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Characterization of adipose factors regulated by body weight

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ABSTRACT

White adipose tissue (WAT) constitutes our most expandable tissue and largest endocrine organ secreting hundreds of polypeptides collectively termed adipokines. Changes in WAT mass induce alterations in adipocyte secretion and function, which are linked to disturbed whole-body metabolism. Although the mechanisms controlling this are not clear they are dependent on changes in gene expression, a complex process which is regulated at several levels. Results in recent years have highlighted the role of small non-coding RNA molecules termed microRNAs (miRNAs), which regulate gene expression via post-transcriptional mechanisms. The aim of this thesis was to characterize global gene expression levels and describe novel miRNAs and adipokines controlling the function of human WAT in conditions with pathological increases or decreases in WAT mass. Obesity and cancer cachexia were selected as two models since they are both clinically relevant and characterized by involuntary changes in WAT mass.

In **Study I**, expressional analyses were performed in subcutaneous WAT from cancer patients with or without cachexia and obese versus non-obese subjects. In total, 425 transcripts were found to be regulated in cancer cachexia. Pathway analyses based on this set of genes revealed that processes involving extracellular matrix, actin cytoskeleton and focal adhesion were significantly downregulated, whereas fatty acid metabolism was upregulated comparing cachectic with weight-stable cancer subjects. Furthermore, by overlapping these results with microarray data from an obesity study, many transcripts were found to be reciprocally regulated comparing the two conditions. This suggests that WAT gene expression in cancer cachexia and obesity are regulated by similar, albeit opposing, mechanisms. In **Study II**, the focus was on the family of fibroblast growth factors (FGFs), members of which have recently been implicated in the development of obesity and insulin resistance. A retrospective analysis of global gene expression data identified several FGFs (FGF1/2/7/9/13/18) to be expressed in WAT. However, only one, FGF1, was actively secreted from WAT and predominantly so from the adipocyte fraction. Moreover, FGF1 release was increased in obese compared to non-obese subjects, but was not normalized by weight loss. Although the clinical significance of these findings is not yet clear, it can be hypothesized that FGF1 may play a role in WAT growth, possibly by promoting fat cell proliferation and/or differentiation. In **Study III**, we identified adipose miRNAs regulated in obesity. Out of eleven miRNAs regulated by changes in body fat mass, ten controlled the production of the pro-inflammatory chemoattractant chemokine (C-C motif) ligand 2 (CCL2) when overexpressed in fat cells and for two, miR-126 and -193b, signaling circuits were defined. In **Study IV**, a novel adipokine, semaphorin 3C (SEMA3C), was identified by combining transcriptome and secretome data. Detailed studies focusing on SEMA3C revealed that this factor was secreted from adipocytes and induced the expression of extracellular matrix and matricellular genes in preadipocytes. Furthermore, SEMA3C mRNA levels correlated with interstitial fibrosis and insulin resistance in WAT derived from subjects with a wide range in BMI.

In summary, the results presented in this thesis have delineated transcriptional alterations in WAT in two clinically relevant conditions, obesity and cancer cachexia. This has allowed the identification of novel adipokines and microRNAs with potential pathophysiological importance. These findings form the basis for further studies aiming at understanding the central role of WAT in disorders associated with metabolic complications.