Multiple SREBs regulate expression of numerous lipid-metabolizing proteins

Low cholesterol $\rightarrow$ cell $\rightarrow$ SREBPs activation $\rightarrow$ turn on gene
Member of the nuclear receptor superfamily contribute to cellular an whole body lipid regulation

SREBP regulated cholesterol and lipid metab
Other hydrophobic molecular (steroid hormone) enter cytosol → nuclear receptor → regulated related gene expression

In liver:
Cholesterol ↑↑ → produce oxysterol → activated LXR (liver X receptor) → cholesterol 7α-hydroxylase → (cholesterol convert to) bile acid → secret excessive cholesterol
LXR → stimulated ABC expression (ABCG5/8; ABCA1) → cholesterol release
LXR → SREBP activation → lipid synthesis related enzyme expression
LXR sense massive cholesterol

Bile acid bind to FXR (nuclear receptor) → activation of FXR → I-BABP, ABCB11, NTCP expression ; inhibited cholesterol 7α-hydroxylase

Role of LXR and FXR

When cholesterol accumulates in cells, cholesterol is oxidized to create oxysterols
Role of LXR and FXR

Oxysterols activate LXR through LXR/RXR heterodimers to activate genes such as the CYP7A1 enzyme that catalyzes the rate-limiting step in bile acid biosynthesis.

In the intestine, LXR also activates ABC-1 to remove cholesterol.

Role of LXR and FXR

In the intestine, FXR activates expression of I-BABP, a protein that increases the transport of bile acids back to the liver from the intestine, reducing their excretion.

18.5 The cell biology of atherosclerosis, heart attacks, and strokes

(a) Normal artery wall

(b) Fatty streak stage

White blood cells adhere and migrate into artery wall to fight infection

Endothelium

Intima

Adventitia

Media (smooth muscle cells)

Macrophage foam cell formation

(c) Atherosclerotic plaque stage

(d) Rupture of endothelium and occlusive blood clot formation

Macrophage foam cell accumulation

Formation of focal lipid core

Occlusive blood clot

Fibrous cap formation
**Endothelial Dysfunction**

Increased endothelial permeability to lipoproteins and plasma constituents mediated by NO, PDGF, AG-II, endothelin.  
**Up-regulation of leukocyte adhesion molecules** (L-selectin, integrins, etc).  
**Up-regulation of endothelial adhesion molecules** (E-selectin, P-selectin, ICAM-1, VCAM-1).  
Migration of leukocytes into artery wall mediated by oxLDL, MCP-1, IL-8, PDGF, M-CSF.

*Ross, NEJM; 1999*

**Formation of Fatty Streak**

SMC migration stimulated by PDGF, FGF-2, TGF-B.  
T-Cell activation mediated by TNF-a, IL-2, GM-CSF.  
Foam-cell formation mediated by oxLDL, TNF-a, IL-1, and M-CSF.  
Platelet adherence and aggregation stimulated by integrins, P-selectin, fibrin, TXA2, and TF.

*Ross, NEJM; 1999*

**Formation of Advanced, Complicated Lesion**

Fibrous cap forms in response to injury to wall off lesion from lumen.  
Fibrous cap covers a mixture of leukocytes, lipid and debris which may form a necrotic core.  
Lesions expand at shoulders by means of continued leukocyte adhesion and entry.  
Necrotic core results from apoptosis and necrosis, increased proteolytic activity and lipid accumulation.

*Ross, NEJM; 1999*

**Development of Unstable Fibrous Plaque**

Rupture or ulceration of fibrous cap rapidly leads to thrombosis.  
Occurs primarily at sites of thinning of the fibrous cap.  
Thinning is a result of continuing influx of and activation of macrophages which release metalloproteinases and other proteolytic enzymes.  
These enzymes degrade the matrix which can lead to hemorrhage and thrombus formation.

