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Author

Cheng, Tik-Chee Jenny

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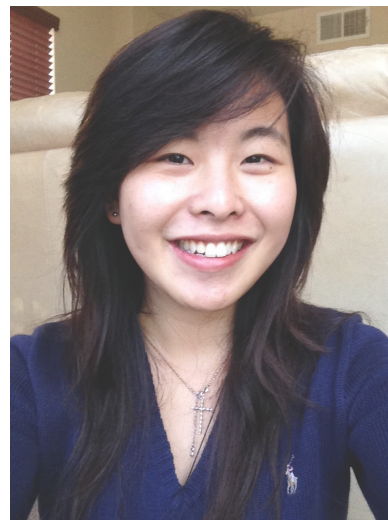
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Effect of CaMKII δ Deletion on Sarcomere Structure

Tik-Chee (Jenny) Cheng, Sukriti Dewan, Andrew McCulloch, Jeff Omens

Jenny Cheng is a senior at Earl Warren College majoring in Bioengineering with a focus in Biotechnology. In Fall 2015, she will be pursuing her PhD in Biomedical Engineering at the University of Wisconsin-Madison, studying cardiovascular pathophysiology for clinical applications.



Heart failure, a progressive condition that is typically undetected and often misdiagnosed, is the leading cause of deaths around the world. The disorder is characterized by the inability of the heart to keep up with the body's demand for blood circulation. It is initiated by structural and functional changes from molecular to systemic levels that result in compensatory physiological changes, commonly termed cardiac remodeling. At first, this remodeling enables the heart to increase its cardiac output to compensate for the change. However, over time, remodeling results in

The disorder is characterized by the inability of the cardiac pump to keep up with the body's demand.

cardiomyopathy, a condition with enlarged left ventricles and/or dilated ventricular walls that can lead to dysfunction and inadequate pumping of blood to the rest of the body. Calcium/calmodulin-dependent protein kinase II (CaMKII) is a protein kinase that can phosphorylate many substrates and regulates a wide range of cellular function. Its role in calcium signaling pathways has been implicated in the pathophysiology of adverse cardiac left ventricular remodeling. Animal models with hypertrophied myocardium showed increased activity and expression of CaMKII δ . Genetically altered mice models with a knockout (KO) elimination of the most abundant cardiac

CaMKII isoform (CaMKII δ) appear to be protected from such dysfunction and hypertrophy.

Normal myocardial function is dependent on the structure of cardiomyocytes, specifically the basic subunits of muscle called sarcomeres. Sarcomeres contract and generate force by utilizing the motor movements of thin and thick filaments, specifically myosin heads and actin filaments. In the intact myocardium, sarcomere length change is assumed to be proportional to muscle cell length changes. This relationship between

cell length and sarcomere length is directly proportional to a decrease in lattice spacing of the myosin-actin filaments as the heart cells, along with the sarcomeres, are stretched. By measuring sarcomere length and lattice spacing in cardiomyocyte-specific CaMKII δ KO mice and wild type (WT) mice (control group), it is then possible to determine how CaMKII δ KO cells change in length and how physiological forces develop.

To measure sarcomere length and lattice spacing, transmission electron microscopy (TEM) was used to image the sarcomeres and myosin-actin filaments of the heart. A contracture solution containing barium chloride and adenosine was used to perfuse

both CaMKII δ KO and WT hearts to stimulate end-systole. This process allows visualization of how CaMKII δ affects heart contraction. Image analysis indicates that sarcomere length and myosin-myosin filament spacing from TEM were greater in the CaMKII δ KO versus WT hearts fixed in the relaxed state. This finding indicates that the contracture solution stimulates contraction at the molecular level, which is the desired effect. Lattice spacing of the myosin-actin filaments in CaMKII δ KO and WT hearts varied between the relaxed and contracted states. Lattice spacing was greater in the CaMKII δ KO versus WT heart fixed in the relaxed state and smaller in CaMKII δ KO versus WT hearts fixed in

the contracted state. Due to the varied results of lattice spacing, further research, such as a more direct approach for measuring sarcomere length and lattice spacing, is needed to understand how loss of CaMKII δ affects the structure and function of the heart. Such studies will allow for a better understanding of how CaMKII can be regulated for prevention or treatment of cardiac hypertrophy and ultimately, heart failure.



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