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"REDUCING SARCOLIPIN EXPRESSION PREVENTS THE PROGRESSION OF DUCHENNE MUSCULAR DYSTROPHY CARDIOMYOPATHY"

By

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Wednesday, Nov 9th, 2022
1:00 P.M.
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ABSTRACT

Aim- Sarcolipin (SLN), an inhibitor of sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) is expressed at high levels in the ventricles of animal models and Duchenne muscular dystrophy (DMD) patients. The major goal of this study is to test the hypothesis that reducing or abolishing SLN expression improves cardiac SERCA function, which improves SR and mitochondrial Ca^{2+} (Ca^{2+}_m) handling and prevents or slows down the development of cardiomyopathy in mouse models of DMD.

Approach- The SLN heterozygous and homozygous knockout mice in *mdx* (*mdx:sln*$^{+/-}$ and *mdx:sln*$^{-/-}$) or SLN heterozygous mice in *mdx:utr*$^{-/-}$ (*mdx:utr*$^{-/-}$*:sln*$^{+/-}$) background were used for this study. Age-dependent disease progression and cardiac function were determined by histopathological examinations and by echocardiography. SERCA function and SR Ca^{2+} handling were measured by Ca^{2+} uptake assays in tissue lysates and by single-cell Ca^{2+} transients in isolated ventricular myocytes respectively. Gene expression changes in the *mdx:sln*$^{+/-}$ ventricles were examined by RNA Seq. To study the effect of SLN reduction in Ca^{2+}_m content and mitochondrial function, we chose *mdx:utr*$^{-/-}$ and *mdx:utr*$^{-/-}$*:sln*$^{+/-}$mice. To determine SR Ca^{2+} handling, and Ca^{2+}_m content, single-cell Ca^{2+} transients, and Ca^{2+}_m efflux were measured in isolated cardiomyocytes, respectively. Ca^{2+}_m content and mitochondrial membrane potential were determined by confocal imaging. Mitochondrial respiration was measured using complex activity assays and Seahorse metabolic profiling in ventricular tissue lysates and isolated mitochondria respectively. The mitochondrial structure was evaluated using TEM. The proteomic analysis of the mitochondrial-associated membrane (MAM) region was carried out using LC-MS/MS instrument.

Results- Reducing or abolishing SLN expression improved the SERCA function and SR Ca^{2+} handling in *mdx* hearts. Histopathological analysis shows that fibrosis and necrosis were significantly decreased in the *mdx:sln*$^{+/-}$ and *mdx:sln*$^{-/-}$ mice hearts at all age groups tested when compared to that of age- and sex-matched mdx controls. The echocardiographic analysis demonstrated that germline reduction/ablation of SLN expression improved the cardiac function in *mdx* mice. Gene expression changes identified the activation of multiple cardioprotective pathways in *mdx:sln*$^{+/-}$ ventricles.

The *mdx:utr*$^{-/-}$*:sln*$^{+/-}$ mice show improved cardiac function and live longer than *mdx:utr*$^{-/-}$ mice. Germline reduction in SLN expression improved SR Ca^{2+} cycling and reduced Ca^{2+}_m overload in *mdx:utr*$^{-/-}$ ventricles. Furthermore, reducing SLN expression prevented structural and functional loss of mitochondria in *mdx:utr*$^{-/-}$ ventricles. Proteomic analysis of the MAM region revealed that SR-mitochondrial junctions were disrupted in *mdx:utr*$^{-/-}$ ventricles, whereas SLN reduction partially rescued the SR-mitochondrial interaction.

Conclusions- The results of the current study demonstrate that reduction in SLN expression is sufficient to improve the SERCA function and SR Ca^{2+} handling, thereby preventing the progression of cardiomyopathy in mouse models of DMD. In addition, our findings demonstrated that reducing SLN expression can prevent Ca^{2+}_m overload and loss of membrane potential, improve mitochondrial function and prevent structural damage. Taken together our findings suggest that SLN reduction could be a potential therapeutic strategy for the treatment of DMD-associated cardiomyopathy.