Dyslipidemia and atherosclerotic disease

Andrew Ying-Siu Lee, MD,PhD.

1. **The lipid transport system:**

Lipoproteins **= water-soluble lipids, for transport of cholesterol and triglyceride in blood**

- ultracentrifugation or electrophoresis seperate lipoproteins into: chylomicron, very low density lipoprotein VLDL, low density lipoprotein LDL, intermediate density lipoprotein IDL, high density lipoprotein HDL and lipoprotein a (Lpa)

2. *Structure of lipoproteins:*

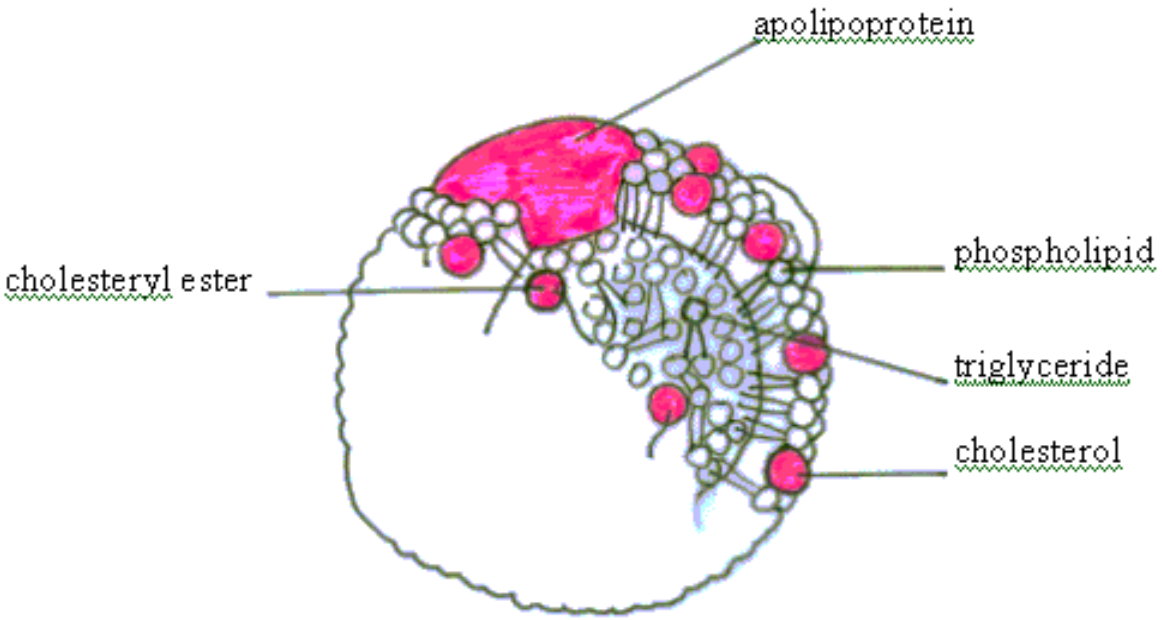
Cholesterol - essential component of cell membrane
- substrate for synthesis of corticosteroid hormones and bile acids

Triglycerides (TG)

phospholipids - essential component of cell membrane
- for signal transduction

apolipoprotein - assemble and secrete lipoproteins
- act as co-activators or inhibitors of enzymes
- bind to receptors or proteins for cellular uptake

Lipoprotein:- **contain lipid core (triglyceride and cholesterol esters) surrounded by phospholipids and apolipopoteins (for structure and enzymatic processes of lipids; ApoA1 = major component of HDL; ApoB = component of other non-HDL proteins)**



Structure of lipoprotein

3. ***Roles of lipoproteins***:
   - **a) transport of triglycerides from gut and liver (chylomicron) to sites of ultilization and storage (fatty acids in fat tissue or muscle) via lipoprotein lipase activity**
   - **b) transport of cholesterol to peripheral tissues for membrane synthesis, steroid hormone production, or to liver for bile acid synthesis**
   - **c) deliver essential fatty acids**
   - **d) atheroprotective effects of HDL via reversed cholesterol transport and decreased lipoprotein oxidation**

Classification of dyslipidemia:

1) ***clinical classification:***

measurement of total plasma lipids (cholesterol and triglyceride),and lipoprotein cholesterol (LDL and HDL “bad” and “good” cholesterols)

LDL(mg/dl) = total cholesterol – HDL – TG/5

2) ***electrophoresis*** → type I = increased chylomicrons, type II = increased LDL, type III = broad beta disease, type IV = increased VLDL, type V = increased chylomicron and VLDL

(3) *genetic classification:*

type II hyperlipidemia (= familial hypercholesterolemia, autosomal codominant)
- **increased LDL**
- **corneal arcus, xanthoma, coronary artery disease**

lipoprotein(a) = Lp(a), consist LDL with apo, correlate with coronary artery disease

familial hypertriglyceridemia: increased VLDL triglycerides, component of metabolic syndrome

familial combined hyperlipidemia: increased total cholesterol and/or triglyceride, LDL, apo B and decreased HDL

