RECOMBINANT ADENO-ASSOCIATED VIRUSES AS A GENE DELIVERY VEHICLE FOR THE USE IN MOLECULAR MEDICINE

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Prospects of using oncolytic viruses in breast cancer therapy

Breast cancer (BC) is a cancer with a high prevalence and mortality among women worldwide. With the current diagnostics methods, BC may remain undetected at its early stages, and the therapies developed for the disease are associated with severe side effects. Oncolytic viruses can be the basis of the new, effective BC treatment approaches. The viruses destroy tumor cells directly and launch the antitumor immune response; this dual action supports their efficacy. It is possible to make the oncolytic virus therapy more effective by designing genetically modified viruses that can target BC cells better and/or induce a stronger antitumor immune response. This review outlines the directions of development of oncolytic viruses in BC treatment, covers the optimal ways of delivering viruses to the tumor and the efficacy of their use in combination with other therapeutic agents (methods) and presents the prospects of using oncolytic viruses in antitumor vaccines.

Keywords: oncolytic viruses, breast cancer, viral vector, chemotherapy, estrogen receptors

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ПЕРСПЕКТИВЫ ТЕРАПИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ С ИСПОЛЬЗОВАНИЕМ ОНКОЛИТИЧЕСКИХ ВИРУСОВ

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Рак молочной железы (РМЖ) — онкологическое заболевание с высокой распространенностью и смертностью среди женщин во всем мире. Диагностика РМЖ не столь эффективна для выявления заболевания на ранних стадиях, а терапевтические методы связаны с тяжелыми побочными эффектами. Онколитические вирусы могут стать новым эффективным средством в терапии РМЖ. Их эффективность обусловлена двумя типами воздействия на раковую опухоль: непосредственным уничтожением опухолевых клеток и запуском противоопухолевого иммунного ответа. Повысить эффективность терапии онколитическими вирусами можно путем конструирования генетически-модифицированных вирусов, обладающих лучшей селективностью к опухолевым клеткам молочной железы и (или) способных к большему усилению противоопухолевого иммунного ответа. Представлены дальнейшие направления применения онколитических вирусов в терапии РМЖ, оптимальные пути доставки вирусов в опухоль и эффективность их использования в комбинации с другими терапевтическими средствами (методами), а также перспектива использования онколитических вирусов в качестве противоопухолевых вакцин.

Ключевые слова: онколитические вирусы, рак молочной железы, вирусный вектор, химиотерапия, эстрогеновые рецепторы

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Breast cancer (BC) is the most common type of malignancy in women [1]. In Russia, the incidence of breast cancer has doubled over 15 years; about 50 thousand new patients with this diagnosis are registered annually [2]. Over 40% of women are diagnosed with BC when the tumor is already at its later stages of development, which adds to the complexity of treatment of this disease [2]. It should also be noted that BC is a group of heterogeneous diseases with different molecular mechanisms of development and cellular origins, which further complicates its diagnosing and treatment [3]. Breast cancer is distinguished by high mortality rates: in 2020, 685 BC fatalities were recorded in the world [4].

The main types of treatment for breast cancer are surgery, chemotherapy, radiation, hormonal and targeted therapies [5]. Hormonal and targeted therapy drugs have better safety profiles, but they are also not without side effects and cannot be used as the only BC treatment method. The effects of other anticancer therapies on the body are more severe. For example, radiation can damage lymphatic vessels close to the chest, causing lymphedema [6]. Breast removal surgery (mastectomy) can adversely affect mental and emotional state of the patients [7]. Chemotherapeutic drugs cause the most massive negative consequences: they are systemic and have effect not only on the cancer cells but also on the rapidly dividing normal cells of the body [8].

Severity and prevalence of the disease, as well as the negative side effects of the existing types of treatment, make the task of developing new groups of anti-BC drugs urgent. Drugs based on oncolytic viruses can form one of such groups. Both naturally occurring and genetically engineered, these viruses can specifically target tumors without harming healthy cells [9]. The investigation of possibilities of using oncolytic viruses as therapeutic agents is a fairly new field of research, yet it is already an intensively developing one. The amount of research and development efforts in this sphere has increased noticeably: from 2015 to 2020, the number of publications returned by PubMed for the "oncolytic viruses" query has grown from 276 to 457, that for the "oncolytic viruses for breast cancer" query — from 11 to 28. Every year, there are more papers published on the subject. This review presents an analysis of the possibilities of using oncolytic viruses as a platform for drugs against BC. The review describes the mechanisms of action of oncolytic

viruses, approaches to increasing the selectivity of their action and enhancing the antitumor effects they trigger. The directions of development of oncolytic therapy are also outlined.

