Oncolytic Immunotherapy:
A Local and Systemic Antitumor Approach
Oncolytic immunotherapy—the use of a genetically modified virus to attack tumors and induce a systemic immune response to cancer—is a rapidly evolving area of therapy, but the basic idea behind it is not new. The ability of viruses to affect cancer was first observed in 1904, and for more than a century potential virus-induced remissions have been observed in a limited number of patients. However, the effect with naturally occurring viruses is limited and short-lived, with the risk of serious infection and death. More recently, there have been attempts to genetically modify these viruses for a more potent, selective, and permanent anticancer effect.  

Oncolytic immunotherapy uses a modified oncolytic virus that selectively replicates in tumor cells for an antitumor effect through a proposed dual mode of action:

- Oncolytic: Direct cytotoxic activity due to the replication of the virus and cell lysis
- Immunotherapy: Indirect induction of a systemic antitumor immune response
Many potential genetic modifications to oncolytic viruses have been identified for enhanced effect. Many viruses have been studied as potential vectors for oncolytic immunotherapy. This includes the insertion, deletion, and/or inactivation of various genes to achieve desired effects. Modifications allow the virus to selectively replicate in and destroy tumor cells and release progeny viruses. The viruses infect, replicate selectively in, and lyse other tumor cells for a potent oncolytic effect. Additional genetic modifications enhance oncolytic cell death and express cytokine genes to activate a systemic immune response.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Virus</th>
<th>Possible gene modifications</th>
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<tbody>
<tr>
<td><strong>SELECTIVITY</strong>&lt;sup&gt;3,6&lt;/sup&gt;</td>
<td>Adenovirus</td>
<td>E1B-55kd and/or E1A CR2 deletion, Use of tissue- or tumor-specific promoters</td>
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<td></td>
<td>HSV-1</td>
<td>ICP34.5 gene or ICPE gene inactivation/deletion, TK gene deletion, Use of tissue- or tumor-specific promoters</td>
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<td></td>
<td>Vaccinia virus</td>
<td>TK gene deletion, Use of tissue- or tumor-specific promoters</td>
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<td>Poxvirus</td>
<td>TK gene disruption</td>
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<td><strong>ENHANCED ONCOLYTIC CELL DEATH</strong>&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>HSV-1</td>
<td>ICP47 deletion and earlier expression of US11</td>
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<tr>
<td></td>
<td>Adenovirus</td>
<td>E3 or FMG gene expression, E1B-19kd gene deletion</td>
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<tr>
<td><strong>CYTOKINE EXPRESSION</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Various</td>
<td>IL-4, IL-12, GM-CSF, MCP-1, and IFN gene insertion</td>
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FMG = fusogenic membrane glycoprotein, GM-CSF = granulocyte-macrophage colony-stimulating factor, HSV-1 = herpes simplex virus 1, IFN = interferon, IL = interleukin, MCP = monocyte chemotactic protein, SPI = spleen focus forming virus proviral oncogene, TK = thymidine kinase.
Genetic modifications reduce the ability of viruses to replicate in healthy cells

Selectivity may be increased by deleting or inactivating genes in the virus that are critical for replication in healthy cells but are not necessary for replication in tumor cells. HSV-1 relies on the neurovirulence factor ICP34.5 to overcome the host cell’s normal response to infection, which includes production of IFNα. IFNα signaling inhibits viral replication. By inactivating the gene in the virus that encodes the neurovirulence factor, the virus will no longer be able to replicate in healthy cells. However, these viruses are able to replicate in tumor cells even without neurovirulence factors.

The chart shows the results of a preclinical model of healthy human cells. Cells treated with HSV-1 modified by the deletion of the neurovirulence factor ICP34.5 and cultured in the presence of IFNα resulted in a 62,000-fold reduction of viral replication (Figure A).

The perpetuated cycle of tumor-selective replication and oncolysis after release of newly synthesized viruses can be visualized in a mouse model of a colorectal carcinoma infected with an oncolytic virus containing the LacZ gene. After staining, LacZ expression was detected as early as day 1, with maximum expression seen on days 2 to 3 and continuing through day 7 (Figure B).
Oncolytic cell death using oncolytic viruses with target gene modifications can result in antitumor activity in preclinical models.

