Atheroma in a human coronary artery

Coronary deaths in Finland

Serum cholesterol in 25-64-year old Finns

Bread spread 1978-2011

It is the LDL level that counts!

LDL cholesterol concentrations


Palomäki ja Kovanen Duodecim 2006
Development of atherosclerotic lesions

<table>
<thead>
<tr>
<th>Foam cells</th>
<th>Fatty streak</th>
<th>Intermediate lesions</th>
<th>Atheroma</th>
<th>Fibrotic plaques</th>
<th>Complicated/ruptured plaques</th>
</tr>
</thead>
</table>

0 10 20 30 40 50 60 70 years


Unsymptomatic development of atherosclerosis

Libby P Circulation 2001

Development of atherosclerotic lesions: (AHA-classification)

LDL carries cholesterol into the arterial wall, HDL carries cholesterol out

Pro-atherogenic lipoproteins

LDL 20-25 nm
IDL 25-35 nm
VLDL 35-90 nm

LDL carries cholesterol into the arterial wall, HDL carries cholesterol out

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4.3.2013

**LDL in the extracellular fluid of tissues**

In physiological conditions, cholesterol does not accumulate intra- or extracellularly.

**The structure of the arterial wall**

- **Intima**
- **Media**
- **Adventitia**

**The concentration of LDL in the arterial intima is the same or even higher than in circulation**

Cells are protected, but LDL accumulates extracellularly.

**Lipoproteins enter the arterial intima by transcytosis**

**Intimal extracellular matrix**

- **LDL**
- **VLDL**

**LDL binds to proteoglycans via ionic interactions**

- **ApoB-100**
- **Glycosaminoglycan disaccharides**

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Atherosclerosis study (20 weeks)

Skälén K et al. Nature 2002

Lipid accumulation is followed by macrophage infiltration

Nakahama, Y et al. ATVB 2007; 27: 1159-1165

Fatty streak: Lipoprotein modification

Aggregated and fused LDL particles within the arterial intima

Intimal lipoproteins induce expression of adhesion molecules in the endothelial cells

Fatty streak: Lipoprotein modification

200 nm
4.3.2013

Foam cell formation

Fatty streak

Endotheium

Monocyte/macrophage

Foam cells

Cholesterol balance in macrophages

Heterogeneity of HDL particles

Pathways of cellular cholesterol efflux depend on the degree of apoA-1 lipidation
4.3.2013

**Cell death in atherosclerosis—Fibrous cap and necrotic core**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead cells</td>
<td>43 ± 9 %</td>
</tr>
<tr>
<td>Dead macrophages</td>
<td>33 ± 5 %</td>
</tr>
<tr>
<td>Dead SMCs</td>
<td>11 ± 6 %</td>
</tr>
</tbody>
</table>

Geng & Libby. Am J Pathol. 1995; 147

**Advanced atherosclerosis: formation of necrotic core**


**Clearance of apoptotic cells in early atherosclerosis**


**Plaque rupture**

**Atheroma**

Stable plaque

- Fibrous cap
- Smooth muscle cells
- Inflammatory cells

Vulnerable plaque

- Thin fibrous cap
- Necrotic core

"Thin-cap fibroatheroma" is the killer

Inflammation

Fibrosis

Macrophages

T-cells

Mast cells

Necrotic core
Atherothrombosis

Coronary atherosclerosis develops in specific areas of the vasculature

Hemodynamics: shear stress

Hemodynamics: shear stress
Mechanisms Relating Insulin Resistance and Dyslipidemia

Fat Cells → Liver
IR ×
Insulin

Liver

Fat Cells

IR

Insulin

Liver

Kidney

Fat Cells

IR

Insulin

Liver

Kidney

LDL particle number vs. LDL cholesterol

Small dense LDL

- Increased entry to arterial intima
- Increased binding to intimal proteoglycans → increased retention in the intima
- Increased modification in the arterial intima → increased inflammatory potential
- Decreased binding to LDL receptor → decreased clearance from circulation
Metabolic syndrome & atherosclerosis

Bornfeldt KE & Tabas I Cell Metabolism (2011) 14: 575-585

Entry of sdLDL ↑
Retention & modification of LDL ↑

eNOS activation ↓
→ NO production ↓
→ adhesion molecules ↑

MCP-1 ↑

ER stress

Necrotic lipid core

ER stress

ER stress-induced apoptosis ↑
• Endothelial dysfunction
• Thinning of fibrous cap
• Increased inflammation & lipid core formation