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Combat between Oncolytic Vesicular Stomatitis Virus and Cancer Cells

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Abstract

Vesicular stomatitis virus is a member of the Rhabdoviridae family that contains enveloped viruses with characteristic rod shapes. These viruses have the efficacy to infect cancer cells and lyse them, there they are called oncolytic viruses. Oncolytic viruses are a specific group of viruses that multiply only in malignant cells and are targeted towards them. The purpose of writing this review is to highlight the importance of the vesicular stomatitis virus as a candidate for oncolytic virus. Among all the viruses, the vesicular stomatitis virus (VSV) has been considered a potent oncolytic virus because it makes slow progression in diseased cells and does not affect normal functioning cells. Due to its remarkable ability to prompt intense antiviral and immune reactions, the compound is better suited as a therapeutic agent based on its natural characteristics. The current advancements in research involve the enhancement of the specificity and efficiency of the vesicular stomatitis virus in the treatment of different kinds of cancer. For example, making genetic modifications in the viral genome (altering of M and G protein) enables it to demolish tumor cells and preserve healthy body cells. This strategy relies on the vesicular stomatitis virus's small size, replication competency, and the virus's competency to trigger anti-tumor immunities, which is why it may be effectively used to treat cancer. This review also guides the mechanism of how viral particles prey on cancer cells and induce apoptosis as well as the combination of vesicular stomatitis virus with other molecules to treat cancer.

Keywords

Oncolytic virotherapy, Oncolytic viruses, Vesicular stomatitis virus, Recombinant vesicular stomatitis virus with tumor lysing properties, Pros and cons of oncolytic viruses

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1. INTRODUCTION

Oncolytic viruses can be considered to be effective anti-tumor agents with the ability to autonomously replicate in tumor tissues and induce tumor cell death without affecting most of the normal cells (Apolonio et al.,2021). Preceding viral progeny to adjacent tumor cells it was believed to enhance anti-tumoral effects by replenishing the therapy in situ. Non-carcinogenic virus replication can be exclusive to one or several species of the tumor viruses as a performant characteristic, appear as a result of selective pressure, or have been biotechnology planned. Reprogramming of the viral replication machinery is made to target the special molecular changes associated with the tumor so that replication of the virus and cell lysis occurs. Virus species that have been used or genetically manipulated for oncolytic purposes include herpes simplex virus, vaccinia virus, reovirus, vesicular stomatitis virus, and adenovirus (Niemann & Kuhnel.,2017).

Another active area of cancer investigation has been the attempt to boost the body's ability to fight tumor cells by stimulating the immune system. Oncolytic viruses (OVs) are one of such tools. Such viruses can be of either a cancer-causing type or a wanted kind that can be designed to target and kill cancerous cells only. Also, the host's immune response appears to be provoked by OVs, which may help to eliminate tumors. Currently, active candidates for oncolytic use are herpesvirus, adenovirus, poxvirus, picornavirus, and reovirus. In 2015 talimogene herparepvec became the first OV to receive approval from the FDA in the USA for human use and there are many other OVs in phase III trials. (Cook & Cauhan.,2017).

Oncolytic viral therapy can be described as viruses that can grow specifically and preferentially in cancer cells and cause the death of the cells without affecting the healthy cells. The first second-generation oncolytic virus drug was recently approved in the USA and Europe; T-Vec– talimogene laherparepvec, an oncolytic herpes simplex virus type 1 (HSV-1) armed with GM-CSF. (Fukhara et al.,2016).

There is growing mechanistic data about OV action that encompasses a selective killing of tumor cells and the induction of antitumor immunity are the hallmarks of therapeutic outcomes (de Gruijl et al.,2015). Immune activation is, therefore, triggered by the tumor microenvironment, where cellular fragments, as well as viral material, are liberated along with antigens. Several factors

contribute to tumor selectivity in the treatment of OV. The first of these is cellular entry during which the virus attaches to specific receptors on the infected cell. Normally, a specific viral entry receptor is usually up-regulated on tumor cells. Nevertheless, some strategies are currently being developed to enhance the tumor's specificity of OVs by entering the cell using tumor-specific receptors.

