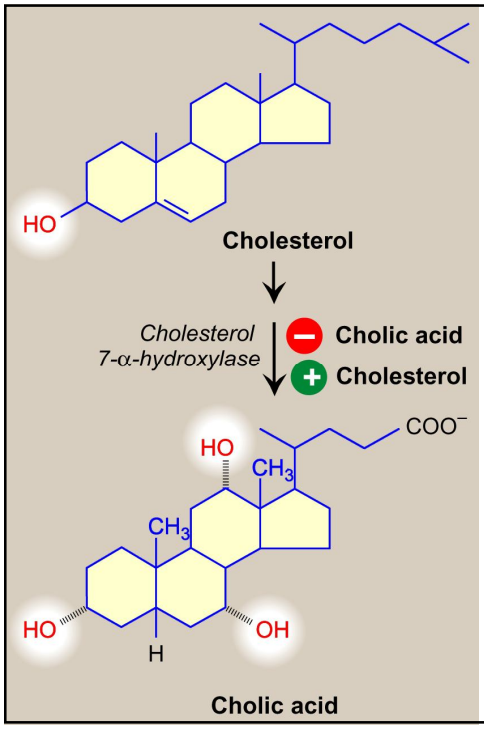
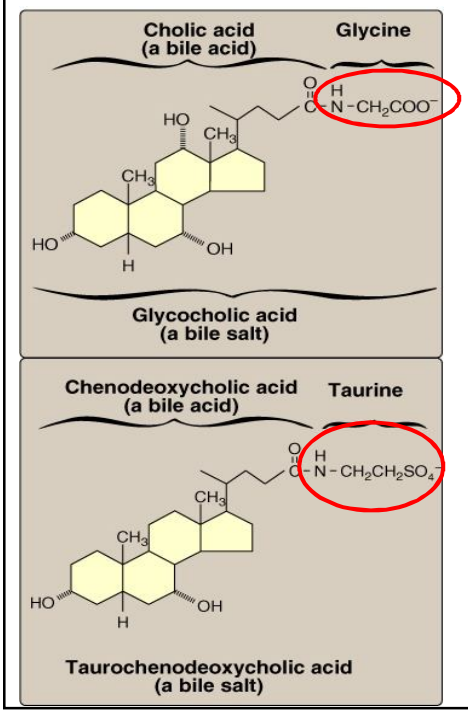
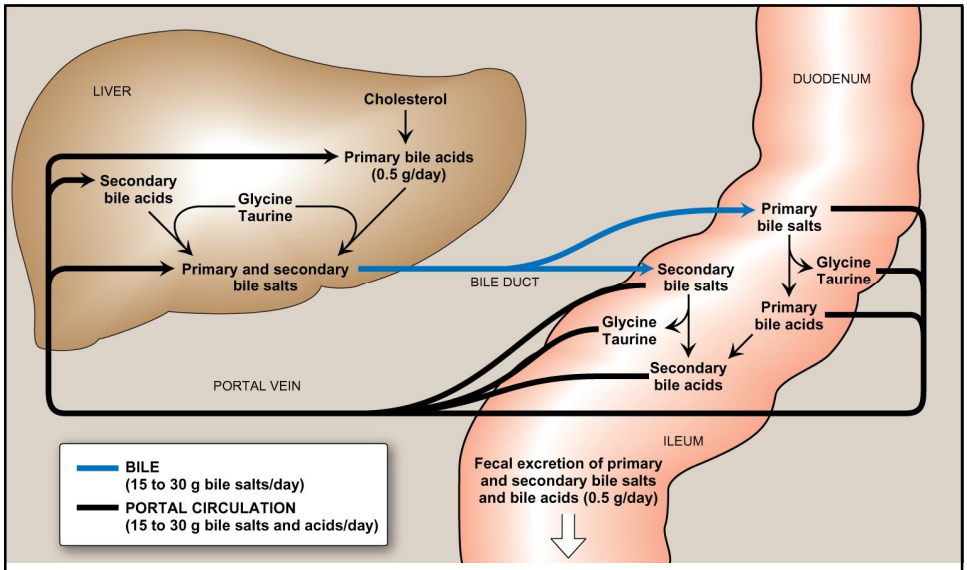



