Low Density Lipoprotein Oxidation Theory as a cause to Atherosclerosis

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Outline:

• Atherosclerosis
• LDL oxidation hypothesis
• Antioxidant Intervention
• Exercise/Diet

Stages of Arteriosclerosis
Starts at a young age (10-14)

• Fatty Streaks = white-gray areas protrude into the lumen
• Intermediate lesions = macrophage infiltration
• Advanced lesion = fibrous plaques (connective tissues, smooth muscle cells, accumulated lipids and lipid laden macrophages - foam cells)

Atherosclerosis

• “Hardening of the Arteries”
• 50% of deaths in the US, Europe, and Japan
• Plaques or atheromas protrude into lumen and reduce blood flow to organs
• Serve as sites for thrombus formation (blood clots)
• Begins as a result of damage to endothelium
The gross appearance of severe coronary atherosclerosis, which involves virtually 100% of the surface of the coronary. There is extensive calcification, especially at the right where the lumen is narrowed.

Factors that promote CVD
- Smoking (lowers antioxidant defenses - free radicals)
- High blood Cholesterol/LDL (LDL-particle LDL-ox)
- High Blood Pressure
- Diabetes (glucose)
- Lack of Exercise
  - (These processes may all interfere with normal healthy maintenance of the endothelial lining)

Risk Factors
- Lack of Exercise
- High Fat Diet: Fast-food meal contains 40-58% of the calories as fats - RDA < 30%
- Smokers
- Heredity
- Stress
- African American Women

Normal human coronary artery with no atherosclerosis and a widely patent lumen that can carry as much blood as the myocardium requires.

The degree of atherosclerosis is much greater in this coronary artery, and the lumen is narrowed by half. A small area of calcification is seen in the plaque at the right.
This is occlusive coronary atherosclerosis. The coronary at the left is narrowed by 60 to 70%. The coronary at the right is even worse with evidence of previous thrombosis with organization of the thrombus and recanalization such that there are three small lumens remaining.

Structure of a lipoprotein (LDL, HDL, VLDL, IDL)

LDL Characteristics
- Transports Cholesterol
- Monolayer phospholipids ~800
- ~1500 cholesterol molecules esterified to long-chain fatty acids
- ~500 unesterified cholesterol molecules
- Apo B-protein 500,000 dalton organizes the particle and mediates the specific binding of LDL to the LDL Receptor

Plasma Cholesterol
- Diet rich in cholesterol and sat. fat (US)
- What is LDL and it’s function?
- Core of cholesterol surrounded by phospholipids and proteins (water-soluble)
- Receptor-mediated endocytosis (RME)
- LDL removed by RME
- Liver usually removes LDL and metabolizes the LDL
Receptor-Mediated Endocytosis

- Specific molecules in extra-cellular fluid interact with specific membrane receptor proteins causing membrane to invaginate, fuse and pinch off to form vesicle
- Example: cholesterol (when attached to specific proteins) is taken into artery cells by this method

General

- LDL receptor diffuse until they associate with clathrin-coated pits
- Coated pits constantly pinch off
- LDL particles bound to LDL receptor
- Form endosomes (hydrolyzes free cholesterol)
  - ↑ Cholesterol
  - 1. Shuts of cholesterol production
  - 2. Synthesis of LDL receptor protein also shuts off
Familial Hypercholesteremia

- Genetic disease Homozygotes and heterozygotes
- (Inherited condition, at young age (20-30y), patients will die from heart attack) Afrikaans
- LDL ~700 mg/dl
- However, FH-patients have "DYSFUNCTIONAL RECEPTORS OR NO RECEPTORS or LOW amounts of Receptor"
- FH strong genetic predisposition impairs LDL uptake. Absence of the LDL receptor in the liver increases LDL in the plasma

LDL Oxidation

- High levels of LDL may result in higher levels of oxidized LDL in the sub-endothelial space
- Scavenger Receptor (protein) on macrophages -binds to LDL particle that has been modified
- Monocytes and macrophages will function as Pac-mans and clean cholesterol

In lipid metabolism, there are two major pathways of "forward" lipid transport in which lipids move from the liver to the peripheral tissues.

