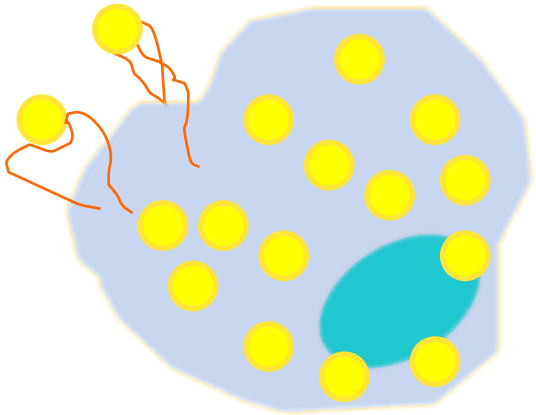
Foam cell



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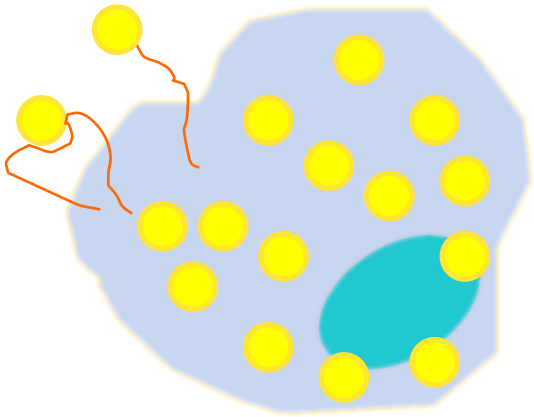
Definition and derivation

Definition:
Fat–laden immune cell of the type macrophage, the lipids in it give it a “foamy” appearance.



Derivation:

- Inflammatory macrophage
- Inflammatory dendritic cell
- Vascular smooth muscle cell
- Resident dendritic cell(?)

