Chemistry of Medicine I

医用化学第一

Lecture III

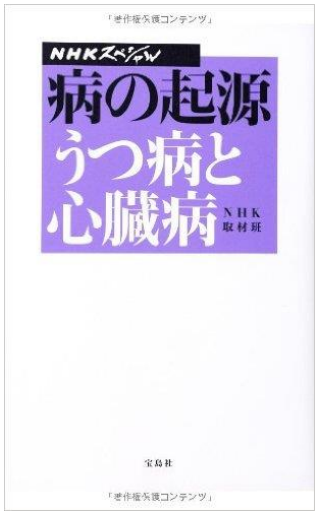
2. Atherosclerosis　動脈硬化

1. What is atherosclerosis 動脈硬化とは
2. biosynthesis and metabolism of lipid 脂質の合成と代謝
3. Cause of Atherosclerosis 動脈硬化の原因
4. Prevention and treatment of atherosclerosis 動脈硬化の予防と治療

2.1 What is atherosclerosis

動脈硬化とは

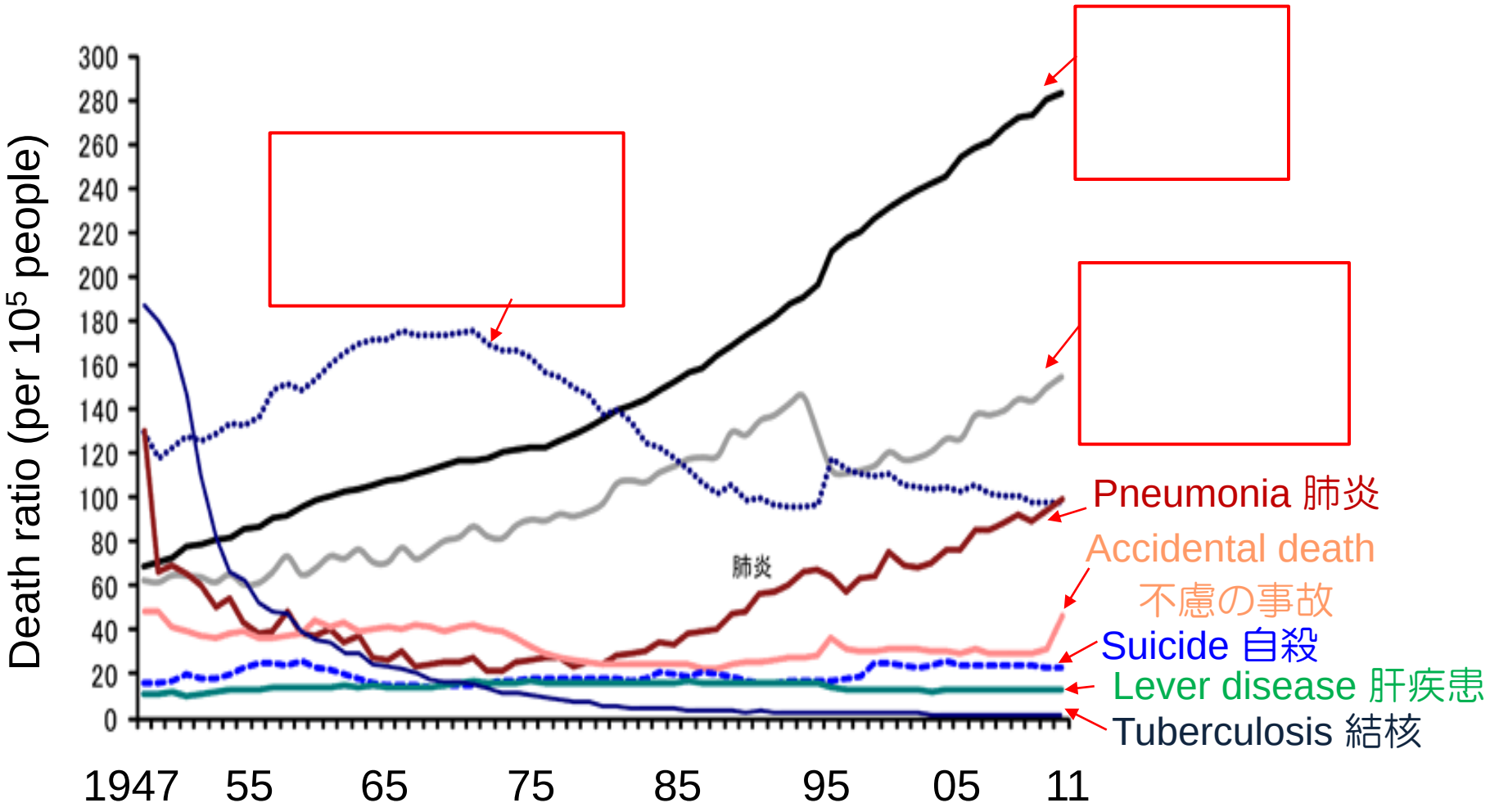
references



“athero-sclerosis”

athero: 粥腫（シュクシュ）。脂肪などからなる塊のこと。
sclerosis: 硬化症。

Cause of death in Japan



Quiz

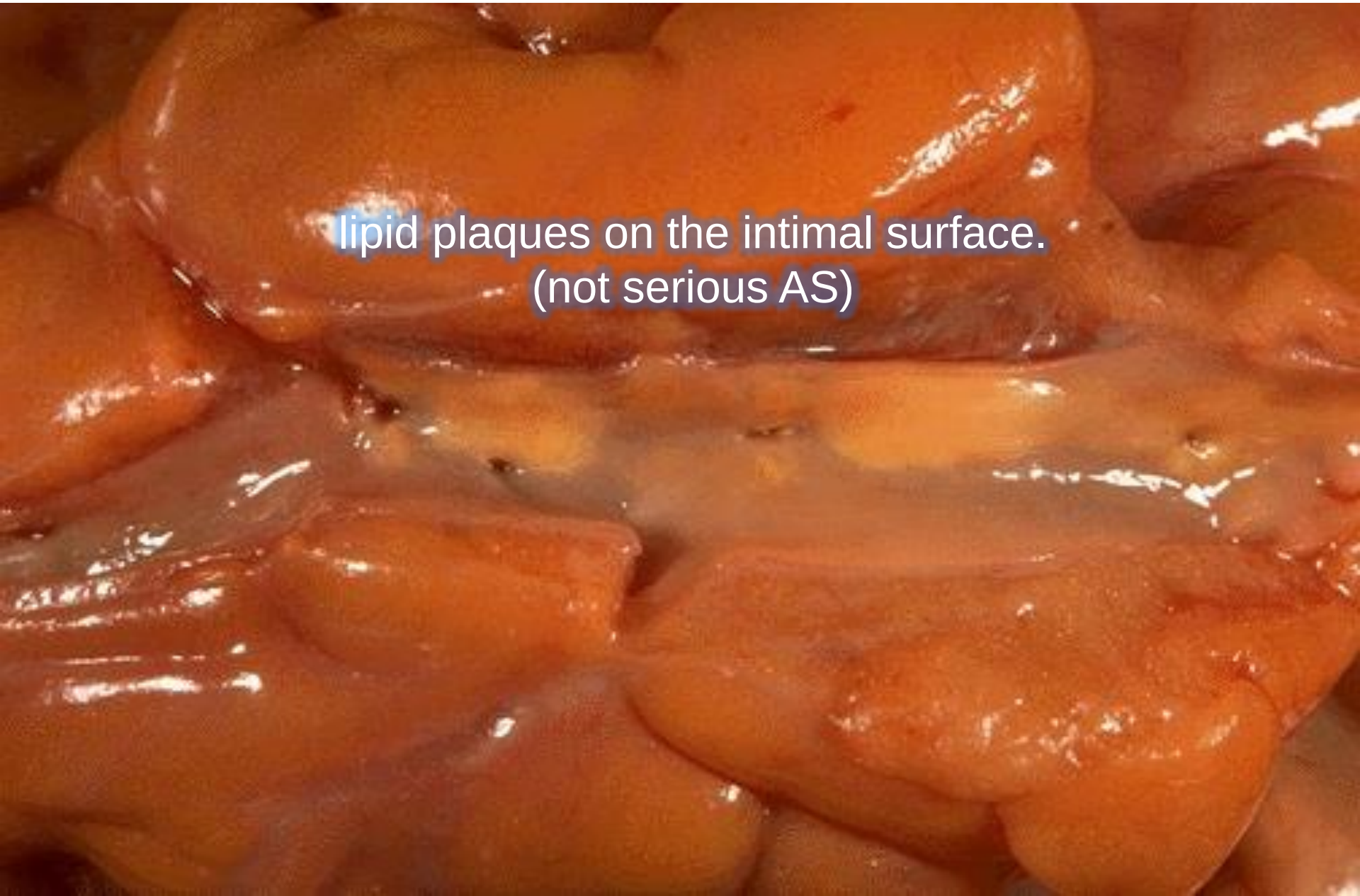
Please speculate the cause of atherosclerosis.

Why artery?
Why accumulation of cholesterol happens?
Why AS is mismatch disease?

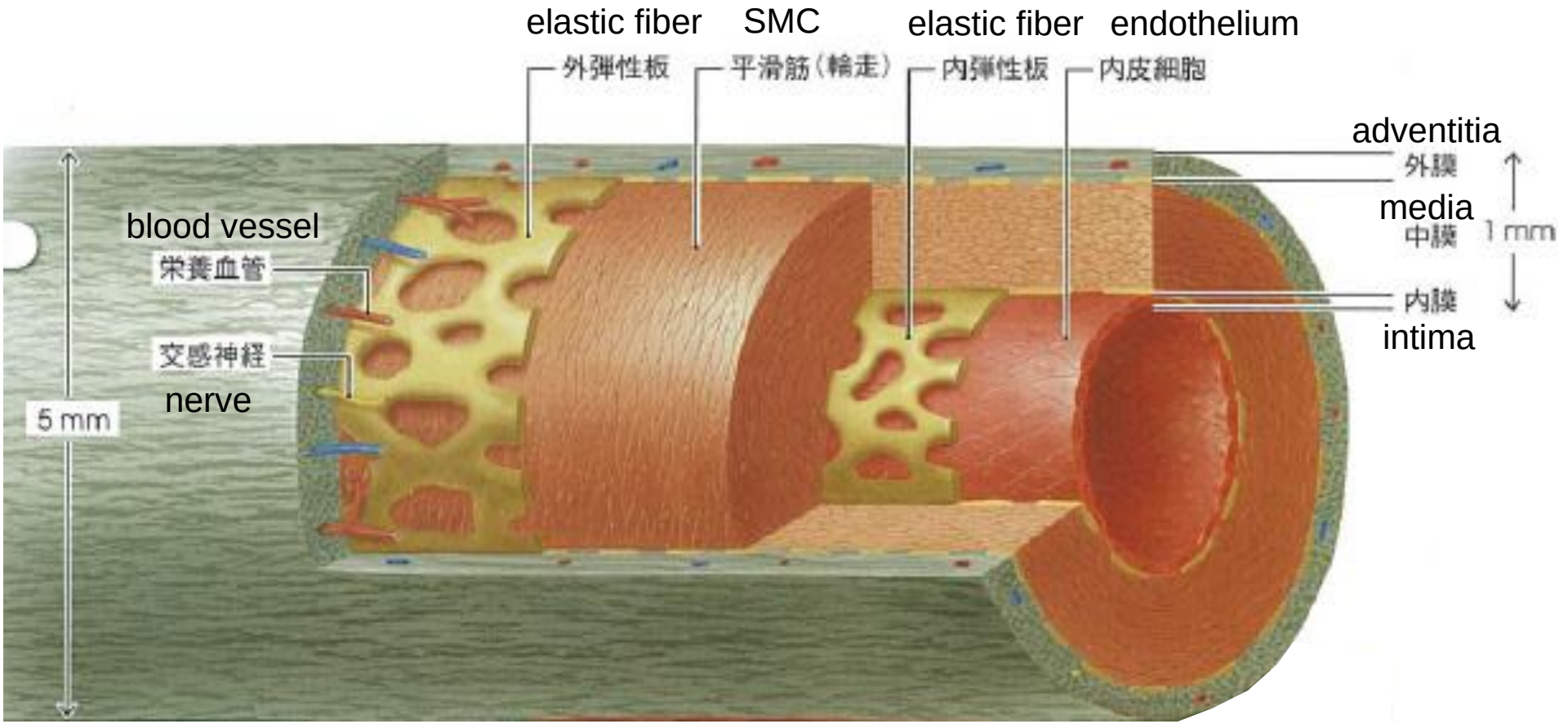
Arteriosclerosis 動脈硬化症
(⊃ Atherosclerosis 粥状硬化症)

- AS related to 75% of all cardiovascular-related death in USA. AS is found in 80% of adults (> 30 years old).
- Thickening, hardening and loss of elasticity (弾性) of the walls of arteries (動脈). This process gradually restricts the blood flow to organs.
- The lesions of arteriosclerosis begins as the intima (内膜) of the walls of arteries.
- Atherosclerosis is a specific form of arteriosclerosis caused by fibro-fatty plaque (線維脂肪性プラーク) created by foam cell (泡沫細胞) and smooth muscle cell (平滑筋細胞). This is a chronic inflammation (慢性炎症), resulting in thrombosis (血栓).
- Thrombosis stopping blood flow is called infarction (梗塞).
- Thrombosis occurs in large high-pressure artery such as coronary (冠動脈：myocardial infarction), cerebral (大脳), femoral (大腿部) arteries.

