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DISSERTATION

"Connexin-43 remodeling: A mechanistic insight into its role in Duchenne muscular dystrophy cardiomyopathy"

by

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10:00 AM
WebEX

ABSTRACT

Duchenne muscular dystrophy (DMD), caused by a loss of function mutation in the dystrophin gene, is the most common and fatal form of muscular dystrophy, affecting 1 in every 3,500 – 5,000 males. Despite the benefit of therapies directed toward skeletal and respiratory muscle improvement, the lack of effective treatments tailored for DMD cardiac failure has limited DMD patient survival. Thus, the focus has shifted toward studying principal DMD-specific cardiac pathomechanisms to better understand the disease and develop novel treatments to improve patient outcomes. Aberrant expression of the cardiac gap junction protein connexin-43 (Cx43) has been suggested to play a role in the development of cardiomyopathy in the mdx mouse model of DMD, however a mechanistic understanding of this association is lacking.

Here, we identified a reduction of phosphorylation of Cx43 serine residues S325/S328/S330 in human and mouse DMD hearts. We hypothesized that hypo-phosphorylation of S325/S328/S330-Cx43 triggers pathological Cx43 redistribution to the lateral sides of cardiomyocytes (remodeling) in DMD hearts, exacerbating the cardiac phenotype. Therefore, we generated knock-in mdx mice wherein the Cx43 serine-triplet was replaced with either phospho-mimicking glutamic acids (mdxS3E) or non-phosphorylatable alanines (mdxS3A). The mdxS3E but not mdxS3A mice were resistant to Cx43 remodeling with a corresponding reduction of deleterious Cx43 hemichannel activity. MdxS3E cardiomyocytes displayed improved intracellular Ca^{2+} signaling and a reduction of NOX2/reactive oxygen species (ROS) production, two prominent features of DMD. Furthermore, mdxS3E mice were protected against inducible arrhythmias, related lethality and the development of cardiomyopathy.

To mechanistically link dystrophin loss to Cx43 remodeling, we next targeted the microtubule cytoskeleton, which transports Cx43 and is pathologically hyper-densified in DMD hearts. Pharmacological reduction of microtubule density by colchicine administration reduced both NOX2/ROS and levels of oxidized Ca^{2+}/calmodulin protein-kinase II (CaMKII), both implicated in negatively regulating Cx43, in mdx hearts. Subsequently, we found S325/S328/S330-Cx43 hyper-phosphorylation and a protection against Cx43 remodeling in unstressed and isoproterenol (Iso)-stressed mdx hearts following colchicine treatment. Colchicine treatment also protected mdx mice against Iso-induced microtubule densification, cardiac hypertrophy and damage and reduced Cx43 hemichannel activity in vitro. Together, these results demonstrate a mechanism of dystrophic Cx43-remodeling and suggest that targeting Cx43 may be a therapeutic strategy to prevent heart dysfunction and arrhythmias in DMD patients.