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A Review of Vaccinia Virus as a New Therapeutic Target Against Cancer

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Abstract

The World Health Organization's smallpox eradication program extensively utilized the Vaccinia virus, which is today regarded as a viable vector for gene therapy due to its distinctive features. Vaccinia virus can specifically reproduce and spread effectively in cancer cells, leading to the destruction of the tumor. Furthermore, the fast generation of viral particles, the ability to infect a wide variety of hosts, the big genome size (about 200 kb), and safe handling make the vaccinia virus an appropriate choice as a vector for gene therapies. Oncolytic virotherapy (OVT) is a highly prospective modality for fighting cancer that involves the use of genetically modified viruses to reproduce specifically inside cancer cells and stimulate an immune response against the tumor. Oncolytic viruses not only destroy cancer cells but may also modify the surrounding tumor microenvironment and trigger a durable defense against the tumor. Vaccinia virus has gained attention as a promising contender because of its capacity to invade a diverse array of cancer cells. In this study, we introduce the vaccinia virus, its molecular mechanism and cell cycle, and its potential to destroy cancer cells.

Keywords: Gene therapy, Cancer, Viral vector, Vaccinia virus.

Introduction

The management of cancer is today a worldwide issue of great importance. Around 7 million people globally succumb to aggressive tumors every year, and it is projected that this figure will rise to 12 million by 2030 (1). The main approaches for treating cancer involve surgical intervention, radiation therapy, and chemotherapy. Nevertheless, even conventional therapeutic approaches have some restrictions. Conventional surgical therapy allows for the quick and direct removal of tumor tissue. However, if the resection is not thorough, there is a risk of residual tumors remaining. In addition, chemotherapy and radiation treatment lack specificity, since they not only target tumor cells but also kill healthy immune cells, resulting in a decrease in patient immunity (2). Hence, there is a need for novel and focused strategies to address these constraints in the management of malignancy. Recently, novel methods have arisen for creating new biological treatments for cancer, such as CAR-T cell therapy and oncolytic viruses (OVs), either on their own or in conjunction

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with conventional treatments. Over the course of more than three decades, OVs have demonstrated exceptional effectiveness in treating many forms of cancer (3).

Ovs exert their therapeutic properties via a complex interplay of sophisticated processes that are specifically engineered to target and destroy cancer cells preferentially. Upon injection, OVs selectively identify and invade cancerous cells (4). This precision is accomplished by using various genetic alterations that capitalize on the intrinsic weaknesses of cancer cells. One main method is the direct destruction of infected cancerous cells, where the multiplication of the virus inside the tumor leads to cell destruction, releasing new viruses and components from within the cell (5). Simultaneously, the transmission of viruses stimulates immunogenic cell death, which releases threat signals and facilitates the activation of immune system reactions against tumors. Once the immune system is mobilized and stimulated, it identifies and eradicates infected and uninfected adjacent cancerous cells, resulting in a widespread immune response against the malignancy. In addition, oncolytic viruses can trigger a series of changes in the tumor environment that affect the immune system. This leads to an increased presence and stimulation of immune cells, including cytotoxic T lymphocytes and natural killer cells. OVs may also hinder the blood flow to tumors by disrupting tumor blood vessels, hence adding to the anticancer impact (6). OVs can induce the production of therapeutic transgenes in the tumor microenvironment (TME) after infecting cancer cells, in addition to their main role. This characteristic enhanced the ability of the treatment to destroy cancer cells and is thus crucial for the subsequent integration of oncolytic therapy and immunotherapy. These methods enable scientists to manipulate the immune system in order to generate antitumor immunity via OV activation (7). The relative roles of each pathway are contingent upon the specific properties of the tumor cell, the viral vector, and the relationships among the virus, tumor environment, and host immune response. The several systems working together result in the specific removal of malignant cells by oncolytic viruses, offering a hopeful path for novel and focused cancer immunotherapies. OVs treatment involves several processes, including connections among cancer cells, viruses, and the immune system (8). OVs' anti-tumor action may be classified into two distinct groups: tumor cell death, which relies on the presence of the receptor on the cell, and the anti-viral response of the host cell. The second method enhances the development of a proinflammatory tumor microenvironment, promoting systemic anti-tumor immunity (9).

