Journal of Biomedical Sciences | ISSN: 2960-9356
Research Article Peer-review, Open Access

Modulation of the Tumor Microenvironment and Immune Response by Oncolytic Viruses in Breast Cancer Immunotherapy

Ani Zhamutashvili [1]

Nino Kemashvili [2]

Luiza Gabunia [3]

Shorena Khetsuriani [4]

Natia Gamkrelidze [5]

Giorgi Varazi [6]

Abstract: The rapid advancement of molecular biotechnology has allowed for the development of novel immunotherapies for cancer. Oncolytic viruses represent a new and exciting approach to cancer treatment. They are genetically modified or naturally occurring viruses that alter the tumor microenvironment and synergize with other anticancer therapies. They selectively affect tumors in multiple ways, not only by directly destroying cancer cells but also by triggering the release of tumor antigens and signals that alert the immune system and induce a specific type of cell death that further activates immunity, ultimately leading to cancer cell death. Furthermore, these viruses can be genetically modified to carry therapeutic genes that further enhance their ability to convert immunologically inactive ("cold") tumors into active ("hot") ones, thereby increasing their effectiveness. Several oncolytic viruses are being investigated for their potential to treat breast cancer. These include adenovirus, vaccinia virus, reovirus, and herpes simplex virus type 1. These viruses are often modified to selectively target and destroy tumor cells while minimizing harm to healthy cells. While various engineered oncolytic viruses show promise for treating different cancers with varying levels of success, combining them with standard therapies in clinical trials suggests that this combination approach can significantly improve cancer treatment outcomes.

Keywords: oncolytic viruses, tumor microenvironment, immune response, breast cancer.

[1, 3,4,5,6] Tbilisi State Medical University, Georgia

[2] Eberhard Karl University of Tubingen, Germany

Breast cancer is one of the leading causes of death in women. Modern treatment approaches, including immunotherapy, surgery, cytotoxic, and hormonal therapies, show limited efficacy in the advanced stages of the disease. They become less effective in the metastatic stage. Additionally, severe side effects and tumor resistance mechanisms pose challenges to these standard approaches [1].

Aggressive systemic therapies, often associated with significant toxic side effects, are less than 50 % effective. These toxic effects can be long-lasting and can damage the cardiovascular and nervous systems, thus impairing patients' quality of life and possibly contributing to the development of new primary tumors. Moreover, the risk of reoccurrence increases as new resistant forms to existing therapeutic combinations emerge. Consequently, ongoing efforts focus on exploring new therapeutic approaches for breast cancer.

Oncolytic virotherapy, as a novel approach to cancer treatment, has grown substantially in recent years [2]. Given all the challenges discussed above, the development of targeted therapies is more important than ever. Recent studies highlight oncolytic virotherapy in a positive light. This innovative approach applies either naturally occurring or genetically engineered viruses to attack and destroy neoplastic cells while preserving healthy tissue. These viruses modify the tumor microenvironment (TME) to trigger immune recognition and enhance sensitivity to other treatments [1].

In this article, we review the potential of oncolytic virotherapy to induce an immune response and modulate the tumor microenvironment, based on evidence from preclinical and clinical trials of oncolytic viruses in the treatment of breast cancer.

Oncolytic viruses selectively target and destroy tumor cells through various mechanisms, including selective binding to tumor-specific cell surface receptors, utilizing defective tumor suppressor pathways, and downregulation of antiviral responses within tumor cells. The use of engineered viral vectors inactivates specific cellular genes. The lytic effectiveness of oncolytic viruses is influenced by several factors, including the specific virus types, viral tropism, and how vulnerable the cancer cells are to various types of cell death, such as apoptosis, necrosis, pyroptosis, and autophagy. Many oncolytic viruses are designed to attach to overexpressed or mutated tumor-associated receptors. For instance, adenoviruses selectively bind to Coxsackie-adenovirus receptors (CARs), which are highly expressed in epithelial tumors, including breast cancer. This strategy ensures precision in viral binding specificity [3].

To overcome tumor cell barriers, oncolytic viruses can also identify and exploit specific genetic mutations or defects characteristic of tumor cells. Adenoviruses seem to target cells with mutated p53 tumor suppressor pathways (impaired DNA damage response and failure to induce cell cycle arrest or apoptosis). Since the lack of functional p53 promotes viral replication in these cells, this process increases viral-induced cell lysis [3,4].

