Cholesterol and Cardiovascular Disease

Cardiovascular (CV) Disease

- Cardiovascular (CV) disease is the leading cause of mortality worldwide, accounting for 31.4% of deaths in 2012.

- In developed countries, age-adjusted CV mortality rates are declining, but CV disease remains the leading cause of mortality due to rapid aging of the population.

- In low-income to middle-income countries, both age-adjusted CV mortality rates and aging of these populations are contributing to a rapid increase in CV mortality (Fuster et al.,2020)

- Low-density lipoprotein cholesterol (LDL-C) has now largely replaced total cholesterol as the primary lipid measurement for evaluation of risk due to atherogenic lipoproteins.

- LDL-C is a measure of the total cholesterol content of LDL particles, reflecting both the number of LDL particles and their individual cholesterol content.

- Most current guidelines include LDL-C as a primary target for initiating and adjusting lipid-lowering interventions

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- Cholesterol, an essential lipid for eukaryotic cells, plays important roles in many cellular processes including membrane properties regulation, steroidogenesis, bile acid synthesis, and signal transduction.

- Accounting for 30%–40% of total cellular lipids, cholesterol is dynamically transported in cells and unevenly distributed in cellular membrane structures.

- Only 0.5%–1% of total cellular cholesterol is present in the ER membrane (Lange et al., 1999) and its concentration is higher in the Golgi apparatus and highest (60%–80%) in the plasma membrane (PM) (Liscum and Munn, 1999).

- In addition, cholesterol exerts diverse cellular functions in different organelles.

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- Sterols in ER control de novo cholesterol biosynthesis by inhibiting SREBP processing and promoting degradation of HMG-CoA reductase (Goldstein et al., 2006).

- Cholesterol is esterified in ER for storage and lipoprotein secretion (Chang et al., 1997; Vance and Vance, 1990) and oxidized and converted to steroids and bile acids in mitochondria and peroxisome (Ishibashi et al., 1996).

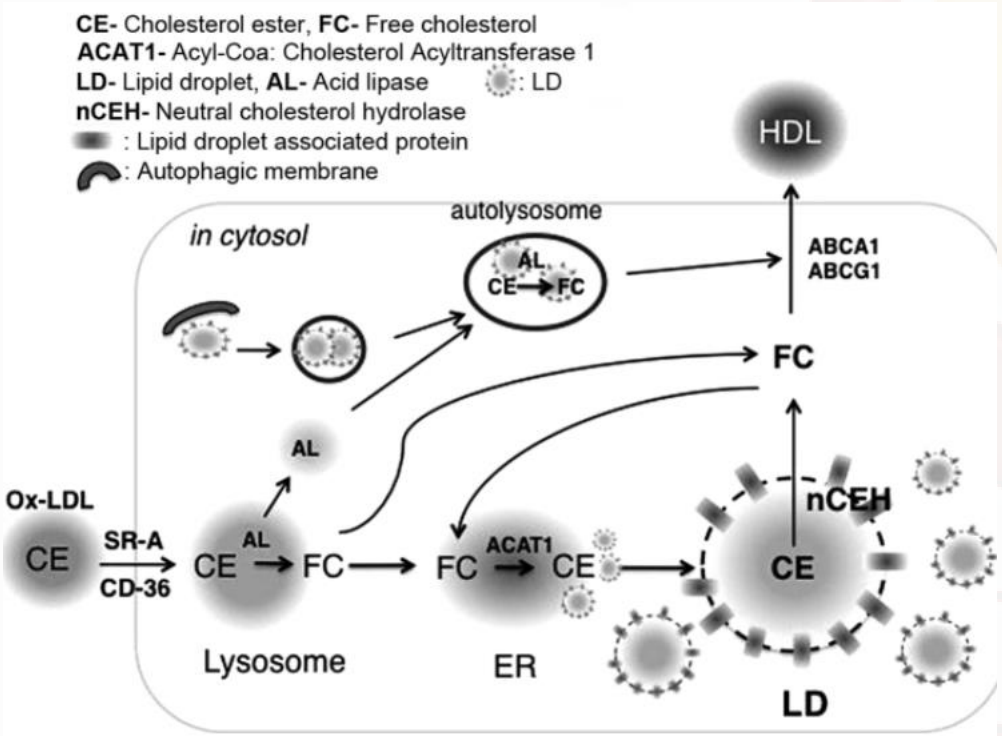
- Thus, dynamic cholesterol transport in cells is pivotal for multiple cellular functions.

