IJBC 2023; 15 (2): 117-127

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

Review

Harnessing the Potential of Vesicular Stomatitis Virus as a Novel Therapeutic Strategy for Cancer Treatment

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ARTICLE INFO

Article History:
Received: 24/04/2023
Accepted: 11/06/2023

Keywords:
Vesicular Stomatitis Virus (VSV)
Cancer Treatment
Oncolytic
Virotherapy
Combination therapy
Oncogene targeting

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Abstract

Background: Oncolytic virotherapy has emerged as a promising approach for the treatment of various cancers. This review article aims to provide an overview of Vesicular Stomatitis Virus (VSV) as an emerging anti-cancer therapy.

Materials & Methods: The article discusses the mechanism of action, preclinical and clinical studies, and challenges in clinical translation of VSV. It also explores potential strategies to enhance the efficacy and safety of VSV-based oncolytic therapy, including combination therapies and genetic modifications

Results: The mechanisms underlying VSV-mediated anti-cancer activity, such as induction of apoptosis, activation of immune responses, and disruption of tumor vasculature, are explored. Additionally, known methods for the preparation of oncolytic VSV, including genetic modifications and combination therapies, are discussed to optimize its anti-cancer effects.

Conclusion: Strategies to enhance VSV efficacy and overcome safety challenges are examined, including the use of VSV in combination with other therapies, such as chemotherapy or immunotherapy, as well as the development of novel viral vectors and engineering approaches to improve tumor-specific targeting and minimize off-target effects. In conclusion, this review highlights the potential of VSV as a novel therapeutic strategy for cancer treatment. Harnessing the unique characteristics of VSV, combined with ongoing research and technological advancements, may pave the way for the development of effective and safe VSV-based therapies in the future.

Please cite this article as: Mousavinasab F, Razani E. Harnessing the Potential of Vesicular Stomatitis Virus as a Novel Therapeutic Strategy for Cancer Treatment. Iranian Journal of Blood and Cancer. 2023; 15(2):117-127.

1. Introduction

Cancer remains a global health challenge, necessitating the development of innovative and effective treatment modalities. Oncolytic virotherapy, which utilizes replicating viruses to selectively target and kill cancer cells, has gained significant attention as a promising therapeutic approach in the field of cancer treatment. Among the various oncolytic viruses, Vesicular Stomatitis Virus (VSV) has emerged as a potential candidate due to its inherent ability to infect and destroy cancer cells while sparing normal cells. This review article aims to provide a comprehensive analysis of VSV as an emerging anti-cancer oncolytic virus therapy, highlighting its mechanism of action, preclinical and clinical studies, and the challenges it faces in clinical translation.

2. Structure and family of Vesicular Stomatitis Virus

The Vesicular stomatitis virus (VSV) is an essentially nonpathogenic, negative-stranded RNA virus that belongs to the order Mononegavirales, family Rhabdoviridae, and genus Vesiculovirus. This family encompasses various pathogens that affect animals and plants (1). The virions of VSV exhibit a characteristic bullet-shaped morphology, with lengths ranging from 100 are essential for viral replication and transcription. Additionally, the RNP includes the heavily phosphorylated phosphoprotein (P) and the RNA-dependent RNA-polymerase (L), which play vital roles in viral RNA synthesis (2, 3). The matrix protein (M) is another integral component found within the VSV virion. M acts as an assembly organizer, facilitating the formation and stabilization of the viral structure (4). Furthermore, VSV possesses a lipid envelope layer, through which glycoprotein (G) spikes protrude (**Figure 1**). The glycoprotein G is responsible for binding the virions to specific receptors on the surface of host cells, initiating the process of viral entry and infection (5).

