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Title: Lactosylceramide Promotes Cardiac and Mitochondrial Dysfunction in a Novel *in vivo* Heart Failure Model of Hypoplastic Left Heart Syndrome

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Background: While heart failure (HF) remains the leading cause of death and indication for transplant in patients with Hypoplastic Left Heart Syndrome (HLHS), the molecular mechanisms associated with HF progression remain poorly understood. Increasing evidence suggests that both inflammation and mitochondrial dysfunction have pathogenic relevance in promoting or potentiating cardiac remodeling in HLHS. Our prior data identified significantly increased levels of lactosylceramide (LacCer) in HLHS patient cardiac tissue and peripheral immune cells. While there are currently no HLHS animal models, this study aimed to assess whether exogenous LacCer can recapitulate *in vivo*, some of the cardio-metabolic derangements seen in HLHS and identify potential novel mechanisms of HLHS HF pathogenesis. We hypothesize that aberrant LacCer-mediated signaling drives maladaptive cardiac, lung, and immune cell responses that predispose HLHS patients to progressive cardiac dysfunction.

Methods: A daily dose of 10mg/kg LacCer was delivered to P2 neonatal SD rats by IP injection for 1 week (n= 10 vehicle, n=12 LacCer). Morphometric data was collected and normalized to tibia length. Cardiac mitochondria were isolated from right ventricular (RV) myocardium, and bioenergetics were assessed using the Seahorse Bioanalyzer (Agilent). Mass-spectrometry was used to quantify lipid levels. Gene expression changes in RV and lung were assessed using next-generation bulk RNA-sequencing.

Results: Exogenous LacCer *in vivo* is sufficient to: (A) induce RV hypertrophy and increase lung mass, with no significant changes in the left ventricle (LV), (B) impair cardiac mitochondrial maximal respiration and energetic reserve capacity (C) promote distinct gene expression in 667 genes in RV tissue, altering canonical pathways related to inflammatory, metabolic, cell signaling, and chemical stimulus pathways, (D) promote distinct gene expression in 1,110 genes in lung tissue, altering canonical pathways related to inflammatory, metabolic, and cell signaling pathways (Figure 1).

Conclusions: Together, these data suggest that even in the absence of hemodynamic stress, LacCer plays a role in modulating cardiac dysfunction and lung inflammation *in vivo.* These data therefore highlight a novel rodent model that recapitulates unique aspects of HLHS which can provide a useful mechanistic platform to investigate signaling pathways altered by HLHS pathophysiology.