- Low density lipoprotein (LDL)-derived cholesterol trafficking is a major part of intracellular cholesterol transport with most mammalian cells acquiring 80% of their cholesterol through receptor-mediated endocytosis of plasma LDL (Brown and Goldstein,1986).

- Upon receptor binding and internalization, LDL is delivered from early endosome to late endosome/lysosome (L/L), where LDL-derived cholesteryl esters are hydrolyzed to unesterifiedcholesterol.

- Free cholesterol then egresses from L/L and is further passed to downstream organelles such as the PM, ER, and mitochondria to fulfill its functions (Chang et al.,2006).

Cholesterol trafficking in macrophages



- Cholesterol trafficking in macrophages. ABCA1, ATP-binding cassette, sub-family A, member 1; ABCG1, ATP-binding cassette, sub-family G, member 1; ER, endoplasmic reticulum; SR-A, scavenger receptor A; CD-36, cluster of differentiation 36

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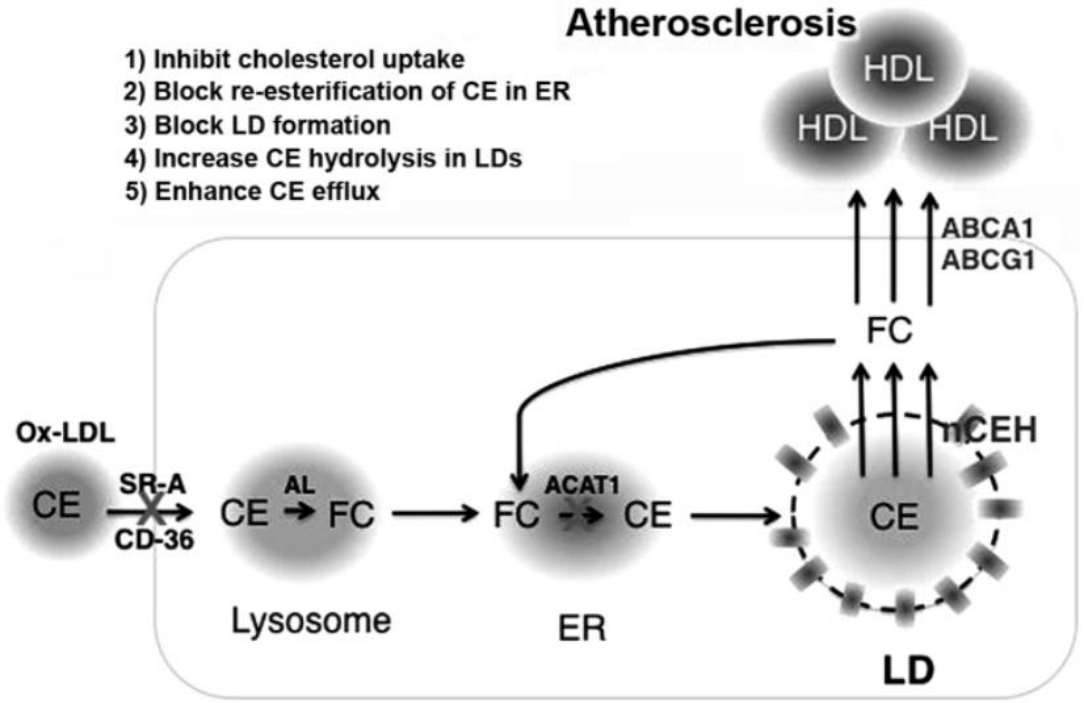
Efforts targeting foam cells to intervene against atherosclerosis



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Efforts targeting foam cells to prevent/intervene against atherosclerosis. CE, cholesterol ester; ER, endoplasmic reticulum; LD, lipid droplet; ox-LDL, oxidized low-density lipoprotein; SR-A, scavenger receptor A; CD-36, cluster of differentiation 36; AL, acid lipase; ACAT1, acyl-CoA:cholesterol acyltransferase

1; nCEH, neutral cholesterol hydrolase; ABCA1, ATP-binding cassette, sub-family A, member 1; ABCG1, ATP-binding cassette, sub-family G, member 1; HDL, high-density lipoprotein.

- To date, most mechanistic knowledge on cholesterol passage from L/L to other organelles has come from studies of the inheritable neuronal degeneration disorder Niemann Pick type C (NPC) disease, which is caused by loss-of-function mutations in NPC1 or NPC2 genes (Carstea et al., 1997; Sleat et al., 2004).

