Maintenance of mitochondrial health becomes a therapy for heart failure

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Heart failure increases with chronological aging. Several processes and pathways contribute for age-related cardiac disease, and these include fibrosis, inflammation, diastolic dysfunction, mitochondrial dysfunction, increased apoptosis and loss of regenerative capacity. In this symposium, I would like to focus on the role of mitochondria in the failing heart. Some patients do not respond to optimized therapies for heart failure and described as “non-responders (non-res)”. We found mitofusion1(Mfn1) was reduced in non-res patients. Cardiac specific Mfn1 depletion resulted in worsening of cardiac phenotype during left ventricle pressure overload. In vitro studies analyzing NRVMs indicated negative regulation of Mfn1 by the β-AR/cAMP/PKA/miR-140-5p pathway, and we also found this mircoRNA increased in non-res patients. Suppression of miR-140-5p, and enhancement of Mfn1 and mitochondrial dynamics would become a therapy for heart failure. We recently found mitochondrial dysfunction developed with a metabolite increased in circulation with aging or heart failure. We did metabolomics studies in aged individuals or patients with heart failure and found oxidized choline increased under these conditions compared to respective controls. We generated murine left ventricular (LV) pressure overload model and found oxidized choline increased both in plasma and failing heart. Administration of oxidized choline deteriorated cardiac function, in contrast, genetic model showed suppression of this metabolite ameliorated systolic dysfunction in LV pressure overload model. Proteomic study indicated that oxidized choline reduced the expression of cytochrome c oxidase subunit1, and metabolomics study showed that both ATP and phosphocreatine level significantly reduced in cardiac tissues of wild type mice administrated with this metabolite. Administration of oxidized choline also reduced muscle strength, induced fibrosis in skeletal muscle, and electron microscopy showed an increase in dysfunctional mitochondria both in the heart and skeletal muscle. Suppression of this metabolite would become a next generation therapy for heart failure.