## Synthesis of Bile Acids

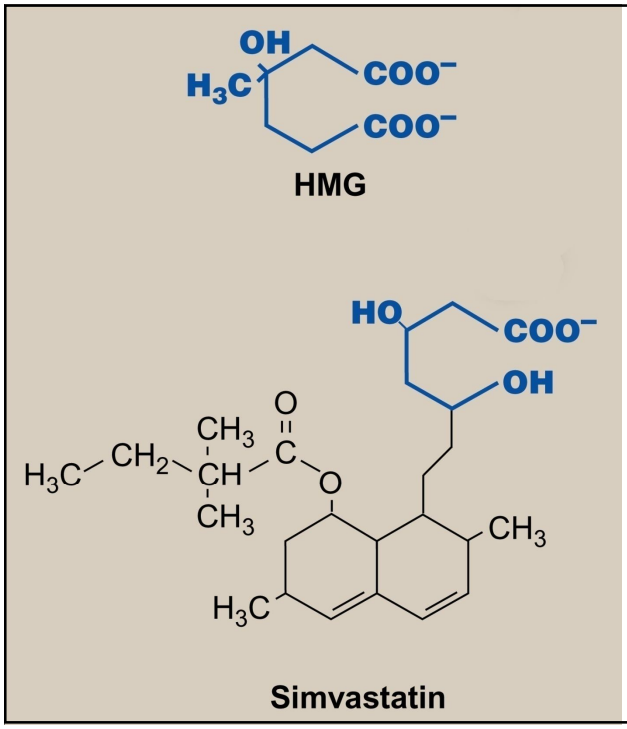
Hydroxylation at Carbon 7 is the Rate-limiting Step






# Lowering Cholesterol Level

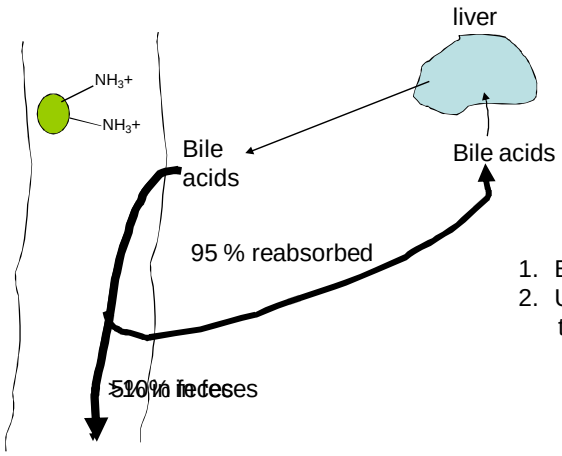
- Dietary
  - ↓Cholesterol intake
  - ↑ PUSFA / SFA
  - ↑ Fiber
  - Daily Ingestion of Plant Steroid Esters
- Inhibition of Synthesis
- ↓ Enterohepatic Circulation of Bile Acids



