Strategic Combinations: The Future of Oncolytic Virotherapy with Reovirus

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Abstract

The dominant cancer treatment modalities such as chemotherapy, radiotherapy, and even targeted kinase inhibitors and mAbs are limited by low efficacy, toxicity, and treatment-resistant tumor subclones. Oncolytic viral therapy offers a novel therapeutic strategy that has the potential to dramatically improve clinical outcomes. Reovirus, a double-stranded benign human RNA virus, is a leading candidate for therapeutic development and currently in phase III trials. Reovirus selectively targets transformed cells with activated Ras signaling pathways; Ras genes are some of the most frequently mutated oncogenes in human cancer and it is estimated that at least 30% of all human tumors exhibit aberrant Ras signaling. By targeting Ras-activated cells, reovirus can directly lyse cancer cells, disrupt tumor immunosuppressive mechanisms, reestablish multicellular immune surveillance, and generate robust antitumor responses. Reovirus therapy is currently being tested in combination with radiotherapy, chemotherapy, immunotherapy, and surgery. In this review, we discuss the current successes of these combinatorial therapeutic strategies and emphasize the importance of prioritizing combination oncolytic viral therapy as reovirus-based treatments progress in clinical development.

Introduction

The last decade has witnessed exciting breakthroughs in a novel treatment paradigm for cancer: oncolytic virotherapy. Oncolytic viruses (OV) are viruses that selectively grow, replicate within, and kill tumor cells while leaving untransformed cells unharmed. Recent advances in molecular biology and genetics have elucidated the mechanisms underpinning viral replication and pathogenicity and spurred the development of therapeutic OV for cancer treatment. The nature of infection with OV makes for a compelling therapeutic strategy: OV replicate exclusively within tumor cells, spreading through the cancerous tissue whereas an inability to replicate in normal tissue can facilitate viral clearance and reduced toxicity. The unique susceptibility of cancer cells to OV infection is a result of the defective immune responses and aberrant cellular signaling that occurs during tumorigenesis. In some tumors, the same mutations that facilitate abnormal and uncontrollable growth also disable the cell’s antiviral defense programs. Without their normal defenses, tumor become susceptible to viral infection. Following virus internalization, OV hijack the cell’s transcriptional and translational machinery and trigger cell death by a variety of mechanisms; apoptotic, and immune-mediated pathways. As viral proteins are translated, viral peptide epitopes are expressed on the surface of cancer cells making them targets for clearance by the immune system. Viral gene expression and replication simultaneously triggers the activation of antiviral defenses within the cell, culminating in apoptosis or virus-replication associated necrosis. Numerous viruses have been shown to possess oncolytic properties and are being investigated as anticancer therapeutics. Among the leading viral candidates are the modified or natural form of herpes simplex (1), poliovirus (2), measles (3), poxvirus (4), vaccinia (5), vesicular stomatitis (6), and reovirus. Reovirus is one of the leading OVs in therapeutic development (REOLYSIN, Oncolytics Biotech Inc.) and is in phase I, phase II, and phase III clinical trials internationally. Reovirus has also been tested in combination with a variety of established treatment modalities. In this review, we provide a background on reovirus oncolytic virotherapy and discuss the evidence for combinatorial treatment strategies pairing reovirus with radiation, chemotherapy, surgery, and immunotherapy. We believe reovirus virotherapy may be an important addition to clinical practice, but the value of reovirus therapy will emerge when synergistic combinations are identified and optimized.

