

**26. Protease pretreatment increases the efficacy of adenovirus-mediated gene therapy for the treatment of an experimental glioblastoma model.**  
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Effective virus-mediated gene therapy for cancer will be facilitated by procedures that enhance the low level of gene transfer mediated by replication-deficient, recombinant viral vectors. We found recently that protease pretreatment of solid tumors is a useful strategy for enhancing virus-mediated gene transduction *in vivo*. In this study, we examined the potential of protease pretreatment to improve the efficacy of a gene therapy strategy for prodrug activation that depends on infection with a recombinant adenovirus encoding herpes simplex virus thymidine kinase (Ad-HSV-tk). Trypsin or a dissolved mixture of collagenase/dispase was inoculated into xenografts derived from the human glioblastoma multiforme-derived cell lines, U87 or U251. Ad-HSV-tk was administered 24 h after protease pretreatment, and animals were then treated for 10 days with ganciclovir (GCV). We found that protease pretreatment increased the efficacy of adenovirus mediated HSV-tk/GCV gene therapy in these experimental tumor models. Mice receiving Ad-HSV-tk/GCV after protease pretreatment demonstrated a significantly greater regression of tumors compared with those treated with Ad-HSV-tk/GCV alone. No adverse effects of protease pretreatment were observed. No signs of metastasis were seen either by histological inspection of lymph nodes or by a PCR-based analysis of selected mouse tissues to detect human tumor cells. Our findings indicate that protease pretreatment may be a useful strategy to enhance the efficacy of virus-mediated cancer gene therapy.