

MOLECULAR MECHANISMS IN OBESITY-ASSOCIATED METABOLIC DISEASE

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Göteborgs Universitet kommer att offentligens försvaras i Sahlgrenska Universitetssjukhusets Aula, Blå stråket 5, Göteborg, torsdagen 31 maj 2007, kl 9.00

av

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Avhandlingen baseras på följande arbeten:

- I **Evaluation of Reference Genes for Studies of Gene Expression in Human Adipose Tissue**
BG Gabrielsson, LE Olofsson, A Sjögren, M Jernås, A Elander, M Lönn, M Rudemo, and LMS Carlsson
Obes Res. 2005 Apr;13(4):649-52
- II **A Microarray Search for Genes Predominantly Expressed in Human Omental Adipocytes: Adipose Tissue as a Major Production Site of Serum Amyloid A**
K Sjöholm, J Palming, LE Olofsson, A Gummesson, PA Svensson, TC Lystig, E Jennische, J Brandberg, JS Torgerson, B Carlsson, and LMS Carlsson
J Clin Endocrinol Metab. 2005 Apr;90(4):2233-9. Epub 2004 Dec 28
- III **A link between *SI00A1* and human resting metabolic rate revealed by a strategy that identifies susceptibility genes for complex diseases**
LE Olofsson, B Olsson, P Jacobson, L Pérusse, L Sjöström, C Bouchard, B Carlsson and LMS Carlsson
Manuscript
- IV **Zn-alpha2-glycoprotein is a susceptibility gene for metabolic disease influencing the cholesterol homeostasis**
LE Olofsson, B Olsson, A Gummesson, P Jirholt, TC Lystig, K Sjöholm, P Jacobson, M Olsson, M Ståhlman, S Romeo, L Sjöström, P Eriksson, A Hamsten, LP Hale, DS Thelle, J Borén, B Carlsson, and LMS Carlsson
Manuscript
- V **C/EBP α regulates genes in lipid and glucose metabolism and is dysregulated in subjects with the metabolic syndrome**
LE Olofsson, L William-Olsson, K Sjöholm, B Carlsson, LMS Carlsson, and B Olsson
Manuscript

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2007

Obesity is associated with increased morbidity and mortality. Subjects with obesity are at risk of developing several serious conditions such as type 2 diabetes, hypertension, coronary heart disease and stroke. This thesis aimed to identify genes that are implicated in the development of these obesity-associated metabolic diseases and to further increase our knowledge about these genes in relation to disease.

Adipose tissue, especially intra-abdominal adipose tissue, is tightly linked to metabolic disease. Identification of genes predominantly expressed in adipocytes can give new insights into adipocyte function and may thereby provide important information about genes involved in the development of obesity-associated metabolic disease. The acute-phase protein serum amyloid A (SAA) was unexpectedly found to be predominantly expressed in adipocytes during the nonacute-phase. Since SAA has been suggested to have multiple atherogenic effects, the production of SAA in adipose tissue may be a link between obesity and atherosclerosis.

Potential susceptibility genes for obesity-associated metabolic disease were identified based on their altered expression in adipose tissue from obese individuals with the metabolic syndrome compared with controls that persisted even when the disease phenotype was temporarily improved by a very low calorie diet treatment. Using this approach, S100 calcium binding protein A1 (S100A1), Zn-alpha2-glycoprotein (ZAG), and CCAAT/enhancer binding protein alpha (C/EBP α) were identified as potential susceptibility genes. Subsequent genetic association study revealed a link between S100A1 and resting metabolic rate. A common ZAG genotype was associated with reduced ZAG gene expression, reduced serum levels of ZAG and low serum total cholesterol levels in humans. This genotype was also associated with coronary artery disease, which may be a result of decreased serum levels of adiponectin or HDL. Furthermore, data from studies in mice suggest that ZAG influences cholesterol synthesis. Thus, studies in both humans and ZAG-deficient mice showed a link between ZAG and cholesterol. Studies of the transcription factor C/EBP α showed that it is induced by insulin and in turn regulates multiple genes in the lipid and glucose metabolism including adiponectin, hexokinase 2, lipoprotein lipase, diacylglycerol O-acyltransferase 1 and 2.

In conclusion, SAA, S100A1, ZAG and C/EBP α were identified as potential susceptibility genes for obesity-associated metabolic disease using two different expression-based approaches. Our subsequent studies of these genes linked them to metabolic parameters known to influence or to be associated with metabolic disease e.g. resting metabolic rate, serum cholesterol levels and glucose and lipid metabolism.

Key words: obesity, metabolic syndrome, cholesterol, resting metabolic rate, insulin resistance, serum amyloid A, S100 calcium binding protein A1, Zn-alpha2-glycoprotein, CCAAT/enhancer binding protein α

ISBN 978-91-628-7180-2