

Cardiac lipids and their role in the diseased heart

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien,
Göteborgs universitet kommer att offentligens försvaras i Hjärtats aula SU, Vita stråket
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av Ismena Mardani

Fakultetsopponent:

Professor Douglas G. Mashek

Department of Biochemistry, Molecular Biology and Biophysics and Department of
Medicine, Division of Diabetes, Endocrinology and Metabolism, University of
Minnesota, USA

Avhandlingen baseras på följande delarbeten

- I. Mardani I, Dalen KT, Drevinge C, Miljanovic A, Ståhlman M, Klevstig M, Scharin Täng M, Fogelstrand P, Levin M, Ekstrand M, Nair S, Redfors B, Omerovic E, Andersson L, Kimmel A.R, Borén J and Levin M.C. **Plin2-deficiency reduces lipophagy and results in increased lipid accumulation in the heart.** *Scientific reports, 2019 May 6;9(1):6909*
- II. Mardani I, Cinato M, Miljanovic A, Drevinge C, Bollano E, Ståhlman M, Levin M, Lindbom M, Scharin Täng M, Klevstig M, Fogelstrand P, Andersson L, Borén J and Levin M.C. **Cardiac-specific overexpression of perilipin 5 promotes physiological hypertrophic remodeling of the heart by fine-tuning calcium-handling regulators.** *Manuscript*
- III. Andersson L*, Mardani I*, Miljanovic A, Cinato M, Koh A, Lindbom M, Klevstig M, Ståhlman M, Fogelstrand P, Swärd K, Ekstrand M, Levin M, Tivesten Å, Adiels M, Bergö M, Proia R, Jeppsson A, Borén J and Levin M.C. **Cardiomyocyte-specific deficiency in glucosylceramide synthase results in dilated cardiomyopathy and premature death in mice.** *Authors contributed equally. *Manuscript*

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Ismena Mardani

Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska akademien, Göteborgs universitet, Sverige, 2019

Abstract

Lipids play an essential role within the heart as they are involved in energy storage, membrane stability and signaling. Changes in cardiac lipid composition and utilization may thus have profound effects on cardiac function. Importantly, the diseased heart is associated with intracellular metabolic abnormalities, including accumulation of lipids. In this thesis, I targeted cardiac lipid droplets (LDs) and membrane lipids using genetically modified mice and cultured cardiomyocytes to investigate how myocardial lipid content and composition affect cardiac function.

In *Paper I*, we investigated the LD protein perilipin 2 (Plin2) and its role in myocardial lipid storage. Unexpectedly, Plin2 deficiency in mice result in increased triglyceride levels within the heart as a result of decreased lipophagy. Even though Plin2^{-/-} mice had markedly enhanced lipid levels in the heart, they had normal heart function under baseline conditions and under mild stress. However, after an induced myocardial infarction, cardiac function reduced in Plin2^{-/-} mice compared with Plin2^{+/+} mice.

We have previously shown in both humans and mice that low levels of cardiac Plin5 are unfavorable for heart function. Therefore, in *Paper II* we tested the hypothesis that forced overexpression of cardiac Plin5 is beneficial for heart function. We found that Plin5 promotes exercise-like effects, inducing physiological hypertrophy with enhanced left ventricular mass, but with preserved heart function. Furthermore, calmodulin-dependent protein kinase II (CaMKII) and phospholamban activities were increased by Plin5 overexpression, indicating enhanced cardiac contractility and calcium handling.

In *Paper III*, we found that the sphingolipid glucosylceramide (GlcCer) accumulates in the human heart following injury. We targeted cardiac *Ugcg* (the gene encoding GlcCer synthase) in mice (h*Ugcg*^{-/-} mice) and found that a significant decrease in GlcCer in cardiomyocytes results in Golgi dispersion and defective autophagy regulation, leading to compromised β -adrenergic signaling. h*Ugcg*^{-/-} mice developed dilated cardiomyopathy and died prematurely from heart failure.

In conclusion, our studies show that dysfunctional cardiac lipid storage plays a role in heart function, both in the healthy and diseased heart. Thus, targeting cardiac lipid accumulation may be a future strategy to delay cardiovascular disease progression.

Keywords: Cardiovascular disease, Lipid droplets, Perilipins, Lipid accumulation, Metabolism, GlcCer.