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**Institutionen för Molekylär Medicin och Kirurgi**

# Gene expression patterns in human adipose tissue in relation to fat mass and adipose depot

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Karolinska Institutet offentligen försvaras i Leksells sal, Eugeniahemmet, Karolinska Universitetssjukhuset, Solna.

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## ABSTRACT

Obesity, especially excess amount of abdominal fat, predisposes to a high risk for cardiovascular disease. Cancer cachexia is characterized by a specific loss of white adipose tissue (WAT) and skeletal muscle mass, and is associated with decreased survival and poor response to chemotherapy. We hypothesize that alterations in WAT function contribute to the negative metabolic consequences and disease outcome, respectively, of these two disorders. In this thesis we apply global transcriptome profiling on patient abdominal WAT biopsies to identify new genes and pathways of relevance for WAT function. In particular we explore gene expression in relation to (i) WAT depot, (ii) a dietary intervention study, and (iv) cancer with or without cachexia. In addition, we select one gene from microarray, Follistatin, for detailed expression profiling and functional evaluation in human fat cells.

***In the first study***, we successfully set up Representational difference analysis to identify a handful of genes differentially expressed between subcutaneous and visceral WAT, e.g. Adipsin, a component in the complement system, and Phospholipids transfer protein (PLPT), which is involved in transfer of phospholipids between lipoproteins. ***Our second study*** was part of a large consortium which compared the effects of a ten week intervention with a low-fat, high-carbohydrate hypoenergetic diet versus a moderate-fat, moderate-carbohydrate hypoenergetic diet. Both diets produced similar weight loss and beneficial changes in blood chemistry parameters. We performed abdominal subcutaneous WAT global transcriptome profiling on a subgroup of patients before and after the dietary intervention. The expression of 96 genes was significantly influenced by hypocaloric diet. Expression of genes involved in the synthesis of polyunsaturated fatty acids was downregulated, and CIDEA was up-regulated by hypocaloric diet. The pattern of gene expression response was almost identical between the two diets. ***In the third study*** we report that subcutaneous WAT Follistatin mRNA decreases with increasing weight, and that weight loss restores Follistatin levels. Furthermore, Follistatin is primarily produced by cells of the stroma vascular fraction in WAT. We show that WAT secretes Follistatin in vitro. Treating precursor cells with Follistatin in vitro stimulates adipogenesis. We cotreated precursor cells with Follistatin and Myostatin under adipogenic conditions, and found that cotreatment reversed the inhibitory effect of Myostatin on adipogenesis. ***The fourth study*** compared cancer patients with or without cachexia. Global transcriptome profiling revealed that genes downregulated by cachexia were overrepresented in pathways related to extracellular matrix, actin cytoskeleton and focal adhesion. By contrast, genes upregulated in cachexia were overrepresented in pathways related to energy turnover, e.g. fatty acid degradation, and oxidative phosphorylation.

In conclusion, variation in WAT size is associated with changes in tissue morphology, fat cell number and metabolism, as well as adipokine secretion. We provide support that the dietary energy intake, and not the macronutrient composition, is associated with changes in WAT gene expression, and highlight the role of CIDEA, which subsequently has been shown to be an important regulator of metabolic switch in fat cells. We identify Follistatin as a new adipokine. Insufficient Follistatin in obesity could possibly contribute to a hypertrophic WAT with large insulin resistant fat cells. We provide support that cachexia is associated with changes in WAT remodeling, which could be involved in WAT loss in this clinical condition.