

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

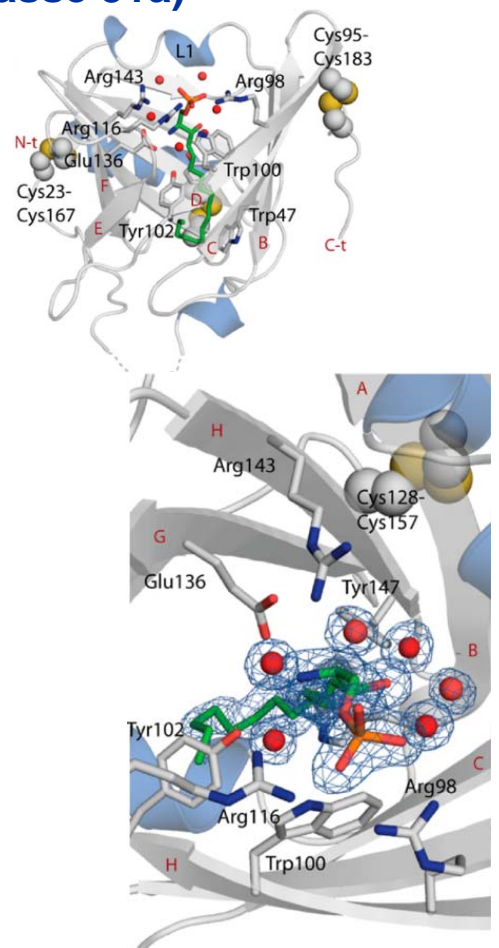
GUEST LECTURE by



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Tuesday, 04.06.2013, 17:00h

Lecture Hall HS 26.K3
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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 overexpressing 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.



The structure of the ApoM-S1P complex reveals the determinants of S1P-binding specificity. Christoffersen et al. PNAS 2011, 108(23) 9613-8

CURRICULUM VITAE

BJÖRN DAHLBÄCK born July 12, 1949

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.

Specialist training in Clinical Chemistry at department of

Clinical Chemistry, Malmö General Hospital, Sweden. Supervisor: Prof. Carl-Bertil Laurell. 1977-1982.

Associated professor at University of Lund, Sweden 1983.

Specialist in blood coagulation disorders, 1987.

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

Professor in Blood Coagulation Research since September 1989.

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.

Supervised 28 Ph.D. thesis students and 23 postdoctoral fellows

304 original papers, 99 reviews, ≈21000 citations, H-index 74

Major Awards:

Eric K. Fernström's Award for younger researchers 1988

The Greenberg Visiting Scholarship, Oklahoma, 1990

The Ham-Wassermann lecture award, 1994

Principal Investigators Award from ISTH 1995

The Göran Gustafsson's Prize, 1995

Louis Jeantet Prix de Médecine, 1996

Söderberg's Prize in Medicine, 1996

Dameshek Prize given by American Society of Hematology, 1997

Honorary Member of the American Society of Hematology, 1997

Distinguished Career Award from ISTH, 1999

"Outstanding achievements in Laboratory Medicine", from Österreichischen Gesellschaften für
Klinische Chemie und Laboratoriumsmedizin, 2002

Professor Lars Werkö prize in medicine, 2003

Engeströmska Guldmedaljen, Kungliga Fysiografiska Sällskapet 2008