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"The Role of Connexin 43 in Cardiac and Skeletal Muscle of Mouse Models of Duchenne Muscular Dystrophy"

by
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BS, 2016, Connecticut College, New London, CT

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Thursday, December 8th, 2022
2:00 PM
G609

Join Zoom Presentation:
https://rutgers.zoom.us/j/98146172929?pwd=NUVJY3dyOHE4bEgxNWFKM2JVdkxiZz09

Meeting ID: 981 4617 2929
Password: 367

ABSTRACT

Duchenne muscular dystrophy (DMD), the most common and severe form of muscular dystrophy (1-in-5,000 males, 1-in-10 carriers), is caused by inherited X-linked recessive mutation(s) in dystrophin, rendering it non-functional. Decades of research have improved skeletal and respiratory muscle-targeted therapies; however, tailored, effective treatments lack for the emergent leading cause of death: DMD-associated cardiomyopathy. In the DMD mouse model (mdx) cardiac and skeletal muscle, gap junction channel protein Connexin-43 (Cx43) is aberrantly expressed. Proper Cx43 localization and function at the cardiac intercalated disc (ID) are regulated by post-translational phosphorylation of Cx43-carboxy-terminus residues S325/S328/S330 (pS-Cx43). In DMD hearts, absence of dystrophin, a microtubule-(MT)-binding protein, results in a hyperdensified, disorganized MT cytoskeleton, yet the mechanistic link with pS-Cx43 remains unaddressed. To gain insight into the MT-pS-Cx43 relationship, mdx and pS-Cx43-deficient (mdxS3A) mice were treated with an MT polymerization inhibitor, Colchicine (Colch). Colch protected mdx, not mdxS3A mice, against Cx43 remodeling, prevented severe isoproterenol-induced arrhythmias, improved MT directionality, and enhanced pS-Cx43/tubulin interaction. In pS-Cx43-mimicking (mdxS3E) mice, MT directionality and density normalized. The data suggest bidirectional regulation: improved MT directionality reduces Cx43 remodeling, and pS-Cx43 is necessary and sufficient to regulate MT organization.

Cx43-copy number reduction has proven to be a novel target for DMD cardiomyopathy, so we investigated its therapeutic potential in our newly established DMD manifesting carrier model (mdx/WT chimeras). In our model, genetic reduction of Cx43 in mdx/WT-Cx43(+/−) chimeras protected against cardiac and, surprisingly, skeletal muscle fiber damage. The data suggest that Cx43(+/-) prevented Cx43 remodeling in the heart and dystrophic cardiac and skeletal pathological markers. The latter corrective effect of Cx43 reduction is not observed in mdx mice. In dystrophic skeletal muscle, immunofluorescence experiments detected an overlap of Cx43 and F4/80+ in the interstitial space neighboring Cx43 non-expressing fibers and aberrant Cx43 hemichannel activity in cell-sorted F4/80+/CD11b+ macrophages. These results suggest targeting Cx43 may be a potential strategy for attenuating dystrophic skeletal muscle manifestation. Collectively, the results demonstrate a mechanism of dystrophic Cx43 remodeling and suggest that modulation of Cx43 may be a crucial, novel cardioprotective target understanding and developing novel, functional treatments for both DMD and DMD carrier-associated cardiomyopathy.