Foam cell formation

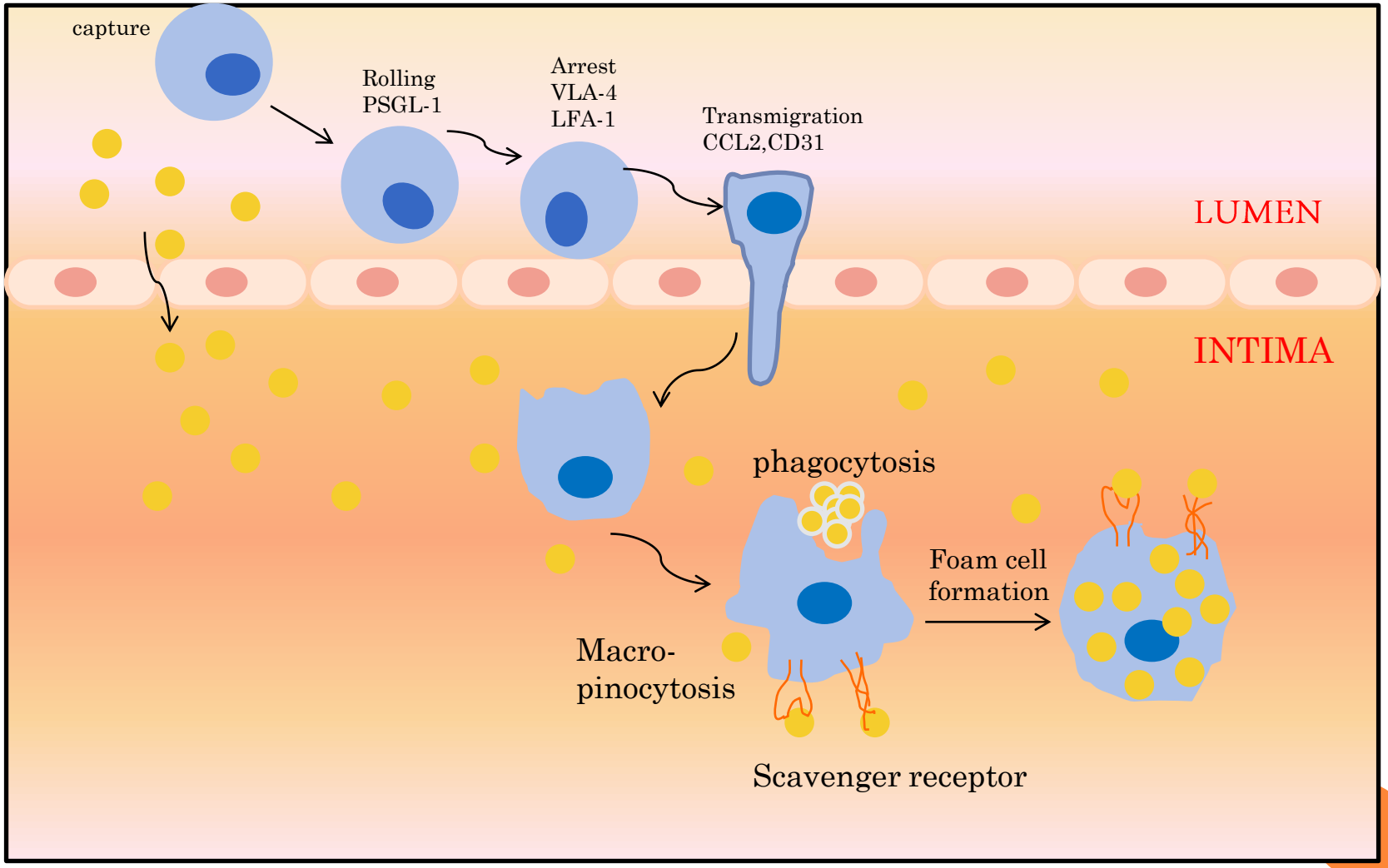
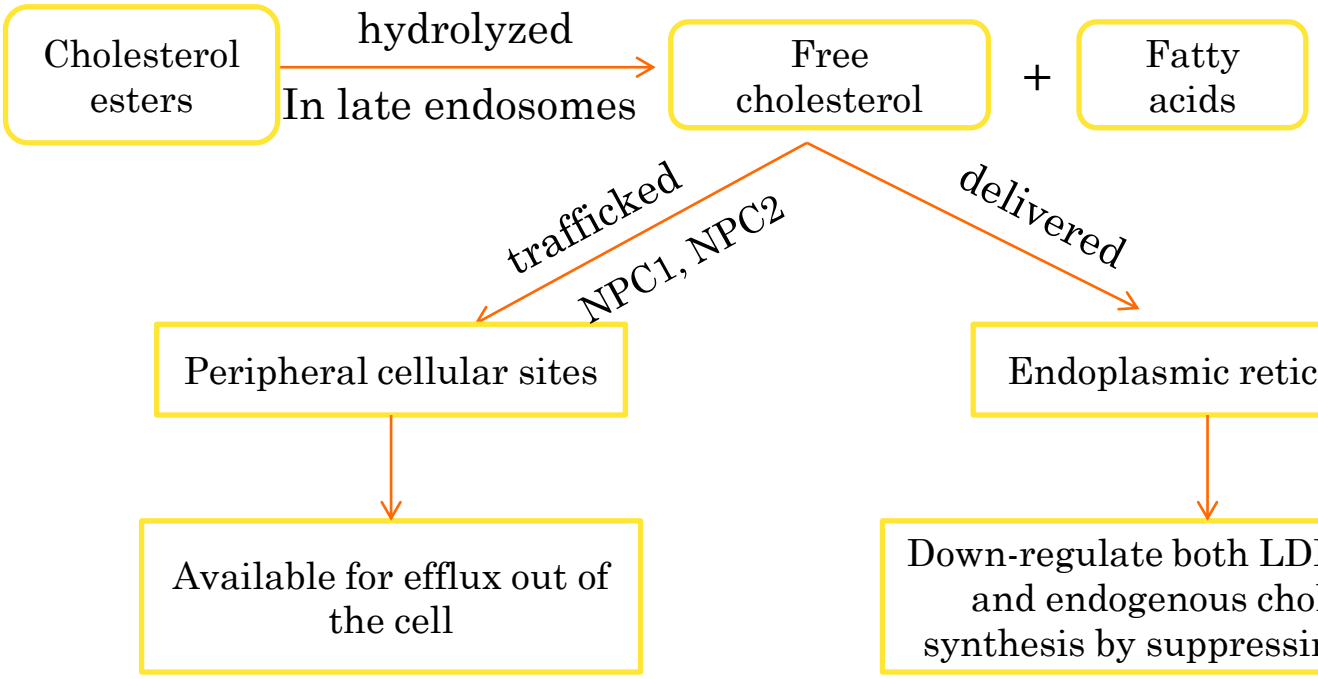