*Ross, NEJM; 1999*
Plaque Rupture with Thrombus

Cholesterol esters in lipoproteins can be selectively taken up by the receptor SR-BI (scavenger receptor, class B type I)

1. cluster on microvilli and in the cell surface lipid raft, not in coated pits as does the LDL receptor
2. Mediate the transfer of lipid across the membrane, not endocytosis of entire LDL particles

LDL Cellular Metabolism

LDL are taken up by the LDL Receptor into clathrin-coated pits

LDL dissociates from the receptor; the receptor recycles to the membrane

Cholesterol and Atherosclerosis, Grundy
Arterial inflammation and cellular import of cholesterol mark the early stage of atherosclerosis

LDLR-independent uptake of LDL (bad cholesterol) leads to formation of foam cell (LDLR play an important role of atherosclerosis? No no no 謊LDLR的錯)

Plasma LDL → LDL in artery high → LDLR-mediated endocytosis ↑ → rapidly foam cell develop ????

However, LDLR-mediated endocytosis is not a factor for the development of atherosclerosis:

Two reasons, still atherosclerosis
1. Intracellular regulation: LDLR gene activity is cholesterol-dependent; High intracellular cholesterol → insig/SCAP/SREBP pathway ↓ → LDLR gene regulation ↓ → low LDLR gene expression
2. In familial hypercholesterolemic patient: LDLR activity is lower, but still has atherosclerosis

Arterial inflammation and cellular import of cholesterol mark the early stage of atherosclerosis (LDLR-independent mechanism)

Generation of macrophage foam cells in an artery wall

A site infection or damage → activated endothelial cell → cell adhesion molecular expression → monocyte adhesion → migration → differentiation to macrophage

High LDL → oxidized to oxLDL → bind to scavenger receptor (macrophage) → degraded → lipid droplets cytosol → formed foam cell → ABCA1 or SR-B1 → transport HDL out
A coronary artery with an atherosclerotic plaque

FC: macrophage contain cholesteryl ester and lipid droplets

Fig 18-22 HDL-mediated reverse cholesterol transport

Atherosclerosis narrows and blocks blood flow through coronary arteries

HDL Function

- Removal of CE from LDL
- Reverse Cholesterol transport
- Apo A-1 prevent seeding of LDL
- Apo A-1 prevent oxidized LDL formation
Reverse Cholesterol Transport

Delivery of peripheral tissue cholesterol to the liver for catabolism Requires HDL, apoA-I and LCAT

Peripheral Cell

- UC = unesterified cholesterol
- CE = esterified cholesterol
- PL = phospholipid
- LDLr = LDL receptor

HDL

- apoA-I
- ABCA1

Peripheral Cell

- UC = unesterified cholesterol
- CE = esterified cholesterol
- PL = phospholipid
- LDLr = LDL receptor

VLDL or LDL

- apoB
- CE
- TG
- apoA-I

Liver

- SR-B1
- LCAT
- Chol
- Bile acids

Bile to gut

UC = unesterified cholesterol
CE = esterified cholesterol
PL = phospholipid
LDLr = LDL receptor

Two treatments for atherosclerosis are based on SREBP-regulated cellular cholesterol metabolism

1. Bile acid-binding resins ("sequestrants")
   - bind tightly to bile acid → inhibits IBAT absorption into int. epith. cell. → increased LDLR expression (Fig 18-23b)
   - Feedback repression by bile acids on 7α-hydroxylase lost; cholesterol to bile acids greatly enhanced to maintain pool of bile acids

2. Statin (inhibitor of HMG-CoA reductase)
   - less cholesterol synthesized
   - increased LDLR expression (Fig 18-23b)
CONSEQUENCES OF BILE SALT SEQUESTERING RESINS (e.g., Cholestyramine)

1) Feedback repression by bile acids on 7α-hydroxylase; cholesterol to bile acids greatly enhanced to maintain pool of bile acids.

2) Lowered liver cholesterol up-regulates LDL receptors via SREBP induction of transcription in the liver

3) More LDL receptors increases the hepatic uptake of LDL with consequent lowering of plasma cholesterol