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VESICULOVIRUSES AS A TOOL OF BIOTECHNOLOGY

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Vesiculoviruses are widely used in various fields of biotechnology. This article analyzes the results of published experimental works devoted to the development of oncolytic and recombinant vaccines against emergent viral infections based on vesiculoviruses. The use of genetic engineering methods makes it possible to strengthen their immunogenicity and oncolytic potential.

Aim. Analysis and summarization of available information devoted to the development of oncolytic and other vaccines based on vesiculoviruses.

Materials and methods. Publications were selected based on the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google Scholar (https://scholar.google.com/) databases published in 2010–2023. They include information on development of oncolytic and other vaccines based on vesiculoviruses.

Results. The article describes in detail the use of vesiculoviruses as a tool for creating highly active recombinant viral vaccines. These vaccines are able to protect people from emergent viral infections in various countries and may find application in anticancer therapy.

Key words: vesiculoviruses; vaccines; oncolysis.

Vesiculoviruses are a large group of rhabdoviruses that are transmitted by insects and in endemic regions infect mammals, birds and reptiles [1]. Recently, a large number of vesiculoviruses have been identified in insectivorous bats using metagenomic analysis [2, 3]. Because there is biological transmission of vesiculoviruses from blood-sucking insects to vertebrate animals, they are arboviruses.

The genomes of vesiculoviruses include linear single-stranded RNA of negative polarity with a size of 10.7–11.3 kb, which contains 5 genes (*N, P, M, G* and *L*) encoding structural proteins. The genome structure and reproduction of vesiculoviruses have been studied in detail using the vesicular stomatitis virus (VSV) model. The leading part of the VSV genome includes 47 nucleotides, the trailing part — 57–59. Genes of structural proteins of all vesiculoviruses are located in the following order: 3′-*N-P-M-G-L*-5′ [1, 3]. Due to the relatively small genome (about 11 kb), the ability to insert small (4–5 kb) foreign genes into it, and accumulation *in vitro* in large quantities, VSV is widely used as a tool of biotechnology, especially as platforms for the creation of recombinant antiviral vaccines [4–6]. This opportunity appeared after the VSV was completely recovered from a full-length cDNA clone of the viral genome in the USA [7]. Currently, there are two types of recombinant VSV (rVSV) viruses that are widely used as biotechnological tools — replication competent and replication incompetent [8]. The latter usually have a genome in which the VSV *G* gene has been deleted (VSVΔG) and replaced by a gene encoding a fluorescent or luminescent reporter (Fig. 1).

Since the genomes of such rVSV do not contain a glycoprotein gene, the viruses are able to replicate only during one round. Conversely, replication-competent rVSV have genomes in which the *G* gene is replaced by a heterologous glycoprotein gene, thus forming a pseudotyped virus capable of several rounds of replication. As vectors for the creation of highly effective vaccines for the prevention of viral diseases of humans and animals, recombinant VSV are used in many laboratories of different countries. One of the advantages

Fig. 1. **Replicationally incompetent recombinant viruses based on the VSV.** *N*, *P*, *M*, *L* — genes of structural proteins; GFP — green fluorescent protein; NIV-G — Nipah virus glycoprotein [8]

of such use is the reproduction of VSV in the cytoplasm, thus eliminating the threat of integration of viral sequences into the genome of the recipient. Usually, such highly effective vectors based on rVSV are intended to protect the population from highly pathogenic viruses. Genetic engineering work on the creation of recombinant vaccines for the prevention of highly pathogenic viruses for humans (Ebola, Zika, Marburg, etc.) is allowed only in laboratories with a BSL-2 level of protection [8]. Below are examples of such application of recombinant viruses based on rVSV.

Recombinant virus vaccines based on VSV

Ebola vaccine. A recombinant vaccine based on VSV was created at Yale University (USA). The viral glycoprotein G of the VSV is replaced in this vaccine by the glycoprotein of the Ebola filovirus (EBOV) (Fig. 2). This vaccine was named VSV-EBOV [8, 9].