Secondary causes of dyslipidemia

- **Metabolic : diabetes, glycogen storage disorders**
- **Renal : chronic renal failure, glomerulonephritis, nephrotic syndrome**
- **Liver disease : cirrhosis**
- **Hormonal : estrogen, progesterone, growth hormone, thyroid disorder**
- **Lifestyle: physical inactivity, obesity, diet, alcohol**
- **Medications: immunosuppressive agents, corticosteroids, thiazides, beta blockers**

Therapy of dyslipidemia

lifestyle modification, treatment of secondary causes, diet, medications

1. **Resin = bile acid-binding resin eg. cholestyramine**
   - for severe hypercholesterolemia due to increased LDL
   mechanism: inhibit enterohepatic resorption of bile acids that contain cholesterol
   side effects: constipation, gastrointestinal discomfort, hypertriglyceridemia

2. **HMG CoA reductase inhibitors eg. statins**
   - inhibit rate-limiting enzyme for cholesterol synthesis
   mechanism: increase LDL receptor and decrease cholesteryl ester formation → increase LDL clearance and decrease hepatic production of VLDL and LDL
   side effects: hepatotoxicity, myositis

3. ***Fibric acid derivatives*** **(fibrate eg. gemfibrozil (lopid)**

- **for hypertriglyceridemia**

mechanism: regulate transcription of LDL and apo gene, and antiinflammatory effect

side effects: cutaneous and gastrointestinal symptoms, erectile dysfunction, elevated serum aminotransferases

4. ***Nicotinic acid (niacin)***

- **effective in increasing HDL and lowering triglyceride**

mechanism: decrease hepatic secretion of VLDL and free fatty acid

side effects: flushing, hyperuricemia, hyperglycemia, hepatotoxicity, gastritis

5. ***Fish oil*** **– lower triglycerides, antithrombotic and antiinflammatory**

mechanism: decrease VLDL and apo B

Atherosclerosis

Structure of normal artery:

3 layers: ***intima*** (endothelial cells of arterial intima = contact surface of blood (vascular homeostasis, endothelial thrombotic balance) containing : 1. anticoagulant factors (prostacyclin, thrombomodulin, heparin sulfate proteogycan molecules) and 2. procoagulant factors (plasminogen activator inhibitor, tissue factor, von Willebrand factor)

media (contains concentric layers of smooth muscle cells, which synthesize arterial extracellular matrix for normal or atherosclerotic homeostasis)

adventitia (contains collagen fibrils, vasa vasorum, nerve endings, fibroblasts and mast cells)

Mechanism of atherosclerosis

1. **atherogenic diet → lipoprotein (LDL) (cholesterol,fat) accumulation in intima**

→ binding of LDL to proteoglycan in intima → oxidation, aggregation, enzymatic processes, glycation of LDL (→ *modified LDL)*

2. **hypercholesterolemia,**

leukocyte adhesion molecules in endothelium (eg.vascular cell adhesion molecules,intercellular adhesion molecules, selectins)

→ **leukocyte adhesion to endothelium**

→ **leukocyte migration to intima (via chemokines eg. monocyte chemoattractant protein-1, interferon-inducible protein 10 etc. induced by oxidative stress from modified LDL)**

- ***foam cell formation*** **(=lipid laden leukocyte or macrophage)**

  due to lipid uptake via scavenger receptors eg. scavenger receptor A, CD36, macrosialin etc.

  = reservoir for excess lipid, proinflammatory mediators (eg. cytokines, chemokines, platelet-activating factor), oxidant species, innate and adaptive immunity → promoting atherosclerosis

- **replication of foam cells forming *fatty streak***

  (via macrophage colony stimulating factor, interleukin 3, granulocyte macrophage colony stimulating factor etc)

- migration of medial smooth muscle cells to intima (due to platelet-derived growth factor PDGF secreted by foam cells)

→ accumulation of intimal smooth muscle cells

a) replication of intimal smooth muscle cells

b) apoptosis of intimal smooth muscle cells (due to inflammatory cytokines present in atheroma)

→ *atherosclerotic plague*

a) plague microvessels (due to angiogenesis via angiogenesis factors eg. fibroblast growth factor, vascular endothelial growth factor)

b) extracellular matrix synthesis (eg. interstitial collagens, elastin fibers, proteoglycans, biglycan, aggrecan, decorin) and dissolution (catalyzed by matrix metalloproteinases)

- ***Plague disruption***

  a) rupture of plague's fibrous cap

  imbalance between mechanical strength and impinging forces on plague's cap

  eg. decreased collagen synthesis (interferon gamma), increased collagen synthesis(PDGF) and extracellular matric dissolution.