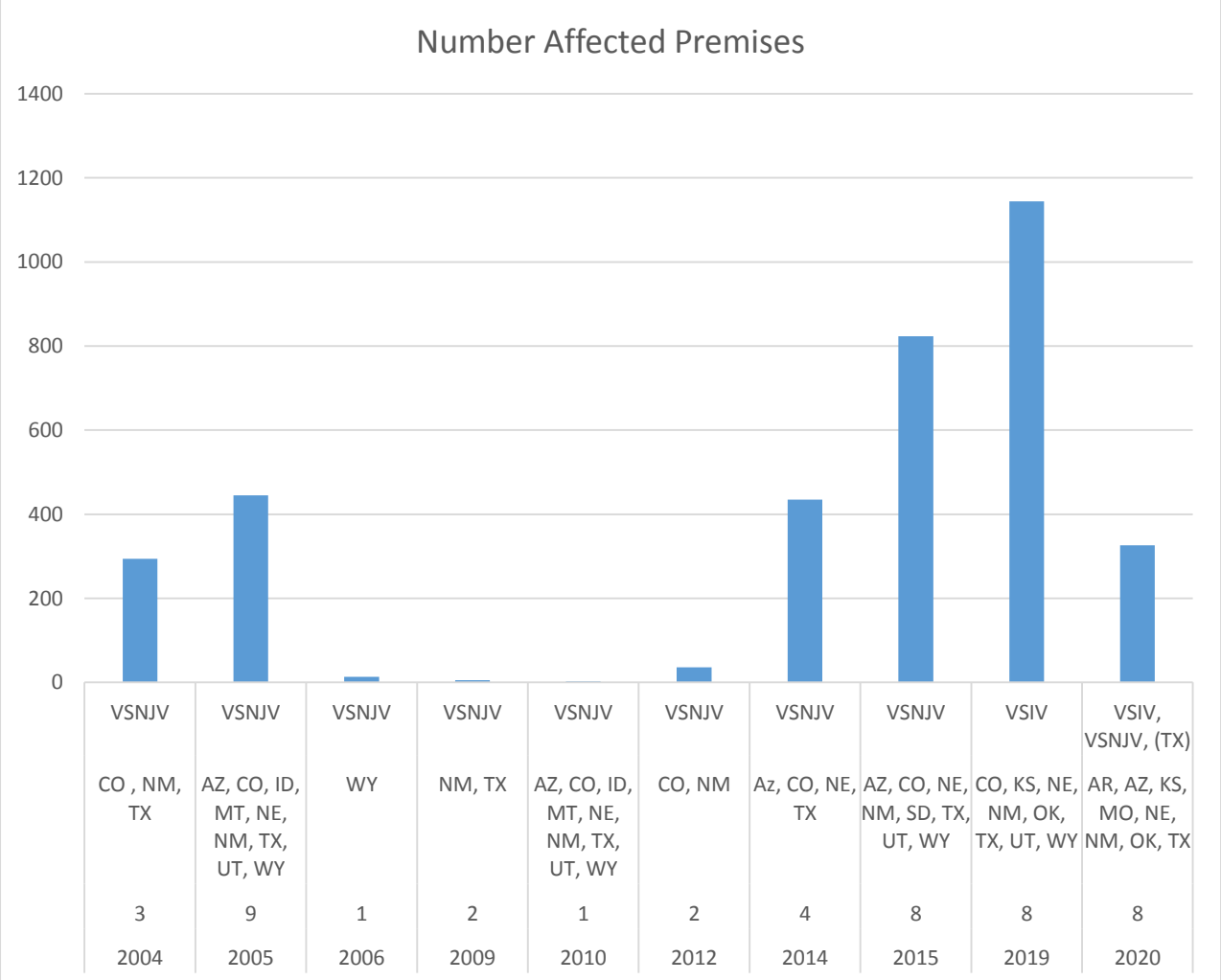
Second, the exponentially dividing and metabolically and replicatively active tumor cells may have enhanced viral replication than distinct non-tumor quiescent cells. Furthermore, tumor-driver mutations also enhance the virus replication only in the tumor cells by increasing the selectivity. Third, multiple tumor cells exhibit impaired signaling through the antiviral type I interferon, and thus, beneficial virus replication is fostered. Viral replication within the tumor microenvironment results in the activation of both innate and adaptive immune systems. This activation would curtail virus replication; however, the occurrence of the virus in addition to cytolysis, which releases tumor-associated antigens and danger signals, would overcome local immunosuppression and induce antitumor immunity. Recognized factors that contribute to the effectiveness of this plan include previous immunity to antiviral and antitumors as well as the addition of immune-stimulating transgenes. (Lawler et al., 2017).

Vesicular stomatitis virus selectivity resides in the interferon deficiency (Alain et al.,2015). An engineered VSV variant that produces interferon β is in the phase I clinical trial for liver cancer. Interferon β will probably work in conjunction with VSV to preserve normal cells from destruction and to induce antitumor impacts and tumor cell-selective cytolysis.

Vesicular stomatitis (VS) is an economically important viral disease of cattle, horses, and swine characterized by vesicular lesions of the gums, tongue, naso-oral mucosa, teats, and coronary bands (Rozo Lopez, 2022). Although VSV is not highly pathogenic and rarely leads to high mortality rates, negative economic impacts are always disastrous to producers of livestock, as well as bans on animal movement due to disease transmission cut the animal production business. In the United States, the economic consequence of an outbreak of VS is calculated at $100 to $200 per cow and a mean of $ 15,565 where a ranch is infected with VSV. Also, VS causes much concern since it is symptomatically very similar to foot and mouth disease, a highly lethal viral

disease affecting cloven-hoofed animals, which was eradicated in the USA in 1929. VSV is sustained in reservoir populations in the tropical areas of Central and South America; annual epizootics result in high prevalence of infection overall species susceptibles. Thus, outbreaks involving other viral strains originating from these southern endemic areas are experienced in the southwestern parts of the United States every 10 years. Some of the factors that could be attributed to such an epidemiological pattern which includes the on-and-off movement of specific strains of the endemic viruses from bases in Mexico to affect those in the U. S.'s northern borders may not be well understood.

Graph: Epidemiological data of different variants of vesicular stomatitis virus in the United States of America. (Modified from (Pelzel-McCluskey et al., 2021).



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Information on transmission, epizootic duration, and geographic range of transmission is gathered from veterinarian reporting of cases and only entails limited entomological sampling during epizootics that are always sporadic. Therefore, to establish that virus transmission routes include direct contact, aerosols, and fomites, insect vector involvement such as mosquitoes, sandflies, black flies, and biting midges is evident.

Stomatitis vesicular viruses are enveloped viruses belonging to the rhabdovirus family, vesiculovirus group. The virions are bullet-shaped and the size is, in general, 180 nm in length and 65nm in width. An external lipoprotein membrane is formed due to the virus envelope derived from the host cell and an inner highly stable ribonucleoprotein core. The genome of VSV consists of a negative sense single-stranded RNA, 11,161 nucleotides in length, encoding five major proteins: Nucleocapsid or ribonucleoprotein, or phosphoprotein, matrix protein, glycoprotein, and large protein or polymerase. Thus, G transmembrane glycoprotein caused the structures named spikes on the surface of the envelope and was involved in the aspect of cellular recognition and fusion for virus entry and exit into the cell. The M protein is situated between the envelope and the nucleocapsid core and has some role in the budding of the virus. The nucleocapsid core is the central part of a virus containing the viral genome that is closely associated with the viral nucleoprotein, N protein that in turn provides an RNase-resistant shell for the viral RNA genome. The P and L proteins are involved in the RdRp of G-RNA and transcription of the mRNAs in the order P-N-M-G-L. (Rozo-Lopez et al., 2018).

