

# Lipid Metabolism

Chapter 29, Stryer Short Course

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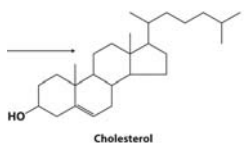
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## Lipid anabolism

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



Cholesterol

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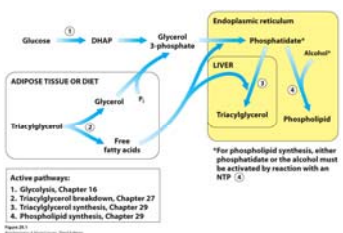
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## TAG Synthesis

- Mainly in Liver
- Packaged in chylomicrons



The diagram illustrates the synthesis of triacylglycerol (TAG) in the liver. It starts with Glucose being converted to DHAP, then to Glycerol 3-phosphate. In the Endoplasmic reticulum, Glycerol 3-phosphate reacts with Phosphatidate\* to form Triacylglycerol. Alternatively, it can react with Alcohol\* to form Phospholipid. Triacylglycerol is then packaged into chylomicrons. A note states: '\*For phospholipid synthesis, either phosphatidate or the alcohol must be activated by reaction with an NTP (Δ)'. Active pathways listed include Glycolysis, Triacylglycerol breakdown, Triacylglycerol synthesis, and Phospholipid synthesis.

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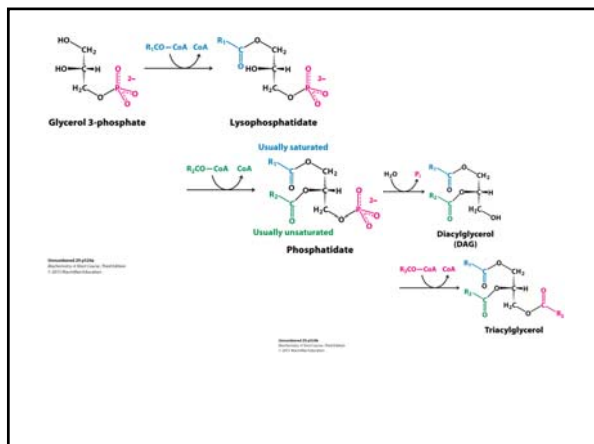
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### Cholesterol Biosynthesis

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

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### Stage 1

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

$2 \text{ CH}_3-C(=O)-SCoA + H-SCoA \xrightarrow{\text{thiolase}} \text{CH}_3-C(=O)-CH_2-C(=O)-SCoA + H-SCoA$

$\text{CH}_3-C(=O)-CH_2-C(=O)-SCoA + H-SCoA \xrightarrow{\text{HMG-CoA synthase}} \text{CH}_3-C(OH)(CH_3)-C(=O)-SCoA + H-SCoA$

$\text{CH}_3-C(OH)(CH_3)-C(=O)-SCoA + 2 \text{ NADPH} + \text{H}^+ \xrightarrow{\text{HMG-CoA reductase}} \text{CH}_3-C(OH)(CH_3)-CH_2-C(=O)-OH + 2 \text{ NADP}^+ + \text{HSCoA}$

