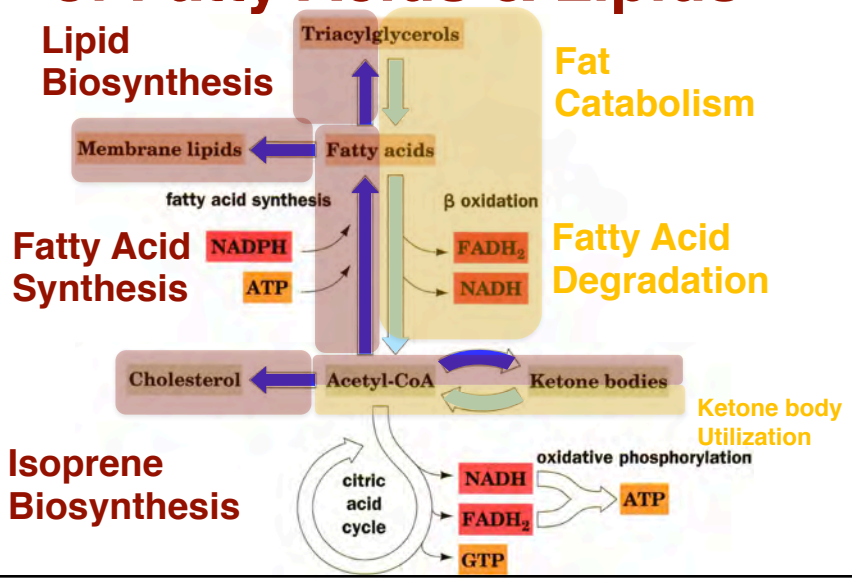
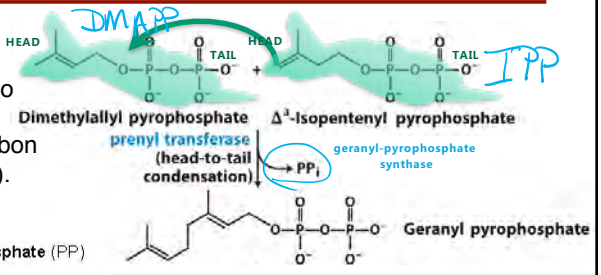
ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

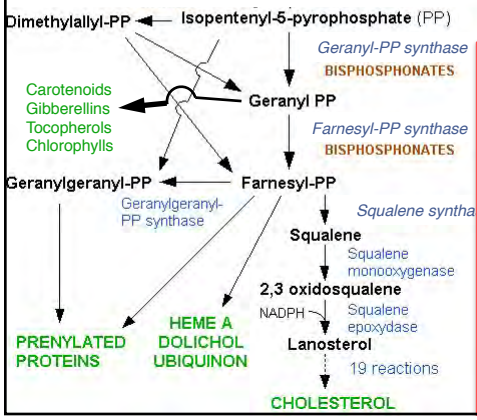


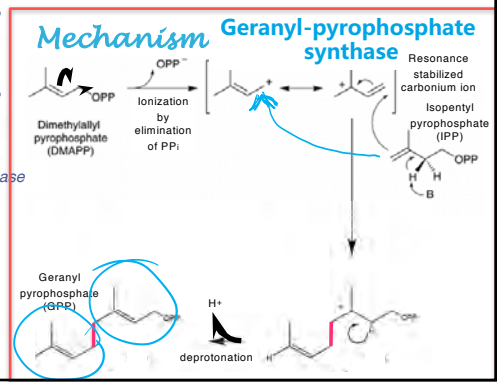
Cholesterol and Steroid Biosynthesis

Joining Isoprenes

- The two isoprenes join head to tail, displacing one set of diphosphates, forming 10-carbon geranyl pyrophosphate (GPP).

