

SPECIAL RESEARCH SEMINAR

Presented by the Center for Vascular and Heart Research at the Fralin Biomedical Research Institute at VTC



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In Person Seminar: Connexin 43: A New Player in Duchenne Muscular Dystrophy and Associated Cardiomyopathy

Aberrant expression of the cardiac gap junction protein connexin-43 (Cx43) has been suggested as playing a role in the development of cardiac disease in the mdx mouse model of Duchenne muscular dystrophy (DMD); however, a mechanistic understanding of this association is lacking. Here, Dr. Fraidenraich and his team identified a reduction of phosphorylation of Cx43 serines S325/S328/S330 in human and mouse DMD hearts. The team hypothesized that hypophosphorylation of Cx43 serine-triplet triggers pathological Cx43 redistribution to the lateral sides of cardiomyocytes (remodeling). Therefore, they generated knockin mdx mice in which the Cx43 serine-triplet was replaced with either phospho-mimicking glutamic acids (mdxS3E) or nonphosphorylatable alanines (mdxS3A). The mdxS3E, but not mdxS3A, mice were resistant to Cx43 remodeling, with a corresponding reduction of Cx43 hemichannel activity. MdxS3E cardiomyocytes displayed improved intracellular Ca²⁺ signaling and a reduction of NADPH oxidase 2 (NOX2)/ROS production. Furthermore, mdxS3E mice were protected against inducible arrhythmias, related lethality, and the development of cardiomyopathy. Inhibition of microtubule polymerization by colchicine reduced both NOX2/ROS and oxidized CaMKII, increased S325/S328/S330 phosphorylation, and prevented Cx43 remodeling in mdx hearts. Together, these results demonstrate a mechanism of dystrophic Cx43 remodeling and suggest that targeting Cx43 may be a therapeutic strategy for preventing heart dysfunction and arrhythmias in DMD patients.

THURSDAY, JAN. 5, 2023 at 11 a.m.

Room R3012, 2 Riverside Circle.
Or watch via Zoom at <https://virginiatech.zoom.us/j/85276935856>



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