

## Microarray Analysis of gene expression in Human Adipocytes and Adipose Tissue

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg, fredagen den 29 februari 2008, kl 09.00

av

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Avhandlingen baseras på följande arbeten:

I **Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression.**

Jernås M, Palming J, Sjöholm K, Jennische E, Svensson PA, Gabrielsson BG, Levin M, Sjögren A, Rudemo M, Lystig TC, Carlsson B, Carlsson LM, Lönn M.  
*FASEB J. 2006 Jul;20(9):1540-2.*

II **The expression of NAD(P)H:quinone oxidoreductase 1 is high in human adipose tissue, reduced by weight loss, and correlates with adiposity, insulin sensitivity, and markers of liver dysfunction.**

Palming J, Sjöholm K, Jernås M, Lystig TC, Gummesson A, Romeo S, Lönn L, Lönn M, Carlsson B, Carlsson LMS.  
*J Clin Endocrinol Metab. 2007 Jun;92(6):2346-52.*

III **Relations of Adipose Tissue CIDEA Gene Expression to Basal Metabolic Rate, Energy Restriction, and Obesity: Population-Based and Dietary Intervention Studies.**

Gummesson A, Jernås M, Svensson PA, Larsson I, Glad CA, Schéle E, Gripeteg L, Sjöholm K, Lystig TC, Sjöström L, Carlsson B, Fagerberg B, Carlsson LM.  
*J Clin Endocrinol Metab. 2007 Dec;92(12):4759-65.*

IV **Changes in adipose tissue gene expression and plasma adipokine levels in patients with critical illness.**

Jernås M, Olsson B, Sjöholm K, Sjögren A, Rudemo M, Nellgård B, Carlsson LMS, Sjöström CD. *Submitted.*

## Microarray Analysis of gene expression in Human Adipocytes and Adipose Tissue

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Obesity has reached epidemic proportions worldwide and is associated with several serious conditions such as insulin resistance, type 2 diabetes, hyperlipidemia and atherosclerosis. Adipose tissue exerts important endocrine and immune functions through the release of adipokines. Adipokines are involved in the regulation of adipose tissue metabolism and associated with alterations in insulin resistance. The aim of this thesis was to identify genes, expressed in adipose tissue and adipocytes, that may contribute to insulin resistance and metabolic diseases related to obesity.

Enlarged adipocytes are associated with insulin resistance and type 2 diabetes. A technique to separate human adipocytes from an adipose tissue biopsy into populations of small and large adipocytes was developed and the expression profiles of the populations were compared. This showed that serum amyloid A (SAA) and NAD(P)H:quinone oxidoreductase 1 (NQO1) were higher expressed in large versus small adipocytes. The expression of both SAA and NQO1 correlated to adipocyte size. SAA has been implicated in inflammation and insulin resistance and NQO1 is known to be involved in oxidative stress suggesting that these findings may provide novel insights into the connection between hypertrophic obesity and insulin resistance/type 2 diabetes. SAA, NQO1 and also the cell death-inducing DFFA-like effector A (CIDE-A) were predominantly expressed in human adipocytes as compared to a panel of 32 other human tissues and cell types. During diet-induced weight loss in obese subjects, adipose tissue expression of NQO1 was reduced and CIDE-A was elevated. NQO1 expression correlated to measures of adiposity, insulin and the markers of liver dysfunction, AST and ALT. These findings indicate a role for NQO1 in the metabolic complications of human obesity. CIDE-A expression was inversely associated with basal metabolic rate independently of body composition, age, and gender. These data suggest that human CIDE-A plays a role in adipose tissue energy balance.

Adipokines may play a key role in the rapid development of insulin resistance during critical illness. We identified gene expression changes in human adipose tissue in subjects with subarachnoidal hemorrhage during intensive care. Zinc-alpha2 glycoprotein (ZAG) was the only adipokine that was increased in adipose tissue during critical illness, and this increase was accompanied by elevated plasma ZAG levels. Plasma levels of SAA and CRP were increased and adiponectin levels decreased of during intensive care.

In summary, gene expression profiling of human adipocytes and adipose tissue during different conditions suggest that SAA, NQO1, CIDE-A and ZAG may be implicated in human obesity-related metabolic disease. During intensive care, increased plasma levels of ZAG, SAA, and CRP together with decreased levels of adiponectin may be involved in the decrease in insulin sensitivity.

Keywords: obesity, adipose tissue, insulin resistance, serum amyloid A, NAD(P)H:quinone oxidoreductase 1, Zinc-alpha2 glycoprotein, cell death-inducing DFFA-like effector A, DNA microarray

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