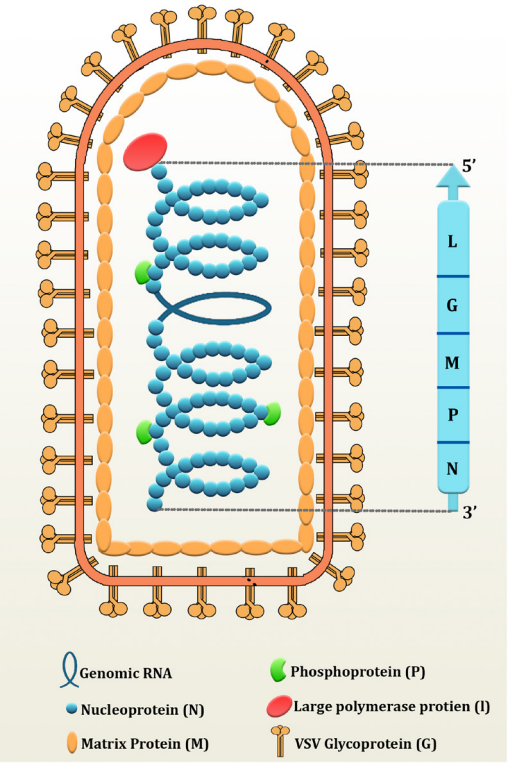

Figure 1. **Illustration of the Structure of Vesicular Stomatitis Virus (VSV).** The image provides an overview of the structure and family of VSV. VSV is a negative-stranded RNA virus with a bullet-shaped morphology. The virions consist of essential components such as the ribonucleoprotein (RNP) complex, which includes the phosphoprotein (P) and the RNA-dependent RNA-polymerase (L) for viral RNA synthesis. The matrix protein (M) acts as an assembly organizer, facilitating the formation and stabilization of the viral structure. VSV also possesses a lipid envelope layer with glycoprotein (G) spikes that bind to specific receptors on host cells, initiating viral entry and infection.

3. Biology and Selectivity of Vesicular Stomatitis Virus

VSV can infect a wide variety of creatures in nature, including mammals and invertebrates. Although there is evidence of spontaneous infection in a variety of wild ruminants, ungulates, carnivores, marsupials, and rodents, overt disease is normally only found in cattle, horses, and pigs. It causes a disease known as vesicular stomatitis, which is characterized by the formation of blister-like lesions on the mouth, tongue, teats, and hooves of infected animals. Animals can infect other animals directly, but this requires an injury or a way to get the virus under the skin. Influenza-like symptoms can also be contracted by humans through contact with vesicular lesions or the saliva of infected animals. It can be transmitted between human by aerosols (6). VSV infection in humans is generally asymptomatic and limited to agricultural and laboratory workers (7). The replication cycle of VSV involves a series of well-defined steps. Upon attachment to specific receptors on the surface of target cells, VSV enters the cell via receptor-mediated endocytosis (8). Its simple genetic composition, the fact that it encodes gene products, and its ability to grow to high titers in most tissue culture cell lines have made it one of the most extensively characterized of all RNA virus. Once inside the host cell, the viral RNA genome is released into the cytoplasm, where it serves as the template for viral replication and transcription. The viral genome is encapsidated by the nucleoprotein (N), forming a ribonucleoprotein (RNP) complex. The RNP also includes the phosphoprotein (P) and the RNA-dependent RNA polymerase (L), which are essential for viral RNA synthesis (3). The matrix protein (M) plays a crucial role in organizing the assembly of new virions and contributes to the budding process. One of the remarkable features of VSV is its selectivity towards cancer cells. Several viral mechanisms contribute to this selectivity, making VSV an attractive candidate for targeted therapy. The envelope glycoprotein (G) of VSV plays a pivotal role in viral entry and host cell specificity. G facilitates viral attachment to specific receptors expressed on the surface of cancer cells, allowing for efficient viral entry and subsequent replication (7).

4. Mechanisms of VSV-Mediated Anti-Cancer Activity

The main goal of virotherapy utilizing replication oncolytic viruses is to facilitate robust viral replication and spread within the tumor, resulting in direct cytotoxicity and destruction of the tumor. (VSV) is an oncolytic virus utilized in oncolytic virus therapy, a treatment approach that employs viruses to specifically target and eliminate cancer cells (9). Unlike healthy cells, cancer cells are often resistant to interferon (IFN), making them vulnerable to oncolytic viruses.The defective interferon response in cancer cells, compared to normal cells, allows VSV to evade the host immune system and replicate more efficiently (10).This approach takes advantage of characteristics commonly found in cancer cells, such as impaired innate immune responses, irregularities in mRNA translation regulation, or dysregulated cellular signaling pathways, to ensure specificity towards cancer cells (10). Cancer cells often exhibit dysregulated signaling pathways and altered cellular environments, which can favor VSV replication. Additionally, VSV has been shown to exploit the upregulated Ras signaling pathway commonly found in cancer cells, which enhances viral replication and oncolytic activity (11). VSV exhibits a unique mechanism of action that contributes to its oncolytic properties. The virus targets cancer cells through the interaction of its envelope glycoprotein with specific receptors, leading to viral entry and subsequent replication within the tumor microenvironment. Replication within cancer cells results in the release of progeny virions, causing direct cell lysis and the induction of immune responses against the tumor. This can trigger immunogenic cell death, promoting anti-tumor immune responses and potential long-term immune memory against cancer cells (**Figure 2**) (12, 13). **Table 1** provides examples of mechanisms involved in VSV-mediated anti-cancer activity and is not an exhaustive list. The specific mechanisms employed can vary based on the unique characteristics of both the cancer cells and the particular strain of VSV utilized in each context.