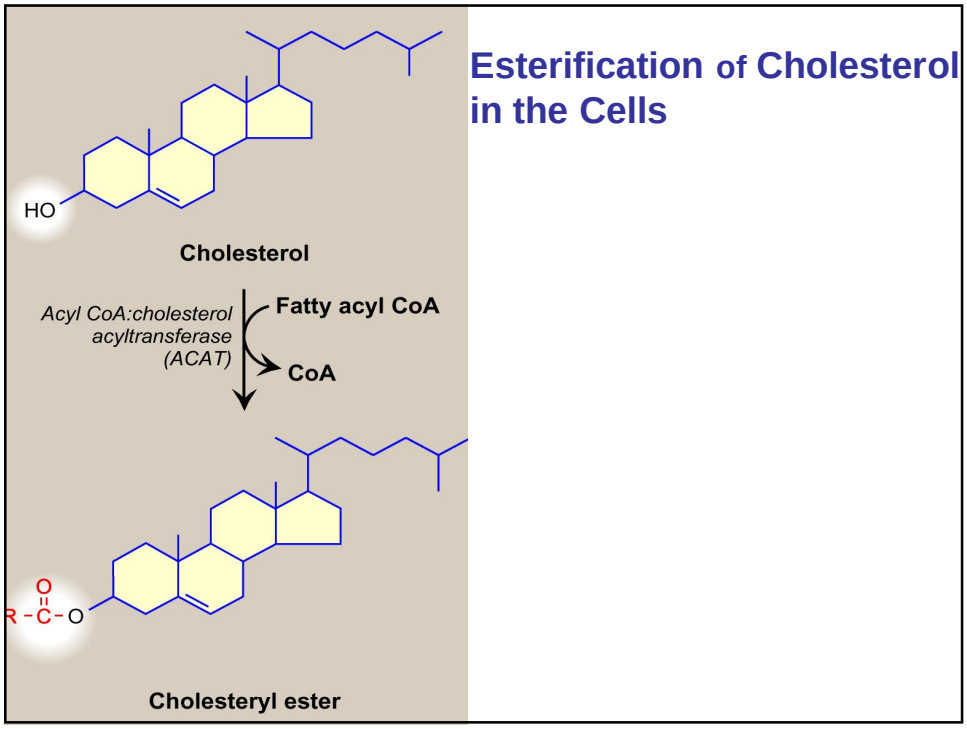

Inhibitors of HMG CoA reductase

# Lowering Cholesterol

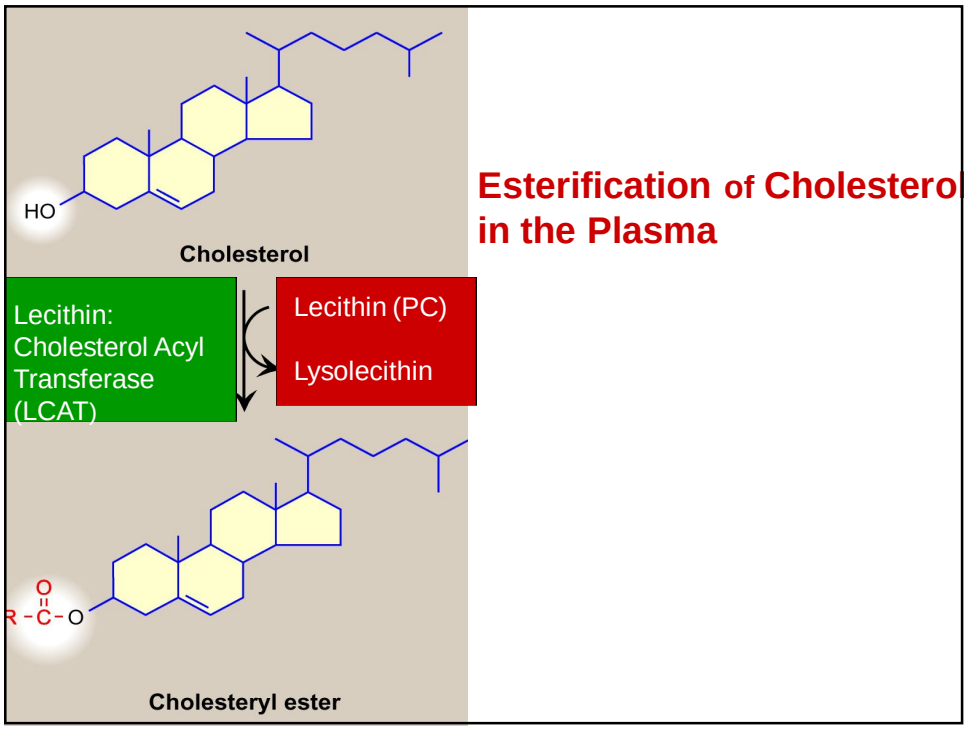
- Bile sequestering agents




1. Bind bile acid
2. Utilize more cholesterol to make bile acids

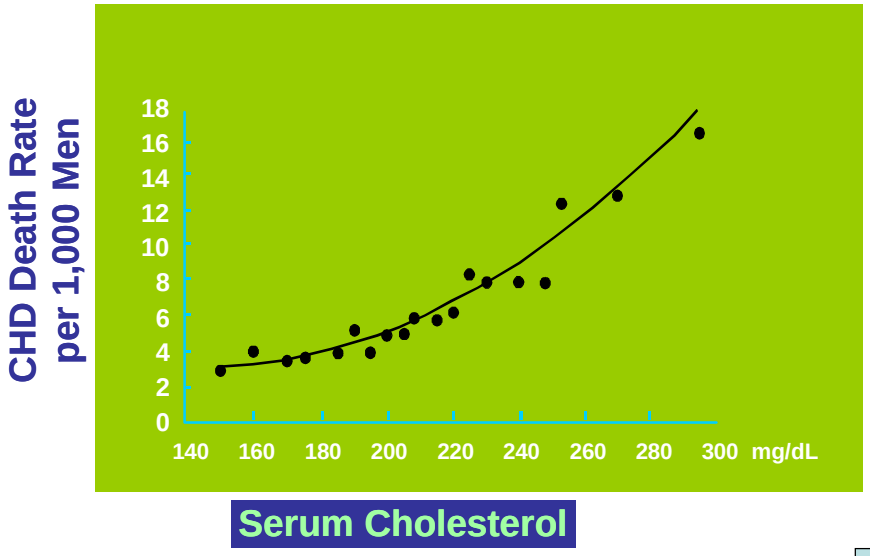



## Esterification of Cholesterol in the Cells




## Esterification of Cholesterol in the Plasma

## Serum Cholesterol and CHD

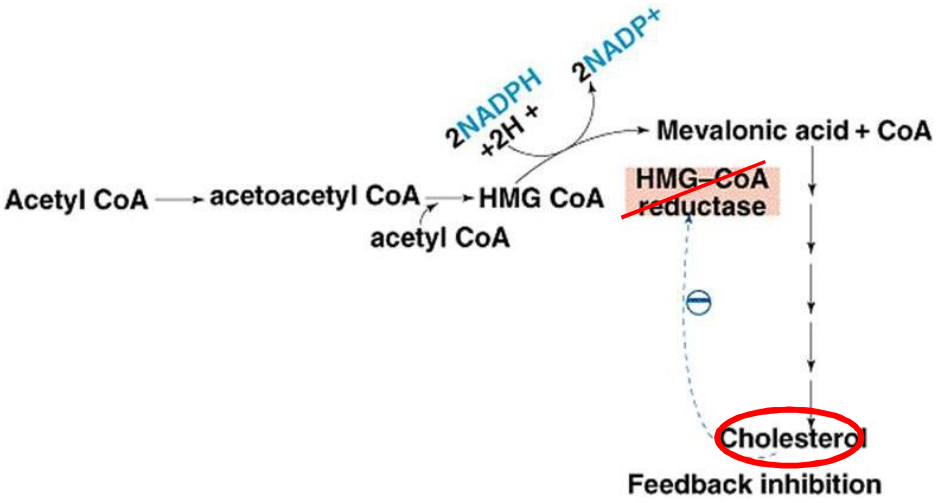



Martin M. Lancet 1986;11:933-

## Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- Proteolytic Regulation