Virotherapy was considered for cancer treatment in the 19th century, but due to the limitations in genetics and a variety of safety issues, its progress was slow till the past two decades. On the concept, the field of oncolytic virotherapy seeks to manipulate the viral genomes to replicate and kill only cancerous cells. Currently, oncolytic virotherapy can be viewed as a form of cancer immunotherapy; this is explained by the induction of immune response concerning the viral epitopes in the tumor cells infected by the virus, as well as oncolytic viral death influence on tumors. Imlygic, or T-VEC, was the first OV, which was approved by the US Food and Drug Administration for its application to melanoma in 2015. (Goradel et al., 2021). This review discusses the features of the vesicular stomatitis virus that help in the destruction of cancer cells,

the modification of its genome, strategies to make it a powerful oncolytic candidate, and conjugation with beneficial molecules.

2. OVERVIEW OF ONCOLYTIC VIRUSES

They are a group of viruses that contaminate and reproduce, particularly in cancer cells but they do not disturb the activity and mechanism of normal cells around them. In the mid-1900s, several viruses were considered clinically important to treat malignancies. In the 1990s, the establishment of genetic engineering boosts the properties of oncolytic viruses (Kelly & Russell, 2007). Nowadays, oncolytic viruses are effective means of cancer treatment using various mechanisms of action. These virus particles break down and target specific human tumor cells. Oncolytic viruses demonstrated natural cancer tropism, including overexploitation of the interstitial molecular marker in cancer cells. As we know, viral disease is the association between virus particles and cell-specific markers but in this case, many oncolytic viruses are selected based on the excessiveness of their detectors in cancer cells as compared to their normal concentrations. Overexpression of the PVR (CD155) receptor in the cancer cells preserves the host's immunity by interacting with the downregulated marker TIGIT (Kucan Brlic et al., 2019). Poliovirus contains innate tropism and over-expressive cancer CD155 receptor is a perfect target for them. Other receptors that can effectively target cancer include CD46 for the measles virus, overstimulation of HVEM, and nectin-1, and 2, which make cancer cells more sensitive to the herpes virus (Fu et al., 2018). Moreover, the coxsackie virus lyses the cancer cells with the upregulation of intracellular adhesion molecules-I and decay-accelerating factors in malignant breast tumors (Au et al., 2007; Shafren et al., 2004). The vesicular stomatitis virus is highly susceptible to type I interferons and can showcase its tumor-destructive performance in the antiviral cytokines (Stojdl et al., 2003). As we know, the activity of type I interferons is inhibited in most cancers so they cause vesicular stomatitis-related tumor lysis in cancer cells. Although oncolytic viruses can suppress malignancies, they also change the genetic code of viruses to produce more authentic, long-term effects specific to cancer (Hemminki et al., 2020).

The ability of oncolytic viruses is that they are targeted specifically towards tumor cells. So, adenoviruses are studied over a longer period because they contain larger genomic DNA and are

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useful as cancer-treating viruses. When they cause infection, adenoviruses synthesize a specific protein E1A capable of regulating the continuance of DNA replication from G1 to the DNA synthesizing stage (S phase) (Loboda et al., 2019). As a result, E1A forms a complex with retinoblastoma by liberating E2F protein (Fueyo et al., 2000). The unbound protein triggers the activation of the E2 viral protagonist and various genes important for the cellular division cycle. Cancer cells induce mutation in the retinoblastoma route and adenovirus contains defective E1A protein that forms a bond with the retinoblastoma and therefore, is not able to replicate in the normal body cells but divides rapidly in the tumor cells along with alterations in the retinoblastoma path. Another adenoviral protein E1B is also studied and investigated to discontinue the reproduction of viruses in the malignant cells (Blackford & Grand, 2009). So E1B attaches to the component p53 and immobilizes its activity. This results in the protection of body cells from programmed cell death. ONYX-15 and H101 are two types of adenoviruses that inhibit the interpretation of E1B and they multiply and burst down in tumor cells with genetic modifications and the suppression of p53 (Lei et al., 2015; Ries & Korn, 2002). Advanced research in cancer shows that ONYX-15 can be replicated in the mutant p53 strain (Edwards et al., 2002; Geoerger et al., 2002; Rothmann et al., 1998). Furthermore, many viruses have been employed to perform flawed antiviral processes in malignant tumor cells. The oncolytic activity of herpes simplex virus-1 includes mutations in the genes of viruses ICP34.5 and US11. They block the PKR activation that inhibits the viral protein synthesis during an infection. Hence, the weakened viral particle is suitable to mutate and reproduce in tumor cells (Poppers et al., 2000).

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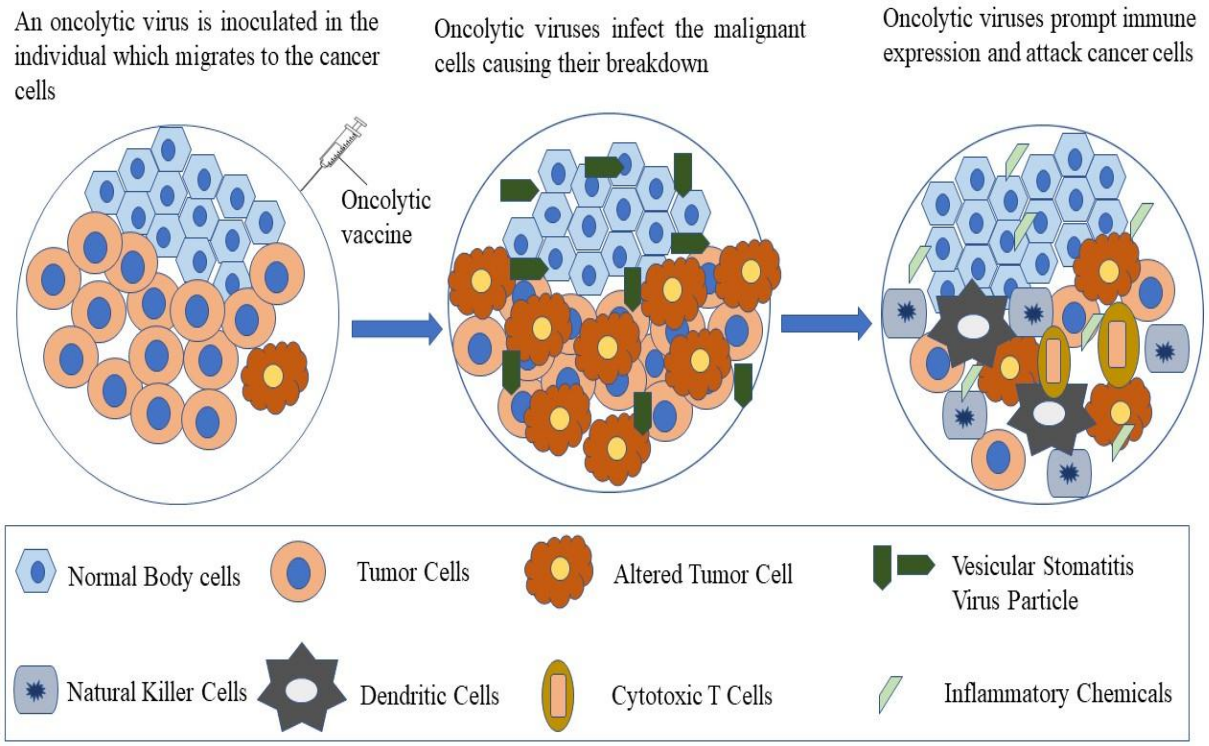