5. Preclinical and Clinical Studies on Mediated Anti-Cancer Activity

Extensive preclinical studies have provided compelling evidence supporting the efficacy of VSV as an oncolytic virus in various cancer models, spanning from solid tumors to hematological malignancies. These studies have consistently demonstrated that VSV can selectively target and eliminate cancer cells, significantly inhibiting tumor growth and induction of tumor regression, both locally and in metastatic settings (21, 22). Additionally, the synergistic effects of VSV with conventional cancer therapies have been extensively investigated in preclinical studies. It has been observed that VSV can enhance the efficacy of traditional cancer treatments, such as chemotherapy and radiation therapy, by potentiating their cytotoxic effects on cancer cells (23, 24). This combination approach has shown promising results in preclinical models, highlighting the potential of VSV to augment the therapeutic outcomes of standard cancer treatments.

Moreover, VSV has demonstrated its ability to synergize with immunotherapeutic approaches, opening up new avenues for combination therapies. The virus has been found to stimulate anti-tumor immune responses, leading to increased infiltration of immune cells into the tumor microenvironment and the activation of immune-mediated cytotoxicity against cancer cells (25-27). This immunomodulatory effect of VSV holds immense potential for enhancing the efficacy of immunotherapies, such as immune checkpoint inhibitors and adoptive T-cell therapies (28, 29). The encouraging results from preclinical studies have paved the way for translating VSV-based oncolytic treatment into clinical trials. These trials aim to evaluate the safety and efficacy of VSV in cancer patients, further exploring its potential as a novel therapeutic approach (30, 31). The preclinical data provide a strong foundation for these clinical investigations, instilling optimism for the future of VSV-based oncolytic therapy in cancer treatment (32). One example of a previously studied application of VSV as a potential therapeutic strategy for cancer treatment is the work conducted by Altomonte et al. (2008). In their preclinical study, the researchers engineered VSV to express a tumor-suppressive protein called IFNα, which has been shown to inhibit tumor growth by inducing apoptosis and promoting an anti-tumor immune response. The study demonstrated that VSV-IFNα effectively targeted and destroyed cancer cells in a mouse model of hepatocellular carcinoma, resulting in significant tumor regression and prolonged survival compared to control groups (33). Another relevant example is a recent clinical study conducted by Andtbacka et al. (2015), which investigated using a modified VSV called talimogene laherparepvec (T-VEC) to treat advanced melanoma. T-VEC is an oncolytic virus that selectively infects and destroys cancer cells while stimulating an anti-tumor immune response. The study demonstrated that intratumoral injections of T-VEC resulted in persistent responses and improved overall survival in patients with

Table 1. **Mechanisms of VSV-Mediated Anti-Cancer Activity**

Mechanism	Description
Direct Oncolysis	VSV directly infects and replicates in cancer cells, leading to their destruction. The viral replication cycle causes cell lysis, resulting in cell death (14).
Immune Response Activation	VSV infection stimulates the immune system, activating various immune cells, including natural killer (NK), dendritic, and cytotoxic T lymphocytes (CTLs). This immune response helps in the elimination of infected cancer cells as well as non-infected tumor cells (15).
Type I Interferon Response	VSV infection triggers the production of type I interferon (IFN) by infected cancer cells. These IFNs induce an antiviral state in neighboring cells, limiting viral spread. Additionally, type I IFNs have direct anti-tumor effects and can inhibit tumor growth (16).
Tumor Vasculature Disruption	VSV infection can cause damage to tumor blood vessels, leading to disruption of tumor vasculature. This disruption can result in reduced blood supply to the tumor, leading to tumor regression (17).
Induction of Apoptosis	VSV infection can induce apoptosis, a programmed cell death, in cancer cells. Various viral proteins mediate this process and can contribute to the elimination of infected cancer cells (11).
Anti-Angiogenic Effects	VSV infection can inhibit angiogenesis; developing new blood vessels is crucial for the proliferation and spread of tumors. VSV-induced anti-angiogenic effects can help in limiting tumor progression (18).
Modulation of Oncogenic Signaling Pathways	VSV infection can modulate various oncogenic signaling pathways in cancer cells, inhibiting tumor growth. This includes inhibiting pathways such as the Ras/MAPK and PI3K/Akt pathways (19).
Tumor-Specific Targeting	Oncolytic VSV can be engineered to selectively infect and replicate in cancer cells while sparing normal cells. This tumor-specific targeting enhances the anti-cancer activity of VSV while minimizing side effects on healthy tissues (20).

