Global Journal of Microbiology Jan. 14, 2021, Vol 2, No 1

Global *Journal of Microbiology*
2021; 2(1): 17-26.
ISSN Online: 2766-9513; ISSN Print: 2766-9505
Website: http://naturescholars.com
Email: glo_j_mic@126.com
Publisher: Scholars Publishing, LLC

Review

Research Progress of Reoviruses in The Treatment of Ovarian Cancer

Jianhua Sun[1], Cunjian Yi [1,✉]

[1]Department of Obstetrics and Gynecology, Jingzhou No1 People's Hospital and First Affiliated Hospital of Yangtze University, Jingzhou, 434023, China.

✉ **Correspondence**
Cunjian Yi, Department of Obstetrics and Gynecology, The First Clinical Medical College of Yangtze University; Jingzhou First People's Hospital, Jingzhou 434023, Hubei, China.Email:Cunjiany@163.com. Telephone number: 13339738010.

Received: October 31, 2020; Accepted: November 30, 2020; Published online: January 14, 2021.
Cite this paper: Jianhua Sun, Cunjian Yi. (2021) Research progress of reoviruses in the treatment of ovarian cancer. *Global Journal of Microbiology*, 2(1):17-26. http://naturescholars.com/gjmic.020102.
https://doi.org/10.46633/gjmic.020102.

Abstract

Ovarian cancer is one of the most common malignant tumors in the female reproductive system. At present, the first choice of treatment is surgery, postoperative adjuvant chemotherapy and radiotherapy. However, advanced ovarian cancer is resistant to current chemotherapeutic drugs, so the treatment of advanced ovarian cancer is still facing great challenges, and there is an urgent need for new treatments. In recent years, with the development of therapeutic methods, oncolytic viruses have attracted more and more attention. Oncolytic viruses can self-replicate, target and replicate in tumor cells, selectively kill tumor cells and induce the body to produce specific anti-tumor immune response pathways to achieve targeted therapy purposes, and ultimately lead to tumor cell lysis and death. At present, the main ones discovered for clinical trials include reovirus, herpes simplex virus-1, adenovirus, vaccinia virus, Newcastle disease virus, measles virus and so on. Among them, in recent years, reoviruses have received more attention in the treatment of tumors. This article mainly reviews the research of oncolytic reoviruses in the treatment of ovarian cancer.

Key words: Oncolytic virus; Reovirus; Ovarian Cancer; Tumor Therapy.

Introduction

Ovarian cancer is the most lethal malignant tumor in the female reproductive system. It is reported that there are about 300000 new cases and 185000 deaths in the world every year (1). About 60% of ovarian cancer patients are diagnosed as advanced, missed the opportunity of surgery, and poor prognosis (2). With the progress of the times, the detection technology and treatment methods are constantly updated, but the mortality of advanced ovarian cancer cells caused by chemotherapy resistance and other factors is increasing year by year. Chemotherapy drugs are the main challenge in the treatment of ovarian cancer, but the effect is not ideal due to the drug resistance of tumor cells. The

standard first-line treatment for patients with ovarian cancer is surgery and radiotherapy combined with platinum and paclitaxel. Although most advanced patients will have remission after standard treatment, most patients will still relapse in a few months or years (3). Oncolytic virus refers to the natural or genetically recombined virus, selectively infects cancer cells, kills and lyses cancer cells through the replication of the virus itself, releases the virus and continues to invade cancer cells to play a role. The tumor antigen released by cancer cell lysis can also cause immune response, which can guide the immune system to attack the cancer cells and even the distal lesions. Oncolytic virus has the advantages of high killing efficiency, good targeting, small adverse reactions and avoiding drug resistance (4).

Reovirus is a pioneer in oncolytic virus (OV) field. At present, phase I, II and III clinical trials are being carried out internationally, and it has been proved to be effective in the treatment of breast cancer, brain cancer, lymphoma and ovarian cancer (5). As a potential new cancer therapy, oncolysis and induction of anti-tumor immune effect are the two mechanisms of reovirus in the treatment of cancer. At the same time, the combination of traditional treatment methods has become a new research hotspot. In this paper, the correlation of reovirus in the treatment of ovarian cancer is reviewed, and it may provide theoretical guidance for further preclinical trials.