Fig1. Diagrammatic overview of oncolytic virotherapy. Oncolytic viruses such as vesicular stomatitis virus target cancer cells and the degradation of cancer cells with time using different immune cells.

3. VESICULAR STOMATITIS VIRUS AS AN ONCOLYTIC VIRUS

Vesicular stomatitis virus is a component of the *Rhabdoviridae* family. The virus causes disease that is followed by lesions formation in the mouth, tongue, nasal cavity, and around the nipples of the infected species. In domestic animals, the infection of the vesicular stomatitis virus occurs periodically and most of them are not fatal (Drolet et al., 2009). The two important wild-type strains of the vesicular stomatitis virus are Indiana and New Jersey cause episodes of the outbreak in Central America and other areas of the United States of America (Lyles et al., 2013). The non-standard variants of the vesicular stomatitis virus produce higher antibody levels in the cell culture.

That is why, this virus is considered the best agent to analyze the biological mechanisms and techniques inside the animal body and outside the artificial environment. The viral genetic material is made of negative-sense single-stranded RNA which is 11000 nucleotides long and consists of five important genes arranged in a 3`-5` direction. When a virus infects a cell, its protein travels back and forth between the cytoplasm and the nucleus, consequently attacking the host RNA polymerases I, II, and III. By targeting the polymerases, the virus inhibits transcription (Ahmad & Lyles, 1998). The viral particle also hinders the activity of messenger RNA by reducing Ran-TC4 GTPase and obstructing the release of mRNA from the host's cell nucleus inducing genetic toxicity (Enninga et al., 2002; Her et al., 1997; Faria et al., 2005). The matrix protein of the vesicular stomatitis virus correlates with nucleoporin and Rae 1 protein which establishes the transcriptional command (Faria et al., 2005; Rajani et al., 2012). Nevertheless, the process of viral protein synthesis remains unchanged as *cis-acting* factors of the virus particle encourage the enlistment of host translational elements. The large ribosomal subunit of the host speeds up the cap-pivoted translation of the virus. This strategy of translation in the host elevates the level of viral proteins in the host cell (Whitlow et al., 2006; Black et al., 1994). Vesicular stomatitis virus causes fast programmed cell death in the corrupted cells making it a good oncolytic virus.

4. MECHANISM OF CELL-DEATH INITIATION BY THE VESICULAR STOMATITIS VIRUS

The pathophysiology of vesicular stomatitis virus in the damaged cells is initiated by the structural modifications in the cells by ceasing the process of RNA synthesis in the host. It is done with the help of M protein which finishes with programmed cell death (Koyama, 1995; Black & Lyles, 1992; Blondel et al., 1990). The initial onset of cell death is devised to restrict viral reproduction and provide protection to the host. Besides this, the viral matrix protein induces the upregulation of the host's anti-apoptotic factor, B-cell lymphoma 2 as it permits the virus to complete its division cycle in the host before its programmed cell death (Gaddy & Lyles, 2005). The M protein inaugurates the process of apoptosis by the mobilization of the factor caspase-9 and it is not linked to the virus-cell cycle and M protein production (Balachandran et al., 2000). However, the M protein lessens the organism's transcriptional and translational activity. It compels cells to suicidal death along with other substituents like the viral envelope made up of glycoproteins and is a

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contributing factor in apoptosis. The cell death activity caused by the M protein varies on the type of cells and that is why, it specifically selects and breaks down the malignant cells (Gaddy & Lyles, 2005). Vesicular stomatitis virus also can cause under-expression of the proteasomal destruction of the B-cell lymphoma 2 group member, myeloid cell leukemia 1 protein. This protein is an important factor that prevents apoptosis and maintains the equilibrium between programmed cellular death and autophagocytosis. The downregulation of myeloid cell leukemia 1 activates the caspase-3 and breaks down light chain 3 which also takes part in the process of apoptosis (Schache et al., 2009). With the help of this strategy, the vesicular stomatitis virus weakens the cancer cells that are resistant to the chemotherapeutic drugs and presents them for apoptosis, becoming a good tool for cancer treatment (Schache et al., 2009).). As we know, the matrix protein is enough to cause cell death but trials are conducted to induce protein in the plasmid of the codocytes (Qi et al., 2016).

