LAMP-2 Deficiency Promotes Mitochondrial Damage in Danon Disease

Sherin Hashem, Emily Gault, Anne Murphy, Neil Chi, Eric Adler, Univ of California San Diego, La Jolla, CA

Danon disease is a familial cardiomyopathy associated with impaired autophagic flux due to mutations in the gene encoding lysosomal associated membrane protein type 2 (LAMP-2). The majority of patients die from progressive heart failure in their twenties, yet to date the mechanisms by which LAMP-2 deficiency leads to cardiomyocyte dysfunction and death are not fully understood. To study the underlying molecular pathogenesis, we created induced pluripotent stem cell-derived cardiomyocytes (hiPSC- CMs) from patients with different *LAMP-2* mutations, and reported an increase in apoptosis and mitochondrial oxidative stress. In Danon hiPSC-CMs, undigested mitochondria within double-membrane autophagosomes were frequently observed suggesting impaired mitophagy. Danon hiPSC-CMs displayed increased translocation of PARKIN and p62 on mitochondria, suggesting increased mitochondrial damage. When mitochondrial bioenergetic profile was assessed, Danon hiPSC-CMs showed a severe impairment in mitochondrial respiratory capacity even when offered various oxidizable substrates, suggesting global mitochondrial damage. In addition, Danon hiPSC-CMs demonstrated excessive mitochondrial fragmentation and low mitochondrial membrane potential. *Lamp-2* knockout (KO) mice recapitulated key pathological features observed in Danon patients and their hiPSC-CMs. *Lamp-2* KO mouse hearts exhibited abnormal mitochondria, increased mitochondrial damage, and impaired mitophagy. Interestingly, altered mitochondrial respiration was observed in *Lamp-2* KO mouse hearts before the onset of significant impairment in contractile function. In summary, we have modeled Danon disease using hiPSC-CMs from patients with *LAMP-2* mutations as well as *Lamp-2* KO mice, allowing us to gain mechanistic insight into the pathogenesis of this disease. We demonstrate that LAMP-2 deficiency leads to impairment in mitophagic flux, accumulation of damaged mitochondria, and deterioration of mitochondrial function. Understanding the mechanisms underlying cardiomyocyte dysfunction will have important implications for the treatment of Danon disease as well as a various cardiovascular disorders associated with impaired autophagy.

Disclosure Block:
S. Hashem: None. **E. Gault:** None. **A. Murphy:** None. **N. Chi:** None. **E. Adler:** None.