High density lipoprotein metabolism
Lipoprotein classes and atherosclerosis

Chylomicrons, VLDL, and their catabolic remnants

LDL

HDL

Pro-atherogenic

Anti-atherogenic
Plasma lipid transport

Liver

FC → CE → TG

CE → FC

FFA

Adipose tissue

VLDL

TG → CE

LPL → FFA

Adipose and other tissues

LDL

LDL receptor

TG → CE

LDL receptor

Bile

FFA

Adipose tissue

HDL

TG → CE

CETP

FFA

New synthesis

LCAT

ABCA1

Cell in peripheral tissue

LDL receptor
HDL and cardiovascular disease
Coronary heart disease and HDL-C

N = 302,430

Hazard Ratio

Adjusted for age and gender
Adjusted for multiple factors

HDL-C (mMol/L)

What are HDLs?
Surface monolayer of phospholipids and free cholesterol

Hydrophobic core of triglyceride and cholesteryl esters

apoA-I

apoA-II

Structure of HDL
HDL are heterogeneous

COMPOSITION

APOLIPOPROTEINS
ApoA-I, apoA-II, apoA-IV, apoE, others

LIPIDS
TG, CE, FC, PL

SIZE: 7.5-15 nm

SHAPE: spherical, discoidal

CHARGE: prebeta, alpha
HDL Charge and shape

- Lipid-poor apoA-I
- Discoidal
- Spherical

Prebeta mobility
 Alpha mobility
HDL Subpopulations

PARTICLE SHAPE
- Discoidal
- Spherical

APOLIPOPROTEIN COMPOSITION
- A-I HDL
- A-I/A-II HDL

PARTICLE SIZE
- HDL$_{2b}$
- HDL$_{2a}$
- HDL$_{3a}$
- HDL$_{3b}$
- HDL$_{3c}$

Lipid-poor apoA-I
This HDL heterogeneity is the result of activity of several factors that assemble and remodel HDL in plasma.
Origin of apoA-I

LIVER

Lipid-poor apoA-I

INTESTINE

Chylomicrons

Lipoplysis
Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
- CETP
- Hepatic lipase
- PLTP
- SRB1
Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
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Lipidation of apoA-I

Lipid-poor apoA-I

Cell membrane

ABCA-1

phospholipid, cholesterol

Discoidal HDL
Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
- CETP
- Hepatic lipase
- PLTP
- SRB1
LCAT
(lecinthin:cholesterol acyltransferase)

LCAT catalyses the reaction:

\[
\text{phosphatidylcholine} \quad \rightarrow \quad \text{lysophosphatidylcholine} \\
\text{unesterified cholesterol} \quad \rightarrow \quad \text{cholesteryl ester}
\]
The LCAT reaction is responsible for most of the cholesteryl esters circulating in plasma.

HDLs are the preferred substrates for LCAT.

LCAT is activated by apoA-I, apoA-IV, apoE.

LCAT NOT activated by apoA-II.
Role of LCAT in formation of spherical HDL

Free cholesterol transferred from cell membranes (including liver and intestine)

Liver
Intestine

apoA-I

Discoidal HDL

free cholesterol

LCAT

cholesteryl esters

Spherical HDL
Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
- CETP
- Hepatic lipase
- PLTP
- SRB1
Role of CETP in plasma cholesterol transport

- Liver
- LDL-R
- VLDL/LDL
- CETP
- Extrahepatic Tissues (including the artery wall)
- Free Cholesterol
Shuttle mechanism

Tall. J. Lipid Res. 1993; 34:1255.
CETP plays a major role in remodelling of HDL, especially when acting in the presence of hepatic lipase.
Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
- CETP
- Hepatic lipase
- PLTP
- PLTP
- SRB1
HEPATIC LIPASE

- Hepatic lipase catalyses the hydrolysis of triglyceride and phospholipids in HDL

- Remodelling of HDL by hepatic lipase is most dramatic when linked to activity of CETP
Role of CETP and hepatic lipase in the remodelling of HDL

Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
- CETP
- Hepatic lipase
- PLTP
- SRB1
PLTP
(phospholipid transfer protein)

- PLTP catalyses the transfer of phospholipids between plasma lipoproteins
- PLTP also remodels HDL
Remodelling of AI-HDL by PLTP

CE

PLTP

CE

CE

CE

lipid-poor apoA-I
Factors that assemble and remodel HDL in plasma

- ABCA1
- LCAT
- CETP
- Hepatic lipase
- PLTP
- SRB1
SRB1
(scavenger receptor type B1)