As an engineered adenovirus, Delta-24-RGD selectively replicates in neoplastic cells with impaired cell cycle regulation, usually mediated by the tumor suppressor protein, Rb protein (retinoblastoma). Another prominent example of a tumor-specific pathway is a defective Ras signaling cascade, which is critical for cell growth and survival [3].

Since alterations in this regulatory system are often present in breast carcinomas, it can be used as a distinctive feature between healthy and malignant cells.

To replicate more freely within the TME, oncolytic viruses can downregulate interferon signaling, which in turn impairs the antiviral defense of tumor cells [5]. Among other viruses, herpes simplex virus (HSV-1) and vesicular stomatitis virus (VSV) both evade immune detection by suppressing type I interferon (IFN-I) response [5,6,7]. Interestingly, in breast cancer cells, viral infection may furtherly suppress the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [8]. STAT3 is highly relevant in breast cancers, as 40 % of breast cancers have phosphorylated STAT3 [9]. Since this type of cytokine signaling route plays a crucial role in immune surveillance and antiviral responses, suppressing

it helps the virus escape immune detection [8].

Immunogenic Cell Death (ICD) - a form of programmed cell death that releases tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) [10].

Given the fact that these molecules activate immune cells, triggering a systemic immune response against the tumor, engineered viruses specifically favor the induction of ICD. To clarify, oncolytic adenoviruses can release calreticulin (a protein that normally resides in the endoplasmic reticulum) and high-mobility group box 1 HMGB1 proteins, both of which act as DAMPs, leading to the activation of dendritic cells and, subsequently, T cells for tumor-specific immunity. As a result, the induction of ICD occurs [4,11,12].

Besides direct effects, oncolytic viruses also indirectly enhance immunotherapy efficacy through modifying the TME.

This TME, comprising tumor cells, stromal elements, immune cells, and vasculature, plays a critical role in tumor progression and therapeutic resistance. A detailed study of how oncolytic viruses alter TME, possibly making it less immunosuppressive and more susceptible to immunotherapy, or how their interaction with TME enhances viral activity, is immensely relevant.

Based on TME, tumors can be classified as either “hot” or “cold” tumors. Hot tumors are characterized by high infiltration of lymphocytes, specifically tumor-infiltrating lymphocytes (TILs), and the expression of programmed death ligand 1 (PD-L1) on the surface of tumor cells. PD-L1 can bind to the PD-1 receptor present on the surface of T cells and natural killer cells, leading to an immunosuppressive interaction that allows the tumor to evade detection by the immune system. In contrast, cold tumors lack PD-L1 expression and T cell infiltration, which makes them less responsive to immunotherapy. Studies have investigated strategies to convert cold tumors into hot tumors. Oncolytic viruses (like reovirus and adenovirus) achieve this by (1) enhancing PD-L1 expression on tumor cells and (2) stimulating the immune response by promoting the infiltration of TILs into the TMI. These actions increase the tumor’s immunogenicity and make it more responsive to immunotherapy [13].

Novel therapeutic approaches for oncolytic viruses are being investigated either alone or in combination with immune checkpoint inhibitors (ICIs) or chemotherapy (CT) in both preclinical and clinical studies. As mentioned, these therapies exhibit synergy and are used in the management of hard-to-treat cancers like breast cancer. Several oncolytic viruses, including adenovirus, protoparvovirus, vaccinia virus, reovirus, and herpes simplex virus type I (HSV-1), have been investigated for their potential in breast cancer treatment. These viruses are specifically engineered to enhance tumor-selective replication, reduce toxicity, and improve oncolytic efficacy. Notably, newer generations of oncolytic viruses, such as Oncoviron and Delta-24-RGD (adenovirus-based), have demonstrated enhanced selectivity and superior antitumor effects in breast cancer models [14].

A key challenge remains in determining the optimal route of administration. Factors such as necrosis, calcification, acidosis, hypoxia, and poor vascularization limit virus distribution within the tumor. Currently, 2 main administration methods are used: intratumoral injection, suitable for surface-accessible tumors and allowing a high viral titer delivery directly into the tumor, and intravenous injection for less accessible tumors, which enables systemic distribution but carries the risk of early clearance and neutralization by serum immunoglobulins, reducing the effective dose. Ongoing research is exploring auxiliary methods like liposomal encapsulation of viruses and the use of immunomodulators such as cyclophosphamide [15].