1. Characteristics of reovirus and its oncolytic mechanism

Reovirus is a kind of nonpathogenic double stranded RNA virus, which exists in human respiratory tract and gastrointestinal tract (6). Reovirus belongs to the genus of reovirus in the family Reoviridae. The gene fragment consists of 10 dsRNA fragments, encoding 8 structural proteins and 4 nonstructural proteins (7). The diameter of reovirus is 80 nm and the length of gene is about 24 Kb (8). As a natural oncolytic virus, reovirus has the characteristics of replication and cleavage in tumor cells, resulting in multiple mutations of genes in abnormal signal transduction pathway during the occurrence and development of tumor. Therefore, reovirus can preferentially replicate in tumor cells by using this abnormal cell signal transduction (9) (Figure 1). In the cell lines transfected with epidermal growth factor receptor (EGFR) gene, the sensitivity of reovirus infection and viral peptide synthesis was significantly increased (10). Ras signaling pathway is a key regulator of eukaryotic cell growth and proliferation (8). About 30% of human cancers are related to the activation of Ras mutation. Ras protein is an important element in regulating cell proliferation signal pathway. If the protein is continuously activated, it can lead to abnormal cell proliferation, which leads to tumor occurrence (11). In transformed cells and tumor cells, EGFR induces Ras phosphorylation and activation through coding receptors erb2 and SOS. The activated Ras inhibits the activity of protein kinase (PKR), resulting in increased sensitivity to reovirus replication (12, 13). In nontransformed cells, the invasion of reovirus can lead to the activation of double stranded RNA dependent protein kinase (PKR), which further phosphorylates eIF2 α (eIF2 α) in eukaryotic cells, thus hindering virus replication. Therefore, reovirus can only proliferate in a few or no normal cells. (Figure 2)

Reovirus can induce the death of tumor cells through different anti-tumor mechanisms. First, reovirus has direct oncolytic effect in tumor treatment. In addition, after the tumor cells are ruptured by reovirus, the release of antigen in tumor cells leads to specific immune response. Secondly, reovirus can also promote the secretion of a large number of inflammatory factors and chemokines, leading to a series of immune response (14). For example, reovirus can stimulate the activation of NK cells in peripheral blood of metastatic rectal cancer, thus enhancing the body's anti-tumor immune response (15). At the same time, it can induce autophagy and promote the infection of host cells by reovirus (16). Thirukkumaran et al had reported the signal pathway of virus therapy for breast cancer and

found that the gene expression profile of htb133 and MCF7 breast cancer cells treated by reovirus shows that the members of nuclear factor kappa B (NF-κB) family are significant, which is the first time to prove that reovirus can play a role in the treatment of breast cancer through NF-κB signal pathway (17).

2. Reovirus therapy for ovarian cancer

2.1 Reovirus monotherapy

The phase I clinical trial using reovirus is an internal single therapy for 18 patients with advanced solid tumors, including soft tissue sarcoma, melanoma, breast cancer and head and neck tumors (18). However, Thirukkumaran and others used reovirus for the first time in the treatment of prostate cancer with safety and good tolerance (19). Reovirus as a single drug treatment method for tumor, a single intratumoral injection of reovirus can lead to the regression of human U87 glioblastoma (20). In addition, for mouse models with Ras activity, multiple injections of reovirus can eliminate 65% of the tumor (20). More than 20% of ovarian cancer is associated with Ras activation (21). However, activated Ras is not a necessary condition for the effective effect of reovirus in the treatment of tumors. It has been reported that the activation of effective regulatory factors of Ras signaling pathway can also lead to the antitumor effect of reovirus (22). There is 47% of ovarian adenocarcinoma peritoneal fluid samples carried a point mutation at codon 12 of K-Ras gene (23). Hwang et al had reported that Ras could regulate the occurrence and development of ovarian cancer through other signaling pathways. Ras MMPs is related to biological activities such as proliferation and migration of ovarian cells. Ras protein mediates Raf-MEK1/2-ERK1/2 signaling pathway to induce cell death and promote metabolism (24).