Reovirus

Respiratory Enteric Orphan virus, commonly known as the reovirus, is widely prevalent in the human population but not associated with any known human disease. Reovirus has been isolated from the respiratory and gastrointestinal tracts and is referred to as an “orphan” virus because infection is asymptomatic (7). In the United States, as many as 63% of adults 20 to 30 years of age carry antibodies against reovirus; in children 1 to 5 years of age, 10% have antibodies against reovirus (8). Taxonomically,
Reovirus is a member of the Reoviridae viral family. The family Reoviridae consists of nonenveloped, double-stranded (ds) RNA viruses with 9 to 12 genome segments, an icosahedral capsid, and range in size from 60 to 80 nm in diameter (9). Reovirus is 80 nm in diameter and has an RNA genome that is 24 kb long. Unlike viruses with a ds DNA genome, like adenoviruses and herpes simplex viruses, the decreased genomic stability provided by an RNA backbone makes genetic engineering more difficult and more prone to hazardous mutation. In DNA viruses, genetic manipulation provides a way to suppress pathogenicity and increase tumor-targeting specificity and oncolytic potency (10). However, even without engineered capabilities, reovirus is pathologically benign and tumor cytotoxic, making it an appealing OV for therapeutic development.

The initial link between reovirus and selective replication within cancer cells dates back to 1977 when reovirus was shown to infect and replicate within mammalian tumors and transformed cell lines, but not untransformed cells (11). The mechanism for selective reovirus infection remained unclear until murine cell lines transfected with genes encoding the EGFR demonstrated an increased likelihood of reovirus infection and viral peptide synthesis relative to cells with a nonfunctional, mutated EGFR (12). Later work used a truncated form of the EGFR lacking the extracellular ligand-binding domain to demonstrate that reovirus infection is facilitated by EGFR-mediated tyrosine protein kinase signaling pathways rather than binding to EGFR itself (13).

The EGFR kinase signaling pathway is one of the dominant regulators of growth, proliferation, and survival in mammalian cells. In short, ligand binding to EGFR results in the autophosphorylation of the receptor's cytoplasmic domain leading to the recruitment of adaptor molecules (Shc and Grb2) that help activate the small G protein Ras by exchanging GTP for GDP on Ras and therefore converting it to an activated state (14). Activated Ras-GTP then activates multiple pathways involved in cellular proliferation, including the pathways for MAPKs, PI3K, and ERKs (15). Eventually, by demonstrating that constitutive activation of the Ras oncogene resulted in enhanced susceptibility to reovirus infection, the Ras signaling pathway was established as the key to reovirus-mediated oncolysis (Fig. 1; ref. 16). When the Ras signaling pathway is activated, the normal cell defenses against viral infection are disrupted (17). The Ras pathway inhibits the phosphorylation of the ds RNA-dependent protein kinase (PKR), which normally is responsible for preventing viral protein synthesis. Without PKR, viral translation and entrance into the viral lytic cycle occurs. Activated Ras signaling is now believed to affect reovirus replication in multiple ways. Ras activation enhances viral uncoating and disassembly, increases the generation of viral progeny with enhanced infectivity, and accelerates the release of progeny through enhanced apoptosis (18).

Although reovirus tumor selectivity has been well documented, it is important to note that infection of untransformed cells does occur. Mutations in the Ras signaling pathway enhance reovirus infectivity, but are not an absolute criteria for infection (16,19). Early reports of reovirus pathogenicity proposed a role for reovirus infection in the development of pediatric conditions including cholestatic hepatitis and extrahepatic biliary atresia (20,21). More commonly, reovirus infects cells in the respiratory and gastrointestinal tracts (22). As many as 50% of adults ages 20 to 30 years carry antibodies against the virus and in some studies up to 100% seropositivity in adult populations has been reported (8,23). The prevalence of seropositivity among potential patients may limit the potency of therapeutic reovirus administration. In the ongoing clinical trials of reovirus, a low level of productive infection of
normal cells is likely responsible for the observed treatment-related adverse events. Reported cases of myalgia, fever, fatigue, nausea, and vomiting are congruent with viral pathophysiology in humans (24). Despite some infection of untransformed cells, reovirus infections are usually benign; the potent cytotoxic functions of reovirus infection occur primarily in tumor tissue.