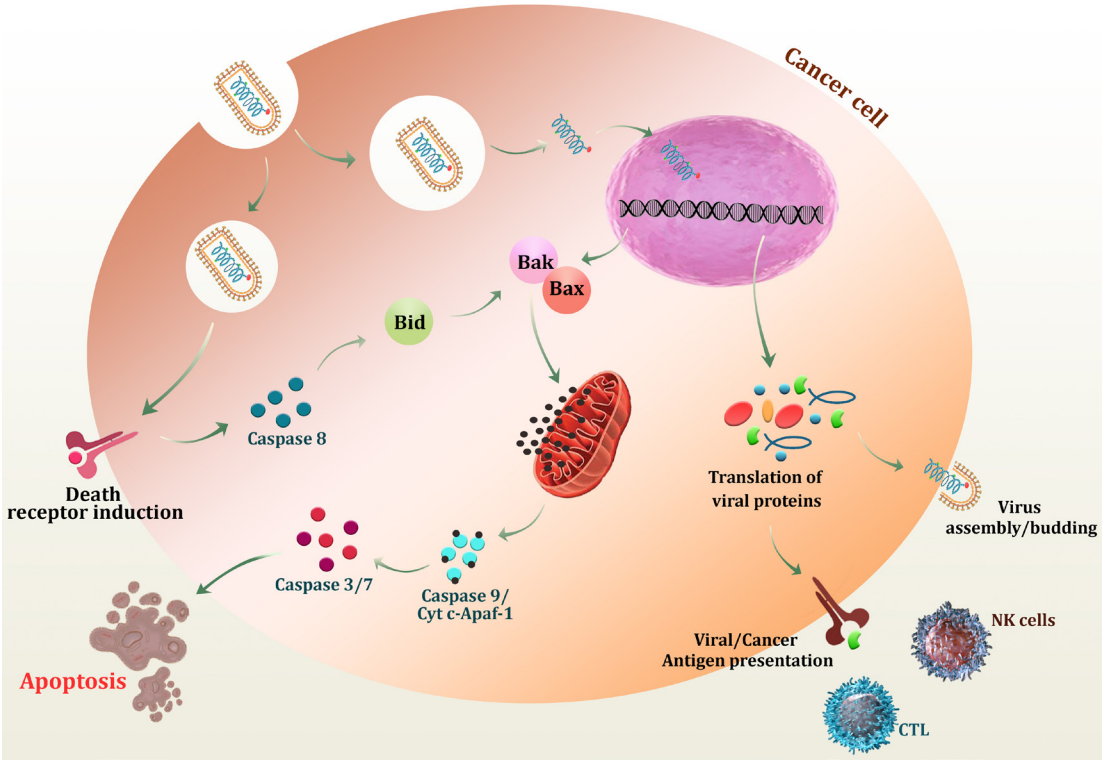

Figure 2. **Illustration of VSV-Mediated Anti-Cancer Activity.** The image depicts the mechanism of VSV-mediated anti-cancer activity. VSV, an oncolytic virus, specifically targets and eliminates cancer cells by exploiting their defective interferon response and dysregulated signaling pathways. The virus enters cancer cells through the interaction of its envelope glycoprotein with specific receptors. Once inside, VSV replicates within the tumor microenvironment, leading to the release of progeny virions. This results in direct cell lysis and the induction of immune responses against the tumor, including immunogenic cell death. The induction of apoptosis by VSV contributes to its anti-cancer activity and potential long-term immune memory against cancer cells.

advanced melanoma compared to standard therapies (34). These findings provide strong evidence for the effectiveness of VSV-based therapies in treating aggressive forms of cancer. These examples highlight the potential of harnessing VSV as a modern therapeutic strategy for cancer treatment. They also emphasize the importance of further preclinical and clinical studies to explore its capabilities thoroughly. By leveraging the unique properties of VSV, such as its ability to target and kill cancer cells selectively, as well as stimulate the immune system, researchers are hopeful that this approach could overcome the limitations of traditional cancer treatments and provide new avenues for personalized medicine (Altomonte et al., 2008; Andtbacka et al., 2015). A clinical trial is underway using VSV against hepatocellular carcinoma (Clinicaltrials.gov, 2012, Trial ID: NCT01628640).

Furthermore, VSV holds promise as a potential treatment option for pancreatic ductal adenocarcinoma, one of the most aggressive and metastatic forms of pancreatic cancer, with most tested cell lines showing high susceptibility to VSV-induced apoptosis. However, resistance to VSV in specific PDA cell lines highlights the need for further research to elucidate the underlying mechanisms and develop strategies to overcome this resistance. Overall, VSV-based oncolytic therapy has immense potential as a novel therapeutic approach in cancer treatment (35, 36).

Therefore, in a fully immunocompetent host, the therapeutic efficacy of local intratumoral virotherapy will be decided by multiple variables and in vivo interactions, many of which are not operative in experiments in animal models lacking complete immune systems. These variables include (a) the amount of viral replication inside the tumor, which will correlate with the levels of direct tumor cell destruction; (b) the immune-based effector mechanisms which will control viral spread both within and outside of the tumor; and will act to restrict viral-mediated tumor cell killing; and (c) the priming of anti-tumor immune effectors, which will contribute to immune-mediated tumor clearance both locally at the injected tumor site, as well as at distant sites of tumor growth. In addition, several reports have described including additional immunostimulatory genes in viral vectors (33, 37-40) or attenuated viral mutants (41, 42) to enhance immune-based clearance of infected tumors. However, relatively few studies have investigated the interactions between these three factors as they apply to antigen-specific T cells in fully immunocompetent hosts undergoing intratumoral virotherapy. **Table 2** and **Table 3** are illustrating some examples of preclinical and clinical studies and do not represent an exhaustive list of all studies and trials on the topic.

