

Reovirus oncolysis of human breast cancer.

[Norman KL](#), [Coffey MC](#), [Hirasawa K](#), [Demetrick DJ](#), [Nishikawa SG](#), [DiFrancesco LM](#), [Strong JE](#), [Lee PW](#).

Cancer Biology Research Group, Faculty of Medicine, University of Calgary, Calgary, Alberta, T2N 4N1 Canada.

We have previously shown that human reovirus replication is restricted to cells with an activated Ras pathway, and that reovirus could be used as an effective oncolytic agent against human glioblastoma xenografts. This study examines in more detail the feasibility of reovirus as a therapeutic for breast cancer, a subset of cancer in which direct activating mutations in the ras proto-oncogene are rare, and yet where unregulated stimulation of Ras signaling pathways is important in the pathogenesis of the disease. We demonstrate herein the efficient lysis of breast tumor-derived cell lines by the virus, whereas normal breast cells resist infection in vitro. In vivo studies of reovirus breast cancer therapy reveal that viral administration could cause tumor regression in an MDA-MB-435S mammary fat pad model in severe combined immunodeficient mice. Reovirus could also effect regression of tumors remote from the injection site in an MDA-MB-468 bilateral tumor model, raising the possibility of systemic therapy of breast cancer by the oncolytic agent. Finally, the ability of reovirus to act against primary breast tumor samples not propagated as cell lines was evaluated; we found that reovirus could indeed replicate in ex vivo surgical specimens. Overall, reovirus shows promise as a potential breast cancer therapeutic.

PMID: 11916487 [PubMed - indexed for MEDLINE]

Reovirus prolongs survival and reduces the frequency of spinal and leptomenigeal metastases from medulloblastoma.

[Yang WQ](#), [Senger D](#), [Muzik H](#), [Shi ZQ](#), [Johnson D](#), [Brasher PM](#), [Rewcastle NB](#), [Hamilton M](#), [Rutka J](#), [Wolff J](#), [Wetmore C](#), [Curran T](#), [Lee PW](#), [Forsyth PA](#).

Department of Oncology, University of Calgary and Tom Baker Cancer Centre, Calgary, Alberta, T2N 4N2 Canada.

Medulloblastoma (MB), the most common pediatric brain tumor, is a highly malignant disease with a 5-year survival rate of only 60%. Tumor cells invade surrounding tissue and disseminate through cerebral spinal fluid, making treatment difficult. Human reovirus type 3 exploits an activated Ras pathway in tumor cells to support productive infection as an oncolytic virus. Here, we examined the ability of human reovirus to kill MB cells lines and surgical specimens in vitro and inhibit tumor growth/metastases in vivo. Most human MB cell lines tested (five of seven = 71.4%), two MB cell lines derived from spontaneously arising tumors in Patched-1(+/-) mice (two of two = 100%) and three MB primary cultures derived from surgical specimens, were susceptible to reovirus infection. Reovirus was internalized and transcribed in both susceptible and resistant cell lines. However, viral protein synthesis was restricted to cell lines with higher levels of activated Ras, suggesting that Ras plays a critical role in reovirus oncolysis in MB. Using an in vivo Daoy orthotopic animal model, we found that a single i.t. injection of reovirus dramatically prolonged survival compared with controls (160 versus 70 days, respectively; $P = 0.0003$). Repeating this experiment with GFP-labeled Daoy cells and multiple i.t. administrations of reovirus, we again found prolonged survival and a dramatic reduction in spinal and leptomenigeal metastases (66.7% in control injections versus 0.0% in the live virus group). These data suggest that this oncolytic virus may be a potentially effective novel therapy against human MB. Its ability to reduce metastases to the spinal cord could allow a reduction in the dose/field of total neuroaxis cerebral-spinal radiotherapy currently used to treat/prevent cerebral spinal fluid dissemination.

PMID: 12810644 [PubMed - indexed for MEDLINE]

Reovirus as an experimental therapeutic for brain and leptomeningeal metastases from breast cancer.

[Yang WQ](#), [Senger DL](#), [Lun XQ](#), [Muzik H](#), [Shi ZQ](#), [Dyck RH](#), [Norman K](#), [Brasher PM](#), [Rewcastle NB](#), [George D](#), [Stewart D](#), [Lee PW](#), [Forsyth PA](#).

Department of Oncology, University of Calgary, Tom Baker Cancer Centre, Alberta, Canada.

Brain and leptomeningeal metastases are common in breast cancer patients and our current treatments are ineffective. Reovirus type 3 is a replication competent, naturally occurring virus that usurps the activated Ras-signaling pathway (or an element thereof) of tumor cells and lyses them but leaves normal cells relatively unaffected. In this study we evaluated reovirus as an experimental therapeutic in models of central nervous system (CNS) metastasis from breast cancer. We found all breast cancer cell lines tested were susceptible to reovirus, with > 50% of these cells lysed within 72 h of infection. In vivo neurotoxicity studies showed only mild local inflammation at the injection site and mild communicating hydrocephalus with neither diffuse encephalitis nor behavioral abnormalities at the therapeutically effective dose of reovirus (intracranial) (ie 10⁷ plaque-forming units) or one dose level higher. In vivo, a single intratumoral administration of reovirus significantly reduced the size of tumors established from two human breast cancer cell lines and significantly prolonged survival. Intrathecal administration of reovirus also remarkably prolonged survival in an immunocompetent ratine model of leptomeningeal metastases. These data suggest that the evaluation of reovirus as an experimental therapeutic for CNS metastases from breast cancer is warranted.