**Mevalonate**

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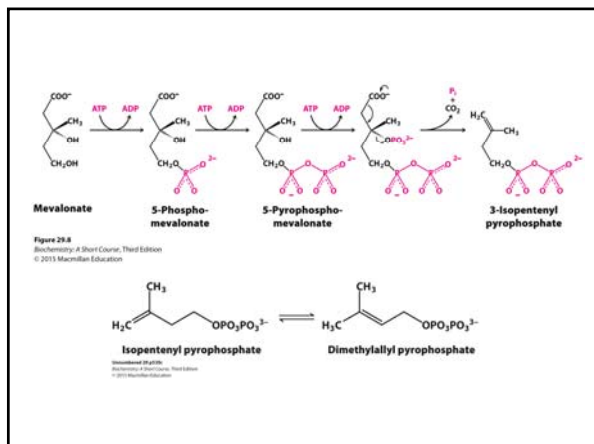
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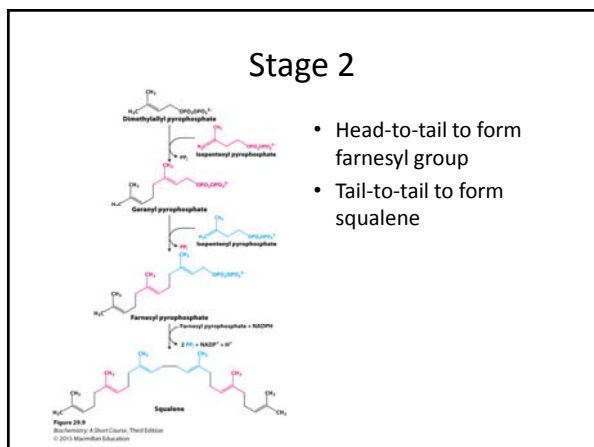
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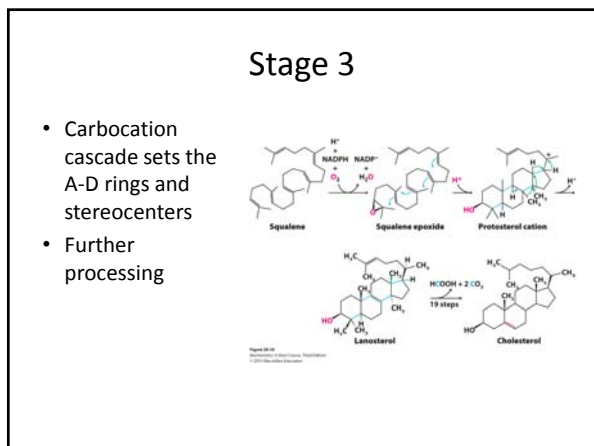
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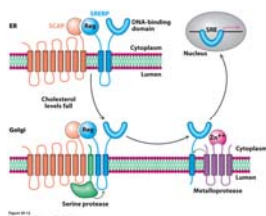
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## Regulation of Cholesterol Synthesis

- **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




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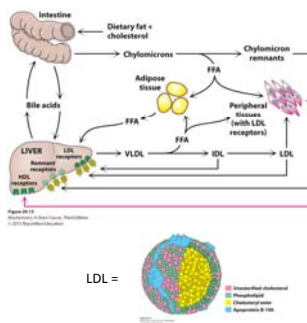
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## Lipoprotein Metabolism



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

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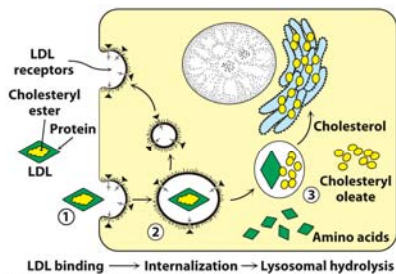
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## LDL receptors




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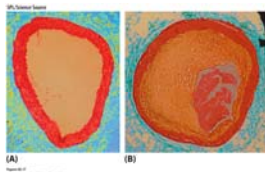
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## Atherosclerosis

- 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




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## Medical Approach to High Cholesterol

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




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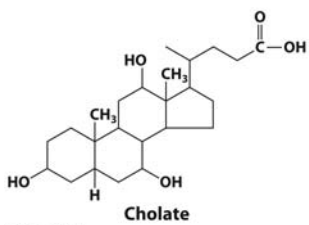
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## Reduce dietary cholesterol

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




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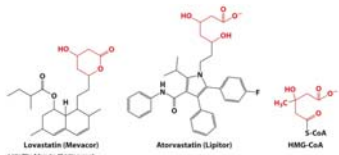
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### Block de novo synthesis



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

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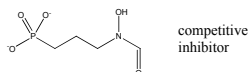
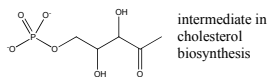
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### Medical Applications

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




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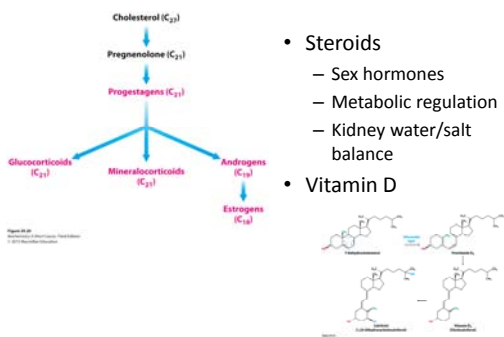
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### Biosynthetic Precursor



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

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