6. Known methods for the preparation of oncolytic VSV

Today, at least eight methods have been demonstrated to enhance the neurotropism safety and oncoselectivity of VSV without degrading its oncolytic properties: (i) altering the VSV G protein; (ii) IFN-b expression driven by VSV; (iii) disrupting the regular gene order to attenuate VSV; (iv) inserting foreign gene into the VSV genome to induce apoptosis, cancer suppression or immune response; (v) altering the VSV M protein; (vi) pseudotyping VSV; (vii) VSV's experimental adaption to cancer cells; and (viii) using semi-replicative VSV(6). **Table 4** provides examples of known methods for preparing oncolytic VSV and is not an exhaustive list. Different laboratories may employ variations or combinations of these methods to generate oncolytic VSV. In this chapter we discuss three most recent papers which have used engineered VSV in anti-tumor therapy:

6-1-Inserting foreign gene into the VSV genome: VSV-S

In 2019, Dr. Ming Luo and his colleagues constructed a novel recombinant VSV in which a transgene encoding Smac (Second Mitochondria-derived Activator of Caspases) was directly introduced into the VSV genome. SMAC promotes apoptosis by binding to inhibitors of apoptosis proteins (IAP) and neutralizing their inhibitory effects on caspases, which are enzymes that play a crucial role in the execution of apoptosis (48, 49). Infection with WT VSV decreases the amount of natural Smac in cells. They introduced VSV-S, which produced a large amount of Smac to restore its levels in the cells. This increased cell death through the caspase-9 pathway and caused significant tumor necrosis in a breast cancer model implanted in mice lacking an immune system. The treatment inhibited tumor growth in a mouse model with a functional immune system. In the next step, they focused on the tumor microenvironment (TME) of the KPC-based mouse model of pancreatic cancer after treatment with VSV-S (50). They induced synergic tumors in male and female C57BL/6 mice by injecting 0.5 × 106 KPC_Luc cells under the skin. VSV-SKPC or PBS control was

Table 2. **Preclinical studies investigating the oncolytic potential of Vesicular Stomatitis Virus (VSV) in various cancer types**

Study	Cancer Type	Findings
Shi W et al. (2009)	Breast cancer	VSV effectively targets and kills breast cancer cells in vitro and mouse models (43).
Schreiber LM et al. (2019)	Lung cancer	VSV demonstrates potent oncolytic activity against lung cancer cells and inhibits tumor growth in mouse models (44).
Kelly EJ et al. (2010)	Colorectal cancer	VSV selectively infects and eliminates colorectal cancer cells while sparing normal cells (45).
Holbrook MC et al. (2021)	Pancreatic cancer	VSV shows promising results in inducing apoptosis and reducing tumor size in preclinical models of pancreatic cancer (46).
Diaz RM et al. (2007)	Melanoma	VSV effectively targets and eliminates melanoma cells in vitro and animal models, including those resistant to other therapies (47).

Table 3. **Clinical trials investigating the therapeutic potential of Vesicular Stomatitis Virus (VSV) in cancer treatment.**

Trial	Cancer Type	Phase	Findings
NCT03226182	Head and neck cancer	Phase I	VSV treatment is safe and well-tolerated in patients, with early signs of antitumor activity observed.
NCT03992474	Glioblastoma	Phase I/II	VSV demonstrates promising efficacy in patients with recurrent glioblastoma, with prolonged survival and tumor regression observed in some cases.
NCT04065941	Prostate cancer	Phase I/II	VSV-based therapy shows potential in patients with metastatic castration-resistant prostate cancer, with some patients experiencing tumor shrinkage and disease stabilization.
NCT04537763	Ovarian cancer	Phase I	Preliminary results show VSV treatment to be safe and tolerable in patients with advanced ovarian cancer, with signs of clinical benefit observed.
NCT04860179	Multiple myeloma	Phase I/II	Patients with relapsed or refractory multiple myeloma have shown encouraging responses to VSV therapy, indicating significant anti-tumor effects. In some cases, partial remissions have been observed.

