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Harnessing oncolytic viruses to overcome immunosuppression in breast cancer: from mechanisms to clinical translation

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Oncolytic viruses (OVs) possess dual advantages in cancer immunotherapy: they selectively replicate within and lyse tumor cells while simultaneously releasing tumor-associated antigens to recruit and activate immune cells within the local tumor microenvironment (TME), thereby inducing robust and sustained antitumor immunity. Furthermore, these viruses can serve as tumor-targeting vectors for immunomodulation and synergize with other immunotherapeutic approaches. As such, oncolytic virotherapy holds significant potential to overcome the low response rates of breast cancer to existing immunotherapies and expand the therapeutic arsenal. This review systematically elucidates the application and mechanisms of this emerging immunotherapy in addressing the challenges of conventional breast cancer treatments. It also discusses engineering strategies to enhance antitumor immunity, highlights recent preclinical and clinical studies on rational combinations of OVs with other therapies, and outlines current challenges and future prospects.

KEYWORDS

breast cancer, oncolytic virus, tumor microenvironment, cancer vaccines, combination therapy

Introduction

Breast cancer remains a leading cause of cancer-related mortality among women (1). Oncolytic virotherapy (OV), which combines the selective infection and destruction of cancer cells with the induction of adaptive immune responses against tumors, has emerged as a promising frontier in the fight against various cancers, including breast cancer (2–4). Additionally, the integration of OVs with other breast cancer treatments to leverage the strengths of each modality has garnered significant attention as a strategy to address tumor heterogeneity (5–7).

Mechanisms of oncolytic viruses in breast cancer

Oncolytic viruses are naturally occurring or genetically engineered immunotherapeutic agents that preferentially replicate in tumors, promoting immunogenic cell death. For instance, the oncolytic mumps virus exhibits potent cytotoxic activity against breast cancer xenografts, and oncolytic peptides demonstrate remarkable antimetastatic properties (8–10). Recombinant OV's have also shown efficacy in triple-negative breast cancer (TNBC) mouse models, a highly aggressive subtype with limited treatment options (11). Beyond direct tumor lysis, OV's primarily exert antitumor effects by activating immune responses (12) **Figure 1**.

The immunosuppressive tumor microenvironment (TME) is a major barrier to cancer immunotherapy (13). By recruiting inhibitory immune cells and upregulating immune checkpoint ligands, the TME fosters immunosuppression and restricts antitumor immunity, facilitating tumor progression and metastasis. OV's remodel the TME by inducing immunogenic cell death, disrupting the dense tumor stroma, and triggering the release of danger signals and tumor-associated antigens. This process attracts antigen-presenting cells, activates and expands lymphocyte populations, and enhances their infiltration into the tumor bed, transforming the TME from an

immunologically “cold” to a “hot” state (14–17). T lymphocytes play a pivotal role in this transition.

Insufficient T cell activation limits the efficacy of immunotherapies. The oncolytic parapoxvirus ORFV and its derivatives induce pyroptosis in breast cancer cells and increase intratumoral cytotoxic T lymphocyte (CTL) populations (18, 19). Similarly, the oncolytic vaccinia virus CF33-hNIS-ΔF14.5 enhances CD8⁺ T cell infiltration in TNBC models (20). A virus-like nanoplateform (PolyIC@ZIF-8) degrades in the acidic TME, releasing PolyIC to induce apoptosis and promote T cell recruitment and activation in an antigen-dependent manner (21). Dendritic cell (DC) activation is also critical for OV-mediated antitumor immunity (22). A GFP-transgenic Newcastle disease virus (NDV-GFP) matures monocyte-derived DCs, priming antigen-specific T cell responses against breast cancer cells (23). Notably, combining high-dose vitamin C with oncolytic adenoviruses (oAds) amplifies T cell activation (24).

Natural killer (NK) cells also contribute to antitumor immunity. An oncolytic vesicular stomatitis virus (VSV)-based vaccine enhances NK cell activity and improves TNBC outcomes (25). OV's engineered to express CCL5 recruit NK cells to tumor sites, synergizing with NK cell-based therapies (26). Moreover, tumor-tropic NK cells can serve as carriers for systemic OV delivery (27). Combining NKT cell immunotherapy with engineered OV's further enhances tumor targeting (28).

