Metabolism and Atherogenic Properties of LDL

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- Astra Zeneca
- Boehringer-Ingelheim
- Lilly
- Meda Pharma
- Merck
- Novo Nordisk
- Roche
- Servier
EPIDEMIOLOGY
Cholesterol and CHD Mortality

Figure 1: CVD mortality (33744 deaths) versus usual total cholesterol
(A) Age-specific associations. (B) Age-specific and sex-specific hazard ratios for 1 mmol/L lower usual total cholesterol. Hazard ratios on the left are plotted on a floating absolute scale of risk (so each log hazard ratio has an appropriate variance assigned to it). The slopes of the age-specific lines on the left are given on the right, subdivided by sex. Each square (left or right) has an area inversely proportional to the variance of the log of the hazard ratio that it represents.

N=900,000

courtesy of Prof. R. Santos

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METABOLISM
Lipoprotein Subclasses
Hepatic Synthesis of ApoB Containing Lipoproteins

Adapted from de Lipids Current Perspectives: Betteridge 1997

courtesy of Prof. R. Santos
Heterogeneity of VLDL and its Remnants

courtesy of Prof. R. Santos
Fig. 1. Hypothetical metabolic scheme incorporating proposed pathways for the production of the major LDL subclasses I, II, III, and IV. As described in the text, a key hypothesis is that the properties of triglyceride-rich lipoprotein species secreted by the liver are determined in large part by the operation of multiple pathways (e.g., those labeled 1 and 2) as well as by hepatic triglyceride availability. Pathway 1: The coordinate production of triglyceride-rich VLDL-1 and triglyceride-poor IDL-2 is based on the reciprocal relationship that we have observed between their hypothesized catabolic products LDL-I and LDL-III (Fig. 2). We propose that production of VLDL-1 results from loading of a discrete quantity of lipid on a precursor particle. Lipolysis of VLDL-1 yields remnants, which in turn yield LDL-III by the action of hepatic lipase. Further remodeling of these particles may occur by CETP mediated triglyceride enrichment and hepatic lipase mediated lipolysis. Pathway 2: We hypothesize that this pathway, which results in production of VLDL-2, is distinct from pathway 1 and gives rise to IDL-I and LDL-II by lipolysis (68). Further processing by CETP mediated transfer of triglycerides into LDL-II and lipolysis by hepatic lipase yields smaller and denser LDL products. Finally, we propose that in an analogous manner to pathway 1, there is loading of a discrete quantity of lipid in hepatic VLDL in pathway 2 (larger VLDL-1) that includes precursors of the smallest and densest LDL IV. TG, triglycerides; CE, cholesteryl esters; LpL, lipoprotein lipase; HL, hepatic lipase; CETP, cholesterol ester transfer protein.
Lipoprotein Metabolism

More Triglyceride → Less Triglyceride

- LPL
- HL

- Apolipoproteins

Lower Cholesterol Concentration → Higher Cholesterol Concentration

- TGs
**LDL Phenotype**

- 7 distinct LDL subclasses
- Two primary LDL phenotypes (pattern A & pattern B)
- Pattern A is predominantly larger, more buoyant LDL
- Pattern B is primarily smaller, more dense LDL

Distribution of LDL particles according to size and density

LDL Particle Size (Diameter nm)

LDL-I II III IV

Density (g/ml)

1.025 1.034 1.044 1.060

Absorbance 280 nm

1.065

Healthy female
Male
CAD patient

B.A. Griffin
LDL size and HDL-c

LDL size and TG

Relationships Between Small Dense LDL Particles, HDL-C, and TG

Gradient Gel Electrophoresis (GGE)
LDL-C Doubly *Underestimates* CV Risk in case of Small, Dense LDL

Large LDL

- Fewer Particles & Less Risk/Particle
- Apo B
- Cholesterol Ester
- LDL-C 130 mg/dL

Small, Dense LDL

- More Particles & More Risk/Particle
- More Apo B

**Lipid profile:**
- TC 198 mg/dL
- LDL-C 130 mg/dL
- TG 90 mg/dL
- HDL-C 50 mg/dL

**Lipid profile:**
- TC 210 mg/dL
- LDL-C 130 mg/dL
- TG 250 mg/dL
- HDL-C 30 mg/dL

Low-Density Lipoprotein (LDL) Consists of Multiple Distinct Subclasses Differing in Size and Lipid Content*

Association with Cardiovascular Disease Risk

- Large:
  1. Less Atherogenic
  2. More Atherogenic

- Small:
  3. clearance by LDL-R
  4. arterial entry
  5. arterial retention
  6. oxidation

* Distribution of subclasses is independent of LDL-C.

Increased small, dense, LDL particles associated with reduced IHD survival

N = 2072 men without IHD at baseline; 13-year follow-up

Survival probabilities

Levels of smal dense LDL
- low
- normal
- high

$P < 0.0001$

$IHD = ischemic heart disease$

“European Panel on Low Density Lipoprotein (LDL) Subclasses”: A
Statement on the Pathophysiology, Atherogenicity and Clinical Signifi-
cance of LDL Subclasses

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Association of Small Dense LDL and Insulin Resistance

BLOOD CHOLESTEROL HOMEOSTASIS
LDL particles consist mostly of cholesteryl esters packaged with a protein moiety called apolipoprotein B (apoB), with 1 apoB molecule in each LDL particle.

LDL particles are the primary carriers of plasma cholesterol in humans, and high LDL levels have a strong and direct relationship with the development of atherosclerosis.

The liver is responsible for the clearance and catabolism of plasma LDL, and hepatocyte expression of LDL receptors (LDLRs) are central to this process by binding and removing LDL from the plasma.

LDL/LDLR complex is internalized into the hepatocyte via clathrin-coated vesicles, thereby removing LDL from the blood. The affinity of the hepatic LDL receptor for apoB on LDL enables LDLRs to clear plasma LDL effectively.

Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles

Clathrin-coated vesicles containing internalized LDL/LDLR complexes fuse with endosomes, resulting in dissociation of the LDLs from LDLRs due to the acidic environment.

The free LDLRs then recycle back to the surface of the hepatocyte to bind and clear additional LDL from the blood.

Free LDL particles in the endosomes are transported to the lysosomes and degraded into lipids and amino acids.

The ability of hepatic LDLRs to be recycled is a key determinant of hepatic efficacy in lowering plasma LDL.
PCSK9 is a proprotein that is produced in hepatocytes, and secreted into the plasma as functional PCSK9.

Extracellular PCSK9 binds to the LDLR on the surface of the hepatocyte and is internalized within the endosome.

LDLR/PCSK9 complex is routed to lysosome for degradation, preventing recycling of LDLR back to hepatocyte surface.

By preventing LDLRs from recycling back to the surface, PCSK9 reduces the concentration of LDLRs on the surface of hepatocytes, resulting in a lower LDL clearance rate and elevated levels of plasma LDL.
EPIDEMIOLOGY
CONCLUSIONS

• Causal Risk factor for CVD
• Heterogeneous group of particles
• Levels regulated by complex mechanisms
• Pro-atherogenic properties
  - Endothelial dysfunction
  - Pro-inflammatory
  - Pro-thrombotic
• *LDL-C reduction is anti-atherogenic*