Breast cancer subtypes and their pathogenesis mechanisms

Breast cancers constitute a group of diseases heterogeneous by both phenotypic and genetic characteristics [10]. BC is classified by histological origins, stages of development, properties of pathological lesions and types of oncogenic markers [10, 11]. Based on the expression of such dominant oncogenes as estrogen receptor (ER), progesterone receptor (PR), epidermal growth factor receptor 2 (HER2) and ki 67 proliferation marker, there are four molecular subtypes of breast cancer distinguished: luminal A, luminal B, HER2 positive and triple negative (Table 1) [10].

Using the statistical data from different countries, we will consider the incidence and mortality rate for each subtype of BC. The most common subtype of BC is luminal A. Its incidence is 50–60%, and it is the most survivable BC subtype: within 3 years from the diagnosis, 95–100% of luminal A BC patients survive the disease [12, 13]. Other subtypes of cancer have a more even incidence of 10–15% [14]. The most dangerous subtype is the triple negative BC: within 3-4 years from the diagnosis, the average patient survival rate is 75–80% [13].

Oncological diseases develop against the background of proliferation, apoptosis, and cell migration mechanisms malfunctioning on the epigenetic and genetic levels [10]. Identification of the signaling pathways that determine pathogenesis of specific cancer subtypes enables deduction of new targets for targeted therapy.

One of the main mechanisms of BC development that is registered in about 70% of cases has estrogen receptors involved in the signaling pathway [15]. It should be noted that there are two types of estrogen receptors: ERα and ERβ. With BC, the expression of ERα is often increased and that of ERβ, contrarily, decreased [10]. Typically, when this pathway is activated, after ERα and estrogen binding the resulting complex dimerizes and interacts with coregulator proteins and specific regions of DNA, the estrogen response elements (ERE). These interactions shape the transcription of a number of genes that regulate the cell cycle, apoptosis, DNA replication, cell differentiation and angiogenesis [15]. Thus, additional activation of the ER pathway stimulates transcription of the cyclin D1 gene, which supports subsequent activation of the CDK 4/6 kinase and transition of the cell from G1 phase to S phase [15]. Increased expression of cyclin D1 is one of the signs of the early pathogenesis of BC and some other malignant tumors [15].

Another important mechanism in the BC pathogenesis is the signaling pathway through HER2, which is a tyrosine kinase [16]. After HER2 and ligand binding and dimerization of the resulting complex there occurs phosphorylation of tyrosine residues of the enzyme's intracellular domain, which leads to the activation of several signaling pathways, such as Ras/MAPK and PI3K/AKT, that triggers cell proliferation acceleration [10].

Cancer treatment with oncolytic viruses: the underlying mechanism

Cancer therapy relying on oncolytic viruses is a fairly new field of research. To date, only one drug based on an oncolytic virus has been made commercially available: Talimogene laherparepvec, which is used to treat melanoma [17]. Some similar drugs are at the clinical trials stage currently. If they are successfully through these trials, there will appear a new niche of anticancer drugs. According to clinicaltrials.gov [18], 12 anti-BC drugs based on oncolytic viruses are undergoing clinical trials today (Table 2). The priority subtype for the researchers is the triple negative BC, the choice probably supported by its high molecular heterogeneity, lack key receptors that can be used in targeted therapy, and the highest mortality among the molecular subtypes of BC. It is also worth noting that most clinical trials have the oncolytic viruses combined with other anticancer therapy options in order to increase treatment efficacy. In addition, many oncolytic viruses are genetically engineered for the same purpose of increasing their efficacy (see Table 2); such efforts are described in the next section.

Oncolytic viruses have a number of useful traits: the resistance to drugs based on them is typically low, they are highly selective in targeting tumor cells, relatively non-pathogenic, capable of replicating in the tumor and thus increasing the dose in action [19]. The viruses used in oncology are those with the efficacy proven in vector vaccines and easily modified genetically [20]. The list of such viruses includes double-stranded DNA viruses (adenoviruses, herpes simplex virus, vaccinia virus), double-stranded RNA viruses (reoviruses), single-stranded (+)-RNA viruses (picornaviruses), single-stranded (-)-RNA viruses (measles virus, viscular stomatitis virus, Maraba virus) [20].