Table 4. **Known methods for the preparation of oncolytic Vesicular Stomatitis Virus (VSV)**

Method	Description
Reverse Genetics	VSV can be generated using reverse genetics, where the viral genome is engineered to express therapeutic genes or mutations that enhance tumor selectivity. This method involves the assembly of a full-length VSV cDNA clone and its transfection into permissive cells for virus production.
Serial Passage	VSV can be passaged serially in cancer cells to select variants with enhanced oncolytic activity. This method involves infecting cancer cells with VSV, harvesting the released viruses, and repeating the process to generate viral populations with increased tumor specificity and potency.
Genetic Engineering	VSV can be genetically modified to enhance its oncolytic potential. This includes the introduction of specific gene deletions or substitutions to improve tumor selectivity or increase immunogenicity. Genetic engineering techniques such as CRISPR/Cas9 or site-directed mutagenesis can be employed for precise modifications.
Pseudotyping	VSV can be pseudotyped with envelope glycoproteins from other viruses, such as the G protein from lymphocytic choriomeningitis virus (LCMV) or the envelope protein from the Indiana serotype of vesicular stomatitis virus (VSV-IND). Pseudotyping can alter VSV tropism and enhance its ability to target specific cancer types
Cell Culture Adaptation	VSV can be adapted to grow in specific cancer cell lines through serial passaging in these cells. This method involves infecting cancer cells with VSV and repeatedly passaging the virus in the same cell line. The resulting adapted VSV strains can exhibit improved replication and oncolytic activity in the selected cancer cell line.

intratumorally injected in each mouse. The overall number of immune cells (CD45+) that penetrated the tumor dramatically rose on day 12 of the trial, and a decline in the size of the KPC tumor accompanied this. The VSV-S therapy generated a considerable infiltration of neutrophils into the tumor, which the researchers discovered to be a marker of a robust inflammatory response in the tumor microenvironment. As a result, significantly fewer MDSCs (myeloid derived suppressor cells) and M2 macrophages were associated with the tumor. These results imply that the immediate inflammatory response and neutrophil-mediated killing played a significant role in quickly eliminating KPC malignancy following VSV-S infection. Treatment with PBS (control) kept the tumor's immunosuppressive milieu, dominated by MDSCs and macrophages, and no neutrophil infiltration.

Furthermore, VSV-S treatment decreases immunosuppressive factors ARG1, TGF-β, and IL-10 levels in tumors. This is a positive outcome as these factors can inhibit the immune system's ability to fight against tumors. By reducing their levels, VSV-S may enhance the immune response to tumors, leading to better outcomes for the treated mice (50, 51).

The other finding of this study demonstrated the role of Anti-PD1 in increasing the efficacy of VSV-S treatment. Anti-PD1 drugs block the interaction between PD1 and PD-L1, allowing the T-cells to recognize and attack the cancer cells more effectively. Following treatment with VSV-S, subsequent treatment with an anti-PD-1 antibody led to complete tumor regression and significantly increased survival of the mice bearing the tumor. This encouraging result indicates that combining VSV-S and anti-PD-1 therapy can amplify the immune system's capacity to identify and eliminate cancer cells. Consequently, this can lead to better outcomes in the mice that received the treatment (52).

While the data for intratumoral injection therapy with VSV-S and anti-PD-1 antibody combination are promising, researchers must give more information about the efficacy of systemic intravenous administration of the same treatment. Systemic administration is often necessary for treating cancer that has spread to other body parts. Therefore, further research is needed to investigate the efficacy and safety of systemic intravenous administration of VSV-S and anti-PD-1 antibody combination therapy. This will help to determine the potential utility of this treatment approach for cancer patients who require systemic therapy.

6.2. Pseudo typing VSV: VSV-GP

VSV is a neurotropic virus, which means it has a particular affinity for nerve cells and can cause neurotoxicity. VSV-GP is a type of oncolytic virus (OV) that has been genetically modified to replace its original envelope glycoprotein (G) with a non-neurotropic envelope glycoprotein (GP) derived from the lymphocytic choriomeningitis virus. This new chimeric OV is live and recombinant, meaning that it is capable of replicating and reproducing itself within host cells. By replacing the neurotropic G protein with the non-neurotropic GP protein, VSV-GP may be able to reduce the neurotoxicity associated with the original VSV virus while still retaining its ability to target and destroy cancer cells selectively (53).

In 2018 Urbiola and his colleagues studied the anti-tumor effects of VSV-GP on a panel of Prostate cancer (PCa) cell lines and patient-derived primary PCa cultures. They analyzed the susceptibility of different cell lines to VSV-GP, an oncolytic virus. They used six humans and one murine prostate cancer cell lines and tested the sensitivity of primary cultures of prostate epithelial cells from patient samples. The results showed that all the primary cultures tested were sensitive to VSV-GP killing, but the killing rates varied from 60% to 20% survival. Overall, the study found that VSV-GP effectively infects and kills both PCa cell lines and patient-derived primary cultures (54).

In the next step, they aimed to determine whether the results of in vitro experiments on the effectiveness of VSV-GP in killing PCa cells correlated with the virus's efficacy in mouse models. The researchers first tested the virus on subcutaneous Du145 tumors with two intratumoral injections of 107 PFUs of VSV-GP. The treated animals experienced complete tumor remission, with no cancer, relapses over the 100-day follow-up period. Then they tested whether VSV-GP was effective when administered systemically to subcutaneous 22Rv1 tumors. The results showed that intravenous treatment with 108 PFU of VSV-GP induced complete responses in all six animals, with an overall survival rate of 100% during the 86-day follow-up period. The study found that, regardless of the level of susceptibility exhibited in vitro, VSV-GP successfully killed PCa cells in vivo. There was also no evidence of viral pathogenicity (54).