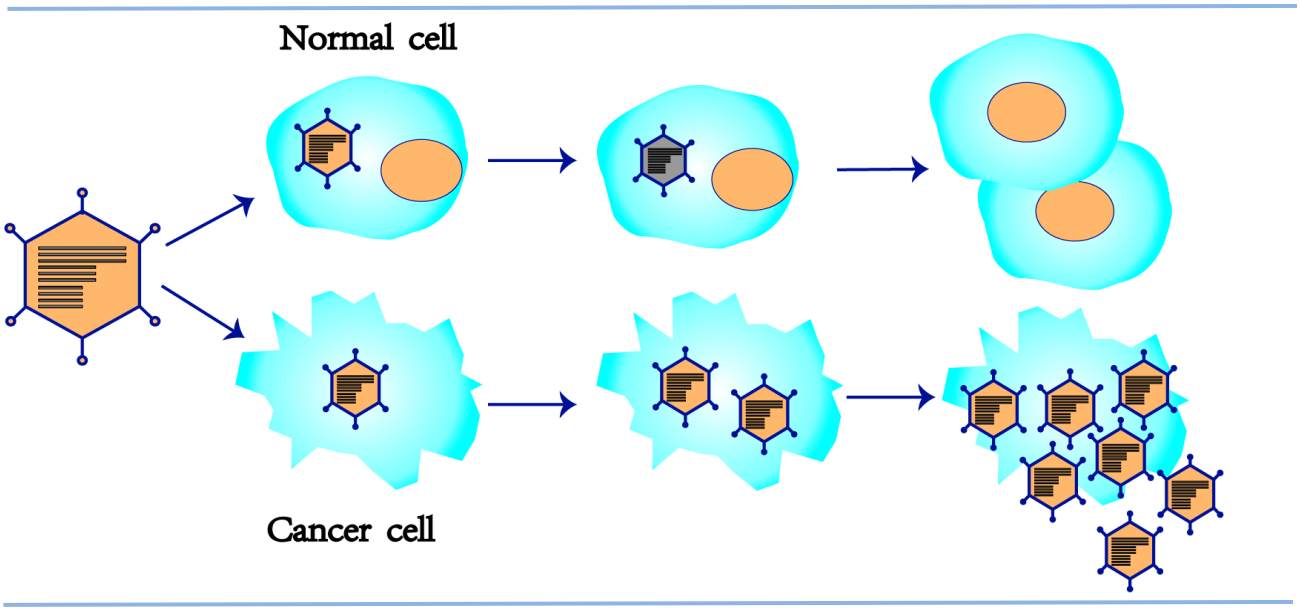

Figure 1 Infection process of reovirus on normal and tumor cells.

It is known that in ovarian tumor cells, EGFR is highly expressed in ovarian cancer (25), and EGFR can regulate and induce the activation of RAS, and the activated Ras can inhibit the activation of PKR, thus reovirus can successfully replicate and proliferate tumor cells, and achieve the oncolytic effect in tumor cells. Hirasawa et al (21) carried out in vivo and in vitro experiments on reovirus in female mice and human ovarian cancer tissue in vitro. When reovirus was directly inoculated into ovarian tumor of mice, the tumor volume was significantly reduced, and the samples in vitro were also found to be susceptible to reovirus infection. At the same time, intraperitoneal injection of live virus every 2

weeks can prolong the survival period (21). Moreover, in the ascites model of human ovarian cancer mice, reovirus has a therapeutic effect of 90% on ovarian tumors with extensive intra-abdominal metastasis (21).

2.2 Reovirus combined with radiotherapy

In clinical application, it is found that the effect of reovirus alone is limited. The data of phase II clinical trial prove that reovirus combined with other anti-tumor therapy may improve or enhance the efficacy and prognosis of patients (5). Radiotherapy is one of the therapeutic methods for various types of tumors, but some tumors are tolerant to radiotherapy; overexpression of EGFR, activation of Ras and phosphorylation of Akt are all related to radiation tolerance (26-28). Radiation can cause single or double strand breaks of DNA (29). However, for oncolytic viruses, isolation of DNA damage proteins and inhibition of DNA repair mechanism play a synergistic role in radiotherapy (30). Ovarian cancer is a kind of radiosensitive malignant tumor (31). Radiotherapy is generally used for patients with ovarian cancer who relapse repeatedly or fail to achieve satisfactory tumor reduction surgery, which is called palliative treatment in foreign countries (32, 33). Several studies have shown that radiotherapy can increase the sensitivity of tumor cells to reovirus and promote the replication function of the virus. Compared with single therapy, combined therapy has better synergistic effect and can increase the apoptosis of tumor cells(28, 34). Phase I and phase II clinical trials combined treatment of advanced solid tumor effect is obvious, phase I first combined treatment proved the safety of both, while the remission is related to the radiation dose. Phase II combined therapy uses low-dose segmented treatment and obtains exciting data. At present, there are few reports about reovirus combined with radiotherapy in the treatment of ovarian cancer, which needs multidisciplinary cooperation and joint efforts.