It does not affect the health of animals and effectively (100%) protects mice from the strain of the Ebola virus adapted to them (MA — EBOV). Similarly, it protects guinea pigs and macaques [10]. Preclinical studies of this vaccine in mice have shown that it effectively protects them against a lethal dose of the Ebola virus, even at very low doses, such as 2 IU and when administered 24 hours before infection. Rhesus macaque VSV-EBOV vaccine protects even when vaccinated 25–30 min before infection [11]. All three required phases (I–III) human clinical trials of the VSV-EBOV vaccine were conducted after the 2013–2016 outbreaks of human Ebola hemorrhagic fever in West Africa [12]. Based on multiple clinical trials, in 2019 this EBV-based Ebola vaccine was licensed in the US by the Food and Drug Administration (FDA) and is being distributed by Merck under the new brand name "Ervebo" [13, 14]. The European Medicines Agency (EMA) also found the evidence of its safety and effectiveness to be quite convincing.

Vaccine against the Marburg virus. Marburg filovirus causes an acute infection of humans, which is characterized by a severe course, generalized damage to blood vessels with the development of hemorrhagic syndrome, damage to the liver, digestive system and central nervous system. A vaccine based on recombinant VSV was created by the joint efforts of Canadian, French and German scientists [15]. As in the Ervebo vaccine, the glycoprotein G of the VSV was replaced with the glycoprotein of the Marburg virus (MARV). The VSV-MARV vaccine protects macaques even after its administration 20–30 minutes after infection with a lethal dose of the Marburg virus (Musoke variant). Other variants of this virus were less effective. The vaccine is not yet registered, clinical trials are underway.

Lassa virus vaccine. Lassa virus (LASV) belongs to the *Arenaviridae* family and causes a highly pathogenic disease called Lassa fever in West Africa. A vaccine based on rVSV against this virus was named rVSVΔG/LASVGPC [15, 16]. As in the other vaccines described above, the glycoprotein G of the VSV is replaced by the glycoprotein G of LASV. The vaccine effectively protects laboratory animals under experimental conditions, but clinical studies have not yet been completed.

The Zika virus vaccine. An experimental vaccine against the highly pathogenic Zika flavivirus (ZIKV) was created in 2018 in the USA on the VSV-EBOV vaccine platform [17], into which the viral envelope protein gene of ZIKV was integrated. This recombinant vaccine, called VSV-ZIKVprMsolE, provides

Fig. 2. **Replication-competent recombinant viruses based on VSV [8]**

100% protection in mice when immunized 28 days before a lethal dose of ZIKV. Mice immunized with this vaccine were also protected against an adapted to them EBOV infection. In another vaccine, in contrast to the removal of glycoprotein G of the VSV, a method of weakening the enzymatic activity of protein L methyltransferase was used [18]. Methyltransferase-defective recombinant VSV, which contained the ZIKV pre-membrane protein and NS1 protein, also protects mice from ZIKV infection.

Vaccines against coronaviruses. Vaccines based on VSV have been developed to protect people against various coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV-2). In these vaccines, the recombinant VSV expressed the spike protein of the SARS-CoV and SARS-CoV-2 viruses alongside the glycoprotein G of the VSV. These vaccines stimulate the development of virus-neutralizing antibodies in mice and protect them from coronaviruses within 4 months after infection [19]. Clinical trials of these vaccines in 2021 were in phase 1/2. Recently, on the basis of the VSV in the USA a VSV-SARS-2(+G) vaccine was developed for the prevention of coronavirus infection, which has a number of advantages over known vaccines, including enhanced immunogenicity, and is administered orally [20].

Oncolytic potential of vesiculoviruses

Animal vesiculoviruses (family *Rhabdoviridae*), especially those that are not pathogenic for humans, have attracted much attention of researchers in recent years. The first report on the ability of rhabdoviruses to inhibit the development of tumors was published in Italy at the beginning of the 20th century. De Pace [25] observed tumor regression after inoculation of an attenuated rabies vaccine in a patient with cervical cancer. Another patient with metastatic melanoma who was vaccinated against rabies after a dog bite also had a prolonged remission [26]. Among animal rhabdoviruses, the largest number of works on oncolysis was performed on the model of representatives of the genus *Vesiculovirus*, such as VSV, Maraba, Morreton, and Jurona [27–31]. Other animal rhabdoviruses, such as Bahia Grande (BGV) and Muir Springs (MSV) baraviruses, also have oncolytic properties [32].