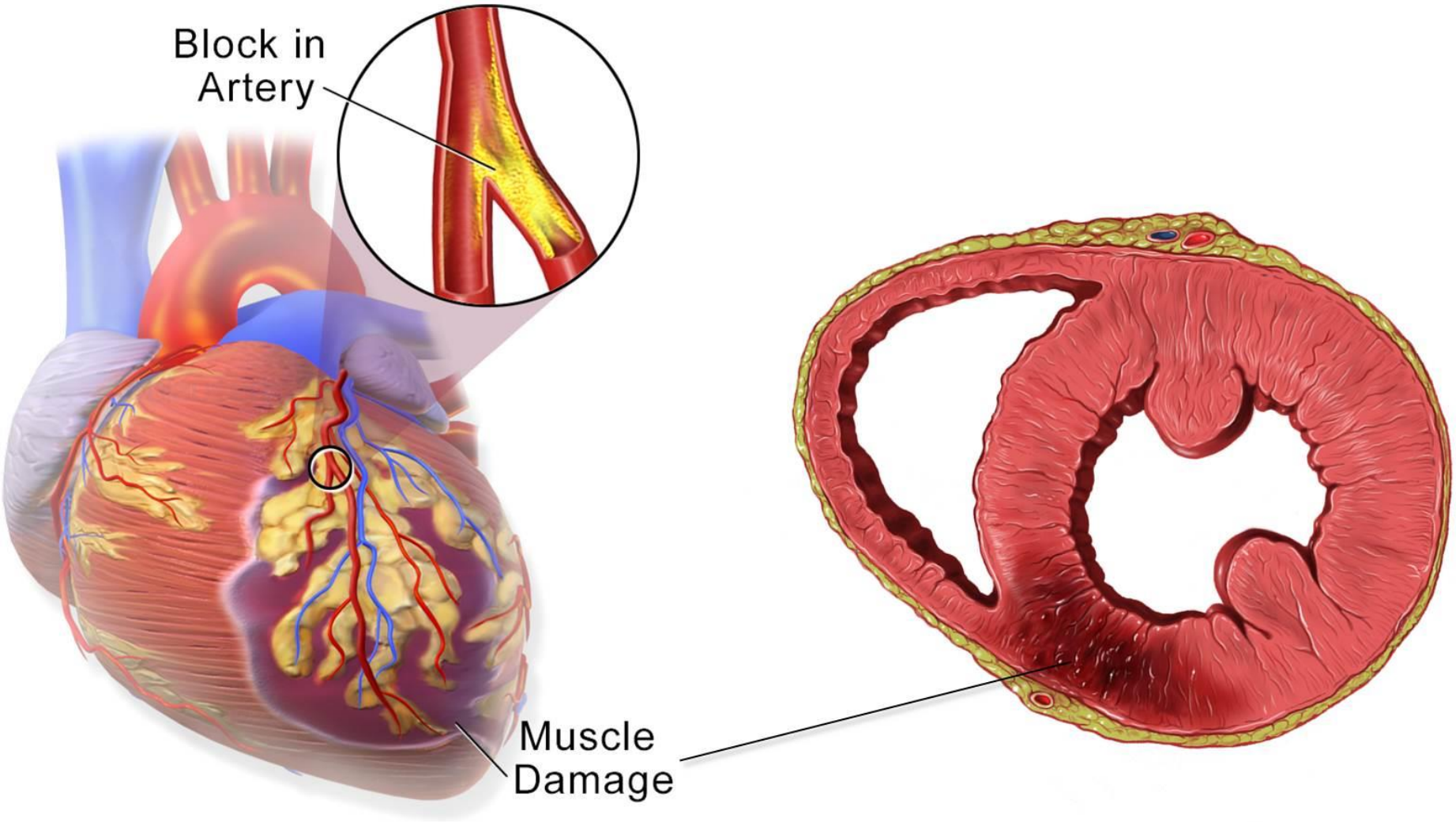
Atherosclerosis 粥状硬化症



Structure of artery



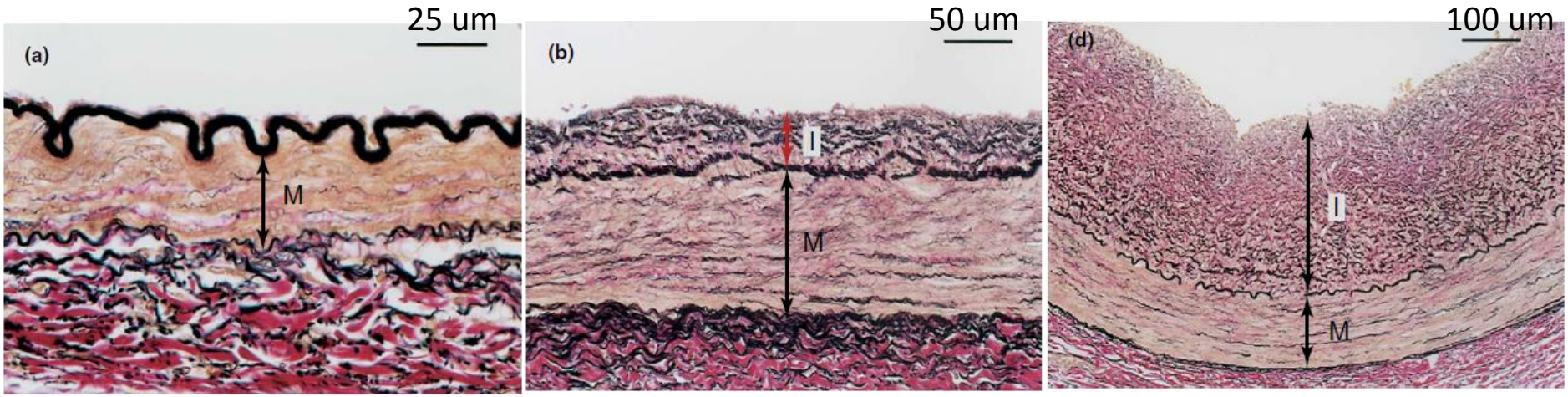
Myocardial infarction



Fine chronic intimal hyperplasia (FC) in coronary artery

び慢性内膜肥厚

- Coronary artery causes FC after birth.
- Thick intima will accommodate more accumulation of LDL.



7-day old

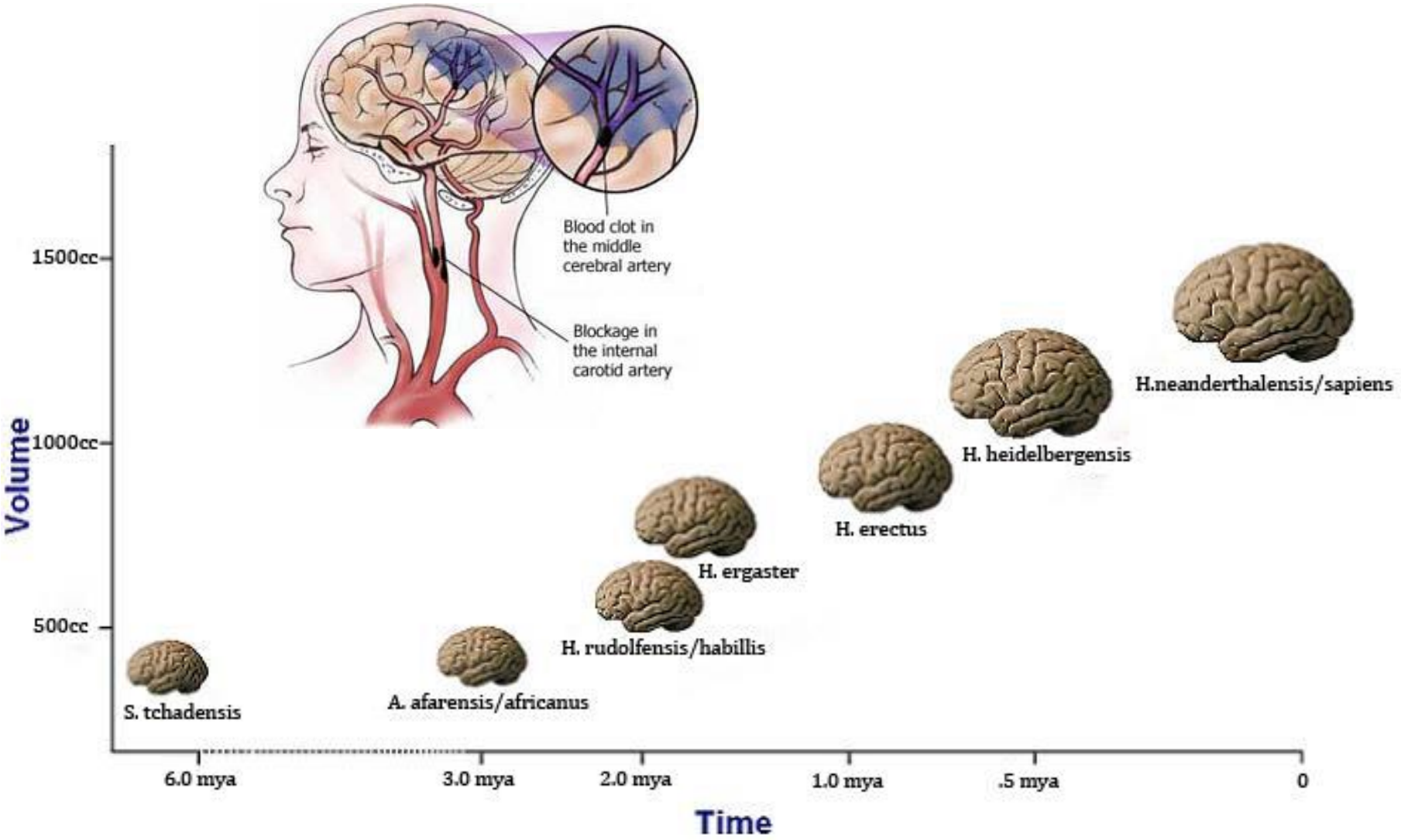
15-year old

29-year old

2016 Drug Discov Today 1578

Cerebral infarction

- Chimpanzee does not cause cerebral infarction.
- Due to the increase of brain volume, blood flow to brain increased.
  -> cerebral infarction.



Atherosclerosis Movies

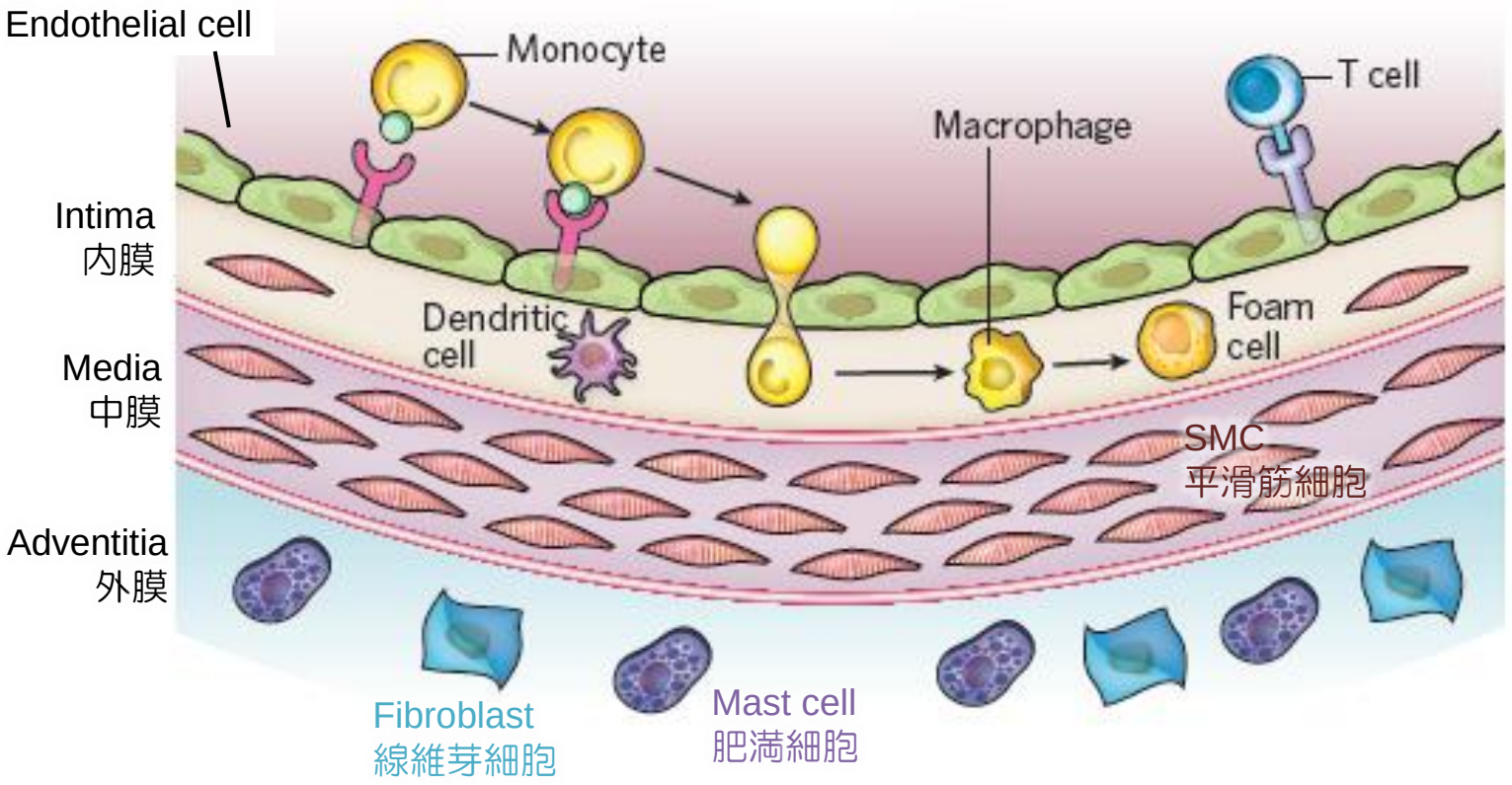
MEDICAL - How cholesterol clogs your arteries