### Mechanism of Tumor Lysis

Ras genes are well established as the most frequently mutated oncogenes in human cancer and it is estimated that at least 30% of all human tumors exhibit aberrant Ras signaling (25). The prevalence of Ras mutations is a strong argument for the adoption of anticancer therapeutics that target cells with overactive Ras signaling. Although the specificity of reovirus for activated Ras pathways is widely accepted, the exact mechanism of reovirus-induced cell death remains controversial. Among the theories behind reovirus cytotoxicity, three mechanistic categories exist: necrotic cell death, apoptotic cell death, and immune-mediated cell death. The evidence of primarily necrotic cell death comes from the examination of pathologic specimens via IHC from mouse xenograft models of human head and neck squamous cell carcinoma (26). The specimens demonstrated extensive cell death caused by viral replication and cell lysis, but evidence of apoptotic signaling was absent. Later work further characterized the necrotic reovirus-induced cell death and reported that it occurs independently of caspase and NF-κB signaling (27). Despite these findings, virus-induced apoptosis is currently believed to be the dominant mechanism of reovirus oncolysis and is initiated by viral capsid proteins during viral endocytosis (28). The viral capsid proteins, including the viral adhesin molecules σ1 and σ1s, trigger apoptotic pathways characterized by activation of initiator caspases-8 and -9 and release of cytochrome c and Smac/DIABLO into the cytosol (29). Efforts to elucidate the exact signaling networks that culminate in tumor cell apoptosis are ongoing (30,31). The immunomodulatory impact of reovirus infection is gaining prominence as a mechanism of oncolysis (32). Reovirus triggers a multi-tiered immune response. As the reovirus viral machinery hijacks protein synthesis pathways in the target cell, viral proteins are expressed in class I MHC. Cytotoxic CD8⁺ T cells recognize the reovirus antigens in the class I MHC; and lyse the infected cell (33). Reovirus infection of tumor has also been shown to stimulate dendritic cell (DC) maturation and induce natural killer (NK) cell recruitment, activation, and cytotoxicity (34). In acute myeloid leukemia samples, reovirus infection induced secretion of the proinflammatory cytokine IFNγ and the chemokine RANTES from the leukemic blasts and simultaneously activated NK cells and peripheral blood mononuclear cells (PBMC; ref. 35). Future work will clarify the mechanisms by which reovirus infection provokes an antitumor adaptive immune response.

Regardless of the mechanism of tumor lysis, reovirus therapy has demonstrated therapeutic applicability. As a monotherapy, reovirus administration generates antitumor responses across a broad range of tumor histologies. Tumor regression has been observed in colorectal and ovarian cancer models (36), xenograft breast cancer models and against primary breast tumor samples (37), prostate xenograft models and six organ-confined prostate cancer patients (38), hamster models of liver metastases from pancreatic cancer (39), and glioblastoma stem-like cells (40). Although the initial monotherapeutic results may indicate some therapeutic activity, OVIs as standalone therapies have rarely been shown to induce complete, durable regressions of established tumors in vivo (41). We believe that the power of reovirus therapy lies in synergistic combinations with complementary treatment modalities.

### Combination Radiotherapy

Ionizing radiation is an important treatment strategy for a variety of tumor types. However, some tumors are resistant to radiotherapy; overexpression of EGFR, activating mutations of Ras, and Akt phosphorylation have all been associated with increased radiation resistance (42–44). Combining radiotherapy with reovirus therapy offers the possibility of spatial synergy whereby the two treatment modalities target and eliminate two different cell populations; reovirus infects and lyzes tumor cells with activated Ras pathways and radiation eliminates tumor cells without Ras activation. Radiation may also increase tumor cell susceptibility to reovirus infection and accelerate viral replication (45). *In vitro* and *in vivo*, in human melanoma, head and neck cancer, and colorectal cancer cell lines, the combination of radiation and reovirus treatment was synergistic and increased tumor apoptosis relative to either treatment as monotherapy (46).

