Oncolytic Virotherapy: Harnessing Nature to Treat High-Grade Gliomas and Metastatic Cancer

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Background

Cancers like glioblastoma remain unmanageable for most patients, and even with the current optimal treatment offered, survival rates are far too low. Fortunately, several preclinical and clinical studies indicate that oncolytic viruses have the potential to effectively eradicate cancers. Data from one such clinical trial, DNX-240, a recently completed first-in-human Phase I clinical trial using Delta-24-RGD to treat recurrent glioblastoma (NC108865376) demonstrated that the oncolytic virus successfully exerts an antitumor immune response. The oncolytic adenovirus Delta-24-RGD includes a deletion in the E1A region that confers tumor-selective infectivity and an RGD peptide motif insertion that improves infective power.

Hypothesis

We hypothesize that the anti-tumor effect might be amplified by the expression of positive immune checkpoints. To test this, we incorporated a costimulatory ligand (OX40L) after the fiber region to maximize T-cell activity, which generated an immune-stimulating oncolytic virus.

Methods

The genome of Delta-24-RGDOX-DH was amplified by PCR and sequenced to ensure the viral construct incorporated the appropriate genetic modifications. Next, the expression of murine OX40L in the membrane of infected cells was assessed using western blot and flow cytometry and the expression of other viral proteins by infected cells was analyzed by western blotting. The presence of immune cell populations in tumor-bearing mice was measured between treatment groups with flow cytometry. Afterwards, the oncolytic effects of oncolytic viruses were tested by infecting A549 human lung carcinoma cells and measuring cell counts over time. Then, studies of mice were conducted to compare the therapeutic effect of viruses on 4T1-derived breast tumors compared to a mock infection.

Results

The Delta-24-RGDOX-DH genome had all the desired genomic alterations that give it the ability to selectively infiltrate and lyse cancer cells, demonstrating reliability in production and utility. Delta-24-RGDOX-DH shows promising signs of efficacy as an anti-cancer therapy, so our data should propel the development of reinvigorate immune lymphocytes.

Conclusions

- The Delta-24-RGDOX-DH genome had all the desired genomic alterations that give it the ability to selectively infiltrate and lyse cancer cells, demonstrating reliability in production and utility.
- Experiments showed that Delta-24-RGDOX-DH produced a substantial infection in vitro and in vivo with effective cancer cell lysis and increased activation of the immune system in tumor-bearing mice.
- Experiments also showed the modified virus produces the necessary costimulatory ligand to maximize infection and reinvigorate immune lymphocytes.
- Delta-24-RGDOX-DH shows promising signs of efficacy as an anti-cancer therapy, so our data should propel the development of clinical trials with Delta-24-RGDOX-DH for patients with high-grade glioma, or other aggressive types of cancer.

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