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Abstract

The heart is the organ with the greatest fatty acid (FA) utilization and heart failure is almost always associated with alterations in cardiac lipid metabolism: diabetes and obesity increase FA use; failing hearts due to increased afterload have reduced FA oxidation. This project focuses on how FAs are acquired for cardiac energy use and why toxicity occurs when excess lipid accumulates. How FAs get from the circulation to parenchymal cells like cardiomyocytes is not known and we will determine why the FA transporter CD36 leads to reduced heart FA uptake. Mice with a deletion of the triglyceride lipolysis enzyme, lipoprotein lipase (LpL, mice denoted hLpL0) have a similar energy use as hearts that are stressed with increased afterload, more glucose and less FA oxidation. hLpL0 mice develop heart dysfunction and compensate poorly to afterload, and we will determine why. Humans with LpL deficiency also have a marked increase in glucose uptake by their hearts, and we will determine how and if subjects with LpL deficiency compensate during exercise. We have created and then corrected several models of lipid accumulation-induced cardiomyopathy, termed lipotoxicity, and have shown that improved heart function and survival does not correlate with the amount of stored triglyceride or FA oxidation. We will study how peripheral tissues modulate heart lipid metabolism and how triglyceride storage in lipid droplets affects heart FA oxidation and lipotoxicity.

This renewal has two aims. Experiments in Aim 1A will study the importance of the FA uptake protein, CD36, in acquisition of lipid by the heart using mice with endothelial and cardiomyocyte specific deletion. We expect to define a basic pathway required for tissue lipid metabolism. We will determine how hearts from hLpL0 mice (Aim1B) and humans with LpL deficiency (Aim1C) compensate for reduced FA uptake. These studies will provide basic information on how hearts adjust in the setting of defective FA uptake. Aim2A will determine why cardiomyocyte specific loss of the triglyceride synthesis enzyme diacylglycerol acyl transferase 1 (DGAT1) causes accumulation of ceramide and diacylglycerol, and cardiac toxicity. Because our previous studies showed a correction of lipotoxicity associated with increased expression of the lipid droplet protein ADRP/Plin2, we will characterize heart lipid metabolism in ADRP knockout mice and then cross them with our lipotoxicity models (Aim2B). The overall objective of our studies is to define pathways that mediate or exacerbate lipotoxic heart disease.