The promising results encouraged them to investigate whether it could treat bone metastasis, one of the most common metastatic PCa presentations that call for systemic therapy. The efficacy of VSV-GP therapy in the metastatic scenario was examined using a well-

established bone metastasis model of PCa. In the study, mice had left tibial bone cancers called PC-3M-Luc. The mice were given a single intravenous injection of 5 x 107 PFUs of VSV-GP, and the amount of tumor growth was assessed using the tumor's luciferase signal. They found that tumor remission was seen in 4 of the five treated mice, demonstrating the effectiveness of VSV-GP treatment in treating bone metastases in the PCa model (54).

While efficacy data for OVs are promising, many of the OVs currently in development must be administered intratumorally because neutralizing antiviral antibodies in the body limits their effectiveness when delivered systemically. However, VSV-GP has several advantages. Specifically, the general population has little pre-existing immunity against VSV-GP, and it does not readily induce neutralizing antibodies. This makes repeated systemic delivery of VSV-GP potentially effective in treating primary tumors and metastases (54).

It has been mentioned in the paper that "We then selected the three cell lines that were susceptible VSV-GP killing and had reduced interferon competence, Du145, 22Rv1, and PC-3M-Luc, for efficacy testing in xeno- transplant mouse models". I believe that is one of the limitations of the VSV-GP treatment. Its efficacy is IFN-dependent. Despite this limitation, their findings were valuable, and according to these results, Porosnicu and her colleagues conducted a phase I clinical trial, which was the first of its kind in humans, to evaluate the effects of VSV-GP as a standalone treatment and in combination with the immune checkpoint inhibitor Ezabenlimab. The study involved patients with advanced, metastatic, or relapsed solid tumors resistant to previous treatments. The trial is recruiting patients and is expected to be completed in August 2025 (53).

6.3. Altering the VSV G protein: VSV-G (K174E and E238K)

In another experiment, the researchers created a new oncolytic VSV that replicates better in virus-resistant pancreatic ductal adenocarcinoma (PDAC) cell lines while remaining substantially attenuated in normal cells (Seegers et al.,2020). They used recombinant VSV, which encodes VSV-p53wt or VSV-p53-CC and matrix protein (M) with a ΔM51 mutation (MΔM51). Functional human tumor suppressor, p53, fused to eqFP650, a fluorescent protein. These viruses were serially passaged 32 times (over 60 viral replication cycles) on SUIT-2 or MIA PaCa-2 human PDAC cell lines. These cell lines were chosen because of their different susceptibility to VSV. SUIT-2 cells are more resistant to VSV infection due to residual type I IFN responses, whereas MIA PaCa-2 cells are very permissive to VSV infection due to inactive type I IFN signaling. Interestingly, the Replication Improved in SUIT-2 while remaining highly attenuated in nonmalignant cells. SUIT-2-passaged viruses acquired two identical VSV glycoprotein (VSV-G) mutations, K174E and E238K, which improved VSV replication, at least in part due to improved virus attachment to SUIT-2 cells. There were no mutations in the M-ΔM51 protein and the p53 or eqFP650 portions of virus-carried transgenes in any of the passaged viruses. These findings demonstrated the long-term genomic stability of complex VSV recombinants carrying large transgenes (55).

Overall, this information highlights the potential of oncolytic VSVs for treating PDAC and the importance of directed evolution approaches to improve their efficacy. While the focus of this study was on the adaptation of oncolytic VSV recombinants to PDAC cells and the stability of VSV transgenes following extended virus passaging, future experiments need to assess the efficiency and safety of the founder and SUIT-2-passaged VSV-p53 viruses in vivo.

7. Strategies to Enhance Efficacy and Safety Challenges in VSV Oncolytic Therapy

Despite promising preclinical and early clinical data, several challenges must be addressed to translate VSV-based oncolytic therapy successfully. These challenges include the development of strategies to enhance viral delivery and replication within tumors, overcoming pre-existing immunity against VSV, and minimizing potential off-target effects. Various approaches, such as engineering VSV for tumor-specific targeting, combining VSV with other therapeutic modalities, and utilizing immune checkpoint inhibitors, are being explored to overcome these challenges and improve the therapeutic outcome of VSV-based oncolytic therapy. However, several challenges need to be addressed to optimize the efficacy and safety of VSV-based treatments. Here we discuss current advances and future directions in strategies to enhance VSV efficacy and safety. Various approaches are discussed, including genetic modifications, combination therapies, and delivery systems. Additionally, the chapter highlights the importance of understanding the interactions between VSV and the tumor microenvironment, as well as the host immune response, to further enhance

the therapeutic potential of VSV. Relevant studies and literature support the information presented in this chapter.

