
Brief Report: Oxidative Stress Mediates Cardiomyocyte Apoptosis in a Human Model of Danon Disease and Heart Failure.

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Authors: Sherin I Hashem, Cynthia N Perry, Matthieu Bauer, Sangyoon Han, Stacey D Clegg, Kunfu Ouyang, Dekker C Deacon, Mary Spinharney, Athanasia D Panopoulos, Juan Carlos Izpisua Belmonte, Kelly A Frazer, Ju Chen, Qiuming Gong, Zhengfeng Zhou, Neil C Chi, Eric D Adler

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Funding Grants: Identification of Novel Therapeutics for Danon Disease Using an iPSC Model of the Disease

Public Summary:

Danon disease is a inherited cause of heart failure due to mutations in a gene called LAMP-2. Patients with Danon disease generally die from heart failure or need heart transplants in their 20s or 30s. In this study we used skin biopsies from patients with Danon disease to make stem cells and then we used the stem cells to make heart cells. We then performed in depth analysis of the Danon disease stem cell derived heart cells and found that they had impaired metabolic and physiologic function. We also treated the cells with a drug called NAC and saw some benefit, but further study is going to be required to determine if this drug has any clinical benefit.

Scientific Abstract:

Danon disease is a familial cardiomyopathy associated with impaired autophagy due to mutations in the gene encoding lysosomal-associated membrane protein type 2 (LAMP-2). Emerging evidence has highlighted the importance of autophagy in regulating cardiomyocyte bioenergetics, function, and survival. However, the mechanisms responsible for cellular dysfunction and death in cardiomyocytes with impaired autophagic flux remain unclear. To investigate the molecular mechanisms responsible for Danon disease, we created induced pluripotent stem cells (iPSCs) from two patients with different LAMP-2 mutations. Danon iPSC-derived cardiomyocytes (iPSC-CMs) exhibited impaired autophagic flux and key features of heart failure such as increased cell size, increased expression of natriuretic peptides, and abnormal calcium handling compared to control iPSC-CMs. Additionally, Danon iPSC-CMs demonstrated excessive amounts of mitochondrial oxidative stress and apoptosis. Using the sulfhydryl antioxidant N-acetylcysteine to scavenge free radicals resulted in a significant reduction in apoptotic cell death in Danon iPSC-CMs. In summary, we have modeled Danon disease using human iPSC-CMs from patients with mutations in LAMP-2, allowing us to gain mechanistic insight into the pathogenesis of this disease. We demonstrate that LAMP-2 deficiency leads to an impairment in autophagic flux, which results in excessive oxidative stress, and subsequent cardiomyocyte apoptosis. Scavenging excessive free radicals with antioxidants may be beneficial for patients with Danon disease. In vivo studies will be necessary to validate this new treatment strategy.

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