## Regulation of Cholesterol Synthesis




## Regulation of Cholesterol Synthesis

- Regulation of Gene Expression

Expression of the HMG CoA Reductase Gene Requires a Transcriptional Factor (Protein):

SRE DNA

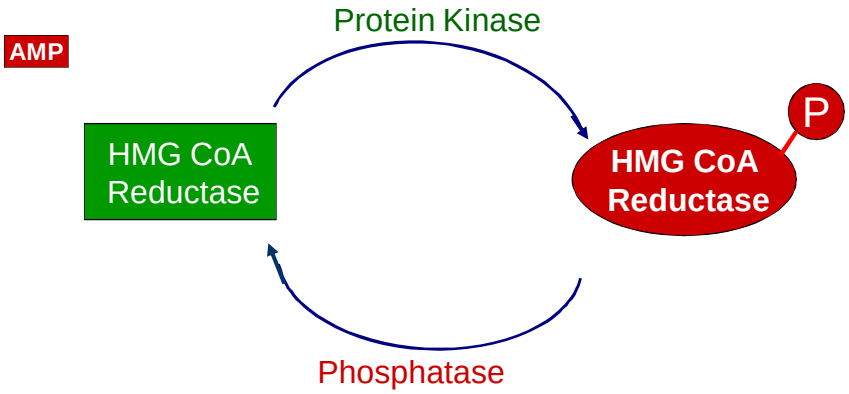
↓Cholestrol

SREBP

mRNA

# Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- **Covalent Modification**




# Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- **Hormonal Regulation**

Glucagon: ↑Phosphorylated Form

Insulin:↑ **Dephosphorylated** Form (↑Phosphatase)

