

# Mechanisms for and consequences of cellular lipid accumulation

## – The role of the Very Low Density Lipoprotein (VLDL) receptor

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssal Hjärtat, Bruna Stråket 5, Göteborg.

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**av Jeanna Perman**

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Avhandlingen baseras på följande arbeten:

- I. The VLDL receptor promotes lipotoxicity and increases mortality in mice following an acute myocardial infarction.**  
Perman JC, Boström P, Lindbom M, Lidberg U, Ståhlman M, Hägg D, Lindskog H, Scharin Täng M, Omerovic E, Mattsson Hultén L, Jeppsson A, Petursson P, Herlitz J, Olivecrona G, Strickland DK, Ekroos K, Olofsson SO, Borén J.  
J Clin Invest. 2011 Jul 1;121(7):2625-40.
- II. Hypoxia-induced regulation of the very low density lipoprotein receptor**  
Jeanna C. Perman, Ulf Lidberg, Ali Moussavi Nik, Peter Carlsson, Sven-Olof Olofsson and Jan Borén  
Submitted
- III. Increased expression of the very low-density lipoprotein receptor mediates lipid accumulation in clear-cell renal cell carcinoma**  
Jeanna C. Perman, Marcus Ståhlman, Max Levin, Sven-Olof Olofsson, Martin E. Johansson and Jan Borén  
Submitted



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# Mechanisms for and consequences of cellular lipid accumulation

## – The role of the Very Low Density Lipoprotein (VLDL) receptor

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### **Abstract**

Lipid accumulation in non adipose tissue is associated with various cases of tissue dysfunction and tissue failure. Reduced availability of oxygen is known to cause intracellular lipid accumulation in cardiomyocytes as well as in hearts. Cardiac lipid accumulation has been shown to cause impaired cardiac function but it is not fully clear how the lipids accumulate in the hypoxic myocardium.

We have studied a model of hypoxic/ischemic myocardium using HL-1 cardiomyocytes incubated in hypoxic condition as well as an *in vivo* model where mice were subjected to a myocardial infarction causing cardiac ischemia.

We found that the Very low density lipoprotein receptor (VLDLr), a member of the low density lipoprotein receptor (LDLr) family suggested to be able to mediate uptake of lipids, was significantly upregulated in response to hypoxia and that this upregulation was mediated through hypoxic activation of transcription factor Hif-1 $\alpha$ . The VLDLr induced an increase in intracellular triglycerides which were mediated not primarily through increased uptake of fatty acids but from an increased uptake of extracellular triglyceride-rich lipoproteins. The uptake of lipoproteins was rapid in response to hypoxia. The increase in intracellular lipids caused an accumulation of cardiotoxic ceramides in the cardiomyocytes which induced myocardial ER-stress. ER-stress initially induces a cardioprotective response but prolonged ER-stress cause apoptosis which was increased when the VLDLr was expressed. Ablation of the VLDLr reduced the ER-stress. The mice lacking VLDLr expression showed a reduced infarct size which could be dependent on a reduced amount of toxic ceramides and apoptosis.

We could also show that it was possible to block the harmful actions of the VLDLr by using VLDLr specific antibodies. Treatment with these antibodies reduced the lipid accumulation, ER-stress and apoptosis otherwise following a myocardial infarction.

The hypoxic VLDLr expression is not restricted to species or tissue. We could see that the VLDLr was increased in human ischemic myocardium compared to non-ischemic biopsies. We could also see that the VLDLr expression was increased in human clear-cell renal carcinoma where in this case the increased VLDLr expression was not due to hypoxia but on constitutive Hif-1 $\alpha$  activation. Like in the myocardium the VLDLr caused an accumulation of intracellular triglyceride in the cancer, which already contained great amounts of cholesterol esters.

These results indicate that the VLDLr is an important mediator of post-ischemic intramyocardial lipid accumulation and that the blocking of this lipid uptake improves survival.

**Keywords:** Very Low Density Lipoprotein Receptor, myocardial infarction, lipid accumulation, lipotoxicity, Endoplasmatic Reticulum-stress.

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