Vesicular stomatitis virus. VSV is a promising oncolytic virus due to its inherent ability to reproduce mainly in cancer cells and the lack of immunity against this virus in humans [33, 34]. VSV has been shown to be highly effective against malignant glioma, melanoma, hepatocellular carcinoma, certain leukemias, breast adenocarcinoma, and prostate tumors [35–37]. Some of the most widely used oncolytic VSVs are recombinants carrying a deletion of the M protein (M-ΔM51) or a substitution (M51R) of methionine at the 51st amino acid residue. These mutations weaken the replication of VSV in normal cells, preventing M protein from inhibiting the release of mRNA from the cell nucleus, including transcripts of virus-induced antiviral genes. As a result, unlike wild-type VSV, M51R VSV mutants have significantly attenuated neurotoxicity, but retain strong oncolytic potential [38]. Since VSV has a wide tropism, experimental vaccines based on it are able to cause neurotoxic manifestations in mice and rhesus macaques [39]. To improve the safety of vaccines against VSV, the interferon beta (IFNb) gene was introduced into its genome [40]. This improved its safety and made it possible to proceed to the second phase of clinical trials. Another obstacle to VSV therapy is the humoral immunity that occurs after therapeutic administration of the virus, because the virus-neutralizing antibodies produced mainly target the viral glycoprotein G [41]. These neutralizing antibodies can nullify the effectiveness of repeated injections of the virus [42].

In the laboratory of Prof. Spivak M.Ya. (Zabolotny Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine) the ability of VSV to inhibit the development of experimentally induced tumors in the Kalanchoe plant was also shown. When plant tumors induced by the bacterium *Agrobacterium tumefaciens* were incubated with the vesicular stomatitis virus, tumor regression was noted by 74.5% [43]. They also showed the effect of buckwheat blight rhabdovirus on Sarcoma 37 cells — apoptotic bodies were observed in 90% of cells under the influence of the virus [44].

Maraba virus. Oncolytic Maraba virus was first isolated from mosquitoes in the Brazilian Amazon River Basin [45]. Maraba virus, like VSV, belongs to the vesiculovirus family, but it has some genetic differences from it [32]. Maraba virus is not pathogenic for humans. In the USA, studies of this vesiculovirus were conducted on the NCI-

60 panel, which contains 60 different cell cultures obtained from cancer patients. As a result of complex studies, it was established that among the 26 rhabdoviruses studied in this panel, the Maraba virus showed oncolytic potential most effectively — it showed oncolytic activity in almost all cells [32, 46]. This ability of this virus is due to the presence of low-density lipoprotein receptors (LDL receptors) in many human cells. In cancer cells with reduced expression of LDL, the penetration of Maraba virus into cells is very rare [47].

To enhance the oncolytic properties of the Maraba virus, two mutations were introduced into its genome using genetic engineering methods, which translated into L123W and Q242R substitutions in the sequence of the M and G proteins, respectively [29]. Such a strain of the Marabo virus was named MG1. Compared to wild-type (wt) and other mutant strains of Maraba virus, it has faster replication and increased ability to kill tumor cells. In addition, in immunocompetent mice, the maximum tolerated dose (MTD) after intravenous administration of MG1 reached the value of 10^9 plaque-forming units (PFU), which is 2 orders of magnitude higher than that of the parental Maraba virus. The oncolytic activity of MG1 has been demonstrated in xenograft models using human cancer cell lines or patient-derived tumors implanted into immunodeficient mice [48].

An interesting fact has been established that the therapeutic efficacy of MG1 largely depends on the ability of large doses of this virus to induce antitumor immunity independent of its replication [49]. Both the parental virus and the replication-incompetent minimally UV-inactivated MG1 showed good results in the treatment of lung metastases in mice under the conditions of high doses of UV-treated virus. Doses of irradiated UV viruses less than 10^8 PFU were not effective.