The inaugural combination reovirus clinical trial treated 23 patients with advanced solid tumors in a phase 1 dose-escalation study using intratumoral reovirus and palliative radiotherapy (47). Trial patients were split into low-dose (20 Gy in five fractions) and high-dose (36 Gy in 12 fractions) cohorts. In the low-dose cohort, 2 of 7 patients obtained a partial response and 5 patients had stable disease. In the high-dose cohort, 5 of 7 patients had a partial response and 2 had stable disease. This trial demonstrated the safety of combination radiotherapy and reovirus therapy and established that reovirus oncolysis is not diminished by concurrent administration of high-dose radiation. In the subsequent phase II trial, 16 pretreated patients with a variety of cancers received intratumoral injection of reovirus and low-dose fractionated radiotherapy (20 Gy of radiation was given in five consecutive daily 4 Gy fractions; Oncolytics Biotech, 2009). Out of 14 patients evaluable for response, 4 patients had partial responses and 9 had stable disease. The encouraging data from combination radiotherapy and reovirus administration increased interest in identifying other therapeutic combinations.

### Combination Chemotherapy

Chemotherapeutic drugs have demonstrated potential in augmenting the cytotoxicity of reovirus therapy. The combination of reovirus and gemcitabine, a deoxycytidine analog, significantly increased the survival of ID8 tumor-bearing C57BL/6 mice compared with either agent as monotherapy (48). Gemcitabine is an FDA-approved antiviral cancer chemotherapy known to inhibit myeloid-derived suppressor cells (MDSC). Although reovirus monotherapy has been shown to induce MDSC accumulation in the tumor microenvironment, combination with gemcitabine eliminated the MDSC accumulation. Reovirus has also demonstrated efficacy in chemotherapy combinations in tumor models of head and neck cancer. Relative to reovirus monotherapy, combination treatment with reovirus, paclitaxel, and cisplatin significantly increased survival.
in nude mouse tumor model of Cal27, a human cell line from tongue epithelium (49). Importantly, the authors report that there was no increased cytotoxicity produced by the combination platin-taxel chemotherapy and reovirus. Paclitaxel and reovirus combination therapy has also been shown to be synergistic in models of non–small cell lung cancer (50). Following these encouraging preclinical results, reovirus therapy moved into multiple clinical studies.

Building off of preclinical work testing gemcitabine, the first combination reovirus chemotherapeutic clinical trial tested gemcitabine and REOLYSIN in 16 patients with advanced malignancies including head and neck, breast, cervical, and colorectal cancers (51). Of the 10 evaluable patients, 1 patient with metastatic nasopharyngeal carcinoma had a partial response whereas 6 other patients had stable disease for 4 to 8 treatment cycles. The authors recommend advancing this therapeutic combination in further platin-taxel chemotherapy and reovirus. Paclitaxel and immune responses (like gemcitabine) must be carefully dosed because they pose the risk of exacerbating reovirus toxicities. This is a major consideration for the ongoing phase II study of REOLYSIN in combination with gemcitabine for patients with advanced pancreatic adenocarcinoma (NCT00998322) and the combination of reovirus and cyclophosphamide, a nitrogen mustard alkylating agent (REO 012).

Other chemotherapeutic agents that have been tested in combination with reovirus include carboplatin, paclitaxel, and FOLFIRI (folinic acid, fluorouracil, and irinotecan). In a phase I/II trial of REOLYSIN and carboplatin and paclitaxel chemotherapy, of the 31 patients who were evaluable, 1 patient had a complete response, 6 patients had partial response, and 9 patients had partial disease (52). The success of this study led to the launch of a phase III, randomized, double-blind study in patients with platinum-refractory head and neck cancers (NCT01166542). The testing of docetaxel and reovirus has also produced positive initial results. In a phase I study of REOLYSIN and docetaxel in 25 patients with a variety of advanced, heavily pretreated cancers, researchers observed one complete response and three partial responses (53). The docetaxel, REOLYSIN therapeutic combination is now in phase II testing in patients with metastatic, castration-resistant prostate cancer (NCT01619813).

