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AAV-mediated cardiac transfer of the desmin cDNA ameliorates progression of cardiomyopathy in desmin-deficient mice

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Background: Desmin is a type III intermediate filament which plays a central role in maintaining the structural integrity of cardiac and skeletal muscle cells. Mutations in the desmin coding gene are associated with a heterogeneous phenotype involving cardiomyopathies, cardiac conduction disease and myopathy. Desminopathies are most commonly diagnosed in adults in their mid 30s and show a progressive course, with cardiac involvement as the most important factor limiting prognosis. As of today, only symptomatic treatment is available for patients. Similar to patients with distinct defects in the desmin gene, knockout mice develop dilative cardiomyopathy compared to wildtype littermates.

Aim of our study was to determine whether an adeno-associated-viral vector (AAV) mediated gene transfer of the intact desmin cDNA can either prevent or slow-down the development of cardiomyopathy in desmin-deficient (des-KO) mice.

Methods: murine desmin cDNA under the control of the TNNT2 promoter was packaged into AAV serotype 9 capsids and were intravenously injected into adult des-KO mice. AAV9-luciferase vectors were used as controls. Left ventricular function was monitored using echocardiography before vector application and 3 months, 6 months and 9 months after treatment. After left heart catheterisation to assess pressure-volume (PV)-loops mice were sacrificed after 10 months for histological and molecular analyses.

Results: AAV9-mediated transfer of the desmin cDNA resulted in an efficient reconstitution of desmin with intact intercalated discs. Echocardiographic analyzes revealed a fractional shortening of 38 ± 4% (n=10) in desmin deficient mice treated with desmin cDNA compared to 28 ± 4% (n=9) in AAV9-luciferase control-treated mice (1-way ANOVA, p < 0.05). PV-loops showed significant improvement in cardiac contractility with increased dp/dtmax in AAV9-desmin-treated mice 7742 ± 539 mmHg/sec (n=7) compared to luciferase-treated mice 5901 ± 466 mmHg/sec (n=9) suggesting an amelioration of the cardiomyopathy phenotype in AAV9-desmin-treated mice.

Conclusion: Our study establishes an approach to specifically treat desmin-related cardiomyopathy by targeting gene expression into the myocardium through systemic application of AAV vectors.