1. Exogenous pathway: Lipids from the gut are packaged in the form of chylomicrons. After being metabolized by lipoprotein lipases (LPLs), chylomicron remnants remain and are taken up by the liver.

2. Endogenous pathway: Triglycerides and cholesterol are packaged into VLDL by the liver, exported into the bloodstream where they are catabolized by LPLs. The products are LDL, which can then be further metabolized by hepatic lipase to yield LDL-LDL can be taken up by peripheral tissue, or taken up by the liver and converted to excretable bile acids, or modified by free radicals in the arterial walls leading to atherosclerosis.

Monocytes Use Inflammatory Cell-derived Oxidants to Convert LDL into an Atherogenic Form


Monocytes Use Cell-derived Oxidants to Convert LDL into an Atherogenic Form


Lipid Oxidation Theory of the Human Coronary Artery


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Lipid Oxidation Theory of the Human Coronary Artery

High Density Lipoproteins (HDL)

- HDL transports cholesterol away from arteries
- High HDL beneficial
- Cells lack the membrane receptor required for cell-mediated endocytosis of the HDL particle

Summary

- Atherosclerosis begins with injury to the endothelium, the movement of monocytes and lymphocytes into the tunica intima, and the conversion of monocytes into macrophages that engulf lipids. Smooth muscle cells then proliferate and secrete extracellular matrix.
- Atherosclerosis is promoted by such risk factors as smoking, hypertension, and high plasma cholesterol concentration. Low-density lipoproteins (LDLs), which carry cholesterol into the artery wall, are oxidized by the endothelium and are a major contributor to atherosclerosis.

Antioxidant Defenses in Human Plasma and LDL

<table>
<thead>
<tr>
<th>Antioxidant Proteins</th>
<th>Typical Plasma Concentrations</th>
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<tbody>
<tr>
<td>Non-Enzymatic:</td>
<td></td>
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<tr>
<td>Fc and C3 Binding Proteins (Albumin, Transferin, Ceruloplasmin, etc.)</td>
<td>300 µg/mL</td>
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<tr>
<td>Enzymatic:</td>
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<tr>
<td>Superoxide Dismutase, Catalase, GSH Peroxidase: mainly intracellular</td>
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<table>
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<tr>
<th>Small Molecule Antioxidants</th>
<th>Typical Plasma Concentrations</th>
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<tbody>
<tr>
<td>Water-Soluble:</td>
<td></td>
</tr>
<tr>
<td>Uric Acid</td>
<td>50 µM</td>
</tr>
<tr>
<td>Ascorbic Acid (Vitamin C)</td>
<td>15 µM</td>
</tr>
<tr>
<td>Albumin-Bound Bilirubin</td>
<td>&lt;2 µM</td>
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<tr>
<td>Glutathione (GSH)</td>
<td></td>
</tr>
<tr>
<td>Lipid-Soluble (Lipoprotein-Associated):</td>
<td></td>
</tr>
<tr>
<td>α-Tocopherol (Vitamin E)</td>
<td>25 µg/mL</td>
</tr>
<tr>
<td>Ubiquinol 10 (Coenzyme Q10)</td>
<td>1.0 µg/mL</td>
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<tr>
<td>β-Carotene (Pro-Vitamin A)</td>
<td>0.5 µg/mL</td>
</tr>
<tr>
<td>Lycopene</td>
<td>0.5 µg/mL</td>
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<td>Modified LDL</td>
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Oxidized LDL & Atherosclerosis

- Oxidized LDL
  - is taken up more readily by macrophages and causes foam cell formation
  - is chemotactic for circulating monocytes
  - inhibits motility of tissue macrophages
  - is cytotoxic to endothelial cells
  - increases vasoconstriction

Mechanism of LDL Oxidation

Summary

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