As REOLYSIN and chemotherapeutic combinations advance in clinical development, greater efforts are being made at preselecting patients who will benefit from therapy. Such "precision medicine" strategies attempt to effectively match patients with therapies based on a patient-specific predictive biomarker. In the case of oncolytic reoviral therapy, the biomarker used to predict response to reovirus is mutation in the Ras signaling pathway. Early clinical trials of REOLYSIN did not prioritize selecting patients with Ras-based molecular abnormalities. However, in more recent clinical trials, patients are screened for KRAS mutation, BRAF mutation, and EGFR mutational status and amplification. By only enrolling patients with a molecular indication of Ras signaling, we may be able to avoid administering reovirus to patients who will not benefit from therapy. The recently completely enrolled phase II trial of paclitaxel and carboplatin in patients with non–small cell lung cancer had the inclusion criteria of KRAS, BRAF, or EGFR activation (NCT00861627). The ongoing trial of reovirus in combination with FOLFIRI and bevacizumab in patients with metastatic colorectal cancer necessitates KRAS mutation (NCT01274624).

**Combination Immunotherapy**

With the advent and clinical successes of anticancer immunotherapeutic agents, there is increasing interest in understanding the immune-mediated component of oncolytic virotherapy (54). Viral infections commonly elicit an inflammatory response marked by the release of cytokines and chemokines and a coordinated action between innate and adaptive immune cells. The hope of OV immunotherapy is that the virus-induced immune response helps redirect the functional innate and adaptive immune responses toward the tumor. With the immune system trained and honed to tumor, greater tumoricidal activity can be initiated and an immunological memory response can prevent cancer recurrence.

One important contribution of oncolytic virotherapy is to localize immune cells near the tumor. Viral replication is a well-established trigger for the chemotaxis and accumulation of cytotoxic lymphocytes to the site of infection (55). During oncology, reovirus-infected melanoma cells secrete RANTES, IL8, MIP-1β, and MIP-1β, thereby creating a proinflammatory milieu that elicits a chemotactic response (56). Reovirus infection induces homing of NK cells, cytotoxic CD8+ T cells, and DCs to the tumor microenvironment and increases tumor antigen expression and presentation by DCs and NK cell activation (57).

However, reovirus infection can also localize suppressive populations. Infection with reovirus initially increases the frequency of MDSCs and Tregs in the spleen and ascites of OC murine models (58). This spike in the numbers of suppressive cell populations may provide a mechanism for minimizing the "collateral damage" incurred during an antiviral immune response. The transience of the observed antiviral immune response is also important for establishing the therapeutic efficacy of reovirus: by day 10 postreovirus injection, the suppressive cells had decreased and increased numbers of CD4+ and CD8+ T cells with elevated IFNy levels within the tumor.

Reovirus is also being used in combination with anticancer mAb therapies. The combination of reovirus and trastuzumab produced augmented antitumor immunity and inhibited tumor growth in a Her2-overexpressing xenograft model of gastric cancer (59). In this model, the cytotoxic synergy of the combination therapy appeared to be mediated by TRAIL signaling: TRAIL levels increased after combination treatment and an anti-TRAIL antibody inhibited cell toxicity caused by the combined treatment. In addition to direct oncolysis, there is early evidence that reovirus virotherapy may increase antibody-dependent cell-mediated cytotoxicity (ADCC), an important mechanism in antibody-mediated tumor clearance (60).

In ADCC, innate immune cells, primarily NK cells, provide antitumor cytotoxicity after the Fc receptor on the immune cell is triggered by binding to the Fc portion of the therapeutic antibody (61). ADCC is an important mechanism of action of mAb therapy with rituximab, trastuzumab, and cetuximab (62–64). Recent work demonstrated that reovirus is not only directly cytotoxic to chronic lymphocytic leukemia (CLL) cells, but also activates NK cells and enhances ADCC-mediated killing of CLL in combination with the anti-CD20 mAb rituximab (65). Additional research is needed to see whether the reovirus-mediated enhancement of ADCC is applicable to other tumor types and other antibody therapies.