(atherosclerosis)

(5:30)

Development of AS lesions (1)

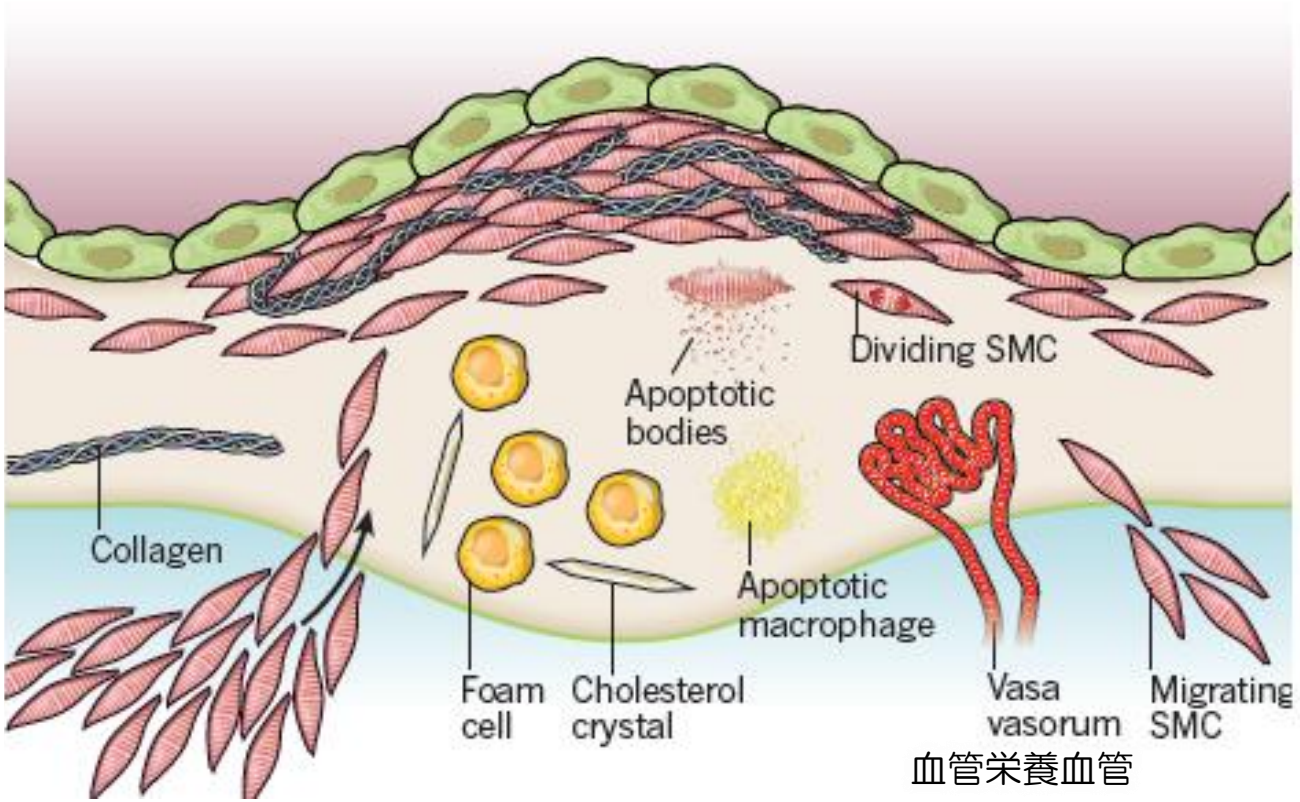
2011 Nature 317



1. Exposure to risk factors (diabetes, hypertension, hyperlipidemia)
2. activation and permeability increase of endothelial layer
3. penetration of LDL to intima and monocyte adhesion
4. oxidation of LDL and conversion of monocyte to macrophage
5. macrophage engulfs oxLDL to become foam cell （泡沫細胞）

Development of AS lesions (2)

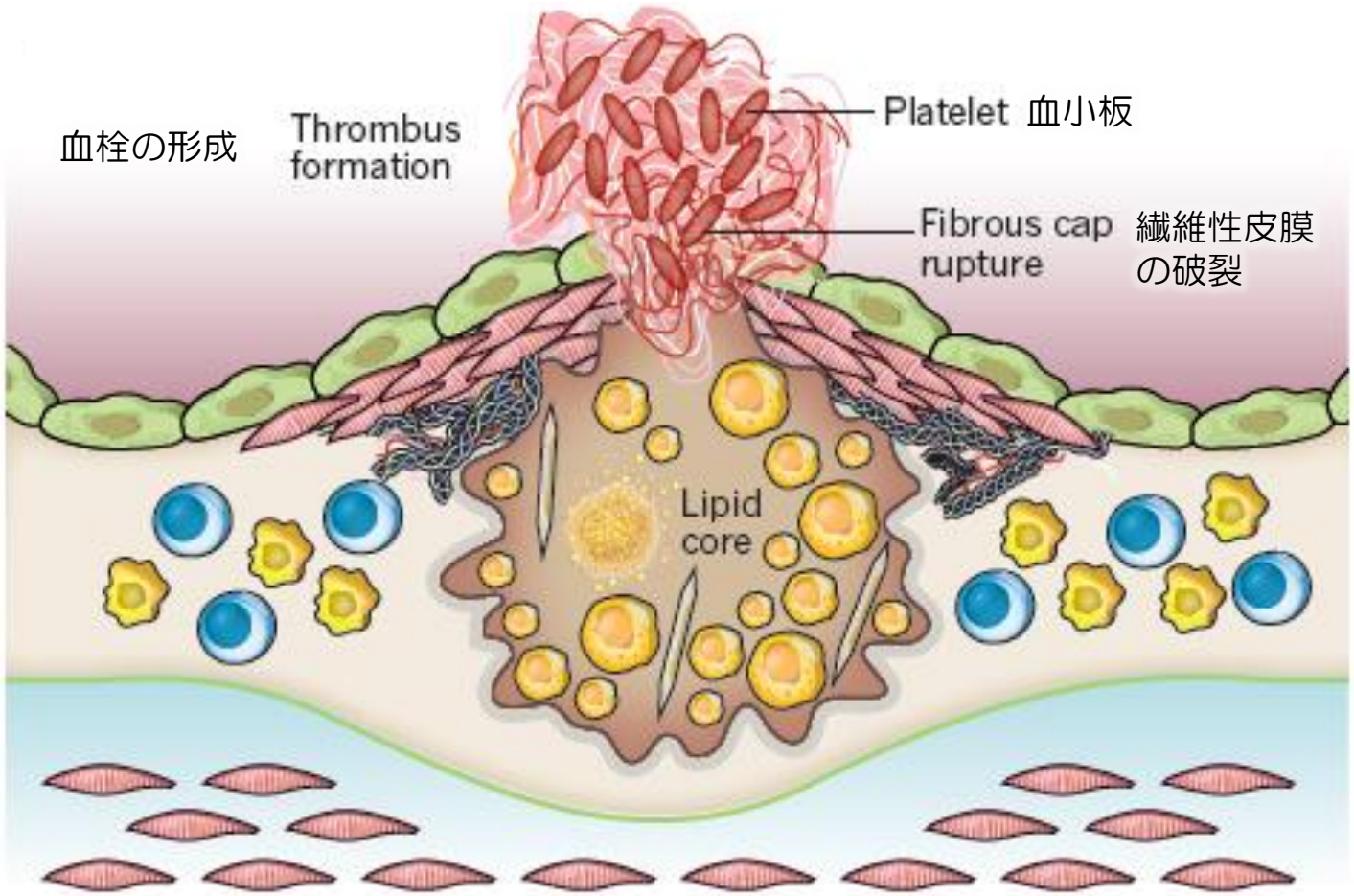
2011 Nature 317



1. SMC migration from media to intima
2. SMC proliferation in intima
3. SMC produces extracellular matrix (ECM:細胞外マトリックス）such as collagen
4. advancing lesion contains apoptotic cells (SMC & MΦ), cholesterol crystal and vasa vasorum (血管栄養血管).

Development of AS lesions (3)

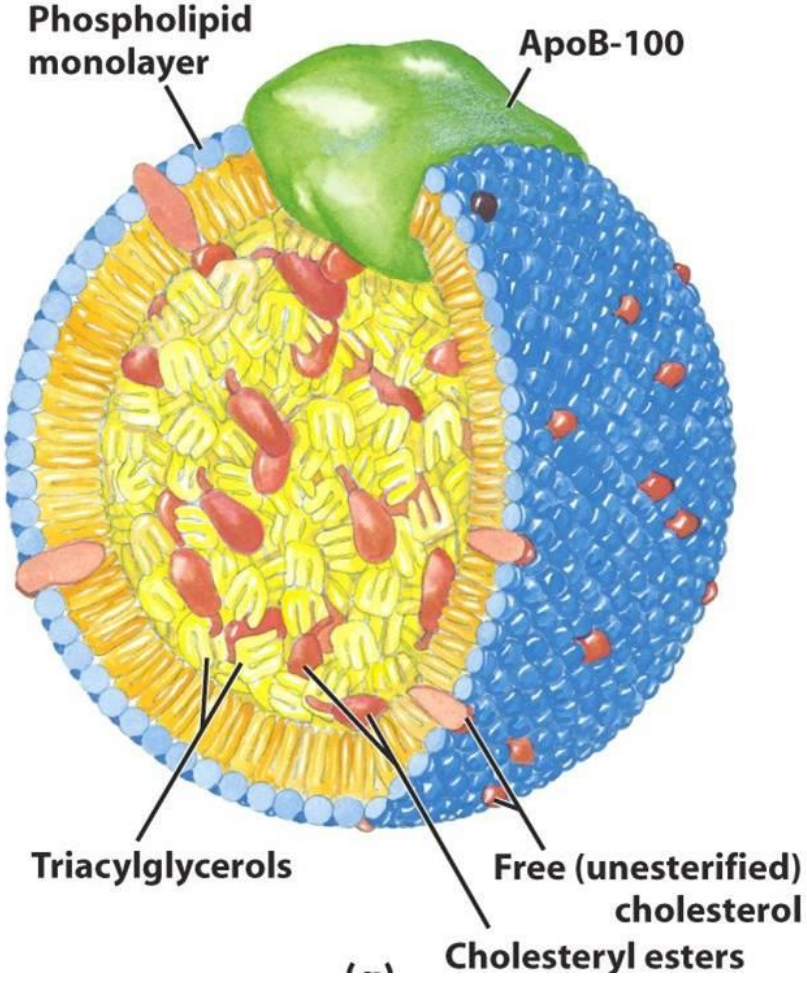
2011 Nature 317



1. Rupture of fibrous cap
2. Thrombus formation on the exposed ECM

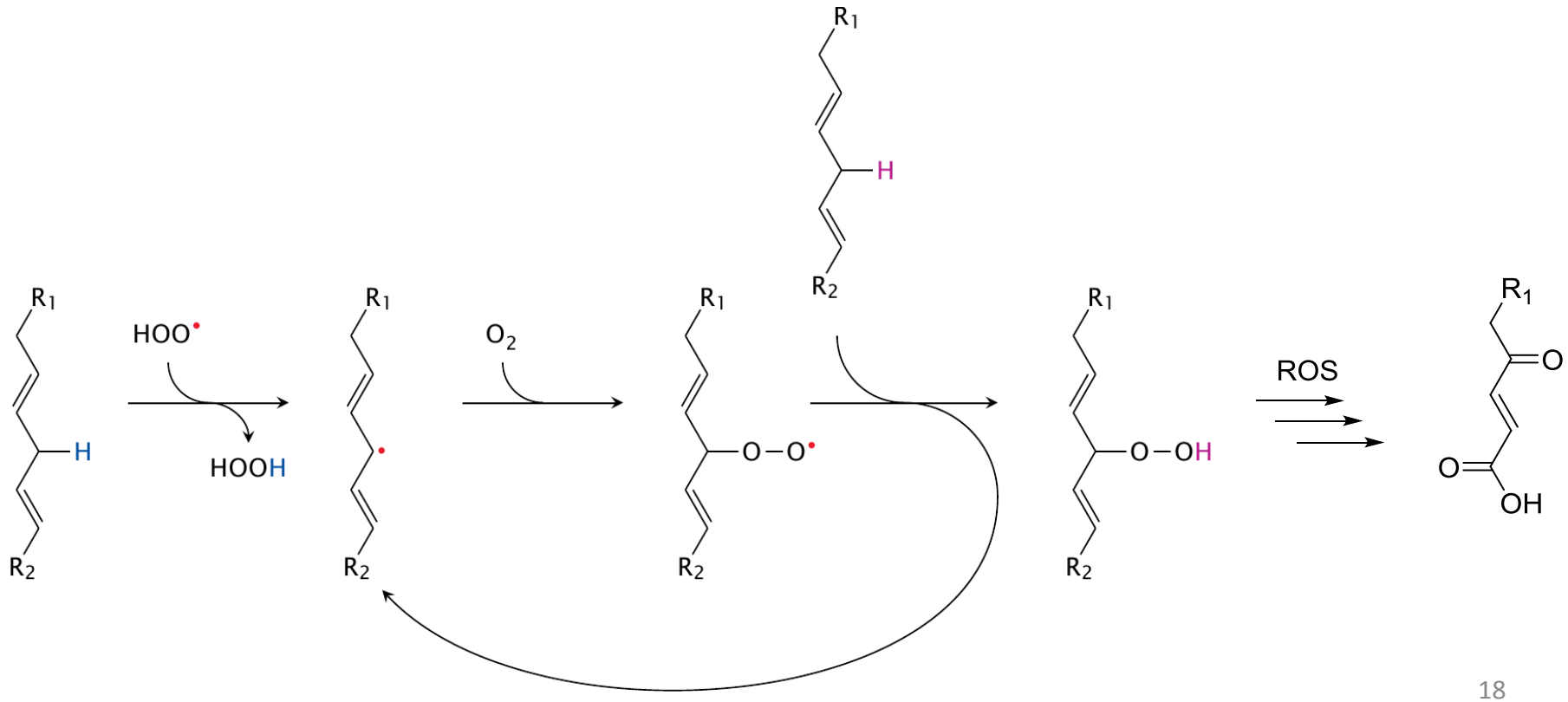
Low density lipoprotein (LDL)

- Water-soluble lipid particle with suitable size for long blood circulation (diameter: 20 nm).
- Secreted from hepatocyte to cells of whole body.
- ApoB-100 works as targeting ligand for LDL receptor which expresses in target cells.



