Oncolytic Virotherapy

see Virotherapy.

The concept of virotherapy for the treatment of malignant tumors dates back more than a century and can be divided into replication-competent oncolytic viruses and replication-deficient viral vectors. Oncolytic viruses are designed to selectively target, infect, and replicate in tumor cells, while sparing surrounding normal brain. A host of oncolytic viruses has been evaluated in early phase human trials with promising safety results, but none has progressed to phase III trials. Despite the 25 years that has passed since the initial publication of genetically engineered oncolytic viruses for the treatment of glioma, much remains to be learned about the use of this therapy, including its mechanism of action, optimal treatment paradigm, appropriate targets, and integration with adjuvant agents. Oncolytic viral therapy for glioma remains promising and will undoubtedly impact the future of patient care [1].

Oncolytic viruses (OV) selectively replicate and kill cancer cells, while not harming normal tissue. In addition to this direct oncolytic activity, OVs are also very effective at inducing immune responses to themselves and to the infected tumor cells. OVs encompass a broad diversity of DNA and RNA viruses that are naturally cancer selective or can be genetically engineered. OVs provide a diverse platform for immunotherapy; they act as in situ vaccines and can be armed with immunomodulatory transgenes or combined with other immunotherapies. However, the interactions of OVs with the immune system may affect therapeutic outcomes in opposing fashions: negatively by limiting virus replication and/or spread, or positively by inducing antitumor immune responses. Many aspects of the OV-tumor/host interaction are important in delineating the effectiveness of therapy: (i) innate immune responses and the degree of inflammation induced; (ii) types of virus-induced cell death; (iii) inherent tumor physiology, such as infiltrating and resident immune cells, vascularity/hypoxia, lymphatics, and stromal architecture; and (iv) tumor cell phenotype, including alterations in IFN signaling, oncogenic pathways, cell surface immune markers [MHC, costimulatory, and natural killer (NK) receptors], and the expression of immunosuppressive factors. Recent clinical trials with a variety of OVs, especially those expressing granulocyte macrophage colony-stimulating factor (GM-CSF), have demonstrated efficacy and induction of antitumor immune responses in the absence of significant toxicity. Manipulating the balance between antivirus and antitumor responses, often involving overlapping immune pathways, will be critical to the clinical success of OVs [2].

Oncolytic adenoviruses, such as Delta-24-RGD (Δ24RGD), are replication-competent viruses that are genetically engineered to induce selective cancer cell lysis. In cancer cells, Δ24RGD induces massive autophagy, which is required for efficient cell lysis and adenoviral spread. Understanding the cellular mechanisms underlying the regulation of autophagy in cells treated with oncolytic adenoviruses may provide new avenues to improve the therapeutic effect. In this work, we showed that cancer cells infected with Δ24RGDundergo autophagy despite the concurrent activation of the AKT/mTOR pathway. Moreover, adenovirus replication induced sustained activation of JNK proteins in vitro. ERK1/2 phosphorylation remained unchanged during adenoviral infection, suggesting specificity of JNK activation. Using genetic ablation and pharmacological inactivation of JNK, we unequivocally demonstrated that cells infected with Δ24RGD required JNK activation. Thus, genetic co-ablation of JNK1 and JNK2 genes or inhibition of JNK kinase function rendered Δ24RGD-treated cells resistant to autophagy. Accordingly, JNK activation induced phosphorylation of Bcl-2 and prevented the formation of Bcl-2/Beclin 1 autophagy suppressor complexes. Using an orthotopic model of human glioma xenograft, we showed that treatment with Δ24RGD induced phosphorylation and nuclear translocation

of JNK, as well as phosphorylation of Bcl-2. Collectively, our data identified JNK proteins as an essential mechanistic link between Δ24RGD infection and autophagy in cancer cells. Activation of JNK without inactivation of the AKT/mTOR pathway constitutes a distinct molecular signature of autophagy regulation that differentiates Δ24RGD adenovirus from the mechanism used by other oncolytic viruses to induce autophagy and provides a new rationale for the combination of oncolytic viruses and chemotherapy [3)].

1)

Foreman PM, Friedman GK, Cassady KA, Markert JM. Oncolytic Virotherapy for the Treatment of Malignant Glioma. Neurotherapeutics. 2017 Mar 6. doi: 10.1007/s13311-017-0516-0. [Epub ahead of print] Review. PubMed PMID: 28265902.

2)

Chiocca EA, Rabkin SD. Oncolytic viruses and their application to cancer immunotherapy. Cancer Immunol Res. 2014 Apr;2(4):295-300. doi: 10.1158/2326-6066.CIR-14-0015. PubMed PMID: 24764576.

3)

Klein SR, Piya S, Lu Z, Xia Y, Alonso MM, White EJ, Wei J, Gomez-Manzano C, Jiang H, Fueyo J. C-Jun N-terminal kinases are required for oncolytic adenovirus-mediated autophagy. Oncogene. 2015 Jan 26. doi: 10.1038/onc.2014.452. [Epub ahead of print] PubMed PMID: 25619840.