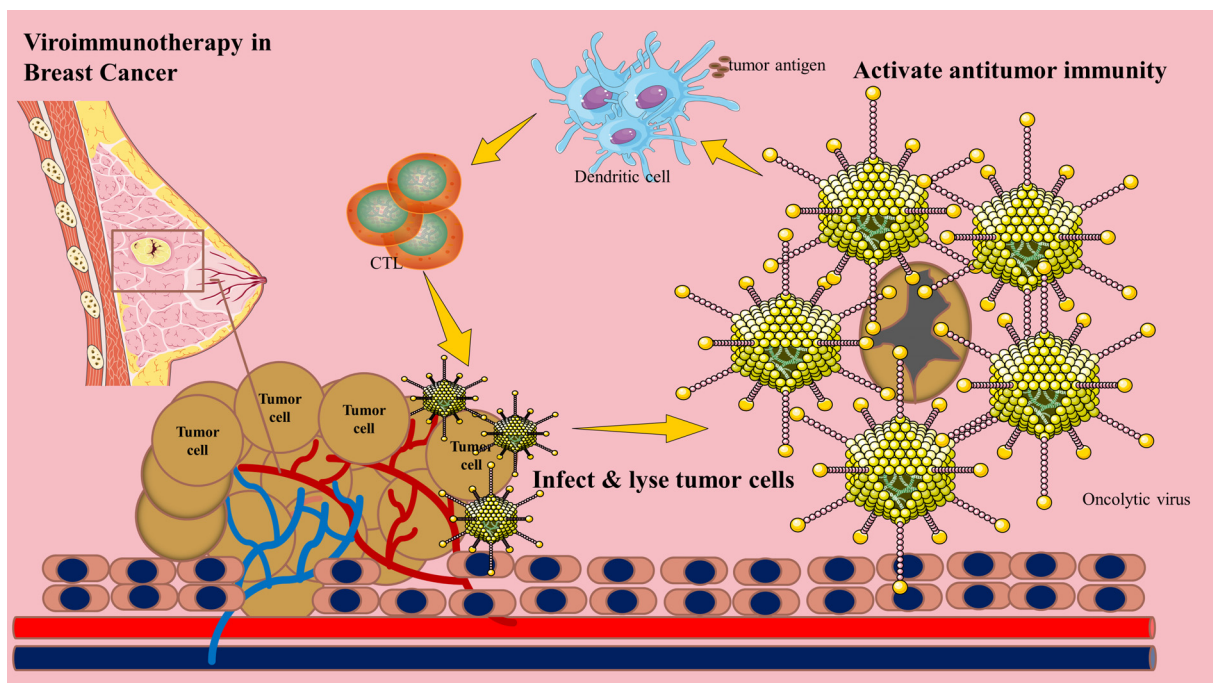


FIGURE 1
Primary mechanisms of oncolytic virotherapy in breast cancer.

Challenges and optimization strategies for oncolytic virotherapy in breast cancer

Limited tumor targeting after systemic administration

Enhancing OV specificity for breast cancer cells is a key research focus. For HER2-positive breast cancer, the HSV-based OV R-LM249 selectively infects and kills HER2-overexpressing cells (29). For HER2-negative tumors, mesothelin (MSLN) is a promising target (30). The recombinant measles virus rMV-SLAMblind suppresses Nectin-4-positive TNBC cells (31). Bispecific T cell engagers (BiTEs) can redirect T cells to tumor antigens, and OV-BiTE combinations represent a novel targeting strategy (32). For instance, a PD-L1-targeting BiTE-armed oHSV-1 selectively kills PD-L1+ tumor cells and macrophages while sparing T cells (33). Intratumoral OV delivery also minimizes off-target toxicity (34).

Host antiviral immune responses

Neutralizing antibodies pose a major challenge to systemic OV delivery. Strategies to evade or repurpose these antibodies are under investigation (35, 36). Antibody retargeting improves intratumoral adenovirus efficacy (37). Magnetic nanoparticles conjugated to HSV1716 shield the virus from neutralizing antibodies and enable magnetic tumor targeting (38). Mesenchymal stem cells (MSCs) serve as effective OV carriers, enhancing tumor delivery and infiltration (39, 40). A liposome-encapsulated NDV expressing MIP-3 α stimulates antitumor immunity and inhibits angiogenesis (41). Exosome-based delivery systems also show promise in TNBC (42).

Engineering multifunctional OVs

Genetic modifications enhance OV specificity and potency. A miR-145/143-modified coxsackievirus B3 (miR-CVB3-1.1) selectively lyses breast cancer cells (43). Combining miR-CVB3 with CpG-melittin suppresses primary and metastatic tumor growth (44). The oncolytic adenovirus AdSVP-lncRNAi9 silences oncogenic miRNAs to inhibit TNBC proliferation and migration (45).

Immunomodulatory OVs amplify antitumor immunity. IL-21- or IL-23-armed vaccinia viruses induce potent immune responses (46, 47). A TK/N1L-deleted vaccinia virus (VV Δ TK Δ N1L) prevents postoperative recurrence and metastasis (48). TGF- β inhibition synergizes with OVs (49), and deleting immune evasion genes enhances efficacy (50). Besides, OVs expressing PD-1/IL-12 remodel the immunosuppressive TME (51).

Immune checkpoint-armed OVs combine virotherapy with checkpoint blockade. An adenovirus suppressing PD-L1 improves checkpoint inhibitor safety and efficacy (52). A TIGIT-targeting

scFv-armed vaccinia virus (VV-scFv-TIGIT) synergizes with PD-1 blockade (53). Another engineered VV- α -TIGIT enhances T cell recruitment and activation (54).