In a preclinical model of glioma, an HSV-1 oncolytic virus was modified with the deletion/inactivation of one or two different genes in order to generate tumor-selective replication and enhance tumor cell kill. These deletions led to significantly slowed or reduced tumor growth over time when injected into mice (Figure A). 5

In a preclinical model of prostate cancer, an oncolytic adenovirus with or without E3 gene expression was injected into mice. Six weeks after a single injection, these modifications resulted in an up to 4-fold reduction in tumor volume (Figure B). 11

Figure A

Figure B
Oncolytic cell death and cytokine expression can initiate a systemic immune response

In addition to releasing newly synthesized viruses, the oncolysis of tumor cells also releases and exposes an array of tumor antigens to initiate a systemic immune response (Figure A). The tumor antigens elicit an adaptive immune response that is patient- and tumor-specific, possibly enhancing efficacy. Further, the virus may be modified to express and release specific cytokines (eg, GM-CSF, IL-4, IL-12, MCP-1, or IFN).3,12

GM-CSF–secreting tumor cells can stimulate dendritic cell expansion and infiltration of tumor tissue. The effect of GM-CSF on dendritic cells and induction of antitumor immunity has been documented in preclinical models. Melanoma cells engineered to express GM-CSF but irradiated to prevent cell division were injected into mice, resulting in an accumulation of tumor-infiltrating dendritic cells (Figure B).13
Systemic effect: Antigen-presenting cells process and present an array of tumor antigens to activate T cells for a systemic immune response

Dendritic cells capture tumor antigens after oncolysis and process them for presentation on MHC molecules. By exposing dendritic cells to an array of tumor antigens, a robust and broad immune response may be achieved. Mature dendritic cells can interact with CD4+ and CD8+ T cells to produce CD8+ effector T cells with cytotoxic potential (Figure A). In a preclinical model of ovarian cancer, treatment with an oncolytic virus can induce tumor infiltration of CD8+ T cells (Figure B). Cytotoxic T cells that recognize different tumor antigens on tumor cells can also disperse throughout the body to destroy tumor cells and lead to destruction of distant tumor cells.18

Local injection may enhance immunotherapeutic response while reducing systemic exposure to healthy cells. Preclinical studies demonstrate that a locally induced, tumor-specific immune response can result in the systemic destruction of distant tumor cells. A modified oncolytic HSV-1 expressing IL-12 injected into a murine colorectal adenocarcinoma tumor on days 0 and 7 resulted in significantly greater antitumor effects compared with a modified oncolytic HSV-1 that did not express the cytokine (Figure A). In addition, significant tumor growth reduction was also observed in a bilateral tumor that had not been injected, demonstrating a systemic immune response (Figure B). 6,20

Systemic effect: In preclinical models, a systemic immune response resulted in destruction of distant tumor cells. 19 Preclinical studies demonstrate that a locally induced, tumor-specific immune response can result in the systemic destruction of distant tumor cells. A modified oncolytic HSV-1 expressing IL-12 injected into a murine colorectal adenocarcinoma tumor on days 0 and 7 resulted in significantly greater antitumor effects compared with a modified oncolytic HSV-1 that did not express the cytokine (Figure A). In addition, significant tumor growth reduction was also observed in a bilateral tumor that had not been injected, demonstrating a systemic immune response (Figure B). 6,20

Oncolytic immunotherapy is an approach that utilizes an oncolytic virus to activate a tumor-specific immune response.

Genetic modifications of the virus result in selective replication in tumor cells while reducing the ability of the virus to replicate in healthy cells. By exposing an array of tumor antigens through tumor cell lysis, oncolytic immunotherapy may induce a robust immune response in patients. In addition, insertion of an immunomodulatory cytokine gene and local cytokine expression attracts and activates dendritic cells and T cells for a systemic immune response to tumor cells. Induction of a systemic immune response can then result in death of distant tumor cells.
References