2.3 Reovirus combined with chemotherapy

At present, the treatment of ovarian cancer is surgical resection combined with platinum chemotherapy, but most patients will still relapse (35). Platinum compounds are DNA destroying substances, and proliferating cancer cells are more likely to be damaged by these platinum compounds (36). For patients with recurrent diseases, retreatment with paclitaxel once a week showed activity, possibly through anti-angiogenesis and direct cytotoxicity mechanisms (37). Combined use of reovirus and cyclophosphamide can reduce the titer of neutralizing antibody and related toxicity in mouse melanoma; however, combined use with cisplatin can significantly inhibit the growth of tumor without affecting the neutralization antibody reaction. At the same time, cisplatin can also reduce the response of inflammatory cytokines to reovirus (38, 39). However, when used in combination with weekly paclitaxel patients, paclitaxel may affect the replication of reovirus in ovarian cancer, which does not improve PFS and other prognostic indicators of patients in this study group (40). Since studies have confirmed that reovirus is cytotoxic under hypoxia (41), weekly use of paclitaxel (proven to target proliferating endothelial cells (42)) may help reverse the hypoxia phenotype. Thereby, reduces the replication of reovirus in ovarian cancer. (44). It was theorized that reovirus and gemitalabine combined to achieve clinical synergetic effect in ovarian cancer treatment.

Reovirus combined with docetaxel can enhance cell apoptosis, and significantly inhibit the growth of ovarian tumor cells and virus replication (43). Reovirus and gemitalabine were combined in ovarian cancer cells implanted in mice to down-regulation of pre-mDSC factors and promote tumor-specific T cell response by inhibiting marrow derived inhibitory cells (MDSCs), resulting in increased survival rate and delayed peritoneal cancer

2.4 Reovirus combined with immunosuppressive therapy

Studies have reported that viral infection in tumors may activate the immune system and produce specific anti-tumor reactions (45). Tumor immune

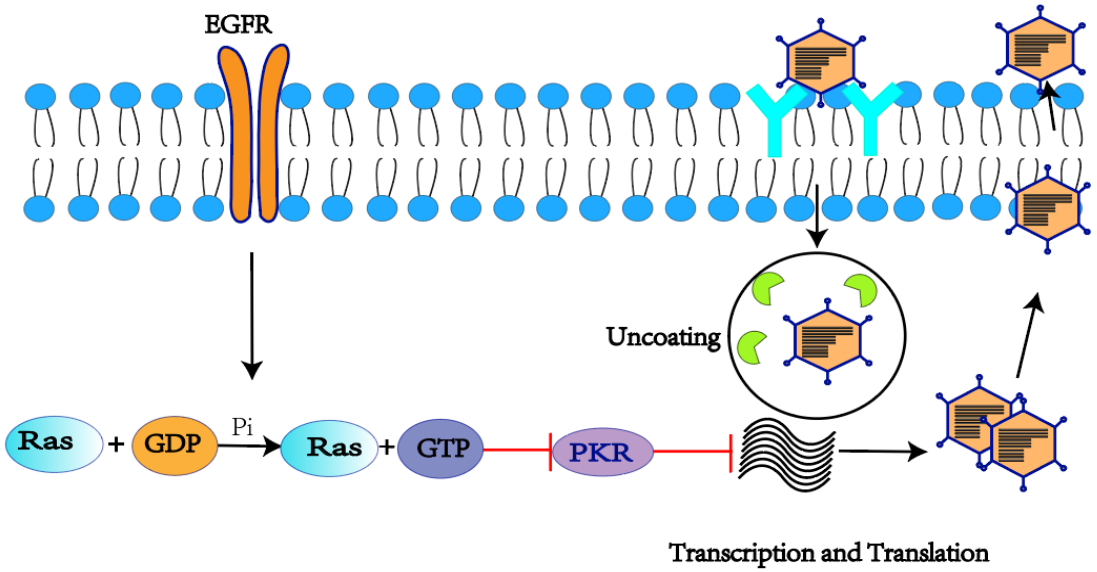

Figure 2. Effect of Ras transformation on reovirus oncolysis

response induced by reovirus: 1) induce the release of many proinflammatory mediators; 2) inhibit the release of immunosuppressant IL-10 and increase the activation of dendritic cells (DC), and recruit effectors from innate immunity and adaptive immunity, including cytotoxic CD8+T lymphocytes (CTL) and NK cells, to promote the lethality of tumor cells (46-48). Reovirus therapy can stimulate pro-inflammatory response, enhance tumor antigen presentation, expose tumor antigen, provide opportunities for dendritic cells and CTLs, and then start tumor specific T cells in vivo and in vitro, and start anti-tumor immunity independent of reovirus (47, 49). Reovirus can anticancer treatment.