Various methods have been devised to modify viruses to make them oncolytic. These methods include reducing the activity of viral genes that are essential for proliferation in normal cells, as well as using promoters that are unique to certain tissues or tumors. According to reports, OVs reproduce more effectively in tumor cells because tumor cells lack proper antiviral type I interferon signaling (10). In general, oncolytic vaccinia virus (VV) can infect both normal and cancerous cells. However, with genetic alterations, it is possible to make these viruses specifically replicate in cancer cells. The VV is a kind of virus that has a protective outer layer and a double-stranded DNA genome that is around 190 kilobases in size (11). It has about 250 genes that code for proteins. The first secure and efficient human vaccination, finally eliminating smallpox. As VV replicates only in the cytoplasm of infected cells, there is no need to worry about the occurrence of mutagenesis inside the nucleus. Vaccinia is known to infect a diverse array of cells (12). The virus infiltrates host cells via an endocytic mechanism by penetrating the cell membrane. VV can accommodate up to 50 kilobases of foreign DNA and can concurrently produce numerous medicinal genes. VV undergoes a quick and destructive replication cycle, stimulating a strong immune system reaction and inflammation in the host (13). VV has become an appealing choice for genetic modification as an oncolytic drug due to recent progress in molecular biology. This article provides a comprehensive review of the vaccinia virus, its cell cycle, and various types of recombinant vectors. In addition, it provides a summary of the progress made in the use of this virus as an oncolytic virus in cancer treatment.

Biology of VV

VV is the most thoroughly studied member of the Poxviridae family, which is the largest and most complex group of animal viruses. The worldwide elimination of smallpox was accomplished with the widespread use of vaccinia virus, which is thought to have evolved from cowpox virus (14). The smallpox vaccination, first described by Edward Jenner in 1798, consists of live VV1 and is largely acknowledged as one of the most effective vaccinations in history. Smallpox is the only human disease that has been completely eradicated. In 1980, the World Health Organization (WHO) recommended the global cessation of smallpox vaccination, except for researchers who face a significant risk of contracting the poxvirus (15). The vaccinia virus genome is composed of two DNA strands organized in a linear shape, measuring about 200 kilobases in length. Inside this genome, there are about 250 potential genes. The virions have an exterior envelope and measure around 200 x 300 nm, displaying a unique rectangular shape. In 1980,

the World Health Organization (WHO) provided guidance The vaccinia life cycle has many unique features that distinguish it as a eukaryotic expression vector. The vaccinia genome can tolerate at least 25 kilobases (kb) of DNA without any detrimental effects on viral replication or assembly (16). Vaccinia virus undertakes complete reproduction inside the cytoplasm of the host cell. Consequently, it either brings in or regulates the production of its own polymerases and transcription factors. Moreover, the virus has a wide range of hosts, enabling it to infect a majority of established mammalian cell lines. The virus can be easily grown and purified in large quantities, and it presents a relatively minimal danger when handling (16).

Reproductive cycle of VV

Considering the size of the vaccinia virus, it is unsurprising that the replication and assembly process is complex. After binding to the host cell, it is believed that the viral envelope immediately fuses with the plasma membrane, resulting in the release of the core virion into the cytoplasm. Although there is little understanding of the uncoating mechanism, the transcription of early genes starts within one hour after infection. Upon entering the cell, the vaccinia virus undergoes DNA uncoating and initiates early transcriptions (17). The virus progresses through three separate phases of transcription, namely early, middle, and late stages, each of which is controlled by various promoters and transcription factors. The enzymes required for the initiation of early transcription are contained inside viral particles and are released upon viral entry. During the first stage of infection, the production of essential proteins required for the replication of the virus takes place (18). The virus introduces a DNA-dependent RNA polymerase into the cytoplasm, leading to the synthesis of early mRNA. The RNA molecule facilitates the synthesis of primary proteins involved in the removal of the viral DNA's protective coating, DNA replication, and the generation of intermediate mRNA by transcription. Afterwards, an intermediate form of mRNA is produced by transcription. This mRNA carries the necessary instructions for the development of late transactivators, which in turn leads to the synthesis of late mRNA. The mRNAs that are produced later are responsible for encoding structural proteins that have a function in the building of membranes (19). In addition, they encode crucial early transcription factors that are necessary for the integration of these proteins into the just-created viral particles. The virus may recruit and use certain cellular proteins throughout the transcription process. An instance of this is the cellular transcription factor YY1, which acts as a stimulator of the vaccinia virus late promoter (19).