Figure1. the process of foam cell formation

Uptake of modified LDL

- ✓Scavenger receptor, such as SR-A, CD36 , LOX-1, CXCL16
- ✓Phagocytosis of matrix-retained and aggregated LPs
- ✓Fluid phase pinocytosis of native and modified LDL

Cholesterol metabolism



Ira Tabas. Macrophage in the pathogenesis of atherosclerosis. Cell, 2011, 145:341-355

Efflux of the cholesterol

RCT pathways in macrophage foam cell

✓Aqueous diffusion
✓Interaction between ABCA1 and cholesterol-deficient and phospholipid-depleted apo A-I complex (pre-β migrating HDL or HDL-VS)
✓Interaction between ABCG1 and spherical, cholesterol-containing α-HDL particles(HDL-S, HDL-M, HDL-L, HDL-VL)
✓SR-BI, mediate bidirectional lipid transport dependent on the content of cholesterol in the macrophage.

Table1. pathways for macrophage-specific cholesterol efflux

Efflux pathways	**Energetics**	**Preferred HDL acceptor**	**characteristics**
Aqueous diffusion	passive	HDL-L~HDL-M~HDL-S	Bidirectional
SR-BI	passive	HDL-L>HDL-M>HDL-S	Bidirectional; create labile pool of cholesterol for efflux; high affinity binding permits cholesterol transfer from plasma membrane to bound HDL particles
ABCG1	active	HDL-L~HDL-M~HDL-S	Undirectional; no high-affinity binding
ABCA1	active	E-HDL HDL-VS(pre-ß1-HDL) Lipid-poor apoE	Create and enlarge labile pool of plasma membrane cholesterol for efflux; undirectional; HDL-VS interaction with high-affinity ABCA1 receptor; active transport from the late endocytic compartment of the endoplasmic reticulum to plasma membrane with formation of HDL-S

Robert S.Rosenson. Cholesterol efflux and atheroprotection : advancing the concept of reverse and cholesterol transport. Circulation, 2012, 125: 1905-1919

ther important proteins

Cholesterol 27-hydroxylase
LXR(LXRα and LXRβ)
LCAT
CETP

functions as sterol sensors by responding to increases in oxysterols with up-regulated transcription of gene products(ABCA1 and ABCG1).

catalyzes 27-hydroxylation of cholesterol to form 27-hydroxycholesterol, which provides a pathway for elimination of intracellular cholesterol by conversion to more polar metabolites that can be transported out of cell orders of magnitude faster than cholesterol.

LCAT, a hepatic synthesized glycoprotein, converts cholesterol to cholesteryl esters. This reaction occurs largely on HDL-VS and HDL-S particles, transforming these particles into the larger spherical α-migrating forms of HDL. It can enhance cholesterol efflux by ABCA1 and by passive exchange.

CETP, a hydrophobic glycoprotein, catalyzes the transfer of cholesterol esters generated by LCAT in HDL to other lipoprotein. Homozygosity for CETP mutation results in dramatic elevations in HDL-C and moderate reductions in LDL-C, which may provide a strategy to increase HDL levels in plasma.

