

Cancer-Killing Viruses: The What, The How, and The What If

Treating cancer has challenged physicians since antiquity. The first recorded, albeit unsuccessful, attempt at surgically excising a tumor dates back nearly 4,000 years to ancient Egypt. Since then, cancer biology has evolved from descriptive pathology to molecular precision medicine. Among the most paradigm-shifting innovations is gene therapy, which has revolutionized oncology by introducing targeted genetic modifications to restore or augment normal cellular functions and immune responses (1). Gene-based therapeutics, particularly cancer immunotherapies, have achieved curative outcomes in previously refractory malignancies.

The most transformative of these immunotherapies is Chimeric Antigen Receptor T-cell (CAR-T) therapy, in which autologous T lymphocytes are genetically engineered to express synthetic receptors that recognize tumor-specific antigens. These chimeric receptors couple an antigen-binding domain (typically a single-chain variable fragment) with intracellular signaling motifs (CD3 ζ , CD28, or 4-1BB) to trigger T-cell activation upon antigen engagement (2). The clinical success of anti-CD19 CAR-T cells in B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL) culminated in the first FDA approval in 2017 (tisagenlecleucel; Kymriah®)(3). Despite remarkable efficacy, the therapy poses notable adverse events, including cytokine release syndrome (CRS), a systemic hyperinflammatory response; immune effector cell-associated neurotoxicity syndrome (ICANS), causing transient encephalopathy; and B-cell aplasia, reflecting on-target off-tumor toxicity against normal CD19⁺ B cells, resulting in prolonged immunodeficiency (4)(5).

Historically, viruses have been viewed as agents of devastation—from smallpox to the COVID-19 pandemic, which claimed over seven million lives worldwide. Yet the same biological entities responsible for pandemics are now being repurposed as precision anticancer agents. The field of oncolytic virotherapy harnesses the innate cytolytic potential of viruses by genetically modifying them to selectively infect, replicate within, and lyse tumor cells, sparing healthy tissue. As these oncolytic viruses (OVs) replicate, they induce tumor-restricted cell lysis, releasing tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) that trigger innate and adaptive immune activation(6). This immunogenic cell death reprograms the tumor microenvironment (TME) from immunosuppressive to immunostimulatory, enhancing antigen presentation and T-cell recruitment (7).

Commonly studied vectors include herpes simplex virus type-1 (HSV-1) and vaccinia virus, both amenable to genetic manipulation and capable of large transgene cargo delivery(8). The first FDA-approved oncolytic virus, talimogene laherparepvec (T-VEC), an engineered HSV-1 expressing GM-CSF, demonstrated durable responses in metastatic melanoma by inducing systemic antitumor immunity(9).

Emerging preclinical and clinical evidence supports the synergistic integration of oncolytic viruses with CAR-T or CAR-NK therapies, combining direct oncolysis with immune modulation. OVVs can remodel the tumor stroma, increase cytokine and chemokine concentrations, and recruit CD8⁺ cytotoxic T lymphocytes into previously “cold” tumors (10). Concurrently, CAR-T or CAR-NK cells provide sustained antigen-specific cytotoxicity. This virus-cell therapy combination enhances tumor infiltration, reduces immune escape, and converts immunologically “silent” tumors into “visible” targets for adaptive immunity (11).

The conceptual analogy is striking: viruses—once the “villains” of biology—are being reprogrammed as biological vectors of justice, analogous to a reengineered Thanos who eliminates malignant rather than healthy cells.

In conclusion, the convergence of oncolytic virotherapy and CAR-T cell technology heralds a new frontier in precision oncology. By leveraging the replicative lethality of viruses alongside the specificity of engineered lymphocytes, scientists are redefining what is possible in cancer immunotherapy. Though still in early clinical exploration, this combinatorial strategy offers a blueprint for durable, system-wide tumor eradication and could transform oncology in the coming decade.

References

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