VV DNA replication occurs inside mini-nuclei, which are enclosed by the endoplasmic reticulum in the cytoplasm. Replication takes place by the creation of many concatamers of the genome. The concatamers are then disassembled into individual genomes, which are then encased, along with the early transcription factors, inside membranes formed by the Golgi (19). The first stage in the formation of infectious particles entails the production of viral crescents, including lipids and viral proteins. The origin of these crescents is still unknown. Currently, it is hypothesized that the crescent consists of a single lipid bilayer that is not linked to cellular membranes. Afterwards, these crescents combine to create an immature virus that lacks the capability to induce infection. The

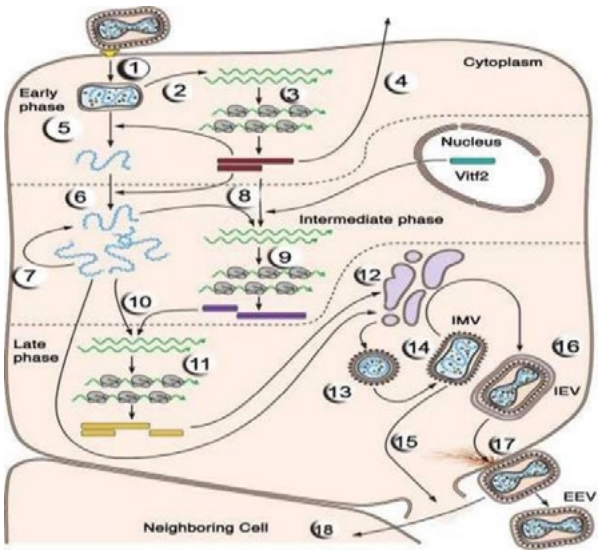

Fig1. The life cycle of the VV. The essential phases of the life cycle that are required for replication and serve as appropriate objectives for drug development include DNA synthesis, transcription, morphogenesis, and cell egress.

nascent virus undergoes maturation by compacting its core and degrading core proteins, leading to the creation of an intracellular mature virus (IMV) (19). The intracellular membrane vesicle (IMV) is then transported to specified locations where it obtains two additional membranes. The membranes in issue originate from the transGolgi network. The proteins encoded by a virus have modified them, causing them to become a part of the outer envelope of the EEV. Internal encapsulated viruses are conveyed to the cell surface, where the outer membrane fuses with the plasma membrane, thus exposing the virus to the cell surface. An intracellular enveloped virus (IEV) has four membranes that are tightly intertwined and can fuse with the plasma membrane. As a consequence of this fusion, virions with three membranes are released into the extracellular space (20).

VV promoters

VV promoters have a concise and straightforward structure, including a central core-initiator region that does not exceed a length of 30 base pairs. Extensive mutagenesis research has definitively found the optimum sequences that trigger both early and late gene transcription (22). Consequently, VV expression vectors have been created that have natural early and/or late promoters or appropriate regulatory sequences. Due to the conservation of several components of the viral transcription machinery within the Poxviridae, the insertion of most promoters into other genera's members leads to their activation. Foreign genes incorporating early promoters should avoid including the TTTTTNT sequence inside the open reading frame. This region serves as a termination signal for the early viral transcription machinery. Unlike early mRNAs, intermediate and late mRNAs do not have a fixed length, indicating that the termination of these gene classes is not dictated by the sequence (22).

Production of recombinant VV vectors

The procedure of incorporating exogenous genes into the vaccinia virus and then verifying the virus's capacity to faithfully express these genes at both the RNA and protein levels is scientifically captivating and engaging. Upon its creation, the recombinant virus has a multitude of applications. The objectives of this study are as follows: (1) to examine the processes involved in the expression of vaccinia genes; (2) to investigate the transcription, translation, and post-translation of foreign gene products without any disruption from natural factors; (3) to generate and separate specific and biologically significant gene products; (4) to carry out immunological analyses of clearly defined antigens; (5) to create live recombinant vaccines; and (6) to explore the possibility of using viruses as carriers for gene replacement therapy (23).

Homologous recombination is the most often used method for producing rVV. The cells are genetically modified by introducing a transfer plasmid that carries the foreign gene positioned next to a suitable VV promoter and surrounded by DNA obtained from VV (24). Subsequently, cells are infected with the wild-type VV, and recombination occurs between the transfer plasmid and homologous areas within the viral genome during replication. The recombined genome is then released from the cell in a packed form. A possible location for recombination was the VV thymidine kinase (Tk) gene, which allowed for selection based on a tk-negative phenotype using BrdU. To improve the efficiency of identifying and selecting recombinant viruses, other flag genes have been added to the transfer plasmids. One of these genes is the neomycin phosphotransferase enzyme (neo) gene from *Escherichia coli* (24).

