



## **Mechanistically Based Proteomics Proteins Involved in the Storage and Secretion of Triglycerides**

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**Project Description:** The storage of triglycerides in lipid droplets has important physiological as well as clinical implications. Thus it both creates our most important energy reserve and is related to insulin resistance and type 2 diabetes with its consequences atherosclerosis and coronary heart disease. The project is focused on the protein machinery involved in this packaging of neutral lipids, such as triglycerides, into lipid droplets in adipocytes.

The triglycerides are synthesized in the ER membrane and are released from the membrane in the form of a lipid droplet. We have demonstrated, using a cell-free system, that a phospholipase D (PLD) activity is needed for the assembly and release of lipid droplets. We have established two systems to follow different parts of the assembly of lipid droplets in intact cells. Moreover we have developed a siRNA system to silence PLD 1. Ongoing results demonstrate that such a silencing of PLD 1 have large impacts on the formation of the lipid droplets.

We have also identified a protein in adipocyte cytosol that is essential for the formation of lipid droplets. Using the cell-free system as an assay system, we have established a chromatographic procedure by which the activator can be purified 40 000 fold. The proteins (2 major) present are being identified using Maldi-tof and Q-tof (at the proteomic centre in Göteborg). The proteins shall be expressed and tested for activity. To finally clarify the role of the proteins in the assembly of lipid droplets, we shall use siRNA to silence the proteins in cells. A long term project is also to investigate the effect of an inducible silencing of the gene in adipose tissue and liver in mice.

Using the activator PLD 1 as well as other proteins that participate in the formation of lipid droplets (caveolin and ADRP) as "tags", we shall try to identify the foci in the endoplasmic reticulum where the assembly of lipid droplets occurs. Using combinations of sub-cellular fractionation and immunoaffinity purification, we shall try to isolate these regions and use proteomics to identify the proteins that are involved in the formation of the lipid droplets.