

Cardiac lipid storage and metabolism following myocardial ischemia

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs Universitet kommer att offentligen försvaras i
hörsal Hjärtat, Vita stråket 12, Göteborg

Torsdagen den 11 juni 2015 kl. 9.00

av Christina Drevinge

Fakultetsopponent: Professor Ellen Aasum
Department of Medical Biology, The Arctic University of Norway, Tromsø

Avhandlingen baseras på följande delarbeten:

I. Cholesteryl esters accumulate in the heart in a porcine model of ischemia and reperfusion

Drevinge C, Karlsson LO, Ståhlman M, Larsson T, Perman Sundelin J, Grip L, Andersson L, Boren J, Levin MC.
Plos One 2013; 8: e61942.

II. Perilipin 5 is protective in the ischemic heart

Drevinge C, Dalen KT, Nastase Mannila M, Scharin-Täng M, Ståhlman M, Klevstig M, Lundqvist A, Wramstedt A, Haugen F, Fogelstrand P, Adiels M, Asin-Cayuela J, Ekestam C, Gådin J, Lee YK, Nebb H, Romeo S, Redfors B, Omerovic E, Levin M, Valen G, Gan LM, Eriksson P, Andersson L, Ehrenborg E, Kimmel A, Borén J and Levin MC.
Manuscript

III. Increased myocardial lipid storage and reduced heart function after a myocardial infarction in *Plin2*^{-/-} mice

Mardani I*, Drevinge C*, Dalen KT, Ståhlman M, Scharin-Täng M, Lundqvist A, Fogelstrand P, Redfors B, Andersson L, Omerovic E, Borén J and Levin MC.

*Equal contribution

Manuscript



UNIVERSITY OF GOTHENBURG

Cardiac lipid storage and metabolism following myocardial ischemia

Christina Drevinge

Department of Molecular and Clinical Medicine , Institute of Medicine
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

ABSTRACT

Myocardial ischemia is associated with cellular- and metabolic adjustments within the heart, including accumulation of lipids. Myocardial lipids are stored in cytosolic droplets, consisting of a core of neutral lipids surrounded by a complex surface containing proteins, such as perilipins. Little is known about how myocardial lipid content and dynamics affect the function of the ischemic heart.

In this study, we investigated cardiac lipid accumulation and the consequences of altered lipid storage and metabolism following myocardial ischemia.

In **Paper I**, we investigated lipid accumulation of in a porcine model of ischemia/reperfusion and we found that cholesteryl esters accumulate in the myocardium following ischemia. The expression of the low density lipoprotein receptor (LDLr) and the low density lipoprotein receptor-related protein 1 (LRP1) was up-regulated, suggesting that cholesteryl ester uptake was mediated by these receptors.

In **Paper II**, we investigated the role of the lipid droplet protein Perilipin 5 (Plin5) in the pathophysiology of myocardial ischemia. In humans, we showed that a polymorphism in the PLIN5 gene is associated with reduced heart function following myocardial ischemia. In mice, Plin5 deficiency dramatically reduced the triglyceride content in the heart. Under normal conditions, *Plin5*^{-/-} mice maintained a close to normal heart function by decreasing fatty acid uptake and increasing substrate utilization from glucose, thus preserving the energy balance. However, during stress or myocardial ischemia, Plin5 deficiency resulted in reduced myocardial substrate availability, severely reduced heart function and increased mortality.

In **Paper III**, we investigated the role of Plin2 in lipid storage and cardiac function following ischemia. We found that deficiency of Plin2 in mice surprisingly resulted in significantly increased levels of triglycerides. The heart function was not compromised in *Plin2*^{-/-} mice in baseline and stress conditions. However, heart function was markedly reduced in *Plin2*^{-/-} mice after induced myocardial infarction.

In conclusion, our findings indicate that dysregulation of myocardial lipid metabolism and storage influences heart function and survival following myocardial ischemia. Furthermore, our findings highlight a role for lipid droplet proteins perilipins in cardioprotection following myocardial ischemia.

Keywords: Lipid accumulation, Myocardial Ischemia, Lipid droplets, Perilipin2, Perilipin5

ISBN: 978-91-628-9370-5