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Development of a Gene Therapeutic Approach to Cardiomyopathy in Desmin-Deficient Mice

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Desmin is a type III intermediate filament, which is mainly ex- pressed in muscle cells and most abundantly found in cardiac muscle cells. Its filamen- tous network is essential for cells in order to cope with mechanical stress as it con- tributes to its structural integrity. Desminopathy represents a form of myofibrillar my- opathies connected to mutations in the desmin-coding gene (DES). Patients suffering from desminopathies typically develop progressive muscle weakness and/or cardiomyopa- thy (CMP) in their mid 20s or 30s. 74% of these patients show muscle weakness combined with cardiac symptoms, while 22% only present with cardiac symptoms. 2% of idiopathic dilated cardiomyopathies can be traced back to an undiagnosed desminopathy. As for most hereditary diseases, no etiologic therapy is currently available.
Aim of this study was to investigate whether an adeno assiciated virus (AAV) mediated gene transfer of the DES-cDNA in desmin-deficient (DKO) mice could prevent or attenuate the development of the desminopathy-associated CMP.
Murine DES-cDNA under the control of the cardiac troponin-T promoter was packaged into AAV serotype 9 capsids (AAV-DES). Dose finding experiments sug- gested the use of a high vector dose (3x1012) to reconstitute desmin expression in DKO mice. In order to study the therapeutic effect, 2 month-old DKO mice were randomly assigned to treatment (AAV-DES, n=10) or vector control group (AAV-LUC, n=10) and a dose of 3x1012 vector genomes was administered into the tail vein. 12 wildtype litter mates were used as controls. Left ventricular function was measured after 3, 6, and 9 months as well as at the end of the study. Finally, pressure volume loops were measured and samples were prepared for histological and molecular analyses.
With an average AAV-DES-mediated desmin expression of 23±3% (mean ± standard error of the mean, SEM) of the median wildtype level, AAV-DES treated animals had a significantly improved fractional shortening (FS) at the end of the study (AAV-DES 46±4% (mean±SEM), AAV-LUC 32±6% (mean±SEM), $p<0.03$). Pressure volume loops confirmed the protective effect on the development of a cardiomyopathy. On the molecular level, ANP and BNP were significantly decreased in DKO mice treated with AAV-DES. Heart weight to tibia length ratios in this group were comparable to wildtype controls and notably reduced when compared to the luciferase control group ($p<0.03$). AAV-DES treatment also attenuated hypertrophy in desmin-deficient animals measured by heart weight to tibia length ratios and myocyte cross sectional areas. In addition, quantification of Masson's trichrome stainings revealed a significant reduction of cardiac fibrosis in AAV-DES treated mice ($p<0.005$).
Systemic administration of AAV-DES resulted in a long term desmin expression and a significant attenuation of CMP in DKO mice. These findings suggest a potential future role for a gene therapeutic approach for desminopathies in patients.