7.1. Genetic Modifications

Genetic modifications of VSV offer a promising avenue to enhance its therapeutic efficacy. These modifications can include the insertion of therapeutic transgenes, such as cytokines or immune checkpoint inhibitors, into the viral genome to augment the immune response against cancer cells. For instance, incorporating interferon genes into VSV has shown enhanced anti-tumor effects in preclinical models. Additionally, engineering VSV to express microRNAs targeting specific oncogenic pathways can further improve its oncolytic activity (56). Moreover, targeted genetic modifications have achieved the development of VSV mutants with enhanced tumor selectivity and reduced neurotoxicity (23, 57, 58).

7.2. Combination Therapies

Combining VSV-based oncolytic therapy with conventional cancer treatments has synergistic effects, improving therapeutic outcomes. Combination approaches can involve chemotherapy, radiation therapy, or targeted therapies complementing VSV's oncolytic activity. For instance, combining VSV with chemotherapeutic agents, such as gemcitabine or cisplatin, has demonstrated enhanced anti-tumor effects in preclinical models. Moreover, combining VSV with immune checkpoint inhibitors has shown promising results by potentiating the immune response against cancer cells and overcoming immunosuppression (30, 32, 59, 60).

7.3. Delivery Systems

Efficient delivery of VSV to tumor sites while minimizing off-target effects is crucial for enhancing its therapeutic efficacy and safety. Various delivery systems, including viral vectors, nanoparticles, and cell-based carriers, have been explored. Viral vectors, such as lentiviruses or adenoviruses, can deliver VSV genes into specific tumor cells, improving tumor targeting. Nanoparticles, such as liposomes or polymeric nanoparticles, can encapsulate VSV and enhance its stability, circulation time, and tumor accumulation. Furthermore, cell-based carriers, such as mesenchymal stem cells or immune cells, can be engineered to deliver VSV selectively to tumor sites, exploiting their natural homing abilities (15, 60-62).

7.4. Understanding the Tumor Microenvironment and Immune Response

The tumor microenvironment is critical in modulating VSV efficacy and safety. Factors include hypoxia, immune evasion mechanisms, and extracellular matrix components (63, 64).

8- Future Directions: Advancing Strategies to Enhance Efficacy and Overcome Safety Challenges in VSV Oncolytic Therapy

There are several methods to improve the neurotropism safety and oncoselectivity of VSV without degrading its oncolytic properties. It leads to about 50 different manipulated VSV used for anti-tumor therapy, some of which are discussed here. However, delivering VSV to the tumor site can be challenging as the immune system clears it and can cause side effects if it infects healthy cells. So in most cases, intratumoral administration is reported, and there are a few reports of successful systemic delivery.

However, intratumoral injection is approximately easy and safe for metastatic tumors systemic delivery becomes essential. There should be an intelligent system that can evade immune components and find even small numbers of malignant cells. To address this problem, I suggest using Nanoparticles. They can help deliver VSV to the tumor site by protecting it from clearance by the immune system and allowing it to target cancer cells specifically. We can encapsulate recombinant VSV in lipid Nanoparticles and decorate the surface of Nanoparticles with Fab fragments of Antibody against specific markers of tumor cells. To track the nanoparticles in the body, we can use nontoxic fluorescent stains like GFP in this construction. After inducing tumors in mice and administering the nanoparticles, the in vivo imaging can show us the accumulation of Nano drugs in tumor sites.

9-Conclusion

Vesicular stomatitis virus (VSV) has shown promising anti-neoplastic action against various human cancers. Because of its broad tropism, rapid replication kinetics, and adaptability to genetic manipulation, VSV is particularly appealing as an oncolytic agent. In addition, VSV-induced oncolysis can trigger a robust antitumor cytotoxic T-cell response to viral proteins and tumor-associated antigens, resulting in a long-lasting anticancer impact. Due to its diverse immunomodulatory ability, VSV has been studied as an immunovirotherapy alone or in combination

with other anticancer treatments, such as immune checkpoint inhibition. Although there have been changes to demonstrate the combined and separate positive effects of oncolytic VSV with current cancer treatments, the FDA has not yet authorized the use of oncolytic VSV in humans. Although challenges remain, ongoing research and clinical trials are expected to provide valuable insights into the optimization and clinical utility of VSV-based oncolytic therapy, potentially revolutionizing the treatment of various malignancies.

Conflict of Interest:

The authors declare that they have no conflicts of interest regarding the publication of this manuscript, entitled "Harnessing the Potential of Vesicular Stomatitis Virus as a Novel Therapeutic Strategy for Cancer Treatment."

Acknowledgement:

The authors would like to express their gratitude to scientific board for Colife Integrated Medical Labs (Tehran, Iran) for supporting this study. Furthermore, we would like to thank the reviewers and editors for their constructive feedback and suggestions, which greatly improved the quality of this manuscript.

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