PMID: 15372068 [PubMed - indexed for MEDLINE]

Oncolytic reovirus against ovarian and colon cancer.

[Hirasawa K](#), [Nishikawa SG](#), [Norman KL](#), [Alain T](#), [Kossakowska A](#), [Lee PW](#).

Cancer Biology Research Group and Department of Microbiology and Infectious Diseases, University of Calgary, Calgary, Alberta, T2N 4N1 Canada.

Reovirus selectively replicates in and destroys cancer cells with an activated Ras signaling pathway. In this study, we evaluated the feasibility of using reovirus (serotype 3, strain Dearing) as an antihuman colon and ovarian cancer agent. In in vitro studies, reovirus infection in human colon and ovarian cell lines was assessed by cytopathic effect as detected by light microscopy, [(35)S]Methionine labeling of infected cells for viral protein synthesis and progeny virus production by plaque assay. We observed that reovirus efficiently infected all five human colon cancer cell lines (Caco-2, DLD-1, HCT-116, HT-29, and SW48) and four human ovarian cancer cell lines (MDAH2774, PA-1, SKOV3, and SW626) which were tested, but not a normal colon cell line (CCD-18Co) or a normal ovarian cell line (NOV-31). We also observed that the Ras activity in the human colon and ovarian cancer cell lines was elevated compared with that in normal colon and ovarian cell lines. In animal models, intraneoplastic as well as i.v. inoculation of reovirus resulted in significant regression of established s.c. human colon and ovarian tumors implanted at the hind flank. Histological studies revealed that reovirus infection in vivo was restricted to tumor cells, whereas the surrounding normal tissue remained uninfected. Additionally, in an i.p. human ovarian cancer xenograft model, inhibition of ascites tumor formation and the survival of animals treated with live reovirus was significantly greater than of control mice treated with UV-inactivated reovirus. Reovirus infection in ex vivo primary human ovarian tumor surgical samples was also confirmed, further demonstrating the potential of reovirus therapy. These results suggest that reovirus holds promise as a novel agent for human colon and ovarian cancer therapy.

PMID: 11912142 [PubMed - indexed for MEDLINE]

Efficacy of oncolytic reovirus against liver metastasis from pancreatic cancer in immunocompetent models.

[Himeno Y](#), [Etoh T](#), [Matsumoto T](#), [Ohta M](#), [Nishizono A](#), [Kitano S](#).

Department of Surgery I, Oita University Faculty of Medicine, Oita 879-5593, Japan.

Liver metastasis is common in pancreatic cancer patients, and the current treatments are insufficient to improve the clinical outcome. Recently, tumor-targeted replication-competent viruses have been developed as cancer therapy. The aim of this study was to clarify the efficacy of oncolytic reovirus against liver metastases from pancreatic cancer in immunocompetent models. Reovirus serotype 3 and three hamster pancreatic cancer cell lines (HPD1NR, HPD2NR, and HaP-T1) were used in this study. The susceptibility of reovirus to these cell lines was examined. The effect of intraportal administration of reovirus against metastatic liver tumors was evaluated *in vivo*. Reovirus infected all cell lines and propagated via an activated Ras signalling pathway *in vitro*. In syngeneic hamster models using the HPD2NR cell line, intraportal administration of reovirus significantly decreased the number and size of treated tumors in comparison with non-treated tumors. Immunohistochemical examination revealed reovirus replication within the tumor cells but not in the surrounding normal tissue and organs. There were no reovirus-related toxicities and deaths. Our results indicate that intraportal administration of reovirus is effective and safe in immunocompetent and syngeneic hamster models of liver metastases from pancreatic cancer, suggesting that reovirus can be developed into an effective therapeutic modality in future.

PMID: 16142304 [PubMed - in process]

Individualized quality of life, standardized quality of life, and distress in patients undergoing a phase I trial of the novel therapeutic Reolysin (reovirus).

[Carlson LE](#), [Bultz BD](#), [Morris DG](#).

Department of Psychosocial Resources, Tom Baker Cancer Centre Holy Cross Site, 2202 Second St, SW, Calgary, Alberta, Canada. l.carlson@ucalgary.ca

BACKGROUND: The purpose of this study was to evaluate the individualized and standardized quality of life (QL) and psychological distress of patients participating in a Phase I trial of the novel therapeutic reovirus (Reolysin). **METHODS:** 16 patients with incurable metastatic cancer were interviewed prior to being accepted into the phase I trial with a semi-structured expectations interview, the Schedule for the Evaluation of Individual Quality of Life--Direct Weighting (SEIQoL-DW), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the Brief Symptom Inventory (BSI), the Beck Depression Inventory (BDI), and the Spiritual Health Inventory (SHI). **RESULTS:** Patients were able to complete all measures. They felt hopeful and excited about the trial, with about two thirds hoping for disease regression and one third hoping for a cure. The most commonly spontaneously nominated areas of QL were family relationships, activities and friends, and the overall SEIQoL mean index score was 69. Health was nominated by only 38% of the sample. Scores on the SEIQoL were correlated with global QL on the EORTC QLQ C-30. Scores on the BDI and BSI were lower than reported for similar populations, and on the SHI scores were similar to other samples. Global QL on the EORTC QLQ C-30 and depression scores were associated with time to death in the nine patients who had died at the time of writing. **CONCLUSIONS:** Individualized QL is easy to assess in seriously ill cancer patients, provides useful information relative to each individual, and is related to standard QL measures. Repeated assessment of individualized QL of patients in Phase I trials would be a useful addition to the research.

PMID: 15676074 [PubMed - in process]