Oxidized LDL (oxLDL)

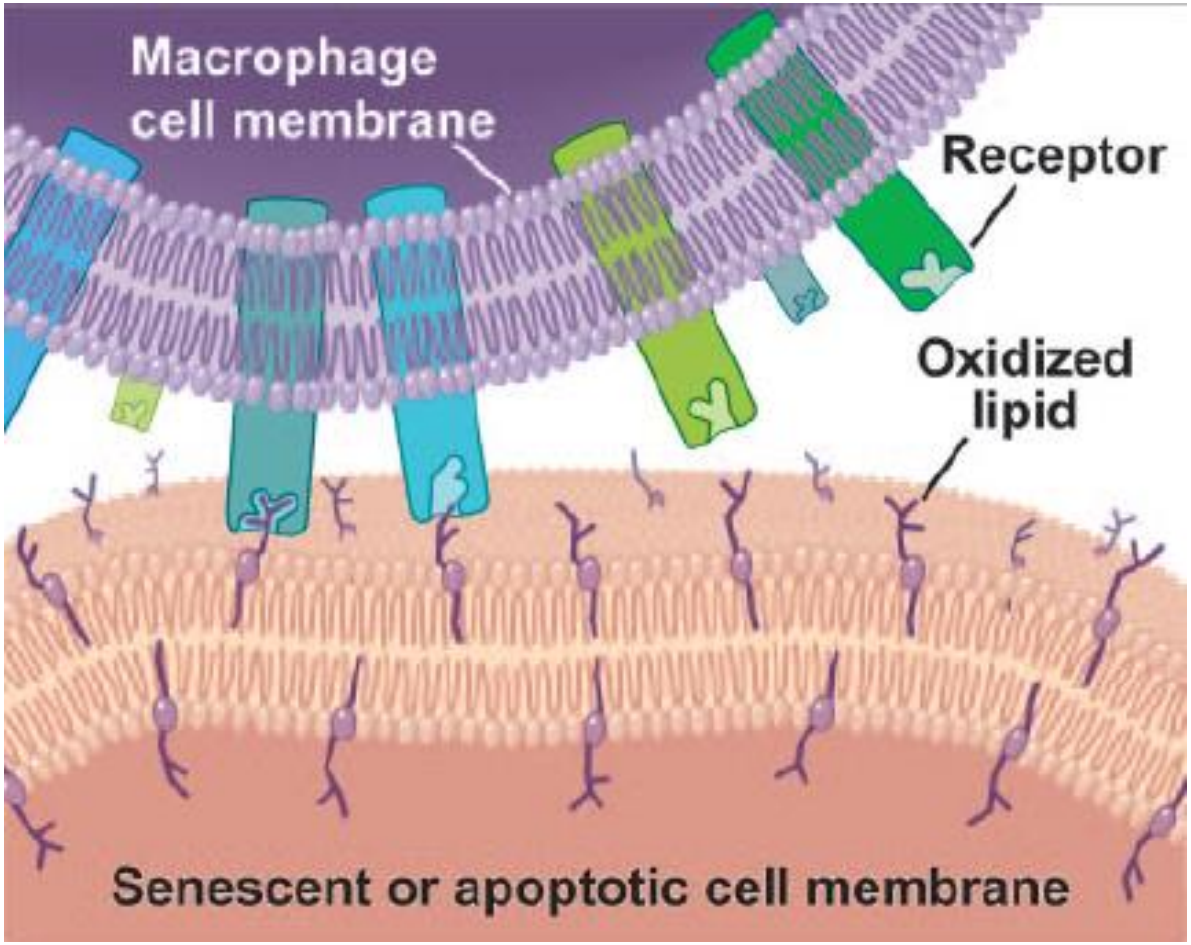
- Oxidization of lipid of LDL results in introduction anionic carboxyl group in the acyl chains.
- Scavenger receptors on macrophage engulf oxLDL to remove it from the blood.
- Oxidation of LDL is accelerated in injured lesions because of high permeability of endothelium and high conc. of ROS.



oxLDL recognition by scavenger receptor (CD32)

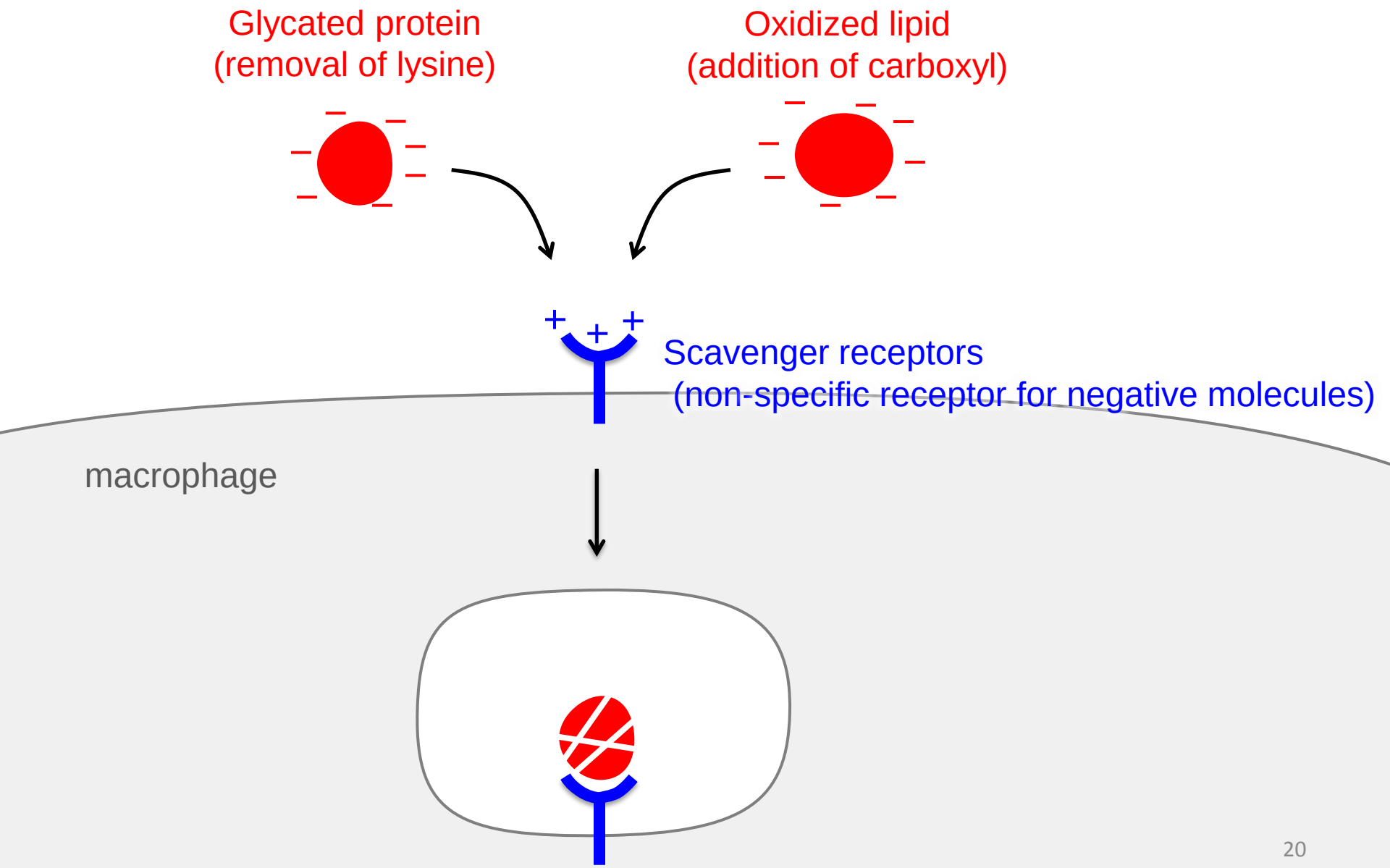
- Exposition of carboxylic acid-terminated acyl chain from the LDL surface.
- Recognized by multivalent interaction.

  (ligand/receptor interaction is weak: Kd > 3 uM).



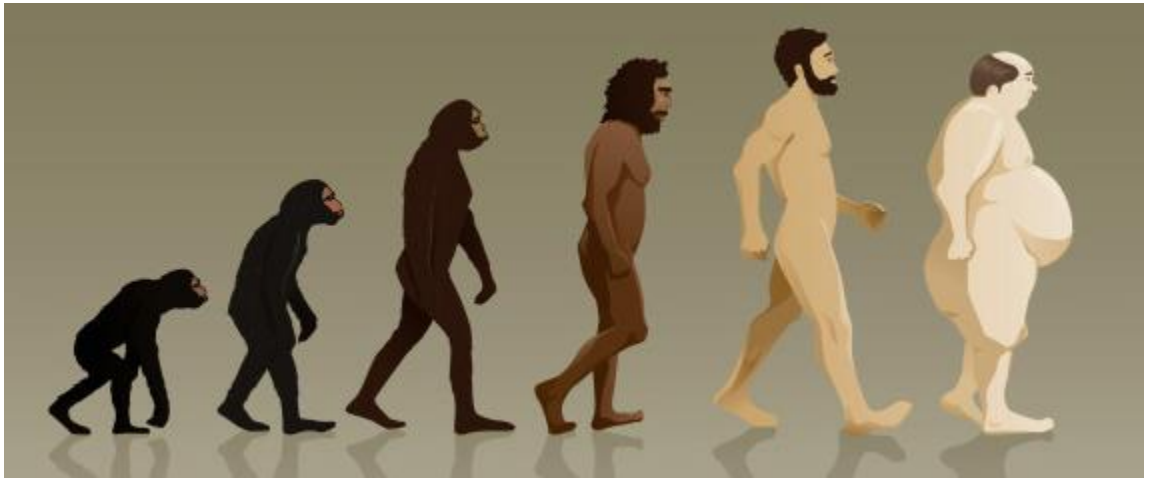
2008 JBC 15527

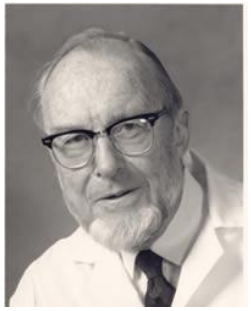
Negatively charged molecules are waste for us



Thrifty gene hypothesis 倹約遺伝子仮説

- In 1962, James Neel (USA) proposed this hypothesis to explain why people are prone to diabetes, although it is disadvantageous genotype for survival.
- Thrifty genotype would have been advantageous for hunter-gatherer population, because it would allow them to fatten more quickly during times of abundance. “Survival of the fattest”.
- However, in modern societies with a abundance of food, this mismatch results in chronic obesity and related problems like diabetes.
- Thrifty gene will be reducing basal metabolic rate (基礎代謝量) and promoting the storage of fat.
- Example of thrifty gene: β3-adrenaline receptor, hormone-sensitive lipase, and lipoprotein lipase which regulate lipolysis.





James Neel
Farther of Darwinian medicine

2.2 biosynthesis and metabolism of lipid

脂質の合成と代謝

Why fatty acid (FA) was chosen?