Experimental data accumulated over the past few years have shown that the antitumor effectiveness of oncolytic viruses depends not only on their direct oncolysis, but may also depend on their ability to stimulate antitumor immunity. According to various estimates, 65–70% of cancer cell lines have defects in interferon (IFN) synthesis [50]. The oncolytic Maraba virus MG1 vaccine has shown a potent ability to enhance pre-existing tumor-specific CD4+ and CD8+ T-cell immunity. When used to treat a syngeneic murine melanoma tumor model, immunization of mice with the MG1 strain resulted in a sharp increase in median survival with complete remission in more than 20% of vaccine-treated animals. MG1 stimulates both innate and adaptive branches of antitumor immunity. Effective immunization occurs using both MG1 itself and in the "prime-boost" mode using adenovirus (the prime-boost mode is when the first component starts the immune response (prime), and the second one accelerates and strengthens it (boost).

Morreton virus. Morreton virus (MorV), like VSV, belongs to the vesiculovirus family. The virus was first isolated in Colombia from mosquitoes [51]. Although antibodies to this virus were found in the blood sera of people and animals in places where mosquitoes spread, this virus does not cause any symptoms of diseases in people and animals. The oncolytic properties of MorV were established experimentally in the USA on a hepatocellular carcinoma (HCC) cell culture model [30].

Intranasal administration of MorV to mice with syngeneic liver cancer at a dose of 1×10^7 $TCID_{50}$ induced a stable cytotoxic T-cell antitumor immune response, which over time resulted in significant tumor regression and disease control in mice in a syngeneic HCC model. VSV also induced tumor regression in model systems, but at much higher (tenfold) doses. In addition, VSV exhibits cytotoxic and hepatotoxic effects in mice and rhesus macaques [30]. Therefore, given the lack of cytotoxic and hepatotoxic effects of MorV in experiments on animals, this vesiculovirus is the most promising for creating an oncolytic vaccine based on it.

With the help of genetic engineering methods, a chimeric virus was created based on the two aforementioned vesiculoviruses, which combined the capabilities of a wider range of VSV hosts and the safe properties of MorV, due to the peculiarities of the structure of glycoprotein G of this rhabdovirus [42]. The virus strain obtained in this way is designated as VMG. This chimeric vesiculovirus causes oncolysis in multiple sarcoma-derived cell lines.

Jurona virus. Jurona virus (JURV) was isolated in the USA from birds during monitoring studies of arboviruses [52]. It also belongs to the vesiculovirus family. Like MorV, Jurona virus exhibits oncolytic properties and does not cause cytotoxicity or hepatotoxicity in mice [31].

Thus, highly active recombinant vaccines have been created on the platform of vesiculoviruses, which are able to protect people from emergent viral infections and will be useful in anticancer therapy.

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Conflict of Interest

Authors declare that there is no conflict of interest.

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ВЕЗИКУЛОВІРУСИ ЯК ІНСТРУМЕНТ БІОТЕХНОЛОГІЙ

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Проведено аналіз результатів опублікованих експериментальних робіт, присвячених розробленню онколітичних та рекомбінантних вакцин проти емерджентних вірусних інфекцій на основі везикуловірусів. Застосування методів генетичної інженерії дозволяє підсилювати їхню імуногенність та онколітичний потенціал.

Мета: аналіз та узагальнення наявної інформації, присвяченої розробленням онколітичних та рекомбінантних вакцин проти емерджентних вірусних інфекцій на основі везикуловірусів.

Матеріали та методи. Підбір публікацій виконано за базами даних PubMed (https://pubmed.ncbi.nlm.nih.gov/) та Google Scholar (https://scholar.google.com/) опублікованих у 2010–2023 рр. У них висвітлено відомості про розроблення онколітичних та інших вакцин на основі везикуловірусів.

Результати. Детально описано застосування везикуловірусів як інструменту для створення вакцин. На платформі везикуловірусів створено високоактивні рекомбінантні вакцини, які здатні захищати людей від емерджентних вірусних інфекцій та будуть корисними в антираковій терапії.

Ключові слова: везикуловіруси, онколізис, рекомбінантні вакцини.