Preclinical studies have shown that PD-1 blockers combined with reovirus have a good anticancer effect. Reovirus therapy combined with immunosuppressive drugs may improve the therapeutic effect of reovirus on metastatic tumors (21). It was reported (21) that reovirus injection combined with immunosuppressive agents showed tumor growth inhibition in ovarian tumors of mice, so it was speculated that reovirus combined with immunosuppressive agents had complementary effects. Immunoregulation of immunosuppressive stimulate the generation of anti-tumor immune response, which can promote the anti-tumor immune response of T cells by inhibiting the recruitment of myeloid suppressive cells into the tumor microenvironment, and promoting the anti-tumor immune response of T cells (44), which can also promote the effect of anti-tumor treatment of reovirus to a certain extent. Zhao et al reported (8) that reovirus therapy can promote the secretion of a series of pro-inflammatory cytokines and chemokines. Immunosuppression is an alternative therapy that combines immunoregulation with reovirus as an

agents such as cyclospore A and cyclophospamide also enhanced the anti-tumor effect of reovirus by weakening neutralizing antireovirus antibody (NARAs). This also revealed the protective effect of NARA response on the toxicity of reovirus system. Therefore, the immune response to reovirus is a double-edged sword, which can not only pose a major obstacle to the tumor seeding and anti-tumor effect of the virus, but also protect the severe toxicity of reovirus and promote anti-tumor cytotoxicity

through innate and adaptive responses and promote the anti-tumor cytotoxicity.

Table 1. Mechanisms of oncolytic reovirus combination therapy.

Disease	Drug	Role or function	Mechanism	Ref.
Ovarian cancer	1. Reovirus 2. Radiotherapy 3. Chemotherapy 4. Immunotherapy	Reovirus and the other two are used together to complement each other	1. In normal cells, viral dsRNA is recognized by PKR, which triggers its own phosphorylation and activation. The activation of PKR phosphorylates eIF2, which results in inhibition of protein synthesis. 2. In Ras transformed cells, the stripping of virus into cells was enhanced by high level of cathepsin. Ras inhibited PKR, promoted the synthesis of viral protein and impaired programmed cell death. Ras can also stimulate the growth and survival of tumor cells. Ras can also be activated by EGFR signaling pathway to enhance the oncolytic effect of reovirus.	1.18-25 2.26-34 3.37-44 4.47-49

3. Summary

Reovirus is a dsRNA virus that selectively replicates and lyses tumors in cancer cells. The oncolytic mechanism of reovirus is still unclear, but the Ras signal pathway transformed and activated by Ras is the keyway to test the sensitivity of reovirus replication. The current phase I / II clinical trials of reovirus in the treatment of metastatic ovarian cancer are phase I / II trials in which patients are resistant to cisplatin. As a single therapy, chemotherapy/ or radiotherapy and immunotherapy, reovirus therapy has achieved good results in the treatment of various types of tumors. However, reovirus infection is characterized by the sensitivity of tumor cells to chemotherapy and radiotherapy (8). It can also stimulate tumor cell-mediated immune response, and combined with immunosuppressants can enhance the therapeutic effect of reovirus (50). The oncolytic mechanism of reovirus is complementary to the use of other drugs due to the different ways of inducing cancer cell death. Reovirus does not rely on the direct oncolytic and replication of the virus but provides further anticancer potential by promoting anti-tumor immune-mediated response. It is characterized by stimulating the pro-inflammatory cascade, activating dendritic cells (DCS), NK cells in the tumor microenvironment and recruitment of CTL to jointly promote cytotoxicity. Reovirus infection can also initiate adaptive tumor specific T cell response, which can provide further tumor immunity and protection against subsequent tumor challenges. In addition to the increased cytotoxicity of chemotherapy, some drugs can also enhance the spread of reovirus in tumor cells due to the reduced adverse reactions of gemcitabine, paclitaxel and platinum. In recent years, it has been found that oncolytic virus combined with photodynamic therapy and photothermal therapy has achieved good results in the treatment of hemangioma, pancreatic cancer, head and neck cancer and oral cancer (51, 52). In recent years, photodynamic therapy combined with ablation and radiotherapy has made progress in

ovarian cancer (53, 54). We hypothesized that if reovirus combined with photodynamic therapy is feasible for ovarian cancer? This requires researchers and clinical staff to work together to provide a new treatment for ovarian cancer.