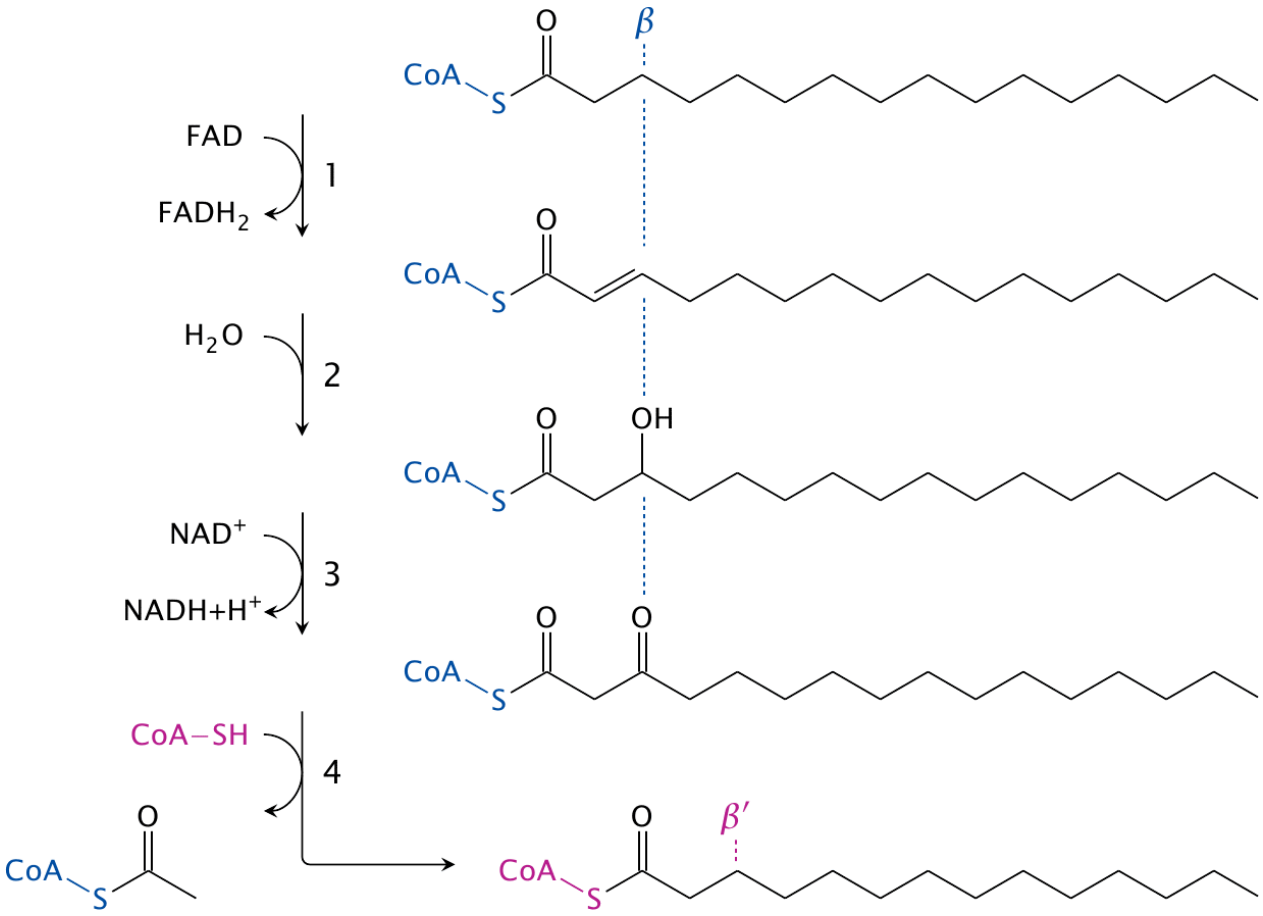
- High oxidation density. 酸化密度が高い。
- Stored with high density because of no solubility in aqueous media.
- Also works as cell membrane.
- Providing stable polymer (polymers of nitrogen or sulfur are not stable)

<u>Why carboxylic acid?</u>

- Able to be stored as neutral ester (triacyl glycerol)
- Activated ester is useful both for cleavage and elongation.

β-oxidation of fatty acid

- Proceeded in mitochondria.
- Producing acetyl CoA which is utilized for TCA cycle.



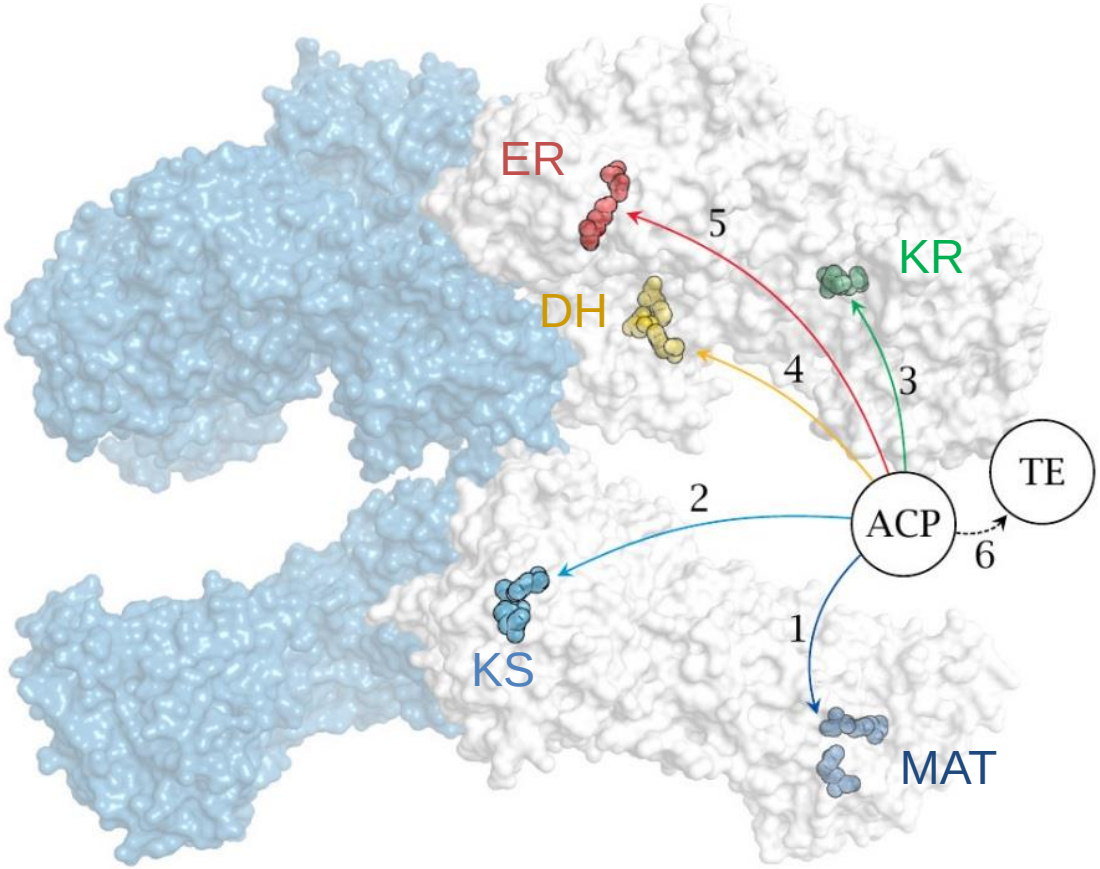
double bond

alcohol

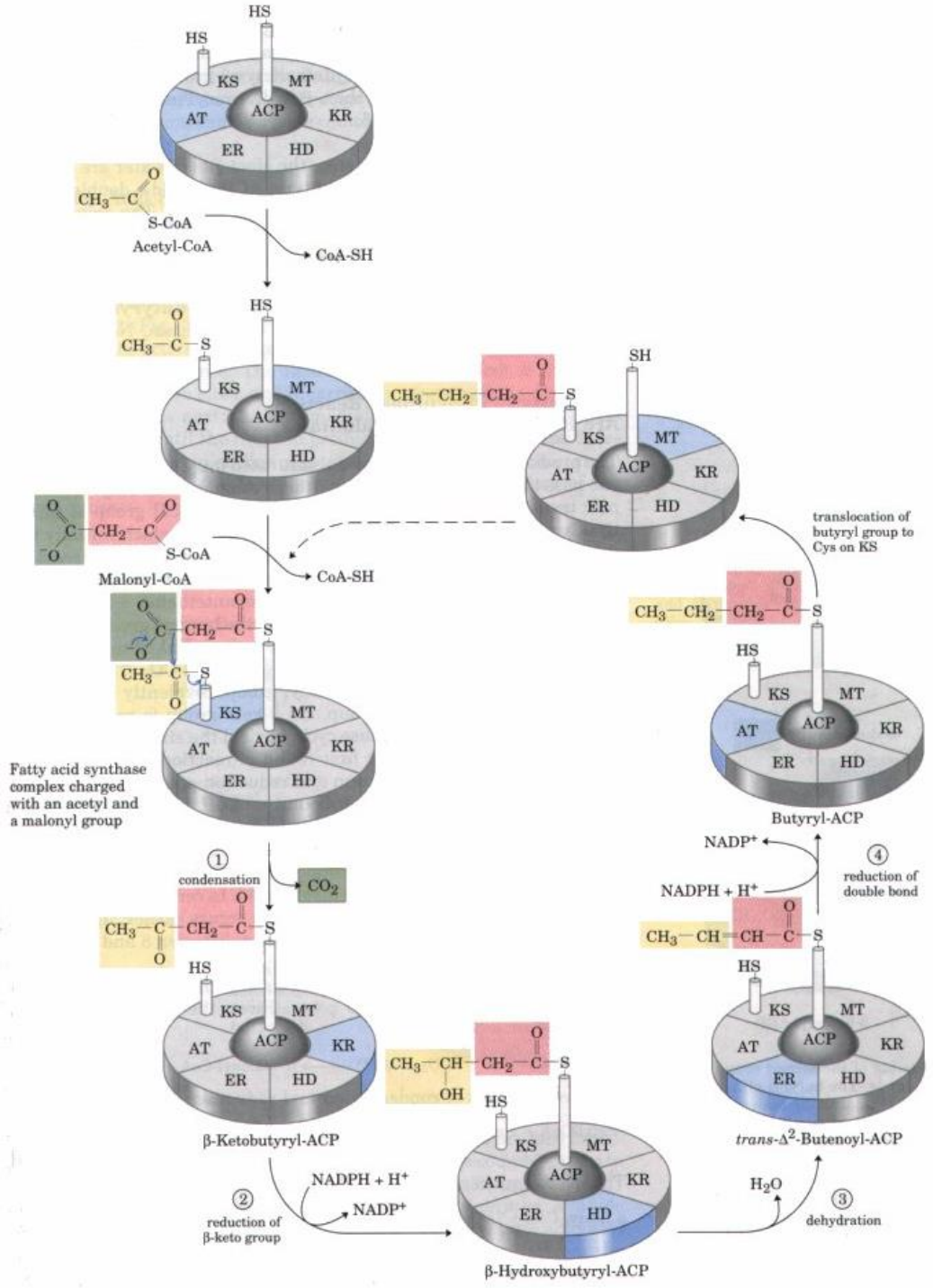
ketone

Lipogenesis by fatty acid synthase (FAS)

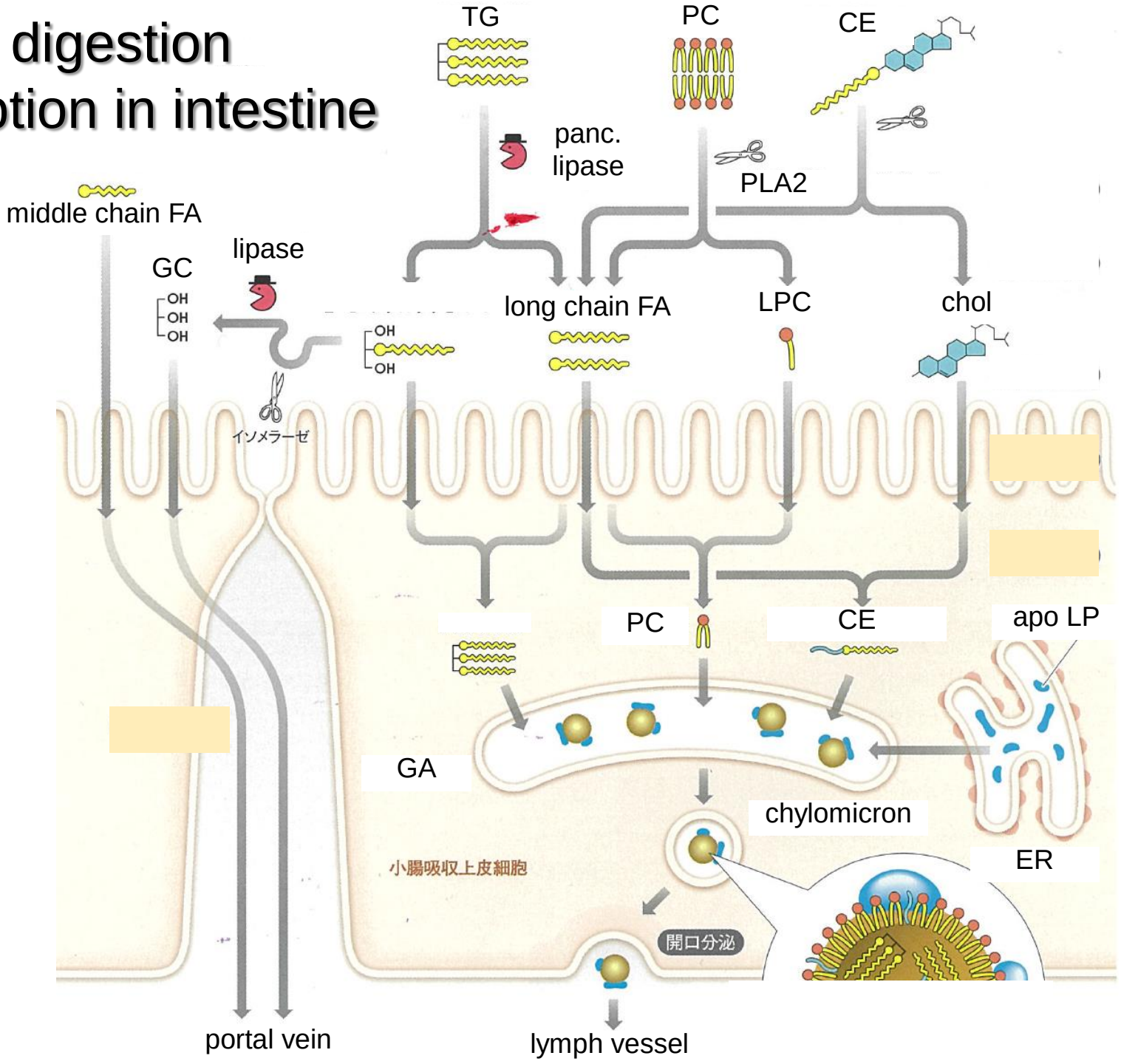
- Huge homodimer (272 kDa x 2)
- Reverse reaction of β-oxidation.
- working in cytosol of adipose, liver and brain to synthesize C16 (palmitic acid). Longer and unsaturated FAs are synthesized from C16 in mitochondria and ER.
- Human's FAS is efficient to support the rapid synthesis of neuron's myelin sheath (髓鞘).