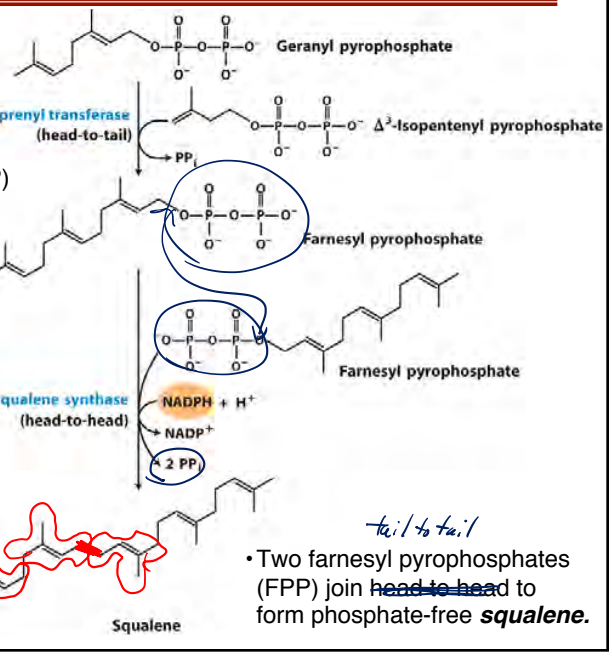






Cholesterol and Steroid Biosynthesis

Formation of S(



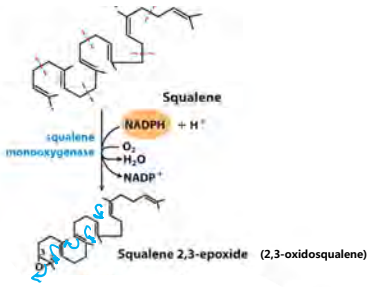
- Geranyl pyrophosphate (GPP) joins to another isopentenyl pyrophosphate.
  → forms 15-C ***farnesyl pyrophosphate***

- Two farnesyl pyrophosphates (FPP) join ~~head-to-head~~ to form phosphate-free ***squalene.***

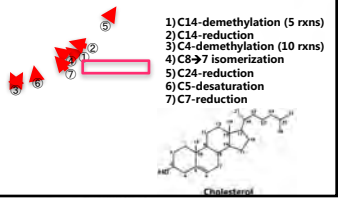
Cholesterol and Steroid Biosynthesis

Synthesis of Cholesterol

Conversion of Squalene to Four-Ring Steroid Nucleus



- Squalene monooxygenase (squalene epoxidase) adds one oxygen to the end of the squalene chain.
  → forms squalene 2,3-epoxide
- Here, pathways diverge in animal cells *versus* plant cells.
- In plants, the epoxide cyclizes to other sterols, such as stigmasterol.
- In fungi, it forms ergosterol.
- The cyclization product in animals is lanosterol, which converts to cholesterol.



Cholesterol and Steroid Biosynthesis

Synthesis of Cholesterol

Conversion of Squalene to Four-Ring Steroid Nucleus

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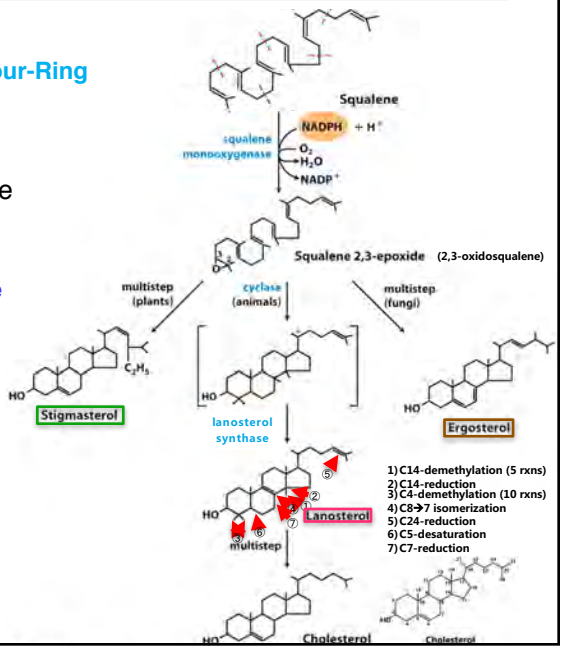
