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Adenoassociated virus-mediated anti-calcitonin ribozyme therapy inhibits growth and metastasis of prostate cancer

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Gene therapy for cancer offers a possibility of targeted destruction of tumor cells in patients. Moreever, gene therapy can be used as a tool to identify new targets or investigate the role of specific gene(s) in carcinogenesis or cancer progression. Most gene therapy studies have used adenoviral vectors and to a lesser extent, retroviral vectors to deliver genes at the targeted site. However, recent studies suggest that AAV-based vectors can serve as potentially powerful delivery vehicle for cancer gene therapy.

We used recombinant adeno-associated virus (rAAV) to target the expression of a neuroendocrine peptide calcitonin (CT) in prostate cancer cells. This is because the expression of CT and its receptor (CTR) is frequently elevated in prostate cancers (PCs), and activation of CT–CTR axis in non-invasive PC cells induces an invasive phenotype. In contrast, inactivation of CT-CTR axis diminishes tumorigenicity and abolishes the ability of highly invasive PC-3M prostate cancer cells to form distant metastases. We employed rAAV to deliver anti-CT ribozymes (RZ) in PC cells in culture as well as in mouse models of PC. Efficacy of rAAV-anti-CT ribozymes (rAAV-RZ) was assessed either by the measurement of calcitonin secretion in conditioned media or CT immunohistochemistry of tumors. rAAV-RZ demonstrated high functional efficacy as indicated by greater than 90% decline in CT secretion from cultured cells or CT immunostaining of tumors. CT silencing led to a dramatic decline in angiogenic activity as assessed by tube formation under in vitro as well as in vivo conditions. Moreover, administration of rAAV-RZ not only abrogated the growth of pre-implanted tumors in nude mice, but also significantly reduced the growth of spontaneous tumors in LPB-Tag mice. These results demonstrate that rAAV can be successfully used to selectively silence genes associated with cancer progression. The rAAV vector offers several additional advantages over other vectors such as the absence of wt genes, relatively easier incorporation of desired gene or shRNA sequences, relatively easier production of high-titer, contamination-free virus with low immunogenicity, and the ability to infect targeted cells in culture or whole animals.

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