

UTROPHIN UP-REGULATION HELPS MAINTAIN NORMAL CARDIAC GEOMETRY IN A GENE THERAPY MODEL FOR DUCHENNE MUSCULAR DYSTORPHY HEART DISEASE

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Duchenne muscular dystrophy (DMD) is the most common childhood muscle wasting disease. DMD sufferers rarely survive past their mid-twenties succumbing to respiratory or heart failure. Skeletal and heart muscle pathology in DMD are caused by mutations in the dystrophin gene. Gene therapy strategies to restore dystrophin expression bring the hope of a cure for DMD. Unfortunately, treatment of the heart remains largely unexplored. A critical question for heart gene therapy is the percentage of cells which must be repaired. We have previously shown that expressing a mosaic pattern of dystrophin in 50% of cardiomyocytes prevents heart disease (Bostick et al 2008 *Cir Res*102:121-130). A surprising finding from this study was up-regulation of a dystrophin homolog, utrophin, strictly in dystrophin-negative cardiomyocytes. This finding implicates a role for utrophin in modulating DMD heart disease. To answer this question, we developed a mouse model expressing 50% mosaic dystrophin in the heart with utrophin expression knocked out. We then analyzed cardiac physiology, anatomical/histological morphology and dystrophin/utrophin expression. We found that 50% mosaic dystrophin in the absence of utrophin normalized electrocardiographic parameters of the heart. Left ventricular catheterization revealed normal stroke volume, cardiac output and markers of contractility. Additionally, dobutamine stress response and mouse survival were normalized. Interestingly, utrophin knockout mice exhibited increased end-diastolic and end-systolic volumes. Our findings support the previous hypothesis that 50% mosaic dystrophin expression in the heart ameliorates DMD heart disease. However, the increased end-diastolic and end-systolic volumes indicate a potential role for utrophin in strengthening the integrity of the heart.

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