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

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BACKGROUND: There is a paucity of data on the physiological, pathological and molecular basis of myocardial dysfunction in NASH. The Diet-induced animal model of NAFLD (DIAMOND) develops fatty liver, NASH and bridging fibrosis after 4, 16 and 36 weeks respectively, on western diet (WD). HYPOTHESIS: NASH-associated cardiomyopathy (NAC) is driven by pathways similar to those seen in NASH. AIMS: (1) To determine if the DIAMOND model reproduces the myocardial dysfunction seen in humans with NASH; (2) To determine the histological, cell signaling and transcriptomic drivers of cardiac physiological changes. **METHODS**: DIAMOND 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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NPR-C Accelerates Obesity Induced NASH and Potentiates the Development of HCC

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BACKGROUND. Natriuretic peptide receptor-C (NPR-C) clears circulating natriuretic peptides e. g. ANP by binding and internalization. ANP is decreased and NPR-C expression is increased in obesity a risk factor for NAFLD. In several cell types, NPR-C increases cell proliferation and inflammation which are known oncogenic signals HYPOTHESIS: NPR-C expression is increased in NAFLD and related HCC and can drive oncogenesis by increased cell proliferation and oncogenic signaling AIMS: To define: (1) if NPR-C is overexpressed in human NAFLD and associated HCC, (2) the effects of high-fat diet on NPR-C expression, upstream regulators of NPR-C and its relationship to NAFLD phenotype and HCC in the diet-induced animal model of NAFLD (DIAMOND) which recapitulates the key elements of human disease, (3) the effects of ANP-binding to NPR-C on oncogenesis-related secretome, and (4) the oncogenic potential of NPR-C and its associated mechanisms. **METHODS**: NPR-C expression in normal, NASH and HCC in humans and DIAMOND mice was determined by qPCR and Western blot. Circulating [ANP] was measured by ELISA in normal, NAFL, NASH and HCC in both humans and mice. The effects of ANP ligation of NPR-C on secreted proteins was measured in HepG2 cells using angiogenesis and cytokine arrays. The oncogenic potential of NPR-C was tested by its effects on cell proliferation, migration, invasion and anchorage-independent growth in QGY-7703 cells. Pathway analysis from array studies was used to identify potential signaling pathways. The role of these were assessed the impact of inhibitors on NPR-C mediated oncogenic properties. **RESULTS**: NPR-C expression increased progressively from control to NAFL to NASH to HCC in both humans and in the DIAMOND mice. This was associated with lower circulating ANP in both humans (Normal vs NASH, $p< 0.05$) and in DIAMOND (CD vs WD, $p< 0.05$) mice. ANP ligation of NPR-C revealed SMAD/TAZ as key transcriptional factors related to its effects on the secretome. High fat diet led to a progressive increase in NPR-C expression in DIAMOND mice along with increased SMAD/TAZ expression which was greatest in NASH and HCC. Loss of function of NPR-C with siRNA in QGY-7703 HCC cells resulted in suppressed proliferation, migration, invasion and anchorage independent growth and down- regulated SMAD/TAZ protein expression. Inhibition of SMAD/TAZ pathway with PKA activators (forskolin and 8-bromo-cAMP) inhibited cell proliferation in these cells. CONCLUSION: Obesity and NAFLD increases hepatic NPR-C expression. NPR-C activation may contribute to HCC formation in NASH by its pro-oncogenic properties mediated by activation of SMAD/TAZ transcriptional factor.

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