- SRB1 promotes the selective hepatic uptake of HDL cholesteryl esters
- SRB1 thus also remodels HDL
Remodelling of AI-HDL by SRB1

Liver

SRB1

CE

TG

Larger HDL

Smaller HDL

Lipid-poor apoA-I

CE

TG
Apolipoprotein-specific HDL

Spherical AI-HDL

Spherical AI/AII-HDL

apoA-I

apoA-II

TG

CE

apoA-I

apoA-II

TG

CE

Apolipoprotein-specific HDL
Origin of AII-HDL

LIVER

Secretion

Lipid-poor apoA-II

phospholipids from cell membranes

Discoidal AII-HDL
LCAT-mediated formation of spherical AI/AII-HDL

Discoidal AI-HDL

Spherical AI-HDL

Discoidal AII-HDL

LIVER

Spherical AI/AII-HDL

LCAT

Fusion

LCAT

TG

CE

CE
Remodelling of HDL generates lipid-poor apoA-I
Remodelling of HDL generates lipid-poor apoA-I

CETP
HL
PLTP
SRB1

Lipid-poor apoA-I
Fate of lipid-poor apoA-I

Lipid-poor apoA-I

Acquire PL from cells (via ABCA1) to form discoidal HDL

Discoidal AI-HDL

Incorporation into spherical AI-HDL

Small, spherical AI-HDL

Large, spherical AI-HDL

Excretion through kidney

LCAT
Cycling of apoA-I between HDL and a lipid-poor pool

HDL

CETP

HL

PLTP

SRB1

Discoidal HDL

Excretion through kidney

Lipid-poor apoA-I

UC  <-->  CE

LCAT
Functions of HDL
Role of HDL in promoting efflux of cholesterol from cells
Efflux of cholesterol from cells

Extracellular space

Lipid-poor apoA-I

Cell membrane

ABCA1

FC, PL
Efflux of cholesterol from cells

Extracellular space

Lipid-poor apoA-I

Discoidal HDL

Cell membrane

ABCA1

FC, PL

Efflux of cholesterol from cells
Efflux of cholesterol from cells

Extracellular space → Cell membrane

Lipid-poor apoA-I

Discoidal HDL

ABCA1

FC, PL

ABCA1

SR-B1

FC
Efflux of cholesterol from cells

Extracellular space

Cell membrane

Lipid-poor apoA-I

Discoidal HDL

LCAT

Small spherical HDL

ABCA1

FC, PL

ABCA1

SR-B1

FC
Efflux of cholesterol from cells

Extracellular space

Lipid-poor apoA-I

Discoidal HDL

LCAT

Small spherical HDL

Cell membrane

ABCA1

ABCA1

SR-B1

SR-B1

ABCG1

FC, PL

FC

FC

FC
Efflux of cholesterol from cells

Extracellular space

Lipid-poor apoA-I

Discoidal HDL

LCAT

Small spherical HDL

LCAT

Larger spherical HDL

Cell membrane

ABCA1

ABCA1

SR-B1

SR-B1

ABCG1

FC, PL

FC

FC

FC
Efflux of cholesterol from cells

Extracellular space

Lipid-poor apoA-I

Discoidal HDL

LCAT

Small spherical HDL

Larger spherical HDL

Cell membrane

ABCA1

FC, PL

ABCA1

SR-B1

FC

SR-B1

ABCG1

Diffusion

FC

SR-B1

ABCG1

Diffusion

FC
Protective properties of HDLs

- Promote cholesterol efflux from macrophages
- Anti-oxidant properties
- Anti-thrombotic properties
- Anti-inflammatory properties
- Improve endothelial function
- Promote endothelial repair
- Improve glycemic control
- Other
Conclusions

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Conclusions

• The concentration of HDL-C correlates inversely with CV risk
• HDL particles have many properties with the potential to protect
• HDL particles are assembled in the plasma compartment
• The HDL fraction in human plasma is heterogeneous in terms of particle size, charge and composition
• HDL particles are extensively remodelled in plasma by a variety of proteins and enzymes
• Deficiencies of these remodelling factors result in major changes to HDL particles
Unanswered questions

Q. Which HDL subpopulations (if any) protect against CV disease?
Answer: We do not know

Q. Which (if any) of the known HDL functions protect against CV disease?
Answer: We do not know

Answers to these questions require much more research