In another method, the vesicular stomatitis virus causes endoplasmic reticulum pressure-interfered cell death. The endoplasmic reticulum is a center where viral proteins are synthesized and assembled. When the cell demands more proteins during virus reproduction in the host cell, the endoplasmic reticulum stress response is activated. The transient endoplasmic reticulum tension regulates the cell expression during the installation of caspase-2. Hence, the stress induced by the endoplasmic reticulum harmonizes with the oncolytic activity of the vesicular stomatitis virus (Mahoney et al., 2011). Apart from provoking the apoptosis, the vesicular stomatitis virus inhibits the progression of the tumor. It infects tumor cells by blocking the blood flow and inhibiting the breakdown of the blood vessels (Qi et al., 2016; Mahoney et al., 2011). The presence of low oxygen levels in cancer cells' surroundings restricts the efficacy of chemotherapeutic drugs and irradiation (Brahimi-Horn et al., 2001). Cells with low blood supply undergo stress conditions inducing a low transcriptional and translational rate (Probst et al., 1999). In these cells, the translational activity of the mRNA is decreased, and hence vesicular stomatitis virus controls the viral protein synthesis (Connor et al., 2004). Thus, the vesicular stomatitis virus is a potential source for the treatment of malignant tumors.

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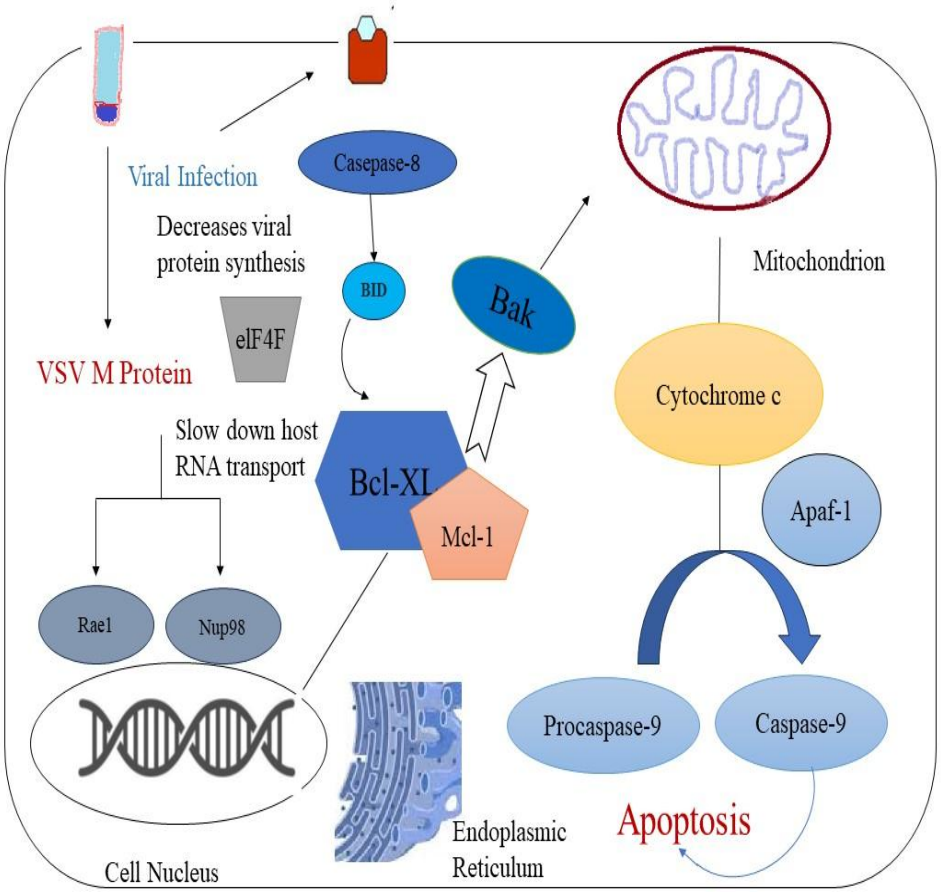

Fig2. Process of apoptosis by the vesicular stomatitis virus in the infected cancer cell. This diagram demonstrates the potential mechanisms by which vesicular stomatitis virus causes programmed cell death in the tumor cells. Apoptosis is induced by external and internal routes utilizing different molecules.

5. ADVANTAGES OF VESICULAR STOMATITIS VIRUS AS A PROMISING ONCOLYTIC VIRUS:

The following features make the vesicular stomatitis virus a good agent as an oncolytic virus to treat cancer cells: (1) deficiency of initial host immunity against vesicular stomatitis virus (2) it is a tiny and uncomplicated source to control the human genetic pool (3) the protoplasmic replication of the virus without any chances of human cells modification (4) fast reproduction of viruses in the in vitro environment aiming to generate large number of viruses (Hastie & Grdzelishvili, 2012;

Hastie et al., 2013). One of the outstanding characteristics of the vesicular stomatitis virus is that it can occupy and influence the nervous system, liver, kidney, and dermal tissues without affecting them. Vesicular stomatitis virus uses cell-mediated substances for cell proliferation such as bad cholesterol molecules, serine phosphoglycerates, and heparitin sulfate (Hastie et al., 2013). The pantropic effect of the vesicular stomatitis virus does not allow it to differentiate between normal body cells and malignant cells. Still, the comparative ability of the virus from the azygous sense organ can be advantageous. It makes the vesicular stomatitis virus a good oncolytic virus for cancer therapy. On the other hand, other oncolytic viruses experience restricted mechanisms of their receptors e.g., adenoviruses and coxsackie viruses (Pearson et al., 1999). The tumor cells' lower type I interferon-related virostatic ability is the basis of oncolytic virotherapy for the vesicular stomatitis virus. Many cancers have non-functional type I interferon communication pathways because they contain anticarcinogenic and programmed cell death-promoting responses (Wang et al., 2011). The wild-type vesicular stomatitis virus is susceptible to interferon and is easily duplicated in tumor cells. It can naturally limit interferon response through the action of M proteins of the vesicular stomatitis virus. This multi-operational M protein is confined in the nuclear membrane and controls the synthesis of mRNA molecules, obstructing the antiviral mechanism in infected host cells (Petersen et al., 2000). Thus, wild-type vesicular stomatitis virus displays actions of toxins and structural changes in the nervous system. Different genetically engineered vesicular stomatitis viruses have been developed to deal with safety concerns (Hastie & Grdzelishvili, 2012). For instance, the vesicular stomatitis virus M51 variants contain a deleted methionine gene at site 51 of the M protein. As a result, the M protein will not adhere to the Rae1-Nup98 mRNA complex required for the viral protein synthesis. All these mechanisms conclude with the inhibition of analgesic reactions in the normal affected cells but not in malignant cells (Coulon et al., 1990; Black et al., 1993).

