History of Cholesterol and The LDL Receptor

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Development of the LDL receptor concept

- 1815 Cholesterol identified as a specific compound
- 1910 Human atherosclerotic plaques contain cholesterol
- 1913 High cholesterol diet causes atherosclerosis in rabbits
- 1933 Feedback inhibition of cholesterol synthesis demonstrated
- 1938 Familial hypercholesterolemia described
- 1954 Elevated LDL identified as primary focus of FH
- 1959 Cholesterol biosynthetic pathway elucidated
- 1959 FH exists in both heterozygous and homozygous forms.
- 1974 Cellular cholesterol control systems defined
- 1976 LDL receptor concept defined
- 1976 Statin effect described in fibroblasts, animals and in FH (1979-80)
The Cholesterol Story

M.E. Chevreul
French chemist discovered cholesterol in 1815. Isolated and chemically purified from bile.

Human atherosclerotic plaques contain cholesterol

Adolf Windaus Circa 1910:
First structural description of cholesterol and identification of its presence in bile and tissues.

Windaus was awarded the 1928 Nobel Prize in Chemistry for studies on:
"Constitution of sterols and their connection with other substances appearing in nature."

From Goldstein, Braun Scientific American 1984
Photomicrograph by L. Maximilian Buja, UTSW.
High cholesterol diet causes atherosclerosis in rabbits

Nikolai Anitchkov (1885-1964)

- Demonstrated that high cholesterol diet was responsible for cholesterol in atherosclerotic lesions in the rabbit arteries. The degree of atheromatous involvement was related to the amount of cholesterol uptake (1913).
- Anitchkov was also the first to describe the foam cell, the lipid-laden macrophage in arterial lesions, which he called the “cholesterinesterphagozyten.”


Feedback inhibition of cholesterol synthesis demonstrated


- Created metabolic cages in which it was possible to study synthesis and destruction of cholesterol quantitatively in serial balance experiments.
- Measuring the input and output and body composition allowed calculation of synthesis.
- When moderate amounts of cholesterol were administered, a smaller amount of cholesterol was synthesized.
- When large amounts of cholesterol were given, a considerable part was destroyed. High fat intake had no effect on the cholesterol balance.

Cholesterol as a Molecule of Interest
Molecular Structure of Cholesterol

Nobel Prize for 1927 for structural work on cholesterol and bile acids.

Heinrich Wieland, PhD

Cholesterol

Summary of biosynthesis pathway in mammalian systems.

Isoprenoids:
- Geranyl-PP
- Farnesyl-PP

Sterol synthesis

From Wikipedia

The Rate Limiting Step in Cholesterol Synthesis: HMG Co-A Reductase

Fig. 1. HMG-CoA reductase reaction.
Mevalonate to Isoprenoids

Prof. G.J. Popjack
Prof. J.W. Cornforth

Isoprenoids to Squalene and Squalene to Lanosterol

The synthesis of squalene and its cyclization to lanosterol was worked out by Konrad Bloch and the final steps published in 1953 by RB Woodward and Block.

Konrad Bloch was awarded the Nobel Prize in Physiology and Medicine in 1964.


Cholesterol Synthesis:

Konrad Bloch and Fyodor Lynen Awarded Nobel Prize in Medicine and Physiology in 1964

Konrad Bloch in his office at Harvard in 1964

Feodor Lynen at Munich University
Xanthomas and Blood Cholesterol

Familial Hypercholesterolemia
Historical Aspects

Case reports of xanthomata:


Familial Occurrence:

Genetic Nature of Familial Hypercholesterolemia

Mueller C: Angina pectoris in hereditary xanthomatosis.
Arch Intern Med. 1939;64:675.

Autosomal dominant inheritance.
First reference to:

**Heterozygous and Homozygous FH**


![Diagram of Homozygotes and Cholesterol Levels]

Hypercholesterolemia becomes Elevated LDL in Ultracentrifuge


Xanthoma Tendinosum. A group of eighteen patients with xanthomatous lesions involving the tendons.

Clinical and lipoprotein data reported.

