Targeting glioblastoma with oncolytic adenovirus delta 24

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ONCOLYTIC VIRUSES

Oncolytic viruses have been introduced in cancer treatment in the last two decades, offering new opportunities and hopes for ultimate therapy. Earlier studies had also tried to take advantage of the antineoplastic activity of natural viral species, but it was genetic engineering that led to the production of modified viral strains selectively infecting and killing neoplastic cells.[1] The two major characteristics of oncolytic viruses are their tropism for malignant cells and their augmented cytotoxicity. The strategies employed to achieve oncotropism involve mainly genetic manipulation of viral vectors in order to either turn them against cells expressing specific surface markers or make them capable to multiply only using the machinery of malignant cells.[2] Despite the capability of specifically targeting neoplastic cells, oncolytic viruses are, usually, not capable to completely demise all malignant cells neither in vivo nor in vitro.[3-5] This inherent limitation of oncolytic viruses is caused principally by restrictions in viral infection due to differential expression of surface viral receptors on different types of malignant cells,[6] by barriers in viral infection in the organism[7,8] as well as by the proliferation of noninfected malignant cells and the development of resistance.[9] In this content, significant effort has been invested to increase the viral cytotoxicity. Thus, genetic engineering has been used to modify viral genome in order to produce molecules toxic for cancer cells, in order to increase the viral cytopathic effect. Furthermore, genes have been employed, causing an augmented immune response against virally infected cells,[10] meanwhile other strategies involve the modulation of vessel permeability for viruses[11] and degradation of extracellular matrix.[12]

DEVELOPMENT OF ONCOLYTIC ADENOVIRUS DELTA 24

Among tens or even hundreds of different viruses that have been used to produce oncolytic viral vectors with different genetic manipulations, oncolytic adenovirus delta 24 (Ad-Δ24) stands out due to its high specificity and toxicity for malignant cells accomplished with simple genetic engineering. Ad-Δ24 is a mutant replication-competent adenovirus containing a 24 base pair deletion in early region 1A gene (E1A), expressing a mutant E1A protein which cannot form complex with the retinoblastoma protein (Rb).[13,14] Thus Ad-Δ24, unlike wild-type adenovirus, is unable to force the progression of infected normal cells in S phase that is required for its replication. On the other hand, the mutant virus can replicate in cells with disrupted Rb cell cycle control, like glioma cells.[15] In 2000, the production of Ad-Δ24 was described for the first time along with a detailed description of its cytopathic effect on different glioma cell-lines.[13] But despite its potent antglioma effect, it was obvious even from the first studies that Ad-Δ24 would need further improvements for optimal therapeutic effect.[16]

ADENOVIRUS DELTA 24 DERIVATIVES

A significant number of modifications have been applied on the initial Ad-Δ24 system trying to enhance its specific targeting or to augment its oncolytic potency. The most important effort that has been made to enhance glioma targeting was the insertion of an Arg-Gly-Asp peptide (RGD) in the Ad-Δ24 fiber knob, increasing its affinity with integrins that are highly expressed in gliomas and other tumor cells.[17] Adenovirus infection in general depends on the initial binding to the coxsackievirus and adenovirus receptor (CAR) on the cell surface, followed by a secondary binding to cell surface integrins.[6] Thus, the effect of Ad-Δ24
on glioma cells depends upon the expression of CARs on their surface. The vector produced by the insertion of RGD peptide, named Ad-Δ24-RGD, can overcome this problem since it can directly bind to cell surface integrins.\(^\text{[17]}\)

Furthermore, a number of studies have focused on augmenting the oncolytic potency of Ad-Δ24. Genetic manipulations were used in order to produce vectors expressing p53,\(^\text{[18]}\) TRAIL and Arresten,\(^\text{[19]}\) cytosine deaminase\(^\text{[20]}\) and the tissue inhibitor of matrix metalloproteinase-3.\(^\text{[21]}\) All these Ad-Δ24 derivatives are claimed to be superior to the initial vector but their efficacy awaits further confirmation.

### COMBINATION TREATMENTS

Other studies have tried to improve the therapeutic effect of Ad-Δ24 and its derivatives through combining treatments with apoptotic and chemotherapeutic agents, as well as radiation. Treatment to glioma with Ad-Δ24 or its derivatives has been observed to enhance when combined with TRAIL,\(^\text{[16]}\) adenovirus expressing p53,\(^\text{[22]}\) temozolomide,\(^\text{[23]}\) radiation\(^\text{[24]}\) and topoisomerase I inhibitor irinotecan.\(^\text{[25]}\) Autophagic induced cell death and induction of apoptosis are well-characterized results of Ad-Δ24 infection giving the erratum for combination treatments.\(^\text{[26]}\)

### ANTITUMOR IMMUNE RESPONSE

Another important aspect of oncolytic virotherapy is the induction of augmented antitumor immune response.\(^\text{[27,28]}\) Ad-Δ24-RGD has been shown to induce antiglioma immunity and to enhance the presentation of tumor-associated antigens to immune cells.\(^\text{[29]}\) These findings provide the base for further genetic manipulation of Ad-Δ24 in order to drive the production of immunostimulatory factors (like granulocyte-macrophage colony stimulating factor) that can possibly mediate more robust therapeutic effects.\(^\text{[30]}\)

### CLINICAL TRIALS

Ad-Δ24 and its derivatives have been tested in clinical trials in patients with solid tumors, and more studies are in progress. The first results show that these agents are safe, but their antitumor efficacy remains modest.\(^\text{[30,31]}\) Ad-Δ24-RGd is also being tested in a clinical trial in patients with malignant gliomas and the results are still pending.

### CONCLUSION

Ad-Δ24 is a promising agent for glioblastoma treatment. The initial vector developed 14 years ago providing a platform for further genetic modifications and combination treatments. Since the first clinical trials have assured its safety, it is important for the future research to seek for enhancements in its genome and combining agents that could refine its effect.

### REFERENCES


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