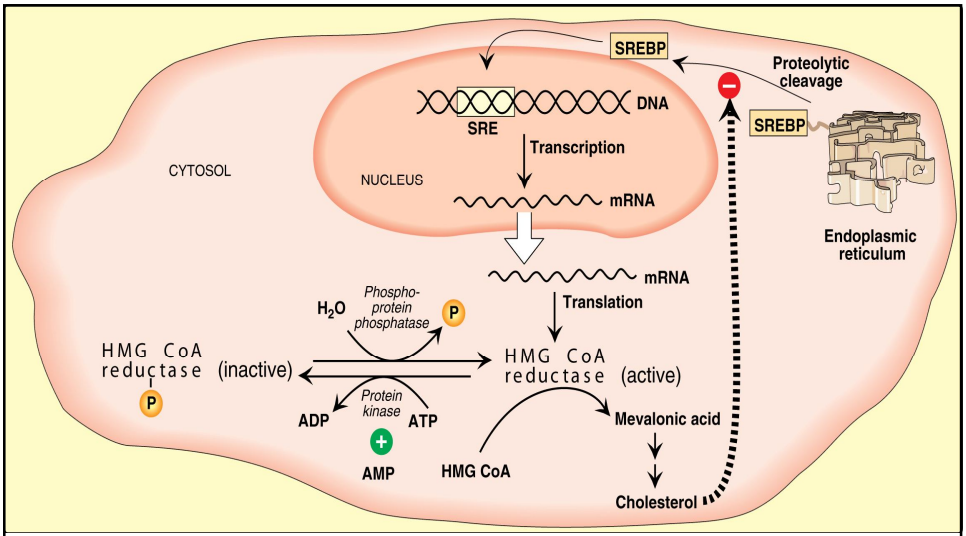
# Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- **Proteolytic Regulation**