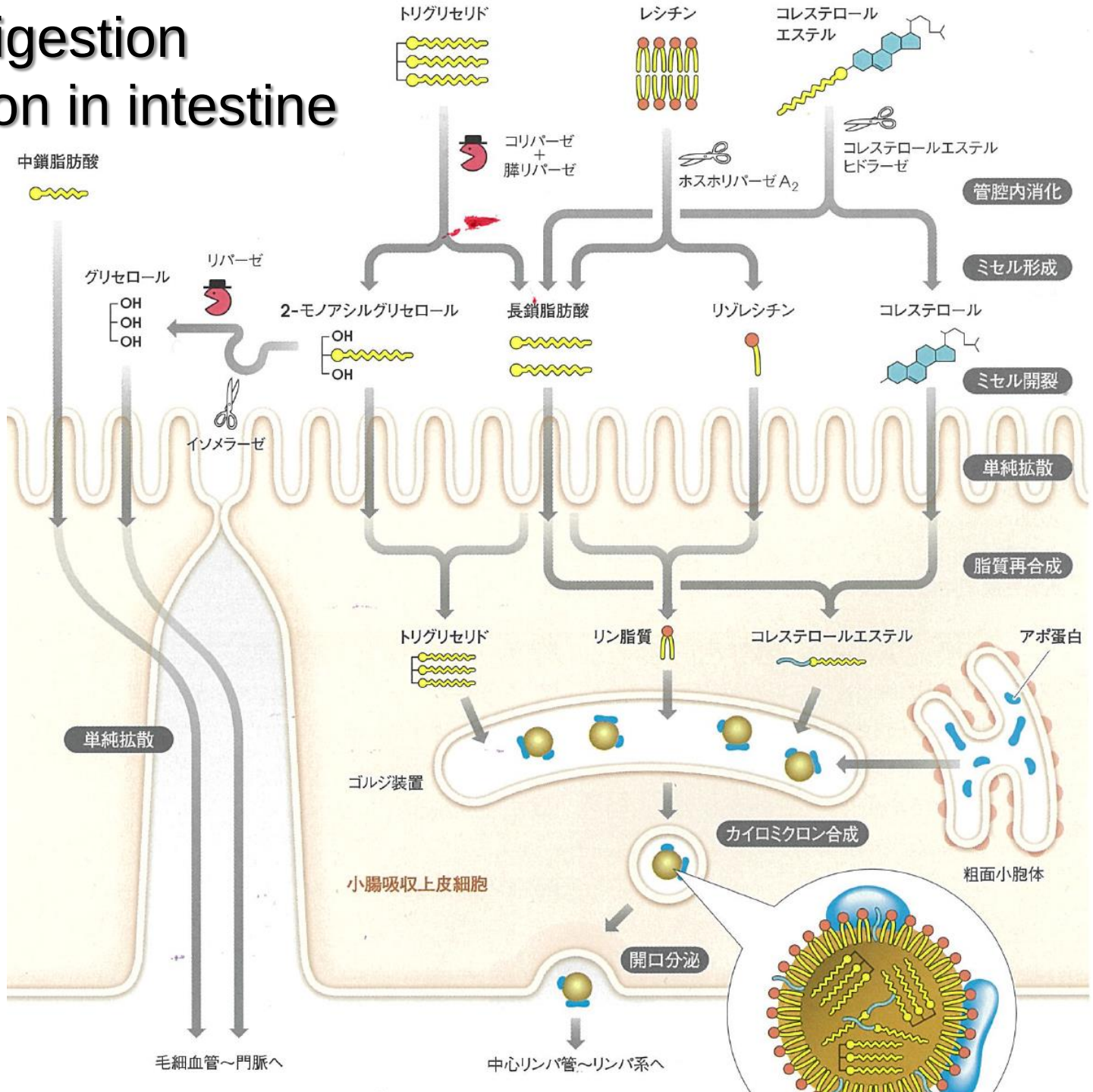
Lipogenesis by fatty acid synthase (FAS)



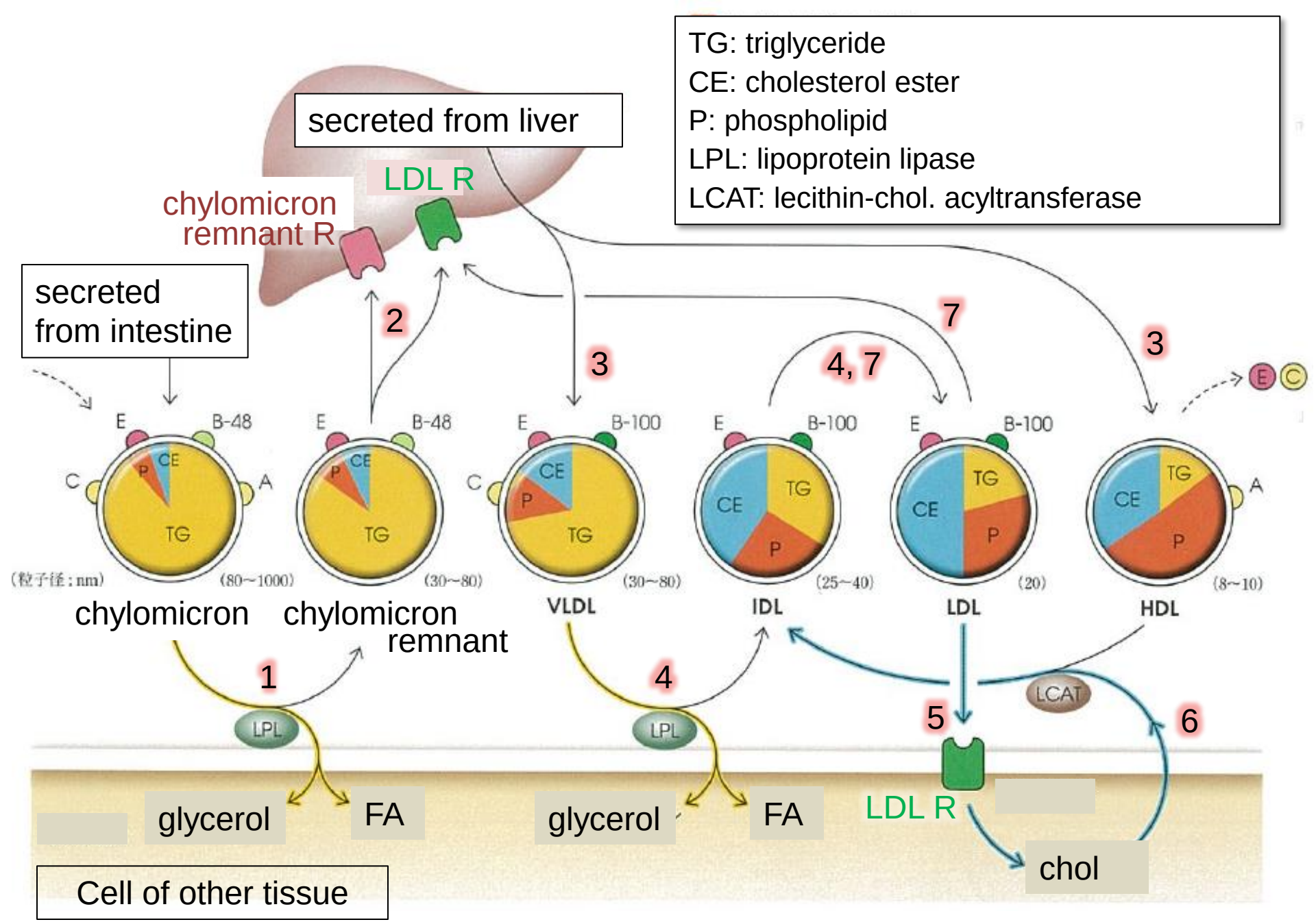
Lipid digestion and absorption in intestine



Lipid digestion and absorption in intestine

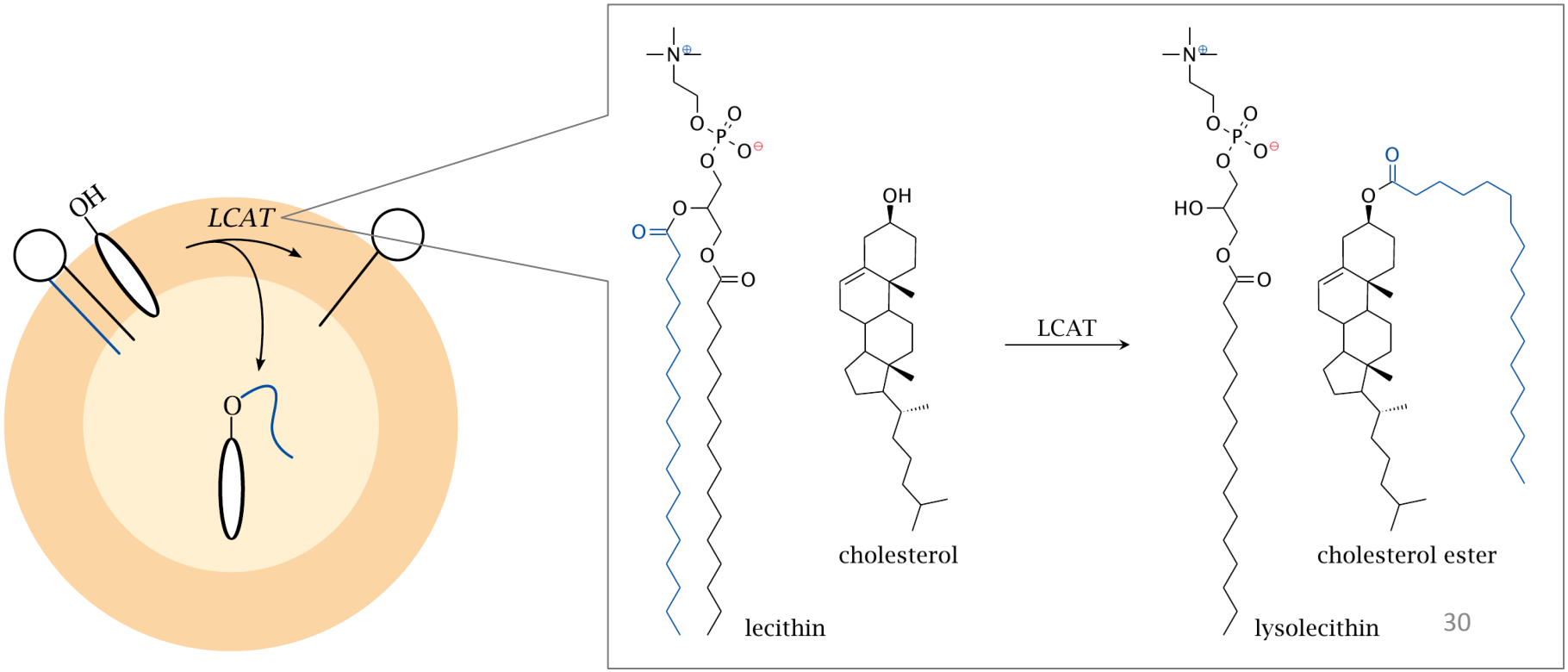


Lipid transport system

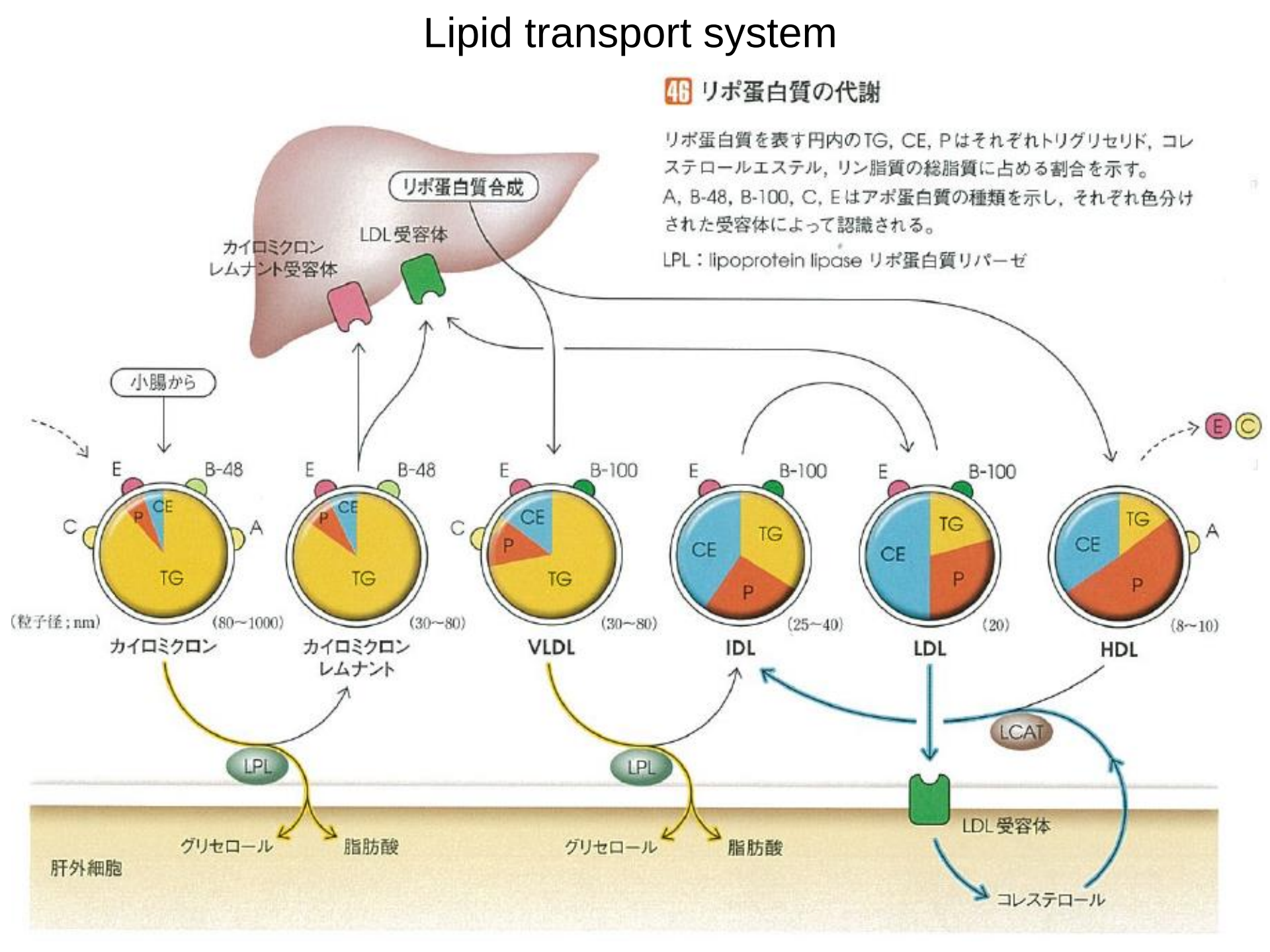


(continued)