Currently, preclinical and clinical trials are evaluating the efficacy of both naturally occurring (e.g., reoviruses, vesicular stomatitis virus) and genetically engineered viruses (e.g., adenoviruses, vaccinia virus, herpesvirus), with several showing promising results. In 2005, China approved adenovirus H101 for the treatment of nasopharyngeal carcinoma, marking the first approval of an oncolytic virus. In 2015, both the US FDA and EU EMA approved talimogene laherparepvec (T-VEC) as an oncolytic virus

therapy for patients with advanced melanoma. T-VEC is the most clinically advanced oncolytic virus derived from HSV-1. It has been studied in clinical trials involving patients with melanoma, pancreatic cancer, head and neck tumors, as well as in a phase I trial for breast cancer. T-VEC shows potential as a valuable therapeutic option when used in combination with immune checkpoint inhibitors, which have shown remarkable antitumor activity across various cancer types [14]. In 2021, Japan initiated a phase 2 clinical trial of Delytact (modified HSV-1) for malignant glioma, while the FDA approved T-VEC (a genetically modified herpes virus) for the treatment of melanoma, though its application for other cancers remains under investigation. Despite these advances, only a limited number of oncolytic virotherapies have been approved for clinical use [16,17]. FDA and EMA approved atezolizumab in the first-line treatment of PD-L1 overexpressing triple-negative breast cancer [18]. A recent preclinical study showed that combining reovirus with anti-PD-1 therapy triggered an immune response against breast cancer cells [19]. A phase I trial using HF10 (spontaneously mutated HSV-1) in patients with metastatic breast cancer showed tumor cell death and fibrosis accompanied by the presence of CD8+ and CD4+ T-cells, suggesting immune activation. Also, oncolytic adenovirus, purified reovirus serotype 3, Vaccinia virus, and some other viruses offer a promising new treatment approach for breast cancer due to their ability to selectively target tumor cells [14].

In conclusion, the promising role of oncolytic viruses as a novel therapeutic strategy for breast cancer is one of the innovative approaches of recent years. Despite advancements in conventional treatments, challenges remain in effectively targeting and eradicating aggressive and metastatic breast cancer subtypes. Oncolytic viruses, self-replicating viruses that selectively infect and lyse cancer cells while stimulating anti-tumor immunity, offer a unique and potentially synergistic approach.

Oncolytic virus immunotherapy has the potential to evolve into a complex treatment strategy at the intersection of virology and immuno-oncology. Its integration with other therapies and precision medicine approaches has demonstrated reliability in ongoing clinical trials for breast cancer treatment.

References:

1. Wu P, Gao W, Su M, Nice EC, Zhang W, Lin J, Xie N. Adaptive Mechanisms of Tumor Therapy Resistance Driven by Tumor Microenvironment. Front Cell Dev Biol. 2021 Mar 1; 9:641469. doi: 10.3389/fcell.2021.641469. PMID: 33732706; PMCID: PMC7957022.)
2. Wu X and Fang S (2024) Comparison of differences in immune cells and immune microenvironment among different kinds of oncolytic virus treatments. Front. Immunol. 15:1494887. doi: 10.3389/fimmu.2024.1494887
3. Chowaniec H, S´ lubowska A, Mroczek M, Borowczyk M, Braszka M, Dworacki G, Dobosz P and Wichtowski M (2024) new hopes for the breast cancer treatment: perspectives on the oncolytic virus therapy. Front. Immunol. 15:1375433. doi: 10.3389/fimmu.2024.1375433) --3
4. Tian, Y., Xie, D. & Yang, L. Engineering strategies to enhance oncolytic viruses in cancer immunotherapy. Sig Transduct Target Ther **7**, 117 (2022). https://doi.org/10.1038/s41392-022-00951-x).
5. Li Q, Tan F, Wang Y, Liu X, Kong X, Meng J, Yang L, Cen S. The gamble between oncolytic virus therapy and IFN. Front Immunol. 2022 Aug 25; 13:971674. doi: 10.3389/fimmu.2022.971674. PMID: 36090998; PMCID: PMC9453641.
6. Aldrak, N.; Alsaab, S.; Algethami, A.; Bhere, D.; Wakimoto, H.; Shah, K.; Alomary, M.N.; Zaidan, N. Oncolytic Herpes Simplex Virus-Based Therapies for Cancer. Cells 2021, 10, 1541. https://doi.org/ 10.3390/cells10061541
7. Marquis KA, Becker RL, Weiss AN, Morris MC, Ferran MC. The VSV matrix protein inhibits NF-κB and the interferon response independently in mouse L929 cells. Virology. 2020 Sep;548:117-123. doi: 10.1016/j.virol.2020.06.013. Epub 2020 Jun 29. PMID: 32838932; PMCID: PMC7447837.)