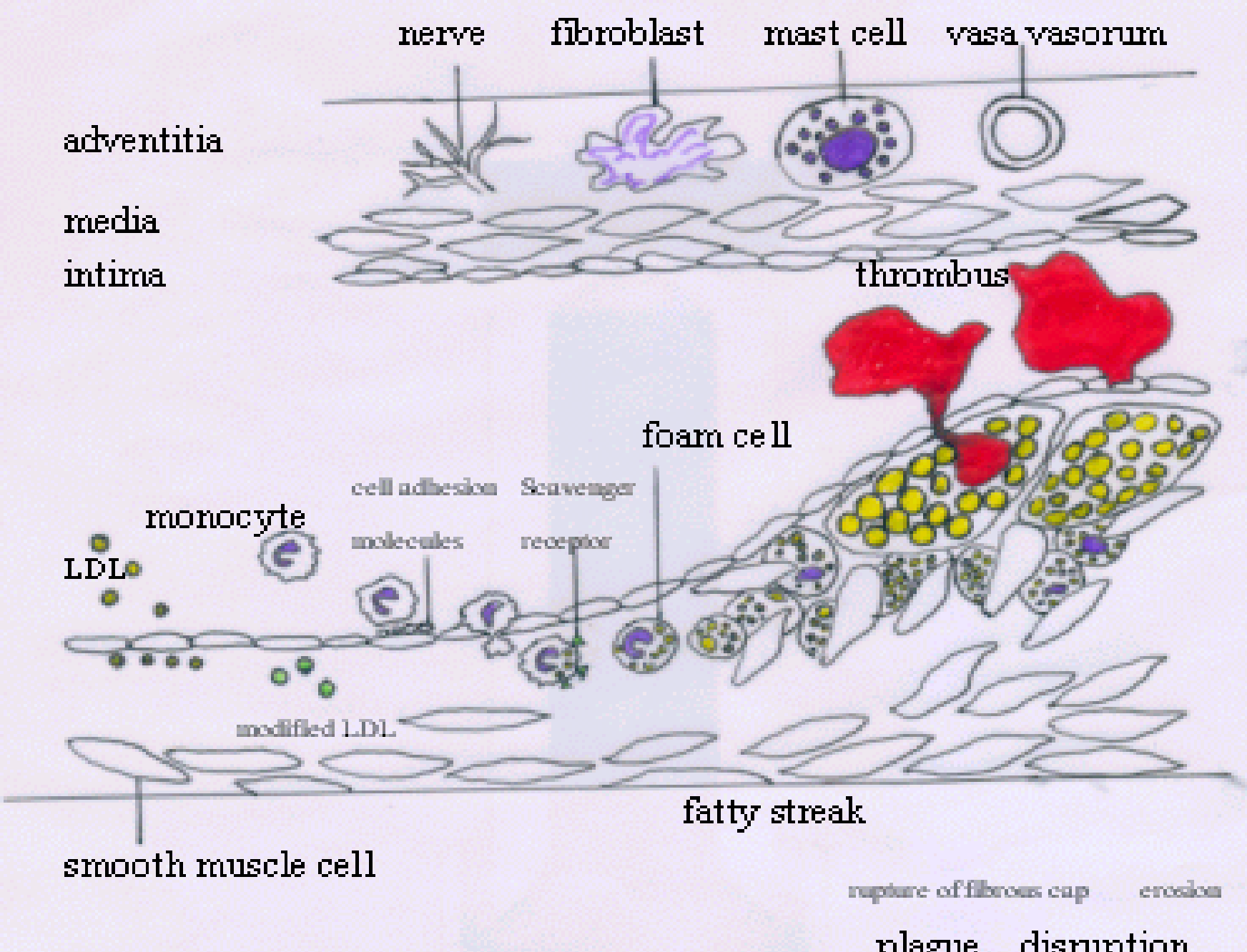
  b) superficial erosion of intima

  apoptosis of endothelial cells,

  matrix metalloproteinases etc.

  c) infections (chlamdydia pneumonia, cytomegalovirus)

→ ***thrombus formation*** **(when blood with its coagulation factors contact tissue factors within plague)**



Mechanism of atherosclerosis

Risk factors for atherosclerotic disease

1. ***Dyslipidemia***

2. ***Smoking*** **= most important modifiable risk factor**
   → **accelerate atherosclerosis**
   oxidation of LDL and decrease HDL
   impair endothelium-dependent vasodilation
   increase inflammation
   platelet aggregation
   increase leukocyte adhesion to endothelium
   coronary spasm
   increase arrhythmias

3. ***Hypertension*** **: increase risk of stroke and myocardial infarction**

4. ***Insulin resistance and diabetes***:
   - promote atherosclerosis
   - impair endothelial and smooth muscle function
   - increase leukocyte adhesion to endothelium

5. ***Exercise and obesity***:
   - exercise lowers cardiovascular risk by improving blood pressure, body weight, lipid, glucose tolerance, endothelial function and fibrinolysis

6. ***Stress***

7. ***Estrogen:***

- decrease LDL, increase HDL, apo A, triglyceride
- improve endothelial-dependent vasodilation, glucose metabolism
- increase risk of endometrial cancer, gallstone, venous thrombosis, breast cancer

8. ***Other atherosclerotic risk factors:***

increased plasma level of homocysteine, fibrinogen, plasminogen activator inhibitor (PAI-1), proinflammatory cytokines (eg. interleukin, tumor necrosis factor), C-reactive protein (CRP)