Expression vectors

There have been two overarching categories of vaccinia expression systems delineated: (a) recombinant viruses, and (b) recombinant plasmids in which transient expression is contingent upon infection with the wild-type vaccinia virus.

Recombinant viruses

Recombinant vaccinia virus production has become a routine technique in several laboratories owing to its straightforward protocols. Firstly, a recombination plasmid is constructed, which contains a foreign gene located downstream of a vaccinia promoter region. This plasmid also has DNA that shares similarities with a dispensable segment of the vaccinia genome, serving as a site for gene integration. Multiple plasmid vectors with distinct viral promoters may be used to introduce genetic material into various sites within the viral genome. Afterwards, the recombination plasmid is extracted and then injected into host cells using transfection. Subsequently, the host cells are invaded by the vaccinia virus. Homologous recombination occurs between the plasmid and the viral genome, with the assistance of the flanking sequences of the plasmid. The infection's development is thereafter allowed, particularly if the plasmid contains a selectable marker. There are many ways available to screen offspring virions that come from unselected or selected transfections, each with its level of effectiveness. The resulting expressing plaques corresponding to recombinant viruses harboring the inserted gene may be later assessed (17, 25).

Recombinant plasmids

The transitory expression of the foreign gene may be achieved by using a plasmid that contains the gene controlled by a VV promoter. This plasmid is then

introduced into cells that have been superinfected with the normal form vaccinia virus. The promoter of the foreign gene is temporarily activated by substances generated by the superinfecting virus. At that point, the cells may be quickly collected and analyzed for protein production. An important advantage of this process is its efficiency; expression may be obtained quickly after cloning, unlike procedures that require the creation of recombinant viruses, which usually take around three weeks. Nevertheless, the levels of expression are somewhat lower in absolute terms when compared to those produced by a recombinant virus. To tackle this difficulty, a heterologous system was used, which consisted of T7 RNA polymerase and bacteriophage T7 promoters. The expression levels obtained with this approach were 10-20 times higher than those acquired by transient expression and a vaccinia promoter that is similar in nature. After introducing plasmids with the T7 promoter upstream of the target gene into cells, these plasmids are then infected with a vaccinia recombinant that carries the T7 RNA polymerase gene. With a high degree of promoter specificity, this highly efficient monomeric enzyme specifically identifies the T7 promoter on the plasmid and starts the production of the matching mRNA. Increased amounts of gene expression may be achieved by combining the target gene and the polymerase on separate recombinant viruses (26, 27).

OVs activity mechanism in cancer cells

Tumor cells undergo constant viral replication, which utilizes the resources, energy, and response sites of the host cells, destroying the tumor cells. In addition, the offspring virus that is produced can infect cancer cells on the periphery, resulting in a constant increase in the effectiveness of the treatment against the malignancy. Vaccinia virus has potent cell lysis activity, resulting in the production of both cell death signs and viral death signals (28). Concurrently, the immune system's response is exposed to tumor-associated antigens and virus-associated antigens at the infection location, which triggers the related inflammatory reactions. Therefore, the inhibition of the immune system in the local area is overcome, allowing the body to generate a targeted immunological response. In addition, the immune response may be delivered to the host via tumor-associated antigens, resulting in immunological impacts occurring locally. Furthermore, VV can invade and infect the vascular endothelial cells inside tumors, leading to their programmed cell death and subsequent breakdown of the tumor's blood vessels. This process indirectly facilitates the programmed cell death of tumor cells (29).

Alteration of OVs

The VV vectors currently employed in oncolytic anticancer experiments consist of the Wyeth strain, Western Reserve (WR) strain, Lister strain, Copenhagen strain, and vaccinia virus Tian Tan strain (VTT) (1). The toxicity and host range of these strains of VV varies due to the global viral evolution that occurred after smallpox vaccination. Enhancing the virus's ability to specifically target tumors and effectively destroy them is crucial for the success of oncolytic viral therapy. To selectively stimulate the growth of VV in tumor cells while sparing normal cells, the genes required for replication in normal cells are often removed, but they are retained in tumor cells. TK plays a crucial role in the production of vaccinia virus DNA. The production of TK is often reduced in normal cells but elevated in rapidly dividing tumor cells (30).

