Familial Hypercholesterolemia: Diagnosis, Treatment and Molecular Basis of a Common Disorder in Children That Causes Premature CAD

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Low density lipoprotein (LDL)

- Phospholipid
- Unesterfied cholesterol
- Cholesteryl ester

Polar surface
Apolar core
Apolipoprotein B

Fig. 18-12, Molecular Cell Biology, Lodish et al., 5th edition
LDL-C and Risk of CHD

Lifecycle of LDL

Fig. 18-13, *Molecular Cell Biology*, Lodish et al., 5th edition
Cholesterol Biosynthesis

Acetyl CoA

↓

↓

↓

↓

↓

↓

HMG-CoA

mevalonate

squalene

lanosterol

cholesterol

HMG-CoA reductase
Induction of Cholesterol Synthesis

FH Defect in HMGR Regulation

J.P. is a 12 year old girl. Had xanthomas from 2 years of age and MI at 11 years of age. Total plasma cholesterol ranged from 700-1000 mg/dL.
Activity of Different Genotypes

FH show a defect in LDL-mediated regulation of HMGR that is not due to defect in enzyme or LDL.

Feedback Regulation of Cholesterol Synthesis

Known:
Cholesterol synthesis is controlled by amount of cholesterol in diet through an end-product, negative feedback mechanism.

Rate-limiting step in cholesterol synthesis is HMG-CoA reductase synthesis of mevalonate.

1973:
Developed *in vitro* assay for HMG-CoA reductase (HMGR) in human skin fibroblasts

Showed that activity of HMGR is regulated by serum lipoprotein (LDL)

Removal increases HMGR activity; addition suppresses.
A Productive Collaboration

Joseph Goldstein and Michael Brown
UT-Southwestern Medical Center in Dallas
Five Functional Classes of LDLR Mutations

Metabolic and Molecular Bases of Inherited Disease, Ch. 120

J.D.
LDL Receptor Internalizes LDL In Clathrin Coated Pits

LDL

LDLR

Clathrin

FXNPVY → C
J.D. mutation

Sequence required for internalization

COATED PIT
Endosomal Release of LDL

Endosome [pH ~5]

Surface of \( \beta \)-propeller domain becomes positively charged, and then binds to the ligand-binding arm

Released LDL particle

\( \beta \)-propeller domain

Fig. 17-30, *Molecular Cell Biology*, Lodish et al., 5th edition
How do cells control levels of LDL receptor and cholesterol synthesis?
Feedback Regulation of Cholesterol Supply

LDL Receptors

Acetyl CoA → Synthase
HMG CoA → Reductase
Mevalonate → Cholesterol

LDL
The SREBP Pathway

SREBP

High Cholesterol

Site-1 Protease

Site-2 Protease

Low Cholesterol
The SREBP Pathway

High Cholesterol

Site-1 Protease

Site-2 Protease

Low Cholesterol

bHLH

SRE
How Statins Work to Lower LDL

LDL Receptors

Acetyl CoA
Synthase
HMG CoA
Reductase
Mevalonate

Cholesterol

SREBP
LDL-C and Risk of CHD

LDL Metabolism in FH

**LIVER**

- LDLR
- LDL
- IDL
- VLDL
  - LDL
  - IDL
  - VLDL

**Peripheral Tissues**

- LDL
- IDL

**Skin Fibroblasts**

- LDL
- IDL

- Bile

**LDL Metabolism Diagram**

- LDLR
- LDL
- IDL
- VLDL
  - LDL
  - IDL
  - VLDL

- Skin Fibroblasts
LDL Receptor Pathway

[Diagram of LDL Receptor Pathway]

Metabolic and Molecular Bases of Inherited Disease, Ch. 120
I. Familial Hypercholesterolemia (FH): An Autosomal Co-Dominant Trait Due to Defects in the LDL Receptor (LDLR). *FH Heterozygotes:*

- Over 900 mutations in LDLR gene that affect the synthesis, transport, LDL-binding ability, clustering (in coated pits) and recycling of the LDLR
- Diagnosis can be made at birth and early in childhood
- Average LDL-C levels (mg/dl) in children 240 and in adults 300
- Triglyceride levels normal or borderline high
- HDL-C levels borderline low
- Elevated Lp(a) levels accelerate risk of CAD
- Tendon and tuberous xanthomas in adults.
- Premature CAD 50 % of males and 25 % of females by the age of 50 years.
- Responsive to statins, resins, niacin and ezetimibe
Familial Hypercholesterolemia (FH):
Defects in both alleles of the LDLR

*FH Homozygotes:*

- LDL-C ranges from 500 to 1,000 mg/dl
- Diagnosis can be made in utero
- Planar xanthomas by age 5 years
- Tendon/tuberous xanthomas by 10 years
- Precocious CV disease before 20 years
- Life threatening aortic stenosis
- Modest response to higher doses of more potent statins and niacin and ezetimibe but often require plasma LDL apheresis
Familial Defective-Ligand apoB-100

- Autosomal dominant disorder affects 1:1,000
- Defect in that portion of the amino acid sequence that binds to the LDL receptor (e.g., residue 3500 of apoB-100)
- LDL levels can be normal, moderately or markedly elevated
- Expression in children also variable
- Only 1/20 adults have tendon xanthomas
- CAD not as malevolent as FH
- Treatment is similar to that used for FH
**Proprotein Convertase Subtilisin-like Kexin Type 9 (PCSK9) Gain-of-Function Mutations**

- PCSK9- Secreted enzyme of serine protease family
- Overproduction of PCSK9 markedly reduces LDL receptors
- PCSK9 targets LDL receptors for degradation
- LDL levels elevated similar to heterozygous FH (FH3)
- Premature coronary artery disease
- Treatment similar to that used for FH
PCSK9 Loss-of-Function Mutations

- PCSK9- Secreted enzyme of serine protease family
- Underproduction of PCSK9 markedly increases LDL receptors
- LDL levels reduced to lower than average, e.g., (70 to 80 mg/dL)
- Prevalence of coronary artery disease reduced over lifetime of 50 to 90%
- These mutations prevalent in African Americans
## Dietary Sterols

<table>
<thead>
<tr>
<th>Cholesterol (ANIMAL)</th>
<th>Sitosterol (PLANT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>20-80%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>&lt; 220 mg/dL</td>
<td>&lt; 1 mg/dL</td>
</tr>
</tbody>
</table>
Phytosteroolemia (Sitosteroolemia)

- Rare recessive sterol storage disease due to two mutant alleles in ABCG5/ABCG8 transporters
- Increased intestinal absorption and decreased hepatic excretion of phytosterols and cholesterol
- Increased amounts of plant sterols such as sitosterol and campesterol in plasma (15-30 fold)
- LDL-C can be normal or elevated 2-3 fold
- Tendon and tuberous xanthomas in first decade of life, premature CAD and aortic stenosis
Mean IMT Changes From Baseline for the Different Carotid Arterial Wall Segments in the Pravastatin and Placebo Groups

Summary

Studies of disease mutations leading to hypercholesterolemia have led to a better understanding of cell biology.

Research is ongoing.

Combination of human disease research and molecular cell biology studies promises to yield future discoveries.