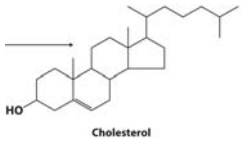
Lipid Metabolism

Chapter 29, Stryer Short Course

Lipid anabolism

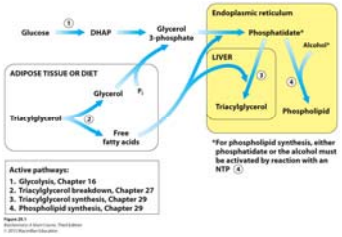
- Triacylglyderides
- ~~Membrane components~~
- **Cholesterol**
  - **Regulation**
- Steroids

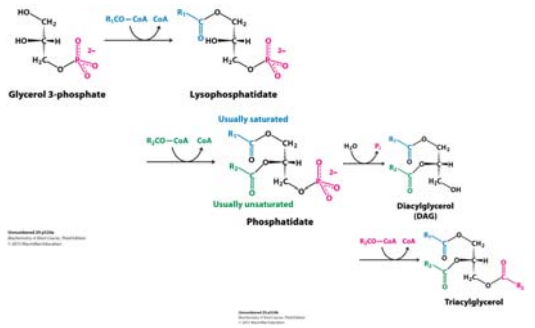


Cholesterol

TAG Synthesis

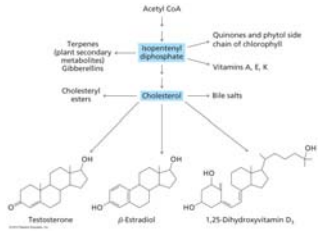
- Mainly in Liver
- Packaged in chylomicrons





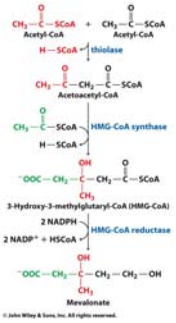
Cholesterol Biosynthesis

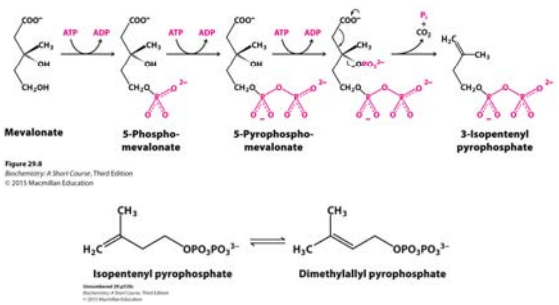
- Three Stages: Acetyl CoA→Isopentyl diphosphate→Squalene→Cholesterol



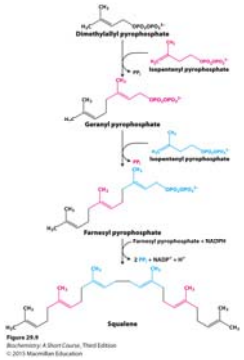
Stage 1

- Similar to ketogenesis, but in cytosol
- HMG-CoA reductase is main regulatory enzyme
- Mevalonate made into isoprene building block for many lipids





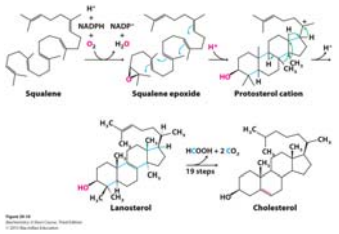
Stage 2



- Head-to-tail to form farnesyl group
- Tail-to-tail to form squalene

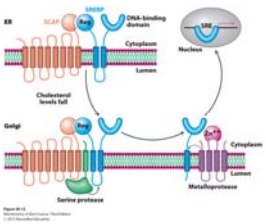
Stage 3

- Carbocation cascade sets the A-D rings and stereocenters
- Further processing

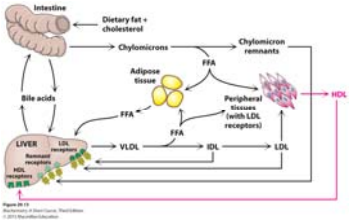


Regulation of Cholesterol Synthesis

- HMG-CoA Reductase
- Local covalent regulation
  - AMP-protein kinase down regulates synthesis (like fatty acid)
- Transcription
  - Low [cholesterol] releases SER (sterol regulatory element) to nucleus to upregulate the Reductase
- Translation inhibition
- Degradation of enzyme

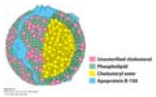


Lipoprotein Metabolism

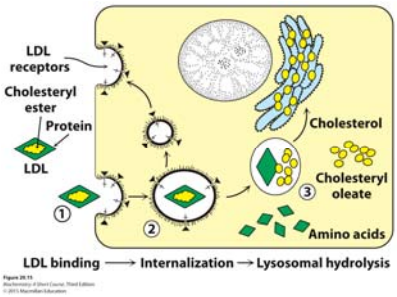


- Liver is the packaging center
- VLDL are sent out of liver
- Constant cycling of LDL in blood
- HDLs are "good cholesterol"

LDL =

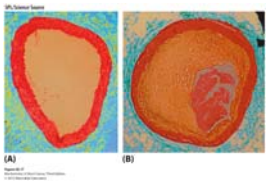


LDL receptors



Atherosclerosis

- Formation of plaques from high LDL
- LDLs oxidize and cause inflammation
- "hardening of the arteries"
- Familial hypercholesterolemia from absence of LDL receptors on cells
- HDL picks up cholesterol scavenged by macrophages
- Low HDL leads to macrophages contributing to plaque/artery damage

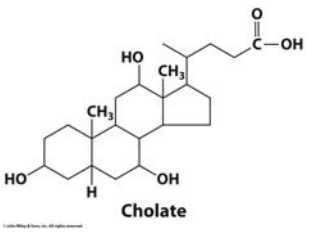


Medical Approach to High Cholesterol

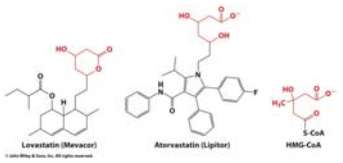
- Deprive cells of cholesterol
  - Dietary
  - *De novo*
- Cell responds by upregulating LDL receptors to pull LDLs out of blood

Reduce dietary cholesterol

- Inhibit reabsorption of bile salts in intestine so that cholesterol is used up making bile salts
- Drug: positively charged polymers that are not absorbed



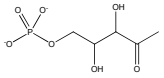
Block de novo synthesis



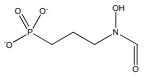
- Statins inhibit HMG-CoA Reductase
- Problem: inhibits all steroid biosynthesis

Medical Applications

- Parasites like malaria make isopentenyl diphosphate through a different mechanism
- A competitive inhibitor can selectively kill malaria

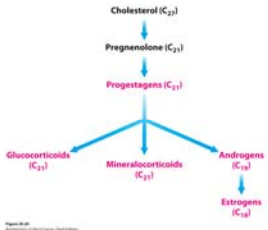


intermediate in cholesterol biosynthesis



competitive inhibitor

Biosynthetic Precursor



- Steroids
  - Sex hormones
  - Metabolic regulation
  - Kidney water/salt balance
- Vitamin D