6. MODIFICATIONS IN THE VESICULAR STOMATITIS VIRUS TO TARGET CANCER CELLS:

The anti-tumor viruses aim at malignant cells and can evade cancer tissues. They can also eliminate the agglutinin abolition and are not cytostatic. The problems of vesicular stomatitis virus as an oncolytic virus are concerned with carcinogenicity and neutralization, so new approaches are

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greatly focused on the mechanisms of the lysis of cancer cells. To carry out this process, the vesicular stomatitis virus is genetically modified by three methods (i) the viral attachment and entrance are maintained by the essential glycoprotein G alterations (ii) oncolytic virotherapy is associated with the duplication of virus cells in the cancer cells. For example, during type I interferon responses the viral M proteins are transformed and their level is controlled in the normal body cells. At the same time, they proliferate and replicate more easily in the cancer cells. (iii) Application of recombinant vesicular stomatitis virus along with monoclonal antibodies strengthens the anticancer activity of viruses. Generally, tumor conducting is a process that is accomplished by demonstrating the cancer-specific polydentate molecules on the virus membrane. The viral proteoglycan is attached to the tumor's particular receptor sites and the unknown external proteins are installed in the glycoproteins of the vesicular stomatitis virus to elevate cancer tropism (Dreja & Piechaczyk, 2006; Guibinga et al., 2004). Small-sized cyclic arginine-glycine-aspartic acid insertions can bind with the cell-mediated integrin proteins, important for the commencement, development, and spread of cancer (Desgrosellier & Cheresh, 2010). The recombinant vesicular stomatitis virus blocks the activity of integrin protein for the treatment of cancer. By modifying the genetic makeup of certain viruses, they show affinity against cancer cells (Padmashali & Andreadis, 2011). Another study suggested that if we substitute the whole viral glycoprotein with the peculiar viral proteoglycan, we can easily get a suitable treatment for the targeted tumor. Vesicular stomatitis virus is pseudotyped with the Sindbis viral glycoprotein that has an association with the human epidermal growth factor that upregulates the breast cancer cells. The resulting vesicular stomatitis virus pseudotype targets human epidermal growth factor receptor-2 express breast tumor cells. The genetically engineered vesicular stomatitis virus spots the breast cancer cells to demonstrate its oncolytic properties in human epidermal growth receptor-2. We can modify the host's immune reaction by administering artificial antibodies against cytotoxic T lymphocytes. In return, the CD4 cells obtain multiple anti-tumor antigenic sites and work with the vesicular stomatitis virus to fight against the tumor cells (Gao et al., 2012). When the receiver with human epidermal growth factor receptor 2 with cancer expression acquires CD4 lymphocytes from the donor helps in the termination of malignant cells in the recipient. Interferon-γ and interleukin-4 and 17 are chemical molecules that help in suppressing the tumor cells (Lv et al., 2023).

7. STRATEGIES TO ENHANCE THE ANTI-TUMOR ACTIVITIES OF VESICULAR STOMATITIS VIRUS:

By understanding the modifications in the recombinant vesicular stomatitis virus, the following mechanisms are adopted to escalate the cancer lytic properties of the virus:

Elevating cancer dissolution efficiency: The creation of recombinant vesicular stomatitis viruses with induced programmed cell death, biological response modification, and suicidal activities are the strategies that increase the lysis of cancer cells (D'agostino et al., 2009; Gao et al., 2009). Scientists develop recombinant vesicular stomatitis virus with the help of horse herpes virus proteoglycan G, which is considered a viral chemokine ligand-protein binding. The function of the viral chemokine binding complex is to attach to the cytokines and limit cell proliferation in the injured area. The function of immune cells is to protect the host organism but in the matter of oncolytic virus therapy, natural killer cells travel to the area of viral reproduction, aiming to remove the virus cells and have a wary effect on the cancer cells breakdown. When recombinant vesicular stomatitis virus is modified with the exuded form of viral chemokine binding proteins, then the relocation of natural killer T lymphocytes to the viral duplication spots is decreased, and a large number of cancer cells lyse in the laboratory investigational animals (Altomonte et al., 2009). Another study shows that the murine herpes gamma virus and viral matrix M protein that downregulates the inflammatory reactions was inoculated in the recombinant vesicular stomatitis virus with M serotype 51. A decreased number of neutrophils and natural killer cells proliferate in the inflammation area and were detected in the mice model of human liver cell cancer (Wu et al., 2008). Another concept was studied where recombinant vesicular stomatitis virus UL-141 is used in conjugation with the human betaherpesvirus-5 to suppress the expression of CD-155 binding protein that initiates the translocation of natural killer cells. This genetically modified virus lysed the tumor cell in a rat clone of human hepatoma.

