AAV Gene Therapy for Alcoholism: Inhibition of Mitochondrial Aldehyde Dehydrogenase Enzyme Expression in Hepatoma Cells

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Resumen

Most ethanol is broken down in the liver in two steps by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH2) enzymes, which metabolize down ethanol into acetaldehyde and then acetate. Some individuals from the Asian population who carry a mutation in the aldehyde dehydrogenase gene (ALDH2*2) cannot metabolize acetaldehyde as efficiently, producing strong effects, including facial flushing, dizziness, hypotension, and palpitations. This results in an aversion to alcohol intake and protection against alcoholism. The large prevalence of this mutation in the human population strongly suggests that modulation of ALDH2 expression by genetic technologies could result in a similar phenotype. scAAV2 vectors encoding ALDH2 small hairpin RNA (shRNA) were utilized to validate this hypothesis by silencing ALDH2 gene expression in human cell lines. Human cell lines HEK-293 and HepG2 were transduced with scAAV2/shRNA, showing a reduction in ALDH2 RNA and protein expression with the two viral concentration assayed (1 x 10(4) and 1 x 10(5) vg/cell) at two different time points. In both cell lines, ALDH2 RNA levels were reduced by 90% and protein expression was inhibited by 90% and 52%, respectively, 5 days post infection. Transduced HepG2 VL17A cells (ADH+) exposed to ethanol resulted in a 50% increase in acetaldehyde levels. These results suggest that gene therapy could be a useful tool for the treatment of alcoholism by knocking down ALDH2 expression using shRNA technology delivered by AAV vectors.

Palabras clave

Palabras clave de autor:gene therapy; AAV; alcoholism; ALDH2; shRNA
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