of tumor that can activate metabolic pathways, it has low selectivity when it comes to non-malignant tumors. The second approach involving pathogenicity modification is widely used in clinical trials and consists of the deletion, insertion, and binding of gene sequences of the viruses to decrease pathogenicity. Prior studies include the deletion of genes such as TK, VGF, hemagglutinin, and B18R in the oncolytic poxvirus, the deletion of the ICP-34.5 gene in HSV1716, and more, offering promising results.^{19,35}

The third method of conduct involves the recombination of types of OV_s. As engineered by Abdullahi *et al.*, the recombination of vesicular stomatitis virus (VSV) and Newcastle disease virus (NDV) into recombinant VSV-NDV (rVSV-NDV) virus by retaining the VSV backbone while replacing its glycoprotein with hemagglutinin-neuraminidase (HN) and the modified envelope proteins of the NVD eliminated the adverse reactions previously observed in the liver and the brain, prevented by the replacement of the glycoprotein.³⁶

Following continuous advancement in oncology and the discovery of other types of OV_s will likely decrease the risk of virus therapy for cancer. Although the possibility of minor post-treatment adverse effects is not entirely gone, there is a high chance of improving the biosafety of oncolytic virotherapy with long-term observations of the cases and further research.

Conclusion

Oncolytic Virotherapy still has unlimited potential that is yet to be studied. Due to tumors' immunosuppressive nature, OV_s play a major role in cancer therapy and combinational therapy. Upon apoptosis, pro-inflammatory cytokines that activate T-cells and NK cells are activated, alerting the innate and adaptive immune systems. Considering their immunosuppression-evoking properties, OV_s are ideal to go hand in hand with other therapies that struggle due to tumor expression. While it is important to consider the dichotomy of certain molecules that carry threats to the prognosis when incorporated into cancer therapy, certain clinical trials have offered worthwhile results in recent years, calling attention to the future of certain combined therapies. Apart from directly triggering the immune response upon injection, OV_s showed positive outcomes when combined with other immunotherapies such as macrophage-targeted therapy and immune checkpoint inhibitors, highlighting that despite the direct effect of these viruses on alerting the immune system, they worked fine as mediators in the host bodies.

Keeping the balance by selective therapies is important not only to eliminate tumors completely but also to avoid feeding them instead, notably calling attention to the different results yielded from M1 and M2 subtype TAMs due to their high plasticity or the differing outcome of acute and chronic inflammation. Therefore, minimizing the possibility of damage is a vital step through continuous *in vitro* and *in vivo* experiments by utilizing complementary therapies in a balance that will suppress tumor hallmarks such as immunosuppression, loss of apoptosis, and evasion of growth suppressors. Furthermore, seeing that all directed and specific treatments against the aforementioned properties of cancerous cells depended on awakening the hosts' immune system, OV_s are a strong candidate for better cancer therapy due to their highly immunogenic features. Undeniably, a better understanding of the properties of oncolytic viruses and their complementary therapies will lead to promising cancer therapies and even cancer prevention in the future.

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■ Author

Asya Yılmaz is a 10th-grade student studying at Tarsus American College. Her greatest aspiration is to become a Pharmacology Research Scientist after attending a Pharmacy College. She currently resides in İzmir, although she stays in Mersin for most of the year due to her high school studies.