Oncolytic Vesicular Stomatitis Virus Rendering a Suicidal Nucleic Acid: To improve the cancer necrotic activity of the vesicular stomatitis virus, it is coupled with the suicidal chromosome. For instance, herpes simplex virus thymidine kinase expresses the suicidal gene. It causes the phosphorylation of the harmless medicine cytovene which is embodied in the nucleic acid and induces cell death by blocking viral reproduction. In this context, recombinant vesicular

stomatitis virus manifesting herpes simplex virus thymidine kinase demonstrates anti-tumor virotherapy (Fernandez et al., 2002). When this recombinant vesicular stomatitis virus is complexed with cytotoxic T cells, it eliminates the malignant cells. The fusion protein of *Escherichia coli*, cytidine deaminase (suicidal gene) is used with the uracil phosphoribosyl transferase and was inoculated in the vesicular stomatitis virus to synthesize reintegration. Cytosine deaminase can remove an amino group from 5-fluorocytosine to produce a novel drug for cancer treatment (Zanna et al., 2014). Uracil phosphoribosyl transferase is an important enzyme that converts ribosyl phosphate to uracil forming 5' uridylic acid. The recombinant vesicular stomatitis virus expresses the action of cytosine deaminase and uracil phosphoribosyl transferase and produces 5-fluorouracil monophosphate. In Balb/c rats, these suicidal cassettes show a decrease in the cancer cells as compared to when treated alone with the recombinant vesicular stomatitis virus (Muik et al., 2014). Moreover, the cytidine deaminase and uracil phosphoribosyl transferase were inoculated in vesicular stomatitis virus M protein serotype 51, limiting the virus's multiplication and targeting tumor cells (Leveille et al., 2011).

Table 1: Best Recombinant Vesicular Stomatitis Virus Used for Cancer Treatment

VSV Modification	Virus Description	References
VSV-IL4	rVSV to make the cytokine IL-4 for oncology with enhanced oncolytic characteristics.	(Bishnoi et al.,2018)
VSV-IFNβ	rVSV with IFN-β gene insert demonstrates anticancer activity against metastatic lung cancer and is capable of producing a T cell immune response.	(Obuchi et al.,2003)
rVSV-UL141	rVSV encoding a protein derived from the human cytomegalovirus which lessens expression of the NK-cell activating receptor CD155 and inhibits the function of NK cells.	(Altomonte et al.,2009)

rVSV(MΔ51)-M3	rVSV encoding the murine gammaherpesvirus-68 chemokine-binding protein M3 in a replacamatric variant of matrix protein with improved tumor necrosis.	(Wu et al.,2008)
VSV-rFlt3L	rVSV encoding the Fms-like tyrosine kinase 3 ligand (rFlt3L). rFlt3L is a growth factor that stimulates the differentiation and proliferation of DC	(Shen et al.,2016)
VSV-mIFNβ-NIS	Combined with rVSV expressing IFNβ and the NIS reporter and the use of an anti-PD-L1 antibody, it exhibits a stronger anti-tumor effect.	(Taha.2024)
VSV-CD133	Enhancement of rVSV to overexpress CD133, a marker for cancer stem cells enhances rVSV specificity to CD133 positive tumors.	(Enadi.2018)
rVSV-gG	rVSV encoding equine herpes virus-1 glycoprotein G as a receptor for viral chemokine and an antiviral agent	(Eckert.2020)
VSV-IL12	Viral replicon Vector rVSV carries the murine IL-12 gene and exhibits an oncolytic effect against SCC.	(Nguyen et al.,2020)
VSV-IL15	rVSV encoding secreted trimer of human IL-15 undoubtedly stimulates both Nk cell and T cell activity.	(Mattapallil.2009)
VSV-CD40L	rVSV delivers CD40L, a cytokine of the TNF family that is upregulated on activated Th cells.	(Ryapolova et al.,2023)
VSV expressing a suicide gene		
VSV-C: U	rVSV to produce the fusion suicide gene from Escherichia coli CD/UPRT that converts 5- FC to the chemotherapeutic 5-FU.	(Porosnicu et al.,2003)

Curcumin and VSV	The combined findings of downregulation of the anti-apoptotic protein, Bcl-XL, the modification of NF-κB, and the increase in the number of virus-infected cells.	(Zhang et al.,2018)
VSV-TK	rVSV with thymidine kinase of herpes virus, enhancement of the oncolytic effect	(Muñoz-Álvarez et al.,2015)
Ruxolitinib and Polycation with VSV	Ruxolitinib and polycation enhance the adsorption and proliferation of VSV in HPAF-II cells	(Felt et al.,2017)

8. COMPREHENDING THE BIOCHEMICAL INTERACTION OF CANCER CELLS TO VESICULAR STOMATITIS VIRUS

To improve the response mechanism of the vesicular stomatitis virus against the cancer cells, it is coupled with different molecules.

Complex of Vesicular stomatitis virus with Small Determents: Pancreatic ductal adenocarcinoma in vitro cultures are resistant to recombinant vesicular stomatitis virus M serotype-51 which illustrates the activity of interferon-stimulated genes (Moerdyk-Schauwecker et al., 2013; Cataldi et al., 2015). A JAK reducer I is a molecule that inhibits the manifestation of interferon-stimulated genes and controls opposition against the vesicular stomatitis virus by activating other halt molecules and enhancing the mechanisms of other viral cell cycles. An exact mechanism was demonstrated by the JAK1/2 inhibitor because it is used to block hindrance against human neck and head tumors against vesicular stomatitis virus. TPCA-1 is an inhibitor that suppresses the expression of interferon-stimulated genes and reduces the performance of the JAK kinase enzyme. So, TPCA-1 stimulates the activity of vesicular stomatitis virus M serotype-51 and blocks the function of JAK kinase (Cataldi et al., 2015).

A mixture of Vesicular Stomatitis Virus with a Complex of Positive Charges: Some cell cultures of cancers are not sensitive to the vesicular stomatitis virus because they show anti-viral properties and interferon-liberated genes. When cells are treated with low-density lipoprotein receptor polycations, then they provide electrostatic forces to the triglyceride membrane as the viral glycoprotein and organism plasma membrane contain electrons. An innovative therapy with

a complex of cations showed that the vesicular stomatitis virus replicates faster in the tumor cells and induces lysis of cells (Felt et al., 2017).

Amalgamation of Vesicular Stomatitis Virus with Anti-cancer Narcotics: Vesicular stomatitis virus is considered best for oncolytic virotherapy as it is highly susceptible to interferon response. G2/M proteins speed up the viral duplication by decreasing the anti-viral reactions. The drug Abraxane provokes the reproduction of vesicular stomatitis virus M protein-51. Cells that express type I interferon decrease the response of interferon type I and III along with the downregulation of interferon-stimulated genes (Bressy et al., 2019). An exact mechanism is demonstrated by the FDA-confirmed drug Colcrys (Arulanandam et al., 2015).