Some of these patients noted that lesions had been present since childhood.

**KHACHADURIAN, A. K.,**


**Family 1.**

![Pedigree of Family 1]

Patient #18 from Family 1

Xanthomata occurring in heterozygotes. Marriage of heterozygotes generated offspring with severe elevations of cholesterol, moderate elevations and normal levels compatible with the inheritance as an autosomal co-dominant or a homozygote.
LDL Physiology in FH versus Normal

The Kinetics of LDL clearance in FH heterozygotes is slower than normal.

Studies of Cellular Cholesterol Metabolism

Endothelial Cells Bind and Degrade $^{125}\text{I}-\text{LDL}$

Normal fibroblasts showing saturation binding followed by degradation. Cells from FH patients show markedly decreased binding and degradation.


LDL inhibits HMG-CoA reductase in Normal cells but not in ho-FH

Pronase digestion of cell surface proteins reduces response to LDL-C in normal cells.

Feedback Regulation of Cholesterol Synthesis and LDL Receptors in Cultured Cells

Normal Subjects (A)
Children with Homozygous FH (B)

(A) Normal cells obtain cholesterol from two sources:
(1) endogenous synthesis and
(2) receptor-mediated uptake and
lysosomal hydrolysis of LDL.

(B) Lacking LDL receptors, FH cells
maintain normal levels of cholesterol
by increasing synthesis of cholesterol,
leaving excess LDL in the culture
medium.


The Role of a Statin in Developing
Receptor Concept


From Citrinin to Compactin (ML-236B)


Compactin as a Tool to Develop the LDL receptor Concept


A LDL receptor activity increases in the presence of compactin

B

Addition in medium

Stimulation

% change

Control

87

100

100

LDL + compactin

91

100

20

C

Cholesterol in cells increases with LDL and compactin

<table>
<thead>
<tr>
<th>Addition to medium</th>
<th>LDL-cholesterol</th>
<th>Cholestyramine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>15.6</td>
<td>7.5</td>
<td>23.1</td>
</tr>
<tr>
<td>Compactin, 5.2 μM</td>
<td>20.6</td>
<td>8.2</td>
<td>28.8</td>
</tr>
<tr>
<td>LDL, 1 μg/ml</td>
<td>20.6</td>
<td>7.7</td>
<td>28.3</td>
</tr>
<tr>
<td>LDL, 1 μg/ml + Compactin, 5.2 μM</td>
<td>33.6</td>
<td>4.2</td>
<td>37.8</td>
</tr>
</tbody>
</table>

First Clinical Tests of Compactin


Seven Compactin like Molecules

The Akira Endo Award

For more information about Dr. Endo’s career and that of Dr. Davis:

For information about the discovery of statins:
A historical perspective on the discovery of statins.

Discussion.
Question #1
Which of the following is NOT Correct?
1. Discovered cholesterol in bile - Chevreul
2. Linked dietary cholesterol to CVD - Anitchkov
3. Revealed structure of cholesterol - Wieland
4. Final steps in cholesterol synthesis - Block
5. Isolated the LDL receptor - Endo

Question #2
Only one of the following is true:
1. Tendon xanthomas occur only in homozygous familial hypercholesterolemia (FH)
2. The cellular defect in FH is due to enzymes of cholesterol synthesis
3. LDL receptors bind one LDL molecule and are then degraded on entry into the liver
4. LDL receptor numbers are controlled by intracellular membrane cholesterol

Question #3
The rate limiting step in cholesterol synthesis is controlled by:
1. The number of LDL receptors on the cell surface.
2. The PCSK9 concentration in the plasma
3. HMG CoA reductase activity
4. HMG CoA synthase activity
5. Acy CoA acyl synthase activity
Question #4
One of the following is true:

1. Statins were discovered by screening fungal cultures for an HMG Co-A reductase inhibitor
2. The initial statin in human studies was pravastatin
3. All statins are derived from fungal cultures
4. Sankyo held the worldwide patent on lovastatin
5. Akira Endo held a PhD in social studies.