Combination therapies with oncolytic viruses

OVs are potent modulators of the TME, and their combination with immune checkpoint inhibitors (ICIs), CAR-T cells, or other immunotherapies represents a highly promising strategy (55–58). For instance, the combination of reovirus and CD3-bispecific antibodies enhances interferon-mediated responses and promotes T cell infiltration, leading to tumor regression in HER2+ breast cancer models (59). Additionally, genome-wide CRISPR-Cas9 screening has identified PARP1 as a key cellular factor that restricts viral replication; accordingly, PARP inhibition sensitizes TNBC to OV-ICI combination therapy (60). Neoadjuvant OV treatment has also been shown to improve surgical outcomes and reduce recurrence rates (61). It is critical to optimize dosing and timing in these combinational approaches, as the synergistic effects between OVs and ICIs are both dose- and schedule-dependent (62, 63). Therefore, establishing optimal dosing regimens and treatment sequences is paramount for the rational design of clinical trials investigating OV-based combination immunotherapies.

OVs also synergize with chemotherapy, radiotherapy, and targeted therapies (64). Table 1 Stereotactic body radiotherapy (SBRT) enhances OV-induced immunogenic cell death (65). Kinase inhibitors, such as BRAF inhibitors, improve OV efficacy (66, 67). Epigenetic modifiers like entinostat augment OV-IL-15 superagonist combinations (68, 69).

Development of potent oncolytic virus cancer vaccines

The development of robust oncolytic virus (OV)-based cancer vaccines relies on the rational design of tumor-selective viruses and the strategic exploitation of their immunostimulatory properties. Utilizing OVs as an adjuvant platform for therapeutic cancer vaccines is particularly attractive for personalized immunotherapy targeting patient-specific neoantigens (79, 80). High-throughput sequencing technologies can be leveraged to optimize viral design, modulate immune responses, and identify predictive biomarkers of clinical efficacy (81). Furthermore, direct imaging and automated analysis using tumor-on-chip systems have elucidated the cooperative antitumor activity between immune cells and oncolytic vaccinia virus, providing novel insights into the mechanisms of action of oncolytic vaccines (82).

Discussion

Oncolytic virotherapy represents a novel multimodal approach bridging virology, oncology, and immunology. While preclinical

TABLE 1 Pre-clinical research of oncolytic virotherapy in breast cancer.

Oncolytic virus	Combined agent	Mechanism of action	Key findings	Ref
Oncolytic alphavirus M1	Doxorubicin	Doxorubicin enhances viral replication and necroptosis	Suppresses TNBC growth <i>in vivo</i>	(70)
Reovirus	Doxorubicin conjugate	Reo-dox promotes innate immune activation and DNA damage	Reduces primary and metastatic TNBC burden	(71)
Talimogene laherparepvec (T-VEC)	NAC	T-VEC + neoadjuvant chemotherapy (NAC) for TNBC (Phase I trial)	55% complete response rate, manageable toxicity	(72)
T-VEC	Paclitaxel + NAC	Intratumoral T-VEC + chemotherapy (Phase II trial)	Increases RCB0–1 rates in TNBC	(73)
VG161 (oHSV-1)	Paclitaxel	Induces proinflammatory TME changes	Inhibits breast cancer growth and lung metastasis	(74)
TG6002 (VV)	5-Fluorouracil	Converts 5-FC to 5-FU, inducing tumor lysis	Effective in canine mammary tumors	(75)
Measles virus (MV)	Baicalein (BAI) + Cinnamaldehyde (CIN)	BAI/CIN sensitize tumor cells to MV	Enhances tumor cell killing.	(76)
VSVΔ51	T-DM1	VSVΔ51 overcomes T-DM1 resistance in HER2+ cells	Improves survival in HER2+ xenografts	(77)
T-VEC	Atezolizumab	T-VEC + anti-PD-L1 for TNBC (Phase Ib trial)	Limited antitumor activity observed	(78)

T-DM1 (Kadcyla®), an antibody-drug conjugate; atezolizumab, an immune checkpoint inhibitor.

and clinical studies validate the antitumor effects of several OV_s, their clinical translation faces challenges, including immune and physical barriers that limit intratumoral delivery, replication, and spread. Beyond improving OV bioavailability and efficacy, developing platforms that synergize with existing therapies is crucial. A deeper understanding of host-virus interactions, particularly in metabolically relevant models, will help bridge the gap between bench and bedside.

Author contributions

KX: Writing – original draft, Formal Analysis, Methodology, Data curation, Writing – review & editing, Software, Conceptualization. LZ: Writing – review & editing, Project administration, Resources. DJ: Writing – review & editing, Software, Investigation. PQ: Methodology, Writing – review & editing. ZL: Validation, Visualization, Writing – review & editing, Conceptualization, Supervision, Writing – original draft. ZF: Writing – original draft, Supervision, Writing – review & editing. SX: Data curation, Resources, Supervision, Writing – original draft, Formal Analysis, Writing – review & editing.

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Conflict of interest

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