The TK-deleted VV has a particular capacity to infect cancerous tissue. In contrast, its infectivity and replicability are significantly diminished in most normal cells due to the loss of the TK gene (31). When normal cells are infected with the vaccinia virus, it triggers antiviral responses, which result in the generation of antiviral substances or the onset of death. These systems can control the activity of infected cells and nearby cells by causing a halt in the cell cycle, encouraging cell death, preventing protein production, and triggering an immune response. These mechanisms can hinder or halt the reproduction and spread of viruses. The JX-594 virus is a variant of the Vaccinia virus (VACV) that produces granulocyte-macrophage colony-stimulating factor (GM-CSF) and lacks the TK domain. It has been used to eradicate metastases in solid tumors, namely stage II liver malignancies (32). The modified vaccinia Ankara (MVA) strain is a variant of the Turkey vaccinia virus Ankara. It has undergone 500 natural passages in chicken embryo fibroblasts (CEF), resulting in the loss of genes associated with immune evasion and determining the spectrum of hosts it may infect. MVA is capable of effectively expressing exogenous genes or antigens and eliciting a robust immune response. Additionally, it may be used in animals with weakened immune systems (33).

Oncolytic VV encoding immunostimulatory genes

As our understanding of immune defense strategies in tumor tissues continues to grow, researchers have enhanced the anti-tumor immune response of oncolytic VV by introducing immunostimulatory genes into its genome. These genes encode for factors such as cytokines, chemokines, and co-stimulatory molecules, which promote anti-tumor immune activity (12). Cytokines, in particular, are water-soluble proteins that play a role in regulating both innate and adaptive immunity, including both inflammatory and anti-inflammatory responses.

Utilizing pro-inflammatory cytokines is a common method to bolster Oncolytic virotherapy by attracting and stimulating immune cells while suppressing immunosuppressive cells. GM-CSF is a highly used cytokine that enhances Oncolytic virotherapy. The process involves the recruitment of both DCs and NK cells to facilitate the maturation of DCs. This, in turn, triggers the activation of anti-tumor immune responses. T-VEC, a herpes simplex virus (HSV) equipped with granulocyte-macrophage colony-stimulating factor (GM-CSF), was granted approval in the United States specifically for the treatment of melanoma in 2015 (34). JX-594, a genetically engineered vaccinia virus that incorporates the GM-CSF gene, has shown encouraging anti-tumor efficacy in clinical studies. IL-21 enhanced the effectiveness of oncolytic VV in fighting tumors by boosting the number of CD8+ T-cells that can kill cancer cells (35, 36).

Certain pro-inflammatory cytokines, such as IL-12, IL-23, and IL-15, when combined with oncolytic VV, have shown a more potent anti-tumor immune response. This is achieved by boosting the activation and cytotoxicity of T-cells and NK cells, as well as raising the generation of IFN-γ. Additional cytokines that have been used in the modification of oncolytic viruses, such as adenovirus and HSV, may further augment the anti-tumor impact of oncolytic VV with deliberate planning. It is important to consider the evaluation of real exposure to prospective payloads and the handling of safety concerns that may result from these payloads when designing oncolytic VV (37, 38).

Due to the significant impact of anti-inflammatory cytokines (such as TGF−β and IL-10) on the host's immune system, they additionally enhance the effectiveness of oncolytic virotherapy as a treatment. Delgoffe and colleagues discovered that the use of oncolytic VV to deliver a TGFβ inhibitor may effectively counteract the immunosuppressive tumor environment. This is achieved by limiting the immunosuppressive effects of TGF−β and enhancing the sensitivity to INF-γ. IL-10 is an acknowledged immunosuppressive cytokine that hinders the synthesis of pro-inflammatory cytokines including IL-12 and INF-γ (39). Hickman and colleagues showed that the production of IL-10 in the immediate area following VV infection restricted the reproduction and spread of VV. A further investigation conducted by Wang and colleagues shown that IL-10 has the potential to improve the effectiveness of oncolytic VV in treating pancreatic cancer. This is achieved by reducing the immune reaction to the virus and extending its presence in tumors (40).