- NPC patients show severe cholesterol accumulation in multiple tissues.
- NPC1 is a polytopic membrane protein on L/L, whereas NPC2 is a luminal protein.

- After cholesteryl ester is hydrolyzed in the lysosomal lumen, NPC2 binds the unesterified cholesterol by recognizing the 8-carbon isooctyl side chain.

- NPC2 then hands over the cholesterol molecule to the N-terminal domain of NPC1, with the 3b-hydroxyl group buried within the binding pocket.

- The NPC1-bound cholesterol projects through the glycocalyx and is inserted into the lysosomal membrane. In NPC1 or NPC2 mutant cells, cholesterol cannot be incorporated into membrane and is therefore accumulated in the lumen (Kwon et al., 2009).

- However, this only accounts for how free cholesterol reaches the L/L membrane, and the mechanisms whereby cholesterol leaves the lysosomal membrane and moves to other organelles remain largely unknown.

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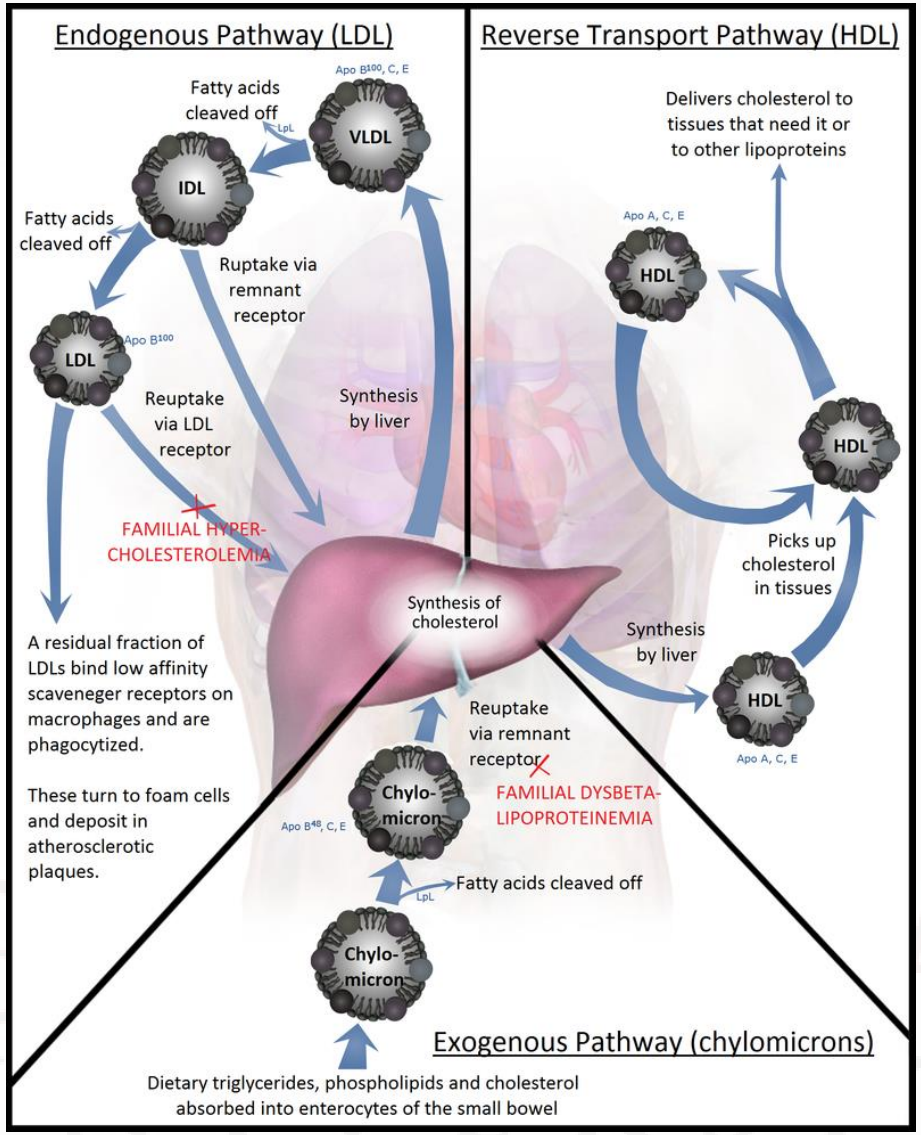

Figure illustrated Pathway of LDL AND HDL taken from Wikipedia

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Thanks