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Delivery of rAAV2/5 to fetal rather than neonatal murine airways allows successful readministration of viral vectors in adult life

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Background

Gene therapy of the fetus rather than the neonate may offer advantages for treatment of genetic pulmonary disorders such as cystic fibrosis (CF). Use of non-integrating vectors such as rAAV for CF gene therapy will require repeated administration. We reasoned that prenatal gene transfer into the lung may induce tolerance allowing repeated administration after birth. In this study we compared gene transfer efficiency of pre- and postnatal rAAV2/5 delivery to the murine airways. We compared immune responses and evaluated the feasibility to readminister rAAV.

Methods

rAAV2/5-β-gal and -fLuc were co-administered to fetuses by intra-amniotic injection or intranasal instillation to neonatal pups. Reporter gene expression was monitored till 3 months by BLI and X-gal staining. Immune response against vector or transgenes was assessed by transduction inhibition assay, ELISPOT, ELISA and FACS.

Results

Transient reporter gene expression was obtained in murine airways. Luciferase expression in lung declined less between 1 and 3 months after fetal (3-fold drop, $p<0.01$) than after postnatal delivery (15-fold drop, $p<0.001$). 3 months after gene delivery transduction efficiency of airways was 4% after fetal and 1.5% after postnatal delivery. Next, we compared readministration of rAAV at 3 months after first delivery. Four weeks after readministration, the BLI signal was 3-fold higher in lung and 7-fold higher in nose in the fetal than in the postnatal group. Analysis of serum neutralizing antibodies (nAb) demonstrated a 16-fold lower titer after fetal delivery. Our initial data indicate that fetal gene delivery outperforms postnatal gene delivery and allows readministration of rAAV.