The combination of reovirus therapy with checkpoint blockade strategies has also demonstrated promising results. In a B16
murine melanoma model, administration of systemic anti-PD-1 antibody along with intratumoral injection of reovirus significantly enhanced survival relative to reovirus alone (66). Immune analysis revealed that PD-1 antibody therapy enhanced the ability of NK cells to kill reovirus infected targets and that the combination therapy led to a reduction in Treg activity. The combination of reovirus and checkpoint blockade is theoretically appealing because it targets two distinct components of tumor immunosuppression. Virally mediated oncolysis can increase immune cell homing to the tumor and generate tumor antigens for uptake by DCs, whereas checkpoint inhibition can bolster effector cell responses by blocking inhibitory signaling. These complementary antitumor mechanisms have the capacity to act synergistically to effect tumor eradication. However, the recent report of augmented toxicities in the combination trial of ipilimumab and nivolumab reinforces the importance of monitoring toxicities when combining immunostimulatory therapies with checkpoint inhibitors (67).

Finally, the combination of reovirus with a cytotoxic adoptive cellular therapy (ACT) offers another promising anticancer therapeutic strategy. ACT involves reinfusing in vitro stimulated and expanded autologous or allogeneic lymphocytes to induce tumor regression (68,69). A variety of different immune effector subsets have been used in ACT: T cells transfused with chimeric antigen receptors, tumor-infiltrating T (TIL) cells, lymphokine-activated killer (LAK) cells, and cytokine-induced killer cells. Combining reovirus administration with ACT may improve reovirus virotherapy by providing a mechanism for avoiding circulating antireoviral neutralizing antibodies (nAb). nAbs bind virus and subsequently block viral attachment to cellular surface receptors, inhibiting viral infection and replication. Immunologic analysis of patients enrolled in reovirus clinical trials has consistently detected circulating nAbs (47,52,70). This humoral immune response presents a significant barrier to intravenously administered reovirus reaching, colonizing, and eliminating disseminated tumor beds.

Interestingly, some OV can conceal themselves within hematopoietic cells and benefit from natural tumor trafficking to deliver virus efficiently to the tumor (71). Recent work has demonstrated the potential of loading reovirus onto “cell carriers” to evade nAb and directly target tumor. In a model of ovarian cancer, using LAK and DCs as cell carriers protected reovirus from the nAb present in the ascites of ovarian cancer patients (72).

Additional research supports the viral carriage capacity of PBMCs and showed that innate immune effector cells, including NK cells, can transport virus and are even stimulated by reovirus to kill tumor targets (73). The prevalence of metastatic disease in cancer patients makes systemic administration a preferable route for oncolytic viral therapy and an improved understanding of how immune cells can shield and deliver OVs will guide how best to administer reovirus in future studies.

**Conclusion**

Oncolytic virotherapy with reovirus has the potential to augment many of the current standard cancer therapies. Exciting results have been observed in combination strategies with all major modalities of cancer treatment, including the burgeoning field of immunotherapy. Similarly to immunotherapy, an attractive element of OV therapy is its capacity to target disseminated tumor tissue throughout the body. Because of its specificity for transformed tissue, systemic administration of reovirus may eliminate dispersed cancer cells and generate an immune response in metastatic tumor sites. This dissipated mechanism of action may be crucial in generating an anticancer immune response to the multiple tumor antigens that exist in the tumor microenvironment. However, to realize the promise of reovirus as a therapeutic partner in rational combination strategies, challenges must be overcome. Primarily, drug combinations must balance antiviral and antitumor immunity. Antitumor immunity is required to clear tumor and sustain a durable response, but antiviral immunity inhibits the viral replication needed for direct oncolysis. Secondly, the ideal route for reovirus administration must be identified. In systemic administration, the virus must evade the circulating complement and nAb of the humoral defense system to act on the tumor. Utilizing cell carriers offers a potential avenue for evading nAb, but more work is needed to identify appropriate carriers and define dosing strategies. Despite these challenges, reovirus oncolytic virotherapy has already demonstrated impressive clinical results and future research will identify additional synergistic combinations that can further augment the clinical benefit of combination reovirus therapy.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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