Declarations

1) ***Consent to publication***
   We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2) ***Ethical approval and consent to participants***
   Not applicable.
3) ***Disclosure of conflict of interests***
   We declare that no conflict of interest exists.
4) ***Funding***
   None
5) ***Availability of data and material***
   We declare that the data supporting the results reported in the article are available in the published article.
6) ***Authors' Contributions***
   Authors contributed to this paper with the design (JHS), literature search (JHS), drafting (JHS), revision (JHS and CJY), editing (JHS) and final approval (CJY).
7) ***Acknowledgement***
   None
8) ***Authors' biography***
   None

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

2. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018;68(4):284-96.

3. Korkmaz T, Seber S, Basaran G. Review of the current role of targeted therapies as maintenance therapies in first and second line treatment of epithelial ovarian cancer; In the light of completed trials. Crit Rev Oncol Hematol. 2016;98:180-8.

4. Bell JC, McFadden G. Editorial overview: Oncolytic viruses--replicating virus therapeutics for the treatment of cancer. Curr Opin Virol. 2015;13:viii-ix.

5. Clements D, Helson E, Gujar SA, Lee PW. Reovirus in cancer therapy: an evidence-based review. Oncolytic Virother. 2014;3:69-82.

6. Rosen L, Evans HE, Spickard A. Reovirus infections in human volunteers. Am J Hyg. 1963;77:29-37.

7. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov. 2016;15(9):660.

8. Zhao X, Chester C, Rajasekaran N, He Z, Kohrt HE. Strategic Combinations: The Future of Oncolytic Virotherapy with Reovirus. Mol Cancer Ther. 2016;15(5):767-73.

9. Maitra R, Seetharam R, Tesfa L, Augustine TA, Klampfer L, Coffey MC, et al. Oncolytic reovirus preferentially induces apoptosis in KRAS mutant colorectal cancer cells, and synergizes with irinotecan. Oncotarget. 2014;5(9):2807-19.

10. Strong JE, Tang D, Lee PW. Evidence that the epidermal growth factor receptor on host cells confers reovirus infection efficiency. Virology. 1993;197(1):405-11.

11. Marcato P, Shmulevitz M, Pan D, Stoltz D, Lee PW. Ras transformation mediates reovirus oncolysis by enhancing virus uncoating, particle infectivity, and apoptosis-dependent release. Mol Ther. 2007;15(8):1522-30.

12. Strong JE, Lee PW. The v-erbB oncogene confers enhanced cellular susceptibility to reovirus infection. J Virol. 1996;70(1):612-6.

13. Strong JE, Coffey MC, Tang D, Sabinin P, Lee PW. The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. EMBO J. 1998;17(12):3351-62.

