Adipose tissue-derived serum amyloid A and adipose tissue macrophages in metabolic disease

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, torsdagen den 19 december 2013 kl. 13.00

av

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Avhandlingen baseras på följande delarbeten:

I. **Macrophage gene expression in adipose tissue is associated with insulin sensitivity and serum lipid levels independent of obesity**
Ahlin S, Sjöholm K, Jacobson P, Andersson-Assarsson J. C, Walley A, Tordjman J, Poitou C, Prifti E, Jansson P-A, Borén J, Sjöström L, Froguel P, Bergman R. N, Carlsson L. M. S, Olsson B, Svensson P-A.
Obesity (Silver Spring). 2013 Mar 20. (Epub ahead of print)

II. **Establishment of a transgenic mouse model specifically expressing human serum amyloid A in adipose tissue**
Olsson M, Ahlin S, Olsson B, Svensson P-A, Ståhlman M, Borén J, Carlsson L. M. S, Sjöholm K.
PLoS One. 2011;6(5):e19609. Epub 2011 May 18. (Open access)

III. **No evidence for a role of adipose tissue-derived serum amyloid A in the development of insulin resistance or obesity-related inflammation in hSAA1$^{+/-}$ transgenic mice**
Ahlin S, Olsson M, Olsson B, Svensson P-A, Sjöholm K.
PLoS One. 2013;8(8):e72204. Epub 2013 August 15. (Open access)

IV. **Adipose tissue-derived human serum amyloid A does not affect atherosclerotic lesion area in hSAA1$^{+/-}$/ApoE$^{-/-}$ mice**
Ahlin S, Olsson M, Wilhelmson A. S, Skålén K, Borén J, Carlsson L. M. S, Svensson P-A, Sjöholm K.
In manuscript

UNIVERSITY OF GOTHENBURG

Adipose tissue-derived serum amyloid A and adipose tissue macrophages in metabolic disease

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Obesity is associated with a low-grade chronic inflammation with increased levels of proinflammatory markers in the circulation and local inflammation in the adipose tissue. In this thesis, two aspects of obesity-related inflammation have been studied. Macrophages in the adipose tissue and the moderately elevated serum levels of serum amyloid A (SAA) derived from the adipose tissue have both been suggested as possible players behind obesity-related comorbidities in humans. The aim of this thesis was to investigate if there are obesity-independent links between adipose tissue macrophages and metabolic dysfunction and to examine if adipose tissue-derived SAA contributes to the development of insulin resistance, obesity-related inflammation and atherosclerosis.

Adipose tissue gene expression of macrophage markers was analyzed in relation to anthropometric and metabolic parameters in the Swedish Obese Subjects (SOS) Sib Pair study. The gene expression of macrophage markers was associated with insulin sensitivity and serum lipid levels and these associations remained, although weakened, when the analysis was adjusted for BMI. The link between adipose tissue macrophages and insulin sensitivity was confirmed by showing that the adipose tissue gene expression of macrophage markers was increased in patients with type 2 diabetes mellitus compared to their BMI-matched non-diabetic controls.

To investigate the effects of adipose tissue-derived SAA, a $hSAA^{+/-}$ transgenic mouse model (hSAA1 mice) where human SAA1 is specifically expressed in the adipose tissue was established. When the hSAA1 mice were fed normal chow or high fat diet, the serum levels of SAA resembled those in lean and obese humans, respectively. The circulating SAA was found in the high density lipoprotein (HDL)-containing FPLC fractions indicating an association of SAA to high density lipoprotein. This is an important finding since lipid-free SAA has other functions than SAA associated with HDL. The hSAA1 mice fed a high fat diet displayed similar glucose and insulin responses during an oral glucose tolerance test compared to their wild type littermates. In addition, the adipose tissue mRNA levels of genes related to insulin sensitivity were not decreased. Circulating levels of proinflammatory markers and gene expression of macrophage markers in the adipose tissue were not increased in hSAA1 mice. Hence, the hSAA derived from adipose tissue did not affect local and systemic insulin sensitivity or obesity-related inflammation in our mouse model. To investigate possible effects of adipose tissue-derived hSAA1 on the development of atherosclerosis, the hSAA1 mice were crossbred with $ApoE^{-/-}$ mice. Analyses of *en face* prepared aortas from $hSAA^{+/-}/ApoE^{-/-}$ mice displayed similar atherosclerotic lesion areas in all sections of the aorta compared to wild type mice.

In conclusion, adipose tissue gene expression of macrophage markers is increased in type 2 diabetes mellitus and linked to insulin sensitivity and serum lipid levels independent of obesity. Furthermore, despite extensive research and several different experimental setups, we find no evidence for a causal role of adipose tissue-derived hSAA in the development of insulin resistance, obesity-related inflammation or atherosclerosis in hSAA1 mice.

Keywords: Adipose tissue, macrophages, serum amyloid A, obesity, insulin sensitivity, atherosclerosis.

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