Endothelium-Protective Sphingosine-1-Phosphate provided by HDL-associated Apolipoprotein M

GUEST LECTURE by

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Abstract: Apolipoprotein M (apoM) is predominantly associated with HDL and to a minor extent with chylomicrons, VLDL, and LDL. Mature apoM (25 kDa) retains its signal peptide, which serves as a hydrophobic anchor for apoM. ApoM has been suggested to be important for the formation of pre-β HDL and reverse cholesterol transport. In accordance with this idea, hepatic overexpression of apoM with an adenovirus in LDL-receptor deficient mice led to ~70 % reduction of atherosclerosis. In addition to the liver, apoM is also expressed in the kidney. ApoM is a member of the lipocalin protein superfamily having a coffee filter-like structure with a hydrophobic ligand-binding pocket, which binds sphingosine-1-phosphate (S1P). In circulation, S1P is bound to HDL and to albumin. S1P activates five G-protein coupled receptors (S1P₁₋₅), which have different cellular distributions. Activation of S1P₁ on endothelium is important for maintenance of vascular integrity. We recently demonstrated that HDL-associated S1P is specifically transported by apoM. The 2.3-Å structure of the S1P-apoM complex reveals that S1P highly specifically interacts with an amphiphilic pocket in the lipocalin fold of apoM. S1P in HDL is exclusively associated with apoM. Thus, HDL in Apom⁻/⁻ mice contains no S1P, whereas HDL in transgenic mice over-expressing apoM has increased S1P. ApoM⁺HDL induced S1P₁ receptor internalization, downstream MAPK- and Akt-activation, endothelial cell migration, and formation of endothelial adherens junctions, whereas apoM-HDL did not. Lack of S1P in the HDL fraction of Apom⁻/⁻ mice decreased basal endothelial barrier function in lung tissue. Our results demonstrate that apoM, by delivering S1P to the S1P₁ receptor on endothelial cells, is a vasculoprotective constituent of HDL.
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Education and Academic training:
- M.D. 1974 – Lund University, Sweden
- Ph.D. 1981 – Thesis supervisor: Prof. Johan Stenflo, MD, PhD.
- Internship at Malmö General Hospital 1974-1976.
- Associated professor at University of Lund, Sweden 1983.
- Professor of blood coagulation research at University of Lund, Sweden. 1989.

Professional Record:
- Licensed to practice medicine 1976.
- Associated Professor in Clinical Chemistry at Department of Clinical Chemistry, University of Lund, Sweden, 1986-1989
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- National Institute of Health International Postdoctoral Fellow at Department of Immunology, Scripps Clinic and Research Foundation, LaJolla, Ca. July 1982- July 1983.
- Greenberg scholar at Oklahoma medical research foundation March-August, 1990.

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Major Awards:
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- The Greenberg Visiting Scholarship, Oklahoma, 1990
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- Söderberg’s Prize in Medicine, 1996
- Dameshek Prize given by American Society of Hematology, 1997
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- "Outstanding achievements in Laboratory Medicine", from Österreichischen Gesellschaften für Klinische Chemie und Laboratoriumsmedizin, 2002
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