1. Chylomicron's lipid is hydrolyzed by LPL (lipoprotein lipase)
2. Chylomicron remnants are taken up by liver
3. Liver secrets VLDL and HDL
4. VLDL is converted to LDL by releasing lipid through LPL.
5. LDL is taken up by cells including liver.
6. Excess cholesterol in cells are picked up by HDL through LCAT. Then HDL is converted to IDL followed by LDL, which is taken up by liver



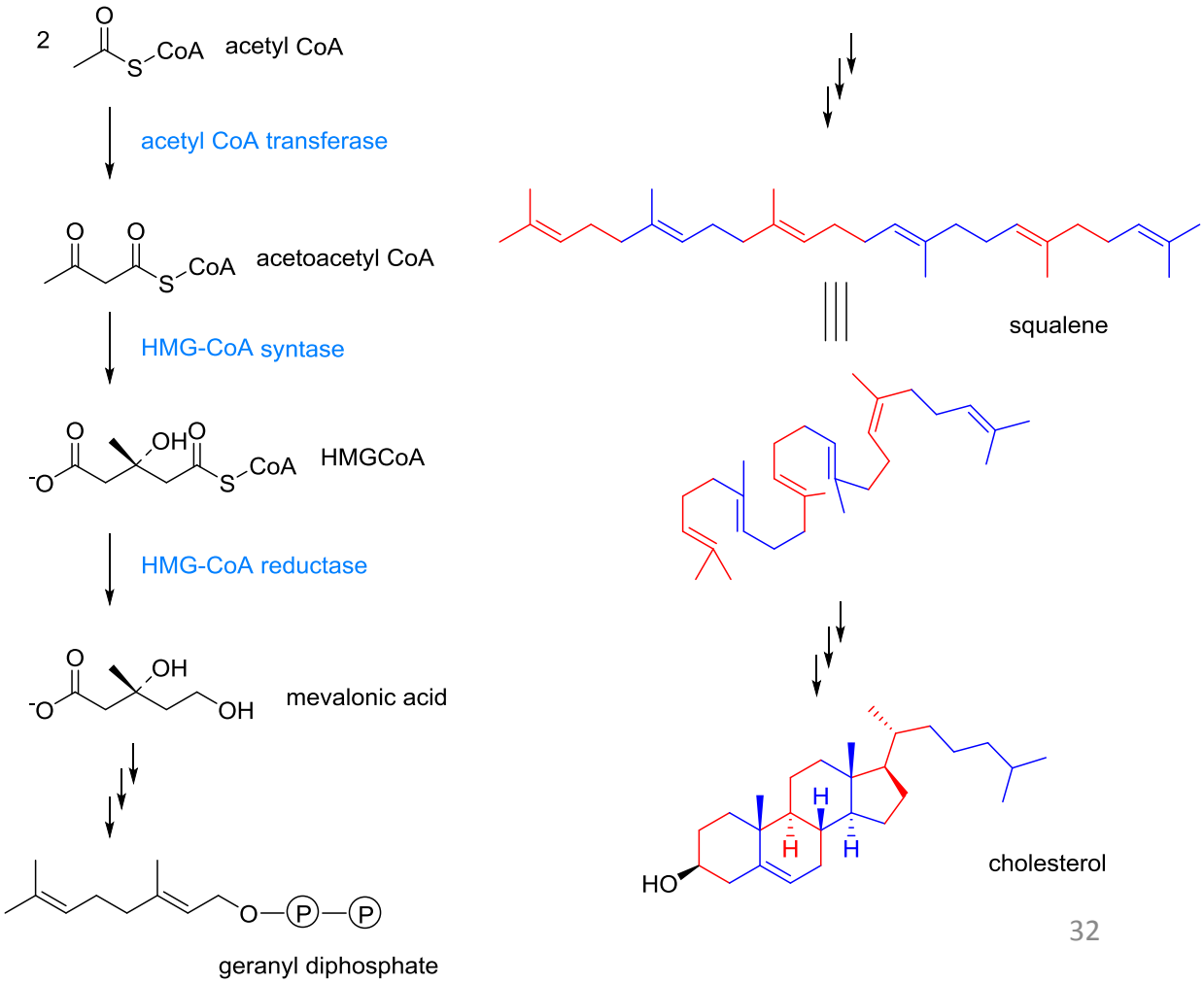
Lipid transport system



Cholesterol synthesis

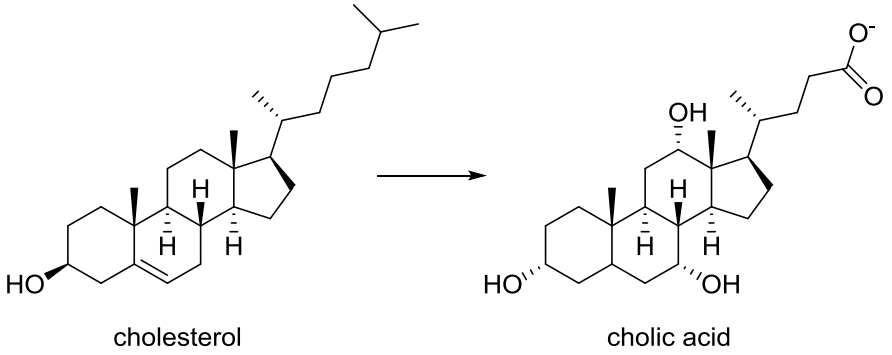
- Three functions of cholesterol:
  1. component of cell membrane to tune membrane fluidity.
  2. synthesis of steroid hormone.
  3. synthesis of bile acids.

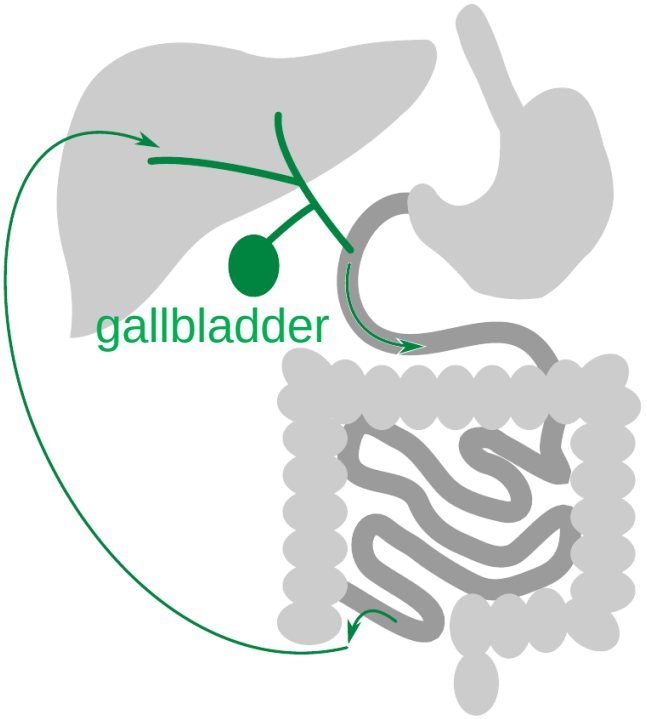
- Mammals synthesize cholesterol in ER of hepatocyte. Plants synthesize a little amount and prokaryotes do not synthesize cholesterol.
- Cholesterol can not be an energy source.



Cholesterol metabolism to bile acid

- Cholesterol is converted to bile acids (胆汁酸) in liver which is secreted to intestine through bile duct (胆管).
- Bile acids allow digestion of dietary fats and oils by acting as a surfactant that emulsifies them into micelles.
- 95% of bile acids are reabsorbed through transporter (ASBT) in ileum (回腸) and recycled back to the liver for further secretion into gallbladder (胆のう) (“enterohepatic circulation”).





