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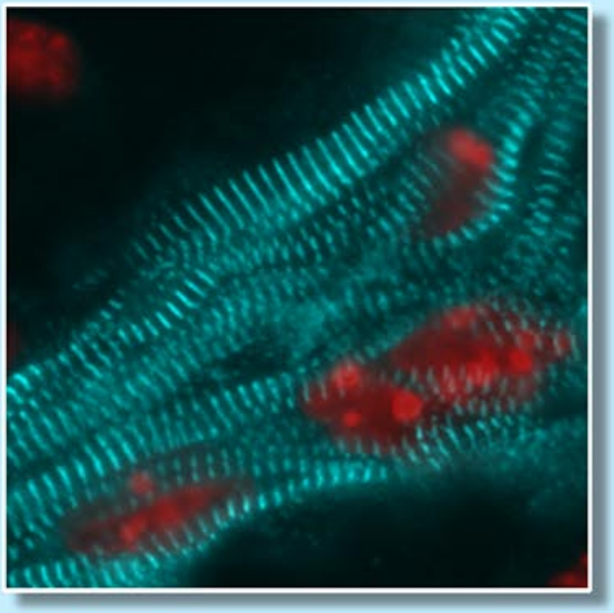

Cardiac Sarcomeres in a Developing Mouse Embryo
(cyan: myomesin, red: DAPI)

Identifying the Role of Non-cardiac Myofibril Isoforms in the Development of Cardiomyopathies

Cardiomyopathies are rare but serious disorders that affect the heart muscle and require lifetime treatment in patients surviving to adulthood. Mutations in cardiac sarcomere components lead to the development of symptomatic cardiomyopathies such as cardiac hypertrophy; however, it has not yet been assessed whether the presence of non-cardiac paralogs of proteins important in sarcomere (and myofibril) structure in the developing heart also contributes to the development of cardiomyopathies. Ablation of CHD4, the catalytic subunit of the Nucleosome Remodeling and Deacetylase (NuRD) complex, a transcriptional repressor, led to the misexpression of non-cardiac isoforms of proteins integral to sarcomere structure. By using a mouse model with a conditional knockout of CHD4 in the developing heart, it could be assessed whether or not the misexpression of these non-cardiac isoforms could lead to impaired cardiac muscle function. Through fluorescent labeling of fast skeletal troponin I2 (TnI2), α-actinin, and smooth muscle myosin heavy chain (SM-MHC), we found that misexpression of non-cardiac sarcomeric isoforms disrupts sarcomere formation, contributing to impaired heart function. Control sarcomeres normally exclude non-cardiac isoforms during formation, but following loss of function of CHD4, developing sarcomeres incorporated misexpressed SM-MHC, and exhibited disrupted structure. Our results suggest that the incorporation of non-cardiac myofibril isoforms in developing cardiac sarcomeres contributes to sarcomere malformation and the development of cardiomyopathies. Identifying the requirement of CHD4 for proper heart development will lead to new treatment strategies for patients with mutations that disrupt this process.