From the point of view of action, oncolytic viruses can selectively damage cancer cells and foster development of antitumor immunity [21]. The overall therapeutic effect depends on the interaction of the virus, the immune system, and the tumor [21]. It is important that the immune response is triggered after the virus enters cancer cells and replicates: in this case, the virus has time to destroy the infected population of cancer cells and cause inflammation in the tumor microenvironment. When the immune cells bind to the virions before interaction with the tumor, therapy fails. Cell carriers and pegylated nanoparticles can help protect the virus from premature neutralization by the immune system [22, 23]. In addition to the time of activation of the immune response, efficacy of oncolytic virus therapy also depends on the type of cancer cells, their sensitivity to the given virus and the structure of the tumor, including the degree of its vascularization that determines the rate of leukocyte inflow, as well as the presence of resident macrophages and the level of expression of tumor markers [19].

There are several factors that influence selective damage to the tumor cells. The first and the most important one is the enhanced tropism of a specific virus to a specific type of tumor cell, which is determined by the affinity of the cell receptor and the virus surface antigen [21]. As a result of the receptor-mediated interaction, the virus enters the cell. Engineered

Table 1. Classification of BC subtypes by molecular oncogenes

Type	Oncogenes
Luminal A	ER^+, PR^+, $HER2^-$, low Ki67
Luminal B	ER^+, PR^+, $HER2^±$, high Ki67
HER2	ER^-, PR^-, $HER2^+$
Triple negative	ER^-, PR^-, $HER2^-$

Table 2. Current clinical trials of drugs based on oncolytic viruses and designed for BC treatment

Drug, therapy	Molecular biological subtype of BC	Stage	ClinicalTrials.gov identifier
Radiation therapy and adenoviral vector expressing herpes simplex virus thymidine kinase	Triple negative	2	NCT03004183
Pelareorep (unmodified human reovirus)	Triple negative	2	NCT04445844
Talimogene laherparepvec (modified herpes simplex virus) and paclitaxel (chemotherapy)	Triple negative	1, 2	NCT02779855
Talimogene laherparepvec in combination with monoclonal antibodies	HER2– and triple negative	1	NCT04185311
Vaccinia virus and pembrolizumab	Triple negative	1, 2	NCT04301011
Pelareorep in combination with paclitaxel and avelumab	Luminal A	2	NCT04215146
Pelareorep in combination with letrozole, atezolizumab, and trastuzumab	All types	1	NCT04102618
HER2-specific CAR-T cells combined with CAdVEC (genetically engineered adenovirus carrying genes of immunity modulating proteins)	HER2	1	NCT03740256
Modified measles virus MV-s-NAP expressing neutrophil activating protein (NAP) Helicobacter pylori (MV-s-NAP)	Not specified	1	NCT04521764
Edmonston strain measles virus genetically modified to express human thyroid sodium iodide symporter (NIS)	$HER2^-$, $HER2^+$	1	NCT01846091
Vaccinia virus encoding human CTLA4-specific antibody 4-E03 IgG1 in combination with pembrolizumab	Triple negative	1, 2	NCT04725331
Recombinant herpes simplex virus in combination with pembrolizumab	Triple negative	1	NCT04348916

pseudotyped viruses have the selectivity enhanced even further: they carry surface antigens of another virus or non-viral ligands with increased affinity to tumor-specific receptors [24]. Besides, the rapid division and accelerated metabolism of tumor cells allows the virus to replicate actively [21]. An additional factor is the disruption of the type I interferon signaling process, which has an antiviral effect. This disruption protects the virus from premature clearance by immune cells [9]. The efficacy can also be increased through direct intratumoral administration of high concentrations of oncolytic viruses [21].

As indicated above, drugs based on oncolytic viruses do not only damage tumor cells directly but also activate the body's antitumor response. In the bloodstream, viral particles can be captured by antibodies and antigen-presenting cells (APCs) before penetrating the tumor cells, which translates into higher antiviral immunity but inhibited antitumor immune response [25]. After the oncolytic virus enters the tumor cell, the viral cycle starts. The final stage of this cycle involves formation of many copies of the virions that, through lysis, leave the cell and thus destroy it and infect the nearby cells. The damaged cells fill the intercellular environment with a large number of DAMP (damage-associated molecular pattern) molecules, which trigger non-infectious inflammation and, consequently, an inflammatory reaction that involves attraction of NK cells and macrophages into the tumor microenvironment. Capture of a tumor-associated antigen (TAA) and its presentation to the lymphocytes by APCs triggers adaptive immunity, predominantly - cytotoxic immune response. The development of the antitumor response is further stimulated by the secretion of viral proteins released into the focus of inflammation [19].