14. Steele L, Errington F, Prestwich R, Ilett E, Harrington K, Pandha H, et al. Pro-inflammatory cytokine/chemokine production by reovirus treated melanoma cells is PKR/NF-kappa B mediated and supports innate and adaptive anti-tumour immune priming. Mol Cancer. 2011;10.
15. El-Sherbiny YM, Holmes TD, Wetherill LF, Black EV, Wilson EB, Phillips SL, et al. Controlled infection with a therapeutic virus defines the activation kinetics of human natural killer cells in vivo. Clin Exp Immunol. 2015;180(1):98-107.
16. Kemp V, Dautzenberg IJC, Limpens RW, van den Wollenberg DJM, Hoeben RC. Oncolytic Reovirus Infection Is Facilitated by the Autophagic Machinery. Viruses. 2017;9(10).
17. Thirukkumaran C, Shi ZQ, Thirukkumaran P, Luider J, Kopciuk K, Spurrell J, et al. PUMA and NF-kB Are Cell Signaling Predictors of Reovirus Oncolysis of Breast Cancer. PLoS One. 2017;12(1):e0168233.
18. Morris DG, Feng X, DiFrancesco LM, Fonseca K, Forsyth PA, Paterson AH, et al. REO-001: A phase I trial of percutaneous intralesional administration of reovirus type 3 dearing (Reolysin(R)) in patients with advanced solid tumors. Invest New Drugs. 2013;31(3):696-706.
19. Thirukkumaran CM, Nodwell MJ, Hirasawa K, Shi ZQ, Diaz R, Luider J, et al. Oncolytic viral therapy for prostate cancer: efficacy of reovirus as a biological therapeutic. Cancer Res. 2010;70(6):2435-44.
20. Coffey MC, Strong JE, Forsyth PA, Lee PW. Reovirus therapy of tumors with activated Ras pathway. Science. 1998;282(5392):1332-4.
21. Hirasawa K, Nishikawa SG, Norman KL, Alain T, Kossakowska A, Lee PW. Oncolytic reovirus against ovarian and colon cancer. Cancer Res. 2002;62(6):1696-701.
22. Gemignani ML, Schlaerth AC, Bogomolniy F, Barakat RR, Lin O, Soslow R, et al. Role of KRAS and BRAF gene mutations in mucinous ovarian carcinoma. Gynecol Oncol. 2003;90(2):378-81.
23. Dokianakis DN, Varras MN, Papaefthimiou M, Apostolopoulou J, Simiakaki H, Diakomanolis E, et al. Ras gene activation in malignant cells of human ovarian carcinoma peritoneal fluids. Clin Exp Metastasis. 1999;17(4):293-7.
24. Hwang CC, Igase M, Okuda M, Coffey M, Noguchi S, Mizuno T. Reovirus changes the expression of anti-apoptotic and proapoptotic proteins with the c-kit downregulation in canine mast cell tumor cell lines. Biochem Biophys Res Commun. 2019;517(2):233-7.
25. Xu H, Zhang Z, Li P, Lu X, Chen B, Lan T. Expression of PKG2 in ovarian cancer and its effect on epidermal growth factor receptor. J BUON. 2020;25(2):729-35.
26. McKenna WG, Muschel RJ, Gupta AK, Hahn SM, Bernhard EJ. The RAS signal transduction pathway and its role in radiation sensitivity. Oncogene. 2003;22(37):5866-75.
27. Gupta AK, McKenna WG, Weber CN, Feldman MD, Goldsmith JD, Mick R, et al. Local recurrence in head and neck cancer: relationship to radiation resistance and signal transduction. Clin Cancer Res. 2002;8(3):885-92.
28. Liang K, Ang KK, Milas L, Hunter N, Fan Z. The epidermal growth factor receptor mediates radioresistance. Int J Radiat Oncol Biol Phys. 2003;57(1):246-54.
29. O'Cathail SM, Pokrovska TD, Maughan TS, Fisher KD, Seymour LW, Hawkins MA. Combining Oncolytic Adenovirus with Radiation-A Paradigm for the Future of Radiosensitization. Front Oncol. 2017;7:153.
30. Kanai R, Rabkin SD, Yip S, Sgubin D, Zaupa CM, Hirose Y, et al. Oncolytic virus-mediated manipulation of DNA damage responses: synergy with chemotherapy in killing glioblastoma stem cells. J Natl Cancer Inst. 2012;104(1):42-55.
31. Dembo AJ. Epithelial ovarian cancer: the role of radiotherapy. Int J Radiat Oncol Biol Phys. 1992;22(5):835-45.
32. Herzog TJ, Pothuri B. Ovarian cancer: a focus on management of recurrent disease. Nat Clin Pract Oncol. 2006;3(11):604-11.
33. Cardenes H, Randall ME. Integrating radiation therapy in the curative management of ovarian