Vesicular Stomatitis Virus Encrypting p53 Genetically Modified Genes: A p53 is a tentative gene that helps in type I immune response in healthy and malignant cells. Current studies have shown that the genetically engineered p53 gene triggers the multiplication of vesicular stomatitis virus M protein-51 in cancer cells (Hastie et al., 2015). Various reasons for existing reports demonstrate the dissimilarities in healthy body cells and several malignant cells in antiviral responses, as well as different amounts of vesicular stomatitis virus, encrypted genes discussed in the study. The vesicular stomatitis virus encoding the p53 chromosome enhances the oncoselectivity and safety of anti-tumor viruses.

Table 2: Clinical Studies and Genetic Alterations of Oncolytic Vesicular Stomatitis Virus

Preclinical Studies Using VSV as an Oncolytic Virus				
Inquiry	**Kind of Tumor**	**Template**	**Main Outcomes**	**References**
Inquiry 1	Carcinoma	Living Body (mouse)	This led to a reduction in the volume of the tumor and enhanced survival rates next to the impact of the VSV.	(Uche et al.,2021)

Inquiry 2	Grade IV astrocytoma	Artificial environment	VSV selectively and specifically infects and kills the glioblastoma without any harm to the normal cells of the body.	(Wollmann et al.,2005)
Inquiry 3	Pancreatic ductal adenocarcinoma	Living Body (mouse)	VSV presents a strong virucidal effect on cancer cells and can enhance the action of chemotherapy.	(SCHINAZI et al.,1992)
Inborn Alterations of Vesicular Stomatitis Virus for Cancer Treatment				
Amendment	**Motive**	**Consequence**		**References**
Reduction of viral matrix-M protein	Decrease nervous diseases caused by microbes	Increased protection and discrimination for malignant cells		(Danhier et al.,2010)
Positioning of interferon-β gene	Provoke innate and adaptive immune systems	Amplified anti-tumor oncolytic immune response.		(Wu et al.,2021)
Introduction of GM-CSF gene	Elevate immune cell recruitment	Enhanced overall anti-tumor immunity.		(Zhang et al.,2015)

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9. LIMITATIONS OF VESICULAR STOMATITIS VIRUS AS AN ONCOLYTIC VIRUS

A vesicular stomatitis virus is a good source of oncolysis but has many disadvantages. To enhance the anti-tumor activity of oncolytic viruses, the virus should be multiplied in a shorter period (Tang et al., 2022). This mechanism protects the host's normal cells from viral attack and infects the tumor cells. However, during this process, oncolytic viruses show mutations and restrict their reproduction in cancer cells causing damage to the healthy body cells (Howells et al., 2017). As compared to the various classes of oncolytic viruses, the vesicular stomatitis virus has a brief cell cycle where the packing of one batch of virions occurs at the same rate as the synthesis of mRNA of the second batch. Besides this, various shots of the vesicular stomatitis virus are required to control the cancer growth in the body. In an immunocompromised patient, the numerous shots of oncolytic vesicular stomatitis virus trigger the adaptive immune response of the host, limiting the suppression of oncolysis (Aurelian, 2016). The adaptive immune system of an organism exhibits antibody-mediated immunity averse to the G proteins and the production of subsequent antibodies causes the accumulation of virus particles in the liver and spleen (Kachanov et al., 2024). The elevated number of antibodies is presented to the antigen-presenting cells that stimulate the B lymphocytes, and decline the activity of the inoculated vesicular stomatitis virus. Another drawback of the oncolytic vesicular stomatitis virus is its neurotropic activity because of M and G proteins. In laboratory animals, the vesicular stomatitis virus multiplies in the brain and causes phrenitis (Van den Pol et al., 2002). We can modify M and G proteins by generating recombinant vesicular stomatitis virus.

Future Prospects and Directions: Since the vesicular stomatitis virus is an excellent tool for eliminating malignant cells, various issues still need to be addressed for future betterment. The genetic modifications in the vesicular stomatitis virus improve the safety of oncolytic virotherapy (Zhang & Nagalo, 2022). Future studies are focused on the development of oncolytic vesicular stomatitis virus in vivo to eradicate the anti-viral immune responses in the host. Vesicular stomatitis virus-luciferase is used to increase the level of viral manifestation in human investigations and the vesicular stomatitis virus is used in conjunction with the iodine isotopes to visualize the viral activity using radioactive isotopes (Naik et al., 2012). The purpose of oncolytic

virotherapy is not only to target tumor cells but also to remove malignant stem cells to avoid the reversion of the cancer. The vesicular stomatitis virus can be an ideal oncolytic virus in the future if it is not cytostatic, and can easily target particular kinds of tumors and produce memory cells (Apolonio et al., 2021). The recombinant vesicular stomatitis virus is clinically significant and their cell cultures are developed in a decontaminated laboratory. A current investigation has demonstrated that administration of the vesicular stomatitis virus-interferon β degraded the Kahler disease in immunocompromised mice (Naik et al., 2012). The future directions in oncolytic virotherapy are aimed at enhancing the oncoselelctivity and security of the vesicular stomatitis virus along with the destruction of tumor cells (Lin et al., 2023).

10. CONCLUSION

This article concludes that the ability of oncolytic virus's especially vesicular stomatitis virus can multiply and destroy tumor cells. This approach has paved the way to disclose novel therapies for cancer control. The vesicular stomatitis virus is a powerful candidate for oncolytic virotherapy that helps in altering cancer chemistry. With time, the development of recombinant vesicular stomatitis virus has helped researchers in the understanding of the mechanism of action of the virus against specific malignant cells. Oncolytic virotherapy is important for the future of cancer treatment because it includes the combination of different oncolytic viruses that target tumor cells and increase the survival rate of patients. Moreover, future studies are focused on the production of that recombinant vesicular stomatitis virus that can fight against lethal tumor cells and enhance the responsiveness of malignant cells against them.

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