Approaches to using oncolytic viruses in breast cancer therapy

Enhanced selectivity of oncolytic viruses for breast cancer cells

To make oncolytic therapy more safe and effective, it is necessary to enhance viral vector's selectivity for cancer cells, breast tumor cells in particular. There are two ways to achieve this goal: through inducing specific binding of the virus surface antigen to the tumor cell receptor and through enabling selective replication of the virus only in tumor cells by extending the genome with a promoter vector that activates upon binding to specific tumor markers [26]. Both approaches had the Ad5 adenoviral vector with chimeric fiber surface protein derived from serotypes Ad5 and Ad3, which improved its tropism, and tissue-specific promoters regulating the expression of protein E1A, which enables viral replication, so that the virus replicated in $CD44^+$ $CD24^-$ /low cell population, the BC stem cells [27].

Viral antigen may be modified not only through insertion of the antigen of another virus with a greater affinity for tumor cells but also by introduction of other ligands for the receptors of tumor cells. For example, the adenovirus fiber protein was modified by insertion of the Lyp-1 peptide, the receptor of which, the p32 protein, is overexpressed in BC cells [28]. The thus engineered oncolytic virus was injected into immunocompetent mice and suppressed tumor growth and slowed down metastasis in them. Another noteworthy effort had the herpes simplex virus tropism genetically altered, retargeting it to $HER2^+$ cells through insertion of a synthetic single-chain anti-HER2 antibody (which served as a ligand) into the gD domain of the herpes simplex virus glycoprotein [29].

It seems promising to modify oncolytic viruses by introducing tumor suppressor sequences or their binding sites into the viral vector genome, thus not only improving selectivity but also enhancing the antitumor effect. In such a way, Ad5 was genetically engineered to enable its selective replication in breast tumor cells: the modification involved introduction of binding sites for miR-145, a tumor suppressor the concentration of which is reduced in tumor cells, into the adenoviral vector genome [30]. As a result, high titers of the virus were registered in the breast tumor cell lines MDA-MB-453, BT-20, and MCF-7, while the normal mammary epithelial cells exhibited a decreased level of HMEpC lines. In another study, a tumor suppressor sequence of the KISS1 gene was inserted into the adenoviral vector genome [31]. The expression of KISS1 resulted in a stronger cytotoxic effect of the virus on breast

tumor cells in combination with the lytic effect of the adenoviral vector.

Antitumor response enhancing through modification of oncolytic viruses

In addition to the direct destruction of cancer cells, oncolytic viruses promote development of the antitumor immune response. This response, as manifesting in the tumor microenvironment in particular, can be further enhanced through introduction of the immunomodulatory proteins into the gene sequences of the virus. In this case, the virus itself acts as a kind of "leukocyte." There are several studies that prove efficacy of this technique. One of them employed mice; the researchers have shown that herpes simplex virus and Newcastle disease virus extended with the IL12 transgene, a proinflammatory cytokine that plays an important role in initiating the antitumor response, can inhibit growth of the tumor [32]. A recombinant adenovirus carrying the IL15 gene, which encodes the cytokine activating proliferation of the natural killer cells and CD8+ T lymphocytes, was also shown to possess the capacity to inhibit BC cells [33]. Antitumor efficacy was also revealed in the oncolytic vaccinia virus the genome of which was extended with the GM-CSF cytokine gene. Analysis of the immune profile of a mouse model showed an increased infiltration of CD8+ T-lymphocytes into the tumor microenvironment, which proves the immunomodulatory effect of this oncolytic virus [34].

In addition to the general inflammation induction through cytokine synthesis, oncolytic viruses, through production of antibodies, can be given specific targets that enable tumor development. Thus, there was engineered an adenoviral vector that contains the sequence of a full-length anti-HER2 antibody [35]. The virus has shown high antitumor efficacy against HER2-positive BC in cell and mouse models. Adenovirus produced antibodies to the HER2 tumor marker, thus reinforcing antibody-dependent cellular cytotoxicity and making the destruction of cancer cells more effective. In another work, the vaccinia virus was modified with a gene encoding the antibody against vascular endothelial growth factor, VEGF (an angiogenesis regulator that promotes tumor growth) [36]. The engineered virus showed oncolytic and antiangiogenic activity in the triple negative BC xenografts implanted in mice.

