The Physiological, Pathological and Molecular Basis of Nonalcoholic Steatohepatitis Associated Cardiomyopathy

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MOND mice were fed chow diet (CD) or WD for 8, 16-24, or 48-52 weeks (n=6-8/ group). Trans-thoracic echocardiography was performed and related to cardiac MRI in humans with NASH. H&E, Sirius Red stains and electron microscopy (EM) were performed. Molecular analysis (PCR/Western blot) of pathways related to NASH pathogenesis, and unbiased analysis (RNA Seq) to evaluate the transcriptome were performed. **RESULTS**: *Physiological Changes*: In WD-fed vs CD-fed mice, diastolic dysfunction (increased isovolumetric relaxation time) occurred by 8 wks (NAFL) and persisted up to 52 wks (NASH with bridging fibrosis). Systolic dysfunction (decreased LV fractional shortening) occurred by 8 wks, corrected, and worsened again at 52 wks. Progressive worsening of myocardial performance index and RV systolic function was noted over time in WD-fed mice. This was similar to humans with NASH. *Histology*: Increasing myocardial fibrosis was seen from week 24 (NASH with fibrosis) onwards, with EM showing disruption of Z line, myofibrillar disorganization, mitochondrial abnormalities, gap junction internalization and fibrosis and microthrombi with megakaryocytes. *Cell Signaling*: At 24 wks, WD-fed (vs CD) mice had no differences in lipid metabolism, but showed significant increase ($p< 0.05$) in markers of oxidative stress (superoxide dismutase, NADPH oxidase, NRF2), endoplasmic reticulum stress (ATF4, GRP78, CHOP), inflam-masome activation (NLRP3, ASC, Caspase 1), inflammation (pJNK, NFKB, pERK), and fibrosis (Collagen I and III, MMP13 and α-SMA). *Transcriptome*: Cell cycle and apoptosis pathways were activated by 8 wks with epigenetic changes (Histone 1 -linked networks). At 24 wks, myofibrillar protein synthetic pathways increased with cytoskeletal remodeling proteins, followed by increased fibrogenic and angiogenic signaling and metabolic reprogramming after 36 wks **CONCLUSIONS**: There are several similarities between the pathogenesis of NAC and NASH, providing potential targets for combined therapeutics in the management of these two important disease processes.

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