

Assembly and Secretion of Atherogenic Lipoproteins

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg,

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av

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Thomas Jefferson University, Philadelphia, USA

Avhandlingen baseras på följande delarbeten:

- Paper I **Relation of the size and intracellular sorting of apoB to the formation of VLDL₁ and VLDL₂**
Pia Stillemark-Billton*, Caroline Beck*, Jan Borén, and Sven-Olof Olofsson
J. Lipid Res. 2005. **46**: 104-114
*contributed equally
- Paper II **B-cell receptor-associated protein 31 (BAP31) interacts with apolipoprotein B48 and directs VLDL₁ secretion**
Caroline Beck, Sven-Olof Olofsson, and Jan Borén
Manuscript
- Paper III **Epigallocatechin gallate increases the formation of cytosolic lipid droplets and decreases the secretion of apoB-100 VLDL**
Lu Li*, Pia Stillemark-Billton*, Caroline Beck*, Pontus Boström*, Linda Andersson, Mikael Rutberg, Johanna Ericsson, Björn Magnusson, Denis Marchesan, Anna Ljungberg, Jan Borén, and Sven-Olof Olofsson
J. Lipid Res. 2006. **47**: 67-77
*contributed equally

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ABSTRACT

The classical dyslipidemia seen in patients with type 2 diabetes is characterized by elevated serum triglycerides (TG), low levels of high-density lipoprotein cholesterol and the appearance of small, dense low-density lipoproteins (LDL). It is now recognized that the different components of diabetic dyslipidemia are not isolated abnormalities but are closely linked to each other metabolically, and are initiated by the hepatic overproduction of large triglyceride-rich very low-density lipoproteins (VLDL₁). Diabetic dyslipidemia frequently precedes type 2 diabetes by several years, indicating that the disturbance of lipid metabolism is an early event in the development of cardiovascular complications of type 2 diabetes. It is thus of key importance to elucidate the mechanisms involved in the production of VLDL₁. The aim of this thesis was to further clarify the molecular mechanisms of the assembly process and secretion of apolipoprotein B (apoB)-containing lipoproteins.

The results indicate that apoB100 assembles into partially lipidated dense pre-VLDL that is retained in the cell unless further converted into VLDL₂ by size-dependent lipidation. VLDL₂ in turn can proceed through the secretory pathway to be secreted or converted to VLDL₁ in the second step of the assembly. Furthermore, an efficient formation of VLDL₁ specifically requires a sequence located between apoB46.8 and apoB48. This sequence interacts with the B-cell receptor-associated protein (BAP31), which seems essential for an efficient secretion of VLDL₁, but not for the secretion of denser particles.

The formation of lipoproteins depends on the availability of lipids. However, the results show that the accumulation of cytoplasmic lipids is not directly associated with increased secretion of VLDL. The phenol epicallocatechin gallate (EGCG) diverts TG from the secretory pathway for storage in cytosolic lipid droplets. While increasing the cytosolic lipid droplet fusion rate and TG content in the cytosol, apoB100 secretion from the cells is decreased. As a consequence, apoB becomes degraded.

The results presented advance our understanding of the complex mechanisms underlying the formation of VLDL. Clarification of these molecular mechanisms will hopefully enable development of targeted treatment for diabetic dyslipidemia, which is of key importance given the high risk for coronary vascular disease (CVD) in patients with type 2 diabetes and the metabolic syndrome.

Key words: very low-density lipoprotein, apolipoprotein B100, B-cell receptor associated protein 31, microsomal triglyceride transfer protein, secretion, assembly

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