8. Jingyi Tan, Jiayu Zhang, Cheng Hu, Gongwei Wang, Qianyao Ren, et al. Pharmacokinetic enhancement of oncolytic virus M1 by inhibiting JAK–STAT pathway, Acta Pharmaceutica Sinica V. 14, Issue 6, 2024, pp. 2554-2566, ISSN 2211-3835, https://doi.org/10.1016/j.apsb.2024.03.007.
9. Dinakar YH, Kumar H, Mudavath SL, Jain R, Ajmeer R, Jain V. Role of STAT3 in the initiation, progression, proliferation and metastasis of breast cancer and strategies to deliver JAK and STAT3 inhibitors. Life Sci. 2022 Nov 15; 309:120996. doi: 10.1016/j.lfs.2022.120996. Epub 2022 Sep 25. PMID: 36170890.
10. Liu J, Hong M, Li Y, Chen D, Wu Y, Hu Y. Programmed Cell Death Tunes Tumor Immunity. Front Immunol. 2022 Mar 30; 13:847345. doi: 10.3389/fimmu.2022.847345. PMID: 35432318; PMCID: PMC9005769.
11. Santos Apolonio J, Lima de Souza Gonçalves V, Cordeiro Santos ML, Silva Luz M, Silva Souza JV, Rocha Pinheiro SL, de Souza WR, Sande Loureiro M, de Melo FF. Oncolytic virus therapy in cancer: A current review. World J Virol. 2021 Sep 25; 10(5):229-255. doi: 10.5501/wjv.v10.i5.229. PMID: 34631474; PMCID: PMC8474975.
12. Muhammad Haris Sultan, Qi Zhan, Hao Jin, Xiaoyuan Jia, Yigang Wang,Epigenetic modulation by oncolytic viruses: Implications for cancer therapeutic efficacy,Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, Volume 1880, Issue 2,2025,189270, ISSN 0304-419X, https://doi.org/10.1016/j.bbcan.2025.189270.
13. Wang L, Geng H, Liu Y, Liu L, Chen Y, Wu F, Liu Z, Ling S, Wang Y, Zhou L. Hot and cold tumors: Immunological features and the therapeutic strategies. MedComm (2020). 2023 Aug 26;4(5):e343. doi: 10.1002/mco2.343. PMID: 37638340; PMCID: PMC10458686.
14. Martini V, D'Avanzo F, Maggiora PM, Varughese FM, Sica A, Gennari A. Oncolytic virotherapy: new weapon for breast cancer treatment. Ecancermedicalscience. 2020 Dec 3; 14:1149. doi: 10.3332/ecancer.2020.1149. PMID: 33574894; PMCID: PMC7864690.
15. Toulmonde M, Guegan JP, Spalato-Ceruso M, Peyraud F, Kind M, Vanhersecke L, Le Loarer F, Perret R, Cantarel C, Bellera C, Bessede A, Italiano A. Reshaping the tumor microenvironment of cold soft-tissue sarcomas with oncolytic viral therapy: a phase 2 trial of intratumoral JX-594 combined with avelumab and low-dose cyclophosphamide. Mol Cancer. 2024 Feb 20;23(1):38. doi: 10.1186/s12943-024-01946-8. PMID: 38378555; PMCID: PMC10877825.
16. Ahamadi M, Kast J, Chen PW, Huang X, Dutta S, Upreti VV. Oncolytic viral kinetics mechanistic modeling of Talimogene Laherparepvec (T-VEC) a first-in-class oncolytic viral therapy in patients with advanced melanoma. CPT Pharmacometrics Syst Pharmacol. 2023 Feb;12(2):250-260. doi: 10.1002/psp4.12898. Epub 2023 Jan 11. PMID: 36564918; PMCID: PMC9931434.
17. Frampton JE. Teserpaturev/G47Δ: First Approval. BioDrugs. 2022 Sep;36(5):667-672. doi: 10.1007/s40259-022-00553-7. PMID: 36098872.
18. Kok M, Voorwerk L, Horlings H, et al. Adaptive phase II randomized trial of nivolumab after induction treatment in triple negative breast cancer (TONIC trial): final response data stage I and first translational data. J Clin Oncol. 2018;36(15) doi: 10.1200/JCO.2018.36.15_suppl.1012
19. Mostafa AA, Meyers DE, Thirukkumaran CM, et al. Oncolytic reovirus and immune checkpoint inhibition as a novel immunotherapeutic strategy for breast cancer. Cancers (Basel) 2018;10(6):205. doi: 10.3390/cancers10060205