cancer: current issues and future directions. Semin Radiat Oncol. 2000;10(1):61-70.
34. Twigger K, Vidal L, White CL, De Bono JS, Bhide S, Coffey M, et al. Enhanced in vitro and in vivo cytotoxicity of combined reovirus and radiotherapy. Clin Cancer Res. 2008;14(3):912-23.
35. Jennings VA, Ilett EJ, Scott KJ, West EJ, Vile R, Pandha H, et al. Lymphokine-activated killer and dendritic cell carriage enhances oncolytic reovirus therapy for ovarian cancer by overcoming antibody neutralization in ascites. Int J Cancer. 2014;134(5):1091-101.
36. Martin LP, Hamilton TC, Schilder RJ. Platinum resistance: the role of DNA repair pathways. Clin Cancer Res. 2008;14(5):1291-5.
37. Cohn DE, Valmadre S, Resnick KE, Eaton LA, Copeland LJ, Fowler JM. Bevacizumab and weekly taxane chemotherapy demonstrates activity in refractory ovarian cancer. Gynecol Oncol. 2006;102(2):134-9.
38. Qiao J, Wang H, Kottke T, White C, Twigger K, Diaz RM, et al. Cyclophosphamide facilitates antitumor efficacy against subcutaneous tumors following intravenous delivery of reovirus. Clin Cancer Res. 2008;14(1):259-69.
39. Pandha HS, Heinemann L, Simpson GR, Melcher A, Prestwich R, Errington F, et al. Synergistic effects of oncolytic reovirus and cisplatin chemotherapy in murine malignant melanoma. Clin Cancer Res. 2009;15(19):6158-66.
40. Cohn DE, Sill MW, Walker JL, O'Malley D, Nagel CI, Rutledge TL, et al. Randomized phase IIB evaluation of weekly paclitaxel versus weekly paclitaxel with oncolytic reovirus (Reolysin(R)) in recurrent ovarian, tubal, or peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2017;146(3):477-83.
41. Gupta-Saraf P, Miller CL. HIF-1alpha downregulation and apoptosis in hypoxic prostate tumor cells infected with oncolytic mammalian orthoreovirus. Oncotarget. 2014;5(2):561-74.
42. Paez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H, Vinals F, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell. 2009;15(3):220-31.
43. Comins C, Spicer J, Protheroe A, Roulstone V, Twigger K, White CM, et al. REO-10: a phase I study of intravenous reovirus and docetaxel in patients with advanced cancer. Clin Cancer Res. 2010;16(22):5564-72.
44. Gujar SA, Clements D, Dielschneider R, Helson E, Marcato P, Lee PW. Gemcitabine enhances the efficacy of reovirus-based oncotherapy through anti-tumour immunological mechanisms. Br J Cancer. 2014;110(1):83-93.
45. Hirasawa K, Nishikawa SG, Norman KL, Coffey MC, Thompson BG, Yoon CS, et al. Systemic reovirus therapy of metastatic cancer in immune-competent mice. Cancer Res. 2003;63(2):348-53.
46. Errington F, Steele L, Prestwich R, Harrington KJ, Pandha HS, Vidal L, et al. Reovirus activates human dendritic cells to promote innate antitumor immunity. J Immunol. 2008;180(9):6018-26.
47. Gujar SA, Marcato P, Pan D, Lee PW. Reovirus virotherapy overrides tumor antigen presentation evasion and promotes protective antitumor immunity. Mol Cancer Ther. 2010;9(11):2924-33.
48. Errington F, White CL, Twigger KR, Rose A, Scott K, Steele L, et al. Inflammatory tumour cell killing by oncolytic reovirus for the treatment of melanoma. Gene Ther. 2008;15(18):1257-70.
49. Prestwich RJ, Errington F, Ilett EJ, Morgan RS, Scott KJ, Kottke T, et al. Tumor infection by oncolytic reovirus primes adaptive antitumor immunity. Clin Cancer Res. 2008;14(22):7358-66.
50. Phillips MB, Stuart JD, Rodriguez Stewart RM, Berry JT, Mainou BA, Boehme KW. Current understanding of reovirus oncolysis mechanisms. Oncolytic Virother. 2018;7:53-63.
51. Gil M, Bieniasz M, Seshadri M, Fisher D, Ciesielski MJ, Chen Y, et al. Photodynamic therapy augments the efficacy of oncolytic vaccinia virus against primary and metastatic tumours in mice. Br J Cancer. 2011;105(10):1512-21.
52. Khaled YS, Wright K, Melcher A, Jayne D. Anti-cancer effects of oncolytic viral therapy

combined with photodynamic therapy in human pancreatic cancer cell lines. Lancet. 2015;385 Suppl 1:S56.
53. Song K, Kong B, Li L, Yang Q, Wei Y, Qu X. Intraperitoneal photodynamic therapy for an ovarian cancer ascite model in Fischer 344 rat using hematoporphyrin monomethyl ether. Cancer Sci. 2007;98(12):1959-64.
54. Rizvi I, Celli JP, Evans CL, Abu-Yousif AO, Muzikansky A, Pogue BW, et al. Synergistic enhancement of carboplatin efficacy with photodynamic therapy in a three-dimensional model for micrometastatic ovarian cancer. Cancer Res. 2010;70(22):9319-28.