↑ **Cholesterol**

↑↑**HMG CoA Reductase** Proteolysis

↓ HMG CoA Reductase



# Transport of Cholesterol in the Blood

Chylomicrons → remenats → Liver

VLDL → IDL → LDL

IDL → Liver

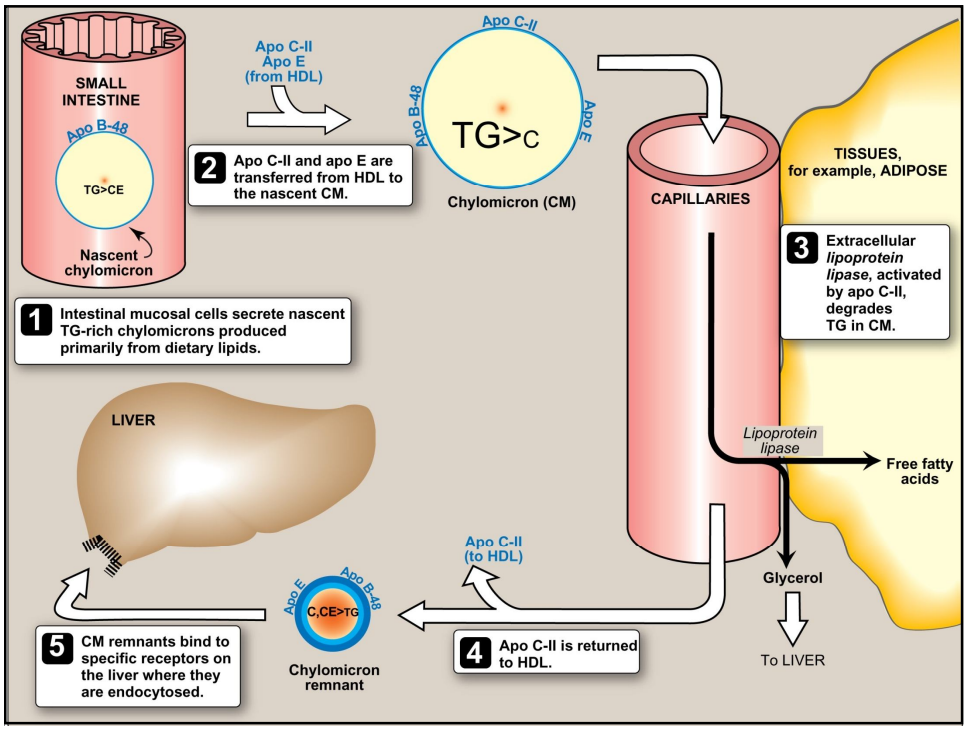
LDL → Liver

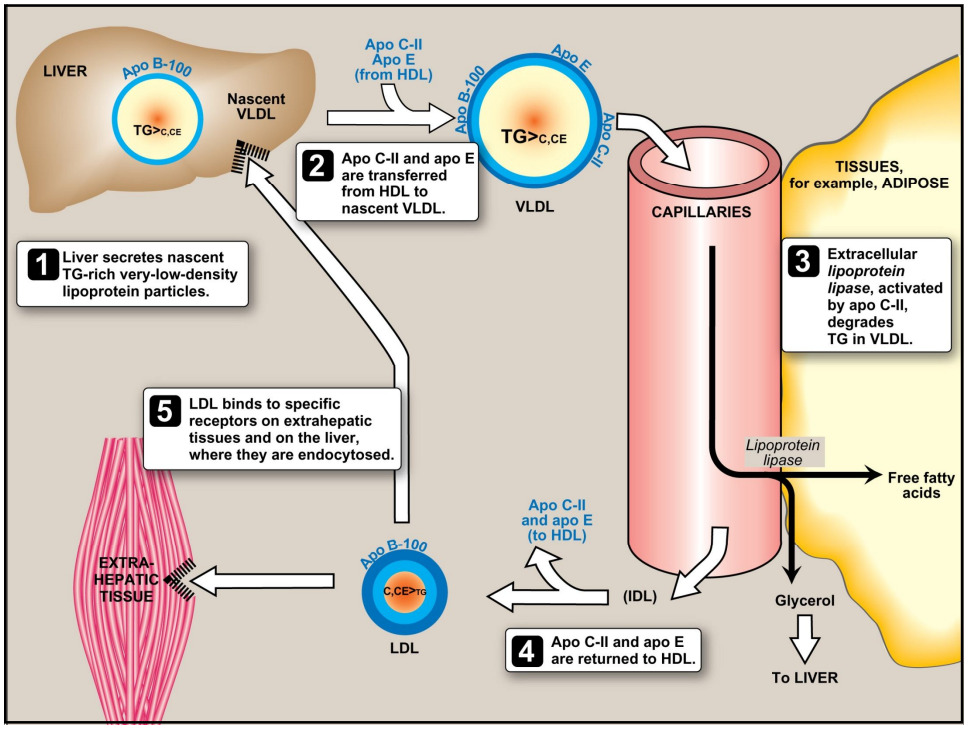
LDL → extrahepatic tissues

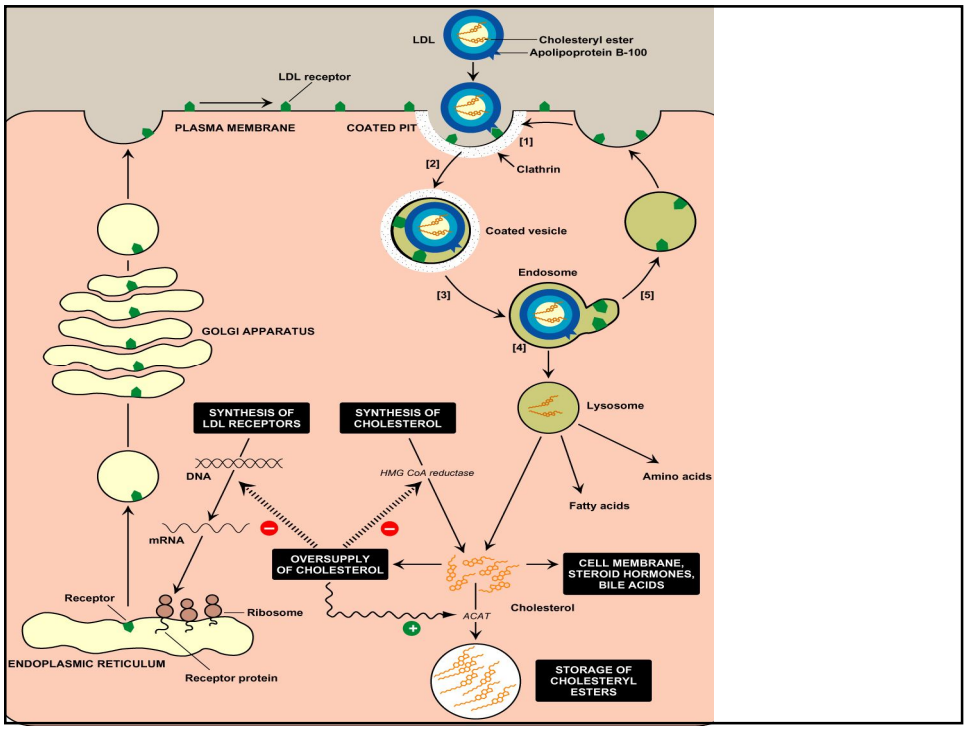
HDL

Importance Vital or lethal ?