BC oncolytic therapy: further development directions

Delivery of viral vectors

To prevent neutralization by antibodies, accumulation in other organs and premature elimination of viral particles, it is important to find the optimal method of delivery of oncolytic viruses to the tumor. The simplest one that mitigates these problems is direct intratumoral injection [37]. For localized and initially local forms of BC, this is the presumably preferred delivery method since the tumor is accessible for injection. However, if there are metastatic lesions, more complex methods of delivery may be required: administration of the viruses together with immunomodulators, use of liposomes and cells as carriers [37]. In a mouse model study, researchers have shown that oncolytic therapy is highly effective when viral vectors are delivered to BC metastatic lesions with the help of dendritic cells [38].

Oncolytic viruses as vaccines

Oncolytic viruses themselves can act as immunomodulatory agents that enhance antitumor immunity. One of the possible strategies is to use an oncolytic virus as a vaccine: a tumor antigen gene is inserted into the virus genome, and when the virus enters the cell, it boosts antigen expression, which increases the likelihood of initiation and enhancement of the antitumor response [26]. This approach has the oncolytic virus acting as a kind of bait for immune cells. In a mouse with ovarian cancer, it was shown that administration of the Maraba virus carrying a tumor antigen caused an increase in the $CD8^+$ antitumor immune response [39]. Accordingly, it is possible to design viral vectors carrying ER, PR and HER2 tumor markers, which will allow targeting the immune response to a specific subtype of BC. Triple negative BC requires special attention as the subtype for which specific tumor markers need to be found. An even more specific triggering of the antitumor immune response is possible with a combination of CAR-T cell therapy (using T-cells carrying chimeric receptors for tumor antigens) and oncolytic viruses delivering the antigenic target for CAR-T lymphocytes [26].

Combination with other therapies

Potentially, the use of oncolytic viruses in combination with other BC treatments may have a synergistic effect. In addition, oncolytic viruses administered as part of a chemotherapeutic protocol often allow reducing the dose of the chemotherapeutic agent, which helps alleviate the severe side effects peculiar to chemotherapy [40]. Most likely, chemotherapy drugs do not have a negative effect on the virus itself. In a mouse model study, it was shown that paclitaxel does not affect the infectious and replicative abilities of the oncolytic virus, and their combined antitumor effect on BC cells was synergistic [41]. According to the results of the second phase of clinical trials, the combined oncolytic reovirus and paclitaxel therapy increased the overall life expectancy in patients with metastatic BC compared to the group taking only paclitaxel [42]. Viruses may also have a synergistic effect with radiation therapy, as was shown in a preclinical study dedicated to the development of a melanoma treatment protocol [43]. Unfortunately, there are no similar studies assessing the effect on BC, but it is assumed that the efficacy of such therapy will be comparable to the results of treatment of other types of tumors. The mechanism underlying the effect has not been identified, however, viruses can interfere with DNA repair after radiation therapy thus promoting a more rapid death of tumor cells [44]. The current direction of therapy is the use of oncolytic viruses in conjunction with monoclonal antibodies. In a phase one clinical trial, some patients exhibited a clinical response with the formation of a pool of reactive $CD8^+$ T cells when solid tumors were treated with vaccinia virus p53MVA in combination with pembrolizumab [45]. In a phase two clinical trial, a combination of Talimogen Lagerparepvec and pembrolizumab proved to have antitumor properties in treatment of sarcoma [46].

CONCLUSION

Oncolytic viruses are a promising platform for BC drugs. Their efficacy is backed by the dual effect they have on a tumor: the lysis of tumor cells — the effector action and the launch (enhancement) of the antitumor immune response — the immunomodulatory action. The effector action can be enhanced by improving the selectivity of the oncolytic virus to BC tumor cells. The immunomodulatory action of the virus can also be enhanced by introducing genes of the immune system proteins into the genome of the virus. Further considerations about the use of oncolytic viruses in the treatment of BC are

related to the methods of delivery of viral particles into the tumor, viral vectors as carriers of tumor antigens accelerating initiation of the antitumor response, and the use of oncolytic viruses in combination with other methods of treatment. However, making the developments in this field practical still requires a significant amount of time, since it is necessary to accumulate a certain amount of evidence on the effectiveness of this approach. Thus, oncolytic viruses are potentially effective and flexible therapeutic tools that may become the basis for a new group of anticancer drugs in the future.

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