2.3 Cause of atherosclerosis 動脈硬化の原因

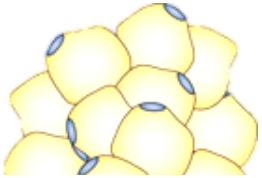
lipid abnormality (obesity)　脂質代謝異常（肥満）

high blood pressure　高血圧

diabetic mellitus　糖尿病

oral bacteria　口内細菌

Atherosclerosis is caused by metabolic syndrome



High visceral fat in adipose

High fatty acid conc. in portal blood

Adipokine secretion

Adiponectin: low
TNF-α: high

TG: high

Apo B

Fatty liver

VLDL: high

insulin resistance

LPL: low

hyperinsulinemia

Na^+ reabsorption: high

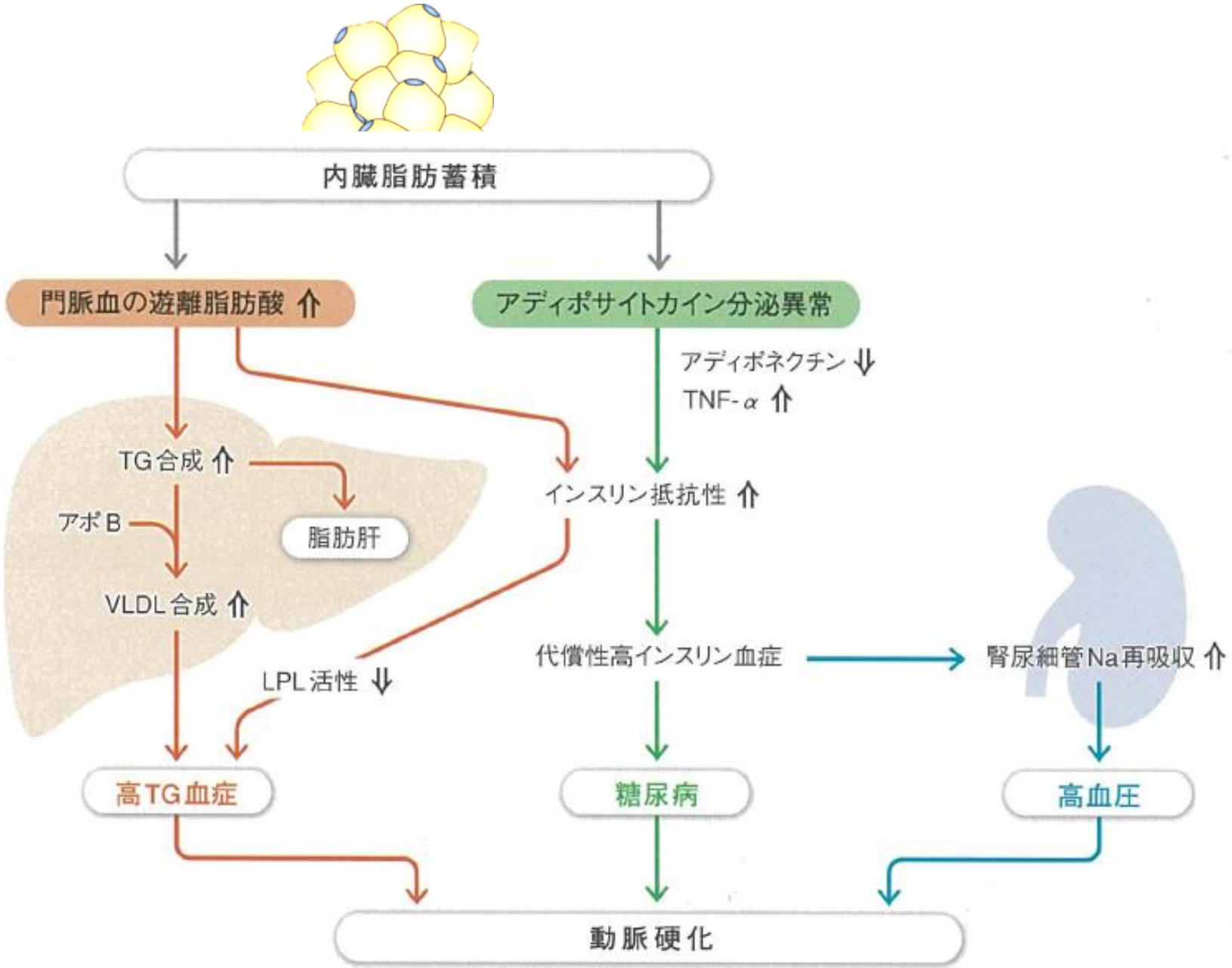
hyperlipidemia

diabetes

hypertension

Atherosclerosis

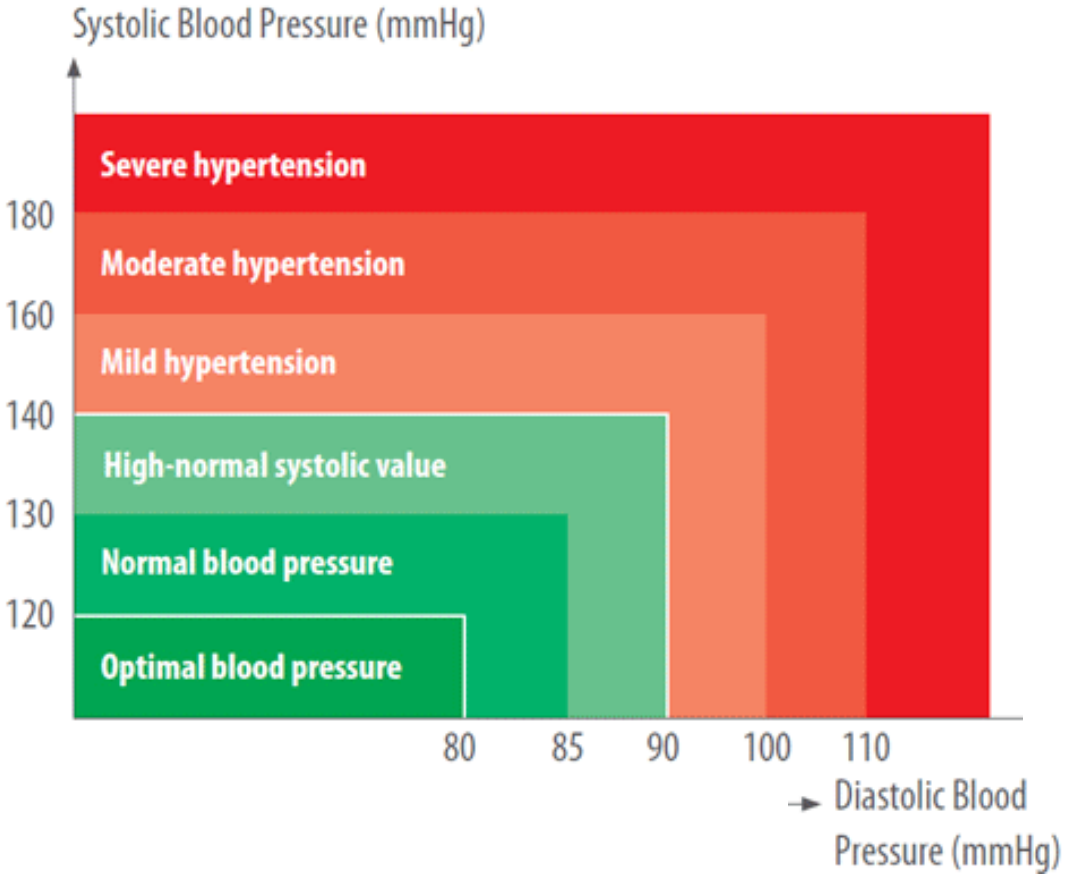
Atherosclerosis is caused by metabolic syndrome

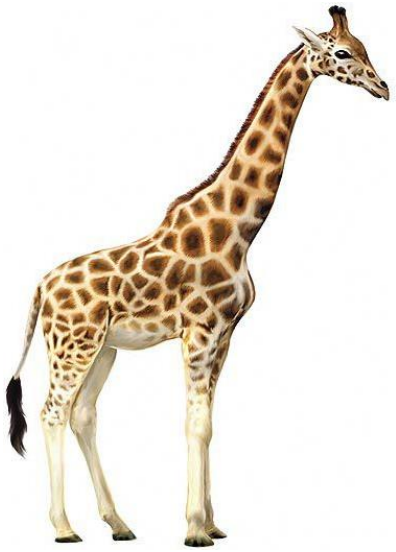


High blood pressure

high blood pressure -> added force against artery wall -> damage arteries

-> plaque formation -> atherosclerosis





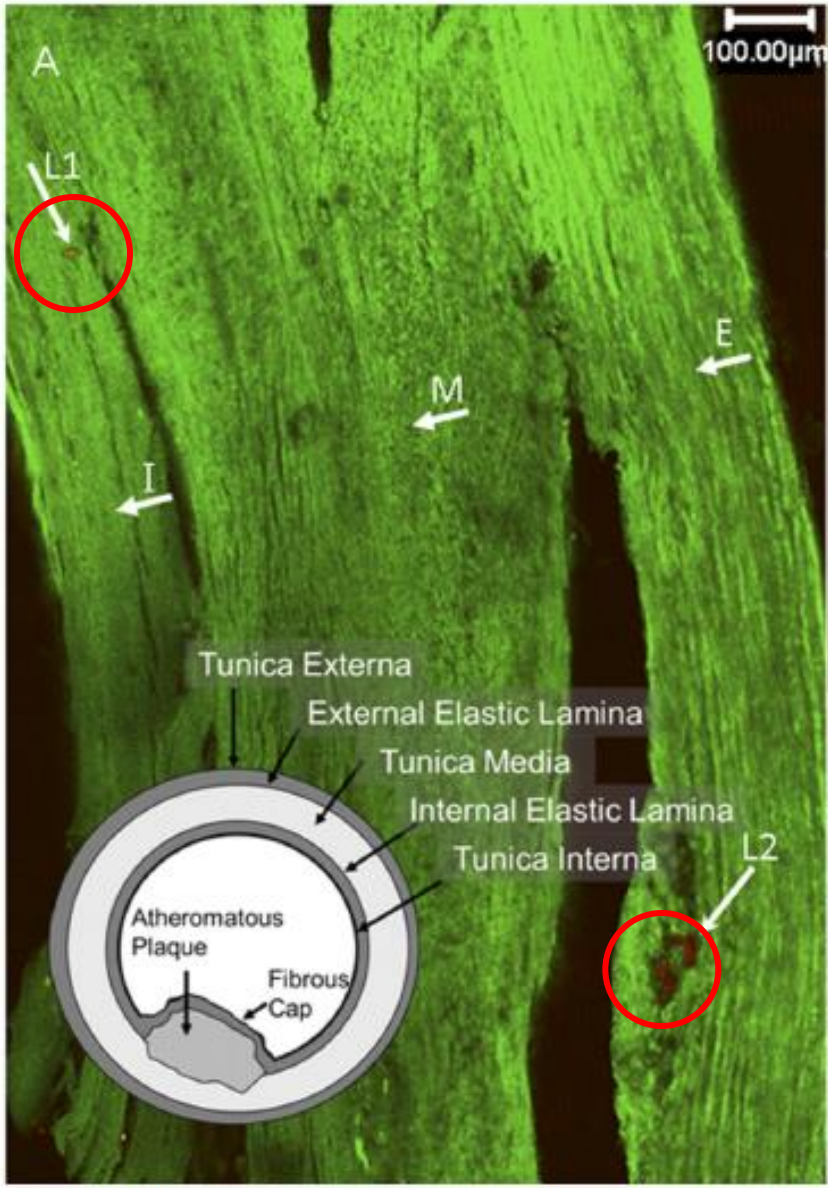
- 300/180 mmHg
- Never die by cardiovascular disease
- Thick SMC-rich medial layer

Lipid abnormality

Element	Optimal	Borderline	High risk
LDL Cholesterol	<100	130–159	160+
HDL Cholesterol	>60	35–45	<35
Triglycerides	<150	150–199	>200

Oral bacteria exist beneath intima

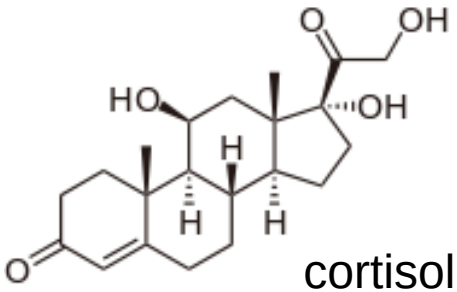
2014 mBio e01206



- ✓ More than 90% of AS patients possess *eubacterium* (pseudomonoas spp) in internal elastic laminal

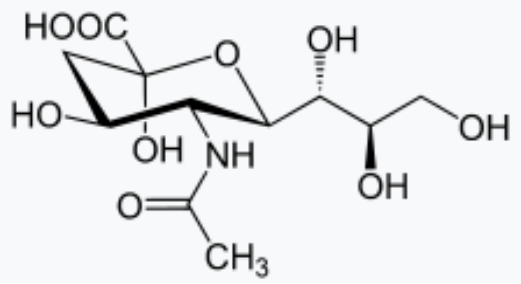
<u>Hypothesis of stress-induced AS</u>

1. Bacteria is dormant in steady state.
2. Under very stressful condition, increase in cortisol secretion from adrenal gland (副腎).
3. Release of free iron from transferrin (ligand exchange reaction?).
4. Abrupt growth of bacteria, then rupture of AS.

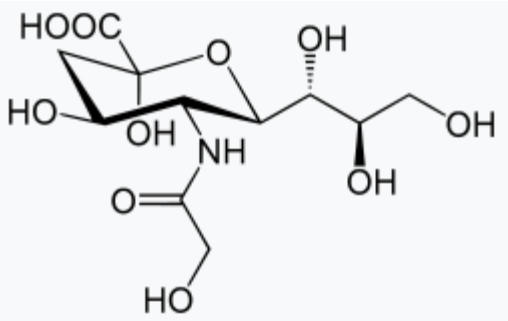


cortisol

Accumulation of anti-Gc antibody



enzyme



N-acetylneuraminic acid (Ac)

N-glycolylneuraminic acid (Gc)

- Human lost the enzyme to be resistant against malaria.

- Food intake Gc can be incorporated into saccharide synthesis.

  -> Attack of Gc by anti-Gc antibody.

  -> Worsen inflammation in AS.

2.4 Prevention and treatment of atherosclerosis

動脈硬化の予防と治療

lipid-lowering medicine 脂質低下薬

anti-hypertensive medicine 抗高血圧薬

anti-obeisty medicine 抗肥満薬

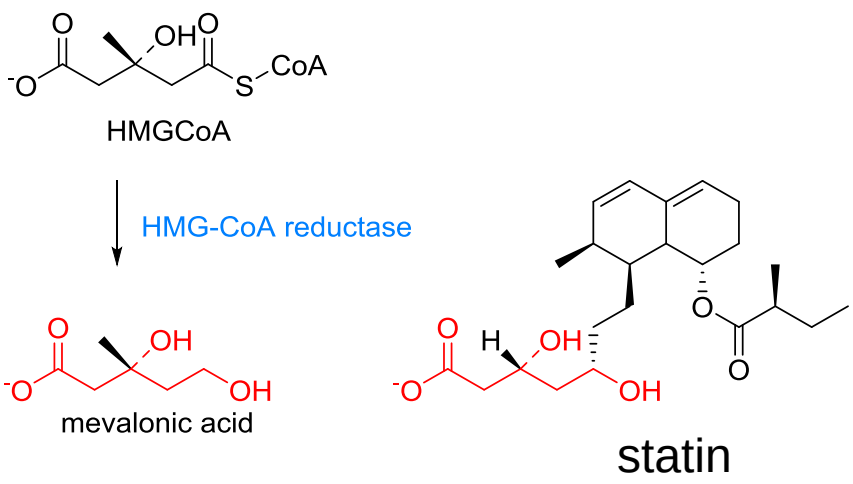
exercise 運動

HMG-CoA reductase inhibitor: statin

- To target rate determining step in mevalonate pathway.
- One of the best selling pharmaceuticals.

<u>Mechanism</u>

1. Reduction of blood conc. of cholesterol.
2. LDL uptake in liver is activated due to the increase of LDL receptor expression.
3. Blood conc. of LDL is reduced.

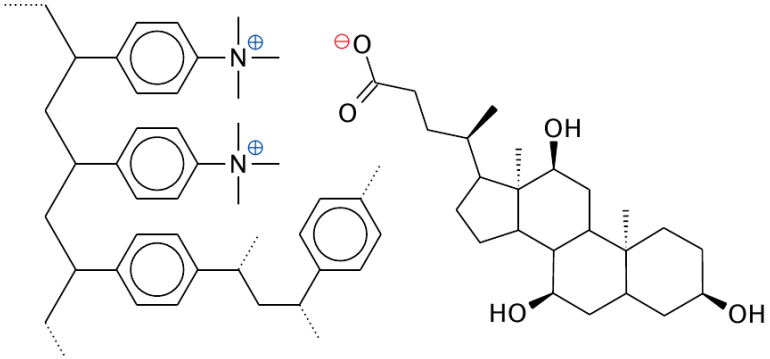


Anion-exchange resin (イオン交換樹脂): cholestyramine

- Polystyrene-based anion exchange resin.

<u>Mechanism</u>

1. Forming complex with bile acids.
2. Preventing the bile acids from being taken up at intestine and remove as feces.



cholestyramine　　cholic acid

PCSK9 inhibitor

- LDLR/LDL complex is recycled back to cell surface after releasing LDL.
- LDLR/PCSK9 complex is not recycled but degraded in lysosomes.
- Blocking the LDLR/PCSK9 complex formation accelerate the cellular uptake of LDL.
- Combination of anti-PCSK9 IgG and statin shows synergetic effect.