Outline

Lipid hypothesis for atherogenesis

Studies in experimental animals:
Early findings that led to these studies
• cholesterol is the substance that accumulates in atherosclerotic lesions
• blood cholesterol was elevated in individuals with premature atherosclerosis,
• cholesterol and saturated fat in the diet together promote atherosclerotic lesion development

Animal models for studies of atherosclerosis:
• Rabbits are hypersensitive to dietary cholesterol and rapidly develop arterial lesions
• Rats and mice are naturally resistant to diet-induced atherosclerosis
• Pigs are large animal models and while some strains are resistant, others are susceptible to diet-induced atherosclerosis with many phenotypic similarities to nonhuman primates
• Several species of nonhuman primates are sensitive to diet-induced atherosclerosis and have many phylogenetic similarities to man
• Genetically engineered mouse models of atherosclerosis are appealing due to the ability to examine molecular mechanisms of diet-induced atherosclerosis in these animals

Diet-induced atherosclerosis in monkeys
• Cholesterol in diet is required
• Demonstrated specificity to type of fat
• Hepatic ACAT2 and CE secretion mediates diet-induced atherogenicity

Atherosclerosis in Mice
• Dietary fat and cholesterol similarities to monkeys
• Gene deletion of ACAT2 reduces atherosclerosis and eliminates hepatic CE secretion
Dietary cholesterol sensitivity is species dependent in primates.
LDL Promote and HDL Protect Against Coronary Artery Atherosclerosis in Primates

LDL Cholesterol (mg/dl) vs. Log Cor. Art. Intimal Area (mm²)

Cyno: $r = 0.82$
AGM: $r = 0.75$

HDL Cholesterol (mg/dl) vs. Log Cor. Art. Intimal Area (mm²)

Cyno: $r = -0.49$
AGM: $r = -0.61$
Coronary Artery Atherosclerosis Develops in Monkeys Only When Diets Contain Cholesterol; Dietary Polyunsaturated vs. Saturated Fat Protects
Fatty Acid Composition of Fats and Oils

- Canola Oil
- Safflower Oil
- Sunflower Oil
- Corn Oil
- Olive Oil
- Soybean Oil
- Peanut Oil
- Turkey Fat
- Chicken Fat
- Lard (Pork Fat)
- Palm Oil
- Beef Tallow
- Cocoa butter
- Butter
- Coconut Oil

Fatty Acid %
Coronary Artery Atherosclerosis is More Advanced in Animals Fed Dietary Saturated and Monounsaturated Fat
Primate Coronary Artery Athero is Related to Dietary Fat Type

![Graph showing the relationship between dietary fat type and coronary artery athero area. The x-axis represents Rank Order (1, 5, 10), and the y-axis represents Log Intimal Area (mm^2). The graph includes bars for SAT, MONO, and POLY dietary fats.](image-url)
LDL Size Predicts Coronary Artery Atherosclerosis Extent in Monkeys

![Graph showing the relationship between LDL Molecular Weight and Log Coronary Art Intimal Area. The graph includes data points for different species, indicated by different markers. The x-axis represents LDL Molecular Weight (g/µmole), and the y-axis represents Log Coronary Art Intimal Area (µm²).]
Plasma LDL Particle Size is Dependent on Dietary Fat Type

Dietary Fat Type

Diameter (angstroms)

<table>
<thead>
<tr>
<th>DIET</th>
<th>Poly</th>
<th>Mono</th>
<th>Sat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>284</td>
<td>300</td>
<td>298</td>
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</tbody>
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Legend:
- a: Significant difference from Poly
- b: Significant difference from Mono and Sat
LDL Size is Highly Correlated to Liver CE Secretion Rate

LDL MW (g/µmole) vs Liver CE Secretion (mg/hg.hr)
Localization of ACAT1 to Kupffer Cells and ACAT2 to Hepatocytes in Liver of African Green Monkeys
Liver Cholesterol Ester Secretion Rate is Strongly Related to Coronary Artery Atherosclerosis

- Perfusate CE (mg/hg.hr) vs. Coronary Art. CE (mg/g wet wt.)
- POLY: Yellow dots
- MONO: Orange squares
- SAT: Red triangles

Correlation coefficients:
- r = 0.73
- r = 0.84
- r = 0.87
Localization of ACAT1 to Goblet Cells and ACAT2 to Enterocytes in Jejunum of African Green Monkeys
Percent Intestinal Cholesterol Absorption is Highly Related to Plasma Cholesterol but not Affected by Dietary Fat Type

\[ r = 0.63 \]
The Extent of Aortic Atherosclerosis in LDLr^-/-, ApoB100 Mice is Dietary Fat Type Dependent
Dietary Fat Dependency of Cholesterol Ester Accumulation is Comparable in LDLr^-/- Mouse Liver and Aorta
Aortic Atherosclerosis is Highly Related to LDL Particle Size as Modified by Dietary Fat Type in ApoB100-only LDLr^-/- Mice

![Graph showing the relationship between LDL particle size and aortic CE (mg/g protein)].

- **Chow**: 0 to 5.00 (g/µmole)
- **FO**: 10 to 20 (mg/g protein)
- **Poly**: 25 to 35 (mg/g protein)
- **Sat**: 30 to 45 (mg/g protein)
- **Trans**: 40 to 50 (mg/g protein)
- **Mono**: 50 to 60 (mg/g protein)

Correlation coefficient: $r=0.97$
Perfused Liver Lipid Secretion Rates in LDLr⁻/⁻ Mice With and Without ACAT2 Fed Low and High Cholesterol Diets

CHOL. ESTER

μg/min/g

LOW CHOL

HI CHOL

TRIGLYCERIDE

LDLr⁻/⁻  LDLr⁻/⁻,ACAT2⁻/⁻  LDLr⁻/⁻  LDLr⁻/⁻,ACAT2⁻/⁻
Aortic Atherosclerosis in LDLr\(^{-/-}\) Mice With and Without ACAT2 Fed Low and High Cholesterol Diets

![Graph showing aortic CE (µg/mgPR) for different genotypes under low and high cholesterol diets.](image-url)
Conclusions

• Dietary cholesterol and fat type are important factors in promoting the development of atherosclerosis

• Monkeys and mice show similar diet dependencies

• Indications are that effects on the liver enzyme ACAT2 may mediate many of the dietary fat and cholesterol effects to promote atherosclerosis