Cytokines and foam cell formation

- Scavenger receptors expression

  TNF-α: LOX-1 ↑, SR-A ↓ ;
  IFN-γ : SR-A ↓, SR-PSOX ↑ ;
  adipokine: SR-A ↓

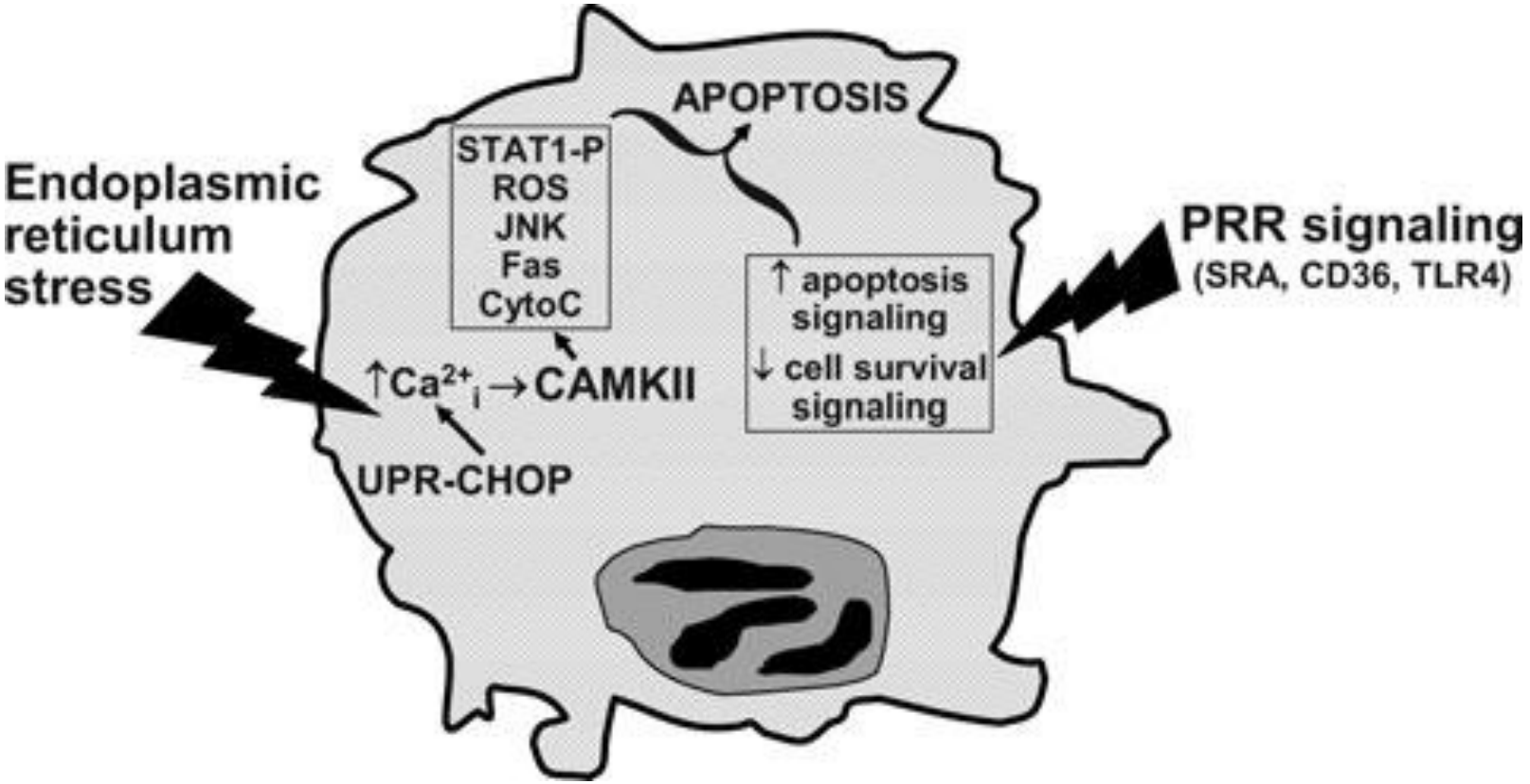
- Lipid transport

  IFN-γ： apo-E and ABCA1 ↓;
  TGF-ß: apo-E and ABCA1 ↑

- Ability of the cell to oxidize LDL

  IFN-γ: oxidation of LDL ↓
  IL-4, IL-13 and TNF-α: oxidation of LDL ↑

Foam cell apoptosis



Ira Tabas. Macrophage apoptosis in advanced atherosclerosis. Integrative physiology, 2009, 1173, E40-E45.

ADK and foam cell formation

ADK: the key enzyme that regulates the intracellular and extracellular concentrations of adenosine

Adenosine: normally at low concentrations in human tissue, but in response to metabolic stress(eg. Inflammatory events , hypoxia), it will be released into the extracellular space.

Potential effects of adenosine stimulation:

✓Monocyte /macrophage , the prime targets of adenosine
✓Up-regulation of the RCT proteins ,such as cholesterol 27-hydroxylase and ABCA1
✓Down-regulation of LOX-1(member of the scavenger receptor)
✓Inhibit expression of inflammatory cytokines
✓Inhibiti macrophage foam cell transformation

Thanks for your attention!