Chemokines are cytokines that are released and function as chemotactic agents, attracting immune cells to tumor lesions and facilitating anti-tumor immune responses. Bartlett's team showed that oncolytic VV carrying CCL5 or CXCL11 genes induced a strong anti-tumor immune response and improved treatment effectiveness by recruiting activated immune cells such T (Th1) and NK cells. In general, chemokine receptors, such as CXCR4, play a role in activating the immune system. However, an imbalance in the control of the signaling pathway might contribute to the formation and spread of tumors. CXCR4 antagonist-armed oncolytic VV shown the capacity to modulate the tumor microenvironment (TME) by reducing the formation of immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs) inside the tumor. In addition to immune stimulators, several genes linked to other signaling pathways have been discovered to stimulate anti-tumor immunity. As an example, the presence of a DNA-dependent activator of IFN-regulatory factors (DAI), which is a sensor for double-stranded DNA located in the cytoplasm, was increased by an oncolytic VV. This resulted in a stronger activation of the innate immune system and an improved immune response against tumors. Collectively, the use of oncolytic VV that carry genes capable of stimulating anti-tumor immune responses can enhance the effectiveness of anti-tumor activity (41, 42).

Oncolytic VV delivery pathway

Thus far, all the authorized oncolytic viruses (OVs) have been administered by injection directly into the tumor, which limits their effectiveness for tumors that are challenging to treat using this method or have already spread to other parts of the body. Creating intravenous oncolytic viruses (OVs) is crucial for expanding the range of medical uses for OVs. The analysis of 97 distinct clinical trials documenting OV investigations conducted between 2000 and 2020 revealed that the predominant method used was intratumoral administration, utilized in 48 trials (49.5%), followed by intravenous administration, employed in 34 trials (35%). During the clinical studies, intravenous oncolytic VV demonstrates favorable safety and promising anti-tumor efficacy. Unlike adenoviruses, oncolytic VV may be administered intravenously in a single dose since the majority of human bodies do not have preexisting neutralizing antibodies. Nevertheless, after oncolytic VV therapy, the production of neutralizing antibodies took place, which restricted the recurrent systemic administration (43).

Lately, scientists have been focused on creating various methods to achieve effective tumor therapy by continuous intravenous infusion of oncolytic VV. Ferguson et al. discovered that temporary

suppression of PI3Kδ, using the PI3Kδ-selective inhibitor IC87114 or the clinically approved idelalisib (CAL-101), before administering a tumor-targeting VV intravenously, can hinder the virus from attaching to systemic macrophages. This inhibition is achieved by disrupting signaling pathways including RhoA/ROCK, AKT, and Rac. However, the internalization of the virus by the macrophages is not affected. Consequently, this approach enhances the effectiveness of intravenous administration of oncolytic VV to cancers (44).

Furthermore, the use of COX-2 inhibitor medication may strengthen the long-lasting protective anti-tumor effects produced by oncolytic VV by preventing the production of neutralizing antibodies against oncolytic VV infection. This allows for the recurrent administration of oncolytic VV (45). A separate study conducted by McCart's team revealed that pretreatment with CP40, a complement inhibitor, resulted in a significant 10-fold increase in the infectious titer in the blood shortly after the JX-594 infusion. This increase was achieved by preventing the neutralization of oncolytic VV, which is advantageous for the repeated intravenous administration of oncolytic VV (46). Oncolytic VV expressing human CD55 protein may enhance viral survival by shielding against complement-mediated lysis and avoiding neutralization by VV-specific antibodies, hence boosting intravenous effectiveness. All the aforementioned methods are both theoretically and practically viable with the use of antiviral inhibitors before the intravenous administration of oncolytic VV. The findings indicate that the use of VV coating might potentially enhance the systemic administration of oncolytic VV. Additional techniques for VV coating must be developed (47).

Conclusions

Presently, the majority of research on oncolytic viruses focuses on adenovirus and lentiviral vectors as prototypes. Nevertheless, the distinctive benefits of the vaccinia virus render it a good vehicle for gene therapy, offering potential for patients with many forms of cancer. For the treatment of various cancer patients, it is recommended to use thorough and personalized techniques. Hence, it is essential to alter the vaccinia virus to decrease its toxicity and enhance its stability for expression. pathogen vector. It has been determined that when foreign genes are incorporated into the TK region of the VV, they have a beneficial impact on cancer cells. Choosing the most suitable gene is likewise a difficult task. Hence, more research on gene therapy, using the oncolytic vaccinia virus as a carrier, may aid in halting the development and decline of cancer. Furthermore, this research is crucial for resolving the current issues and establishing the foundation for future therapeutic applications.

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Authors' Contribution

Akram Sadat Ahmadi and Yasaman Vojgani were involved in the conceptualization, design and writing of the manuscript draft. All authors read and confirmed the final manuscript.

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