Studies of Atherogenic Lipoproteins Using Mass Spectrometry–Based Lipidomics

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssal Arvid Carlsson, Medicinaregatan 3, Göteborg.
Fredagen den 24 september 2010, kl. 09.00

av Marcus Ståhlman

Fakultetsopponent: Professor Robert Murphy
Department of Pharmacology, University of Colorado

Avhandlingen baseras på följande arbeten:

I. **Proteomics and lipids of lipoproteins isolated at low salt concentrations in D_2O/sucrose or in KBr**
Ståhlman M, Davidsson P, Kanmert I, Rosengren B, Borén J, Fagerberg B and Camejo G.
Journal of Lipid Research; 2008; 49(2): 481-490

II. **ApoCIII-enriched LDL in type 2 diabetes displays altered lipid composition, increased susceptibility for sphingomyelinase, and increased binding to biglycan**
Hiukka A*, Ståhlman M*, Pettersson C, Levin M, Adiels M, Teneberg S, Leinonen ES, Mattson Hultén L, Wiklund O, Orešič M, Olofsson SO, Taskinen MR, Ekroos K and Borén J.
Diabetes 2009; 58(9): 2018-2026
*These authors contributed equally

III. **Lipidomics of apoB-containing lipoproteins reveal that dyslipidemia is associated with alterations in molecular lipids leading to increased proinflammatory properties**
Ståhlman M, Pham H, Adiels M, Mitchell TW, Blanksby SJ, Fagerberg B, Ekroos K and Borén J.
Manuscript

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Abstract

The prevalence of type 2 diabetes is increasing worldwide and is about to reach epidemic proportions. The disease is often associated with dyslipidemia which is characterized by an atherogenic lipoprotein profile including elevated serum triacylglycerol levels, low high-density lipoprotein levels and high levels of small low-density lipoproteins. Several large clinical studies have shown that this change in serum lipoprotein profiles constitutes a major cardiovascular risk factor, but the molecular mechanisms are still not completely understood. It has been proposed that the intrinsic properties of the particles, such as protein and lipid composition, might be responsible for the increased risk, mediated through an increased accumulation of lipoproteins in the artery wall, leading to atherosclerosis. The primary aim of this thesis was to isolate and, with a lipidomics approach, characterize the atherogenic lipoproteins from patients with type 2 diabetes. A secondary aim was to link compositional changes to atherosclerotic processes *in vitro*.

Initially, an ultracentrifugational method was developed for the isolation of lipoproteins at physiological settings. Then, in order to make a comprehensive lipid characterization of the lipoproteins, an analytical platform for lipidomics analyses was established. This platform consists of a normal-phase HPLC system with an evaporative light scattering detector that is used in combination with a hybrid quadrupole time-of-flight instrument, equipped with a chip-based nanoelectrospray interface.

By using this platform the atherogenic lipoproteins from patients participating in two major studies were characterized. The results revealed several alterations in the lipid and protein composition of the atherogenic lipoproteins isolated from patients with type 2 diabetes. Several of these alterations could, by the use of different *in vitro* systems, be linked mechanistically to proatherogenic processes such as lipoprotein retention and tissue inflammation. We also showed that changes in lipoprotein lipid composition were mainly associated with dyslipidemia.

Keywords: lipids, lipoproteins, atherogenesis, lipidomics, type 2 diabetes, mass spectrometry.

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