Risk factor for coronary heart disease.




LIVER
Apo B-100
TG>C,CE
Nascent VLDL
Apo C-II
Apo E
(from HDL)
Apo B-100
TG>C,CE
Apo E
Apo C-II
VLDL
2 Apo C-II and apo E are transferred from HDL to nascent VLDL.
CAPILLARIES
TISSUES, for example, ADIPOSE
1 Liver secretes nascent TG-rich very-low-density lipoprotein particles.
3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TG in VLDL.
5 LDL binds to specific receptors on extrahepatic tissues and on the liver, where they are endocytosed.
Lipoprotein lipase
Free fatty acids
Apo C-II
and apo E
(to HDL)
EXTRA-HEPATIC TISSUE
Apo B-100
C,CE>TG
LDL
(IDL)
Glycerol
4 Apo C-II and apo E are returned to HDL.
To LIVER


LDL
Cholesteryl ester
Apolipoprotein B-100
LDL receptor
PLASMA MEMBRANE
COATED PIT
[1]
[2]
Clathrin
Coated vesicle
Endosome
[3]
[4]
[5]
GOLGI APPARATUS
Lysosome
SYNTHESIS OF LDL RECEPTORS
SYNTHESIS OF CHOLESTEROL
DNA
HMG CoA reductase
Amino acids
Fatty acids
mRNA
OVERSUPPLY OF CHOLESTEROL
CELL MEMBRANE, STEROID HORMONES, BILE ACIDS
Receptor
Ribosome
Cholesterol
ACAT
ENDOPLASMIC RETICULUM
Receptor protein
STORAGE OF CHOLESTERYL ESTERS

# Macrophage Scavenger Receptor

Non specific

modified (damaged) LDL

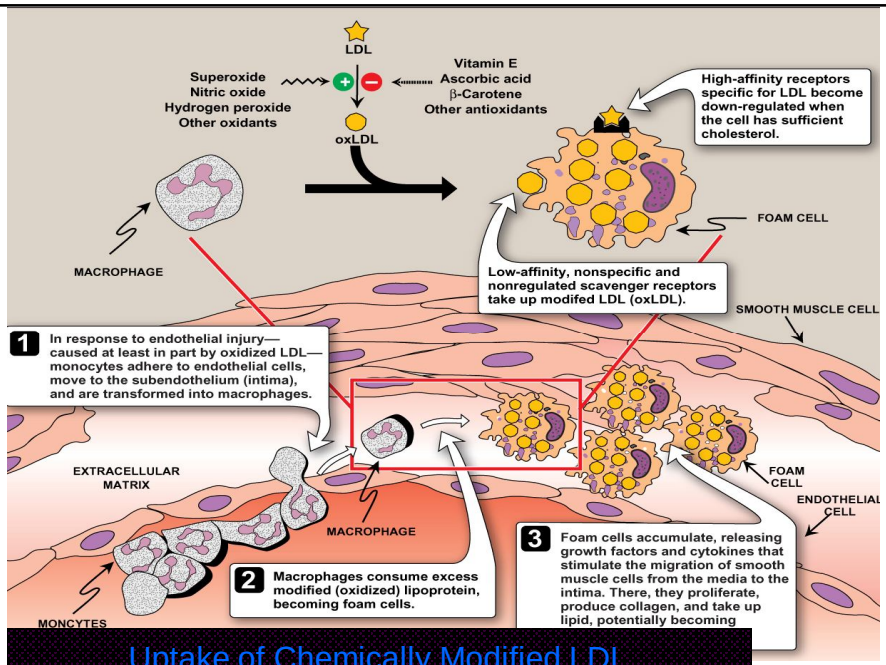
No down regulation

LDL

Macrophage → foam cells

Accumulation of foam cells in the subendothelial space

→ Early evidence of atherosclerotic plaque




Uptake of Chemically Modified LDL by Macrophage Scavenger Receptors

## Modifiable and non-modifiable CAD risk factors

| | |
|---|---|
| Cigarette smoking | Males > 45 years<br>Females > 55 years |
| Obesity | Males |
| Hypertension (blood pressure >= 140 / 90 mmHg) | Family history of coronary artery disease |
| Physical inactivity | |
| Kidney disease | |
| Diabetes mellitus | |
| Alcohol consumption | |
| Stress | |
| Elevated LDL | |
| Reduced HDL | |

## Familial Hypercholesterolemia

Homozygotes 680 mg/dl

Heterozygotes 300 mg/dl

Absence of LDL receptor / Abnormal Receptor

Homozygotes No Receptors

Hetero ½ Normal Number

Accumulation of lDL more IDL ⟶ LDL

Cholesterol deposition in tissues

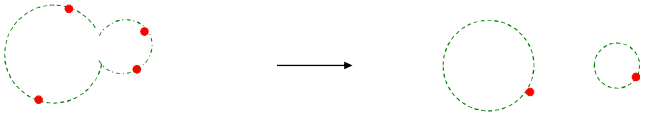
Atherosclerosis Death in childhood

# HDL

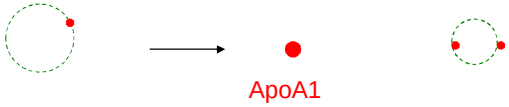
Origin

- Liver and Intestine: Nascent Discoid Shape

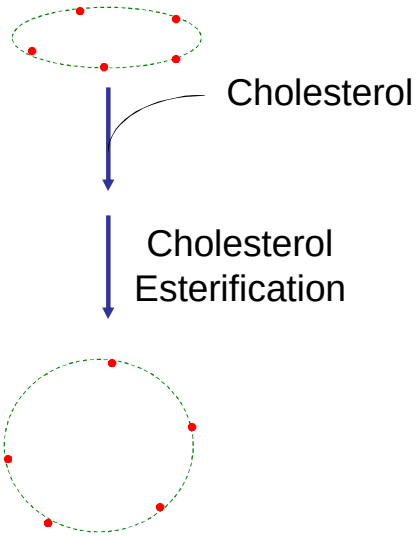

- Budding from other Lipoproteins Particles



- From Free Apo A




# Maturation of HDL

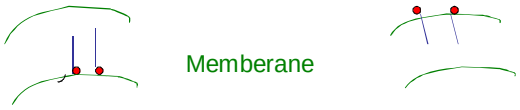


# Reverse Transport of Cholesterol

From Cells to Liver

Foam Cells in Vascular Tissues

1) Directional Movment; Role of ABC1

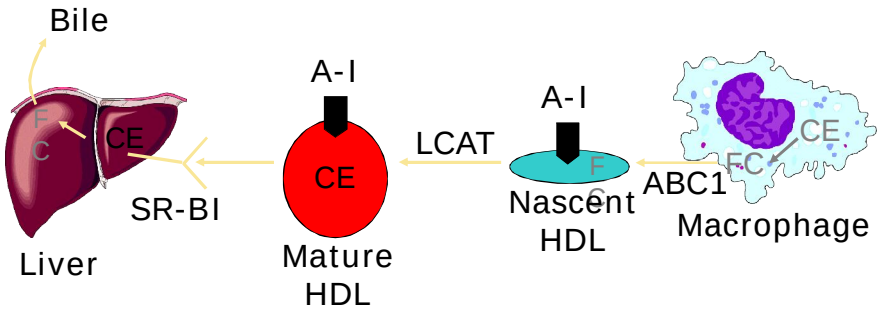



2) Esterification of Cholesterol

Ch $\xrightarrow{\text{LCAT}}$ Ch-FA

cholesterol is trapped within the core of HDL

# HDL Metabolism and Reverse Cholesterol Transport




ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I; CE = cholesteryl ester; FC = free cholesterol; LCAT = lecithin:cholesterol acyltransferase; SR-BI = scavenger receptor class BI

# Fate of HDL cholesterol

* Uptake by liver

Binding to Specific Receptor on Hepatocytes

* Transfer of cholestrol into cells scavenger receptor SR_B1
  - On many cell types
  - Can be upergulated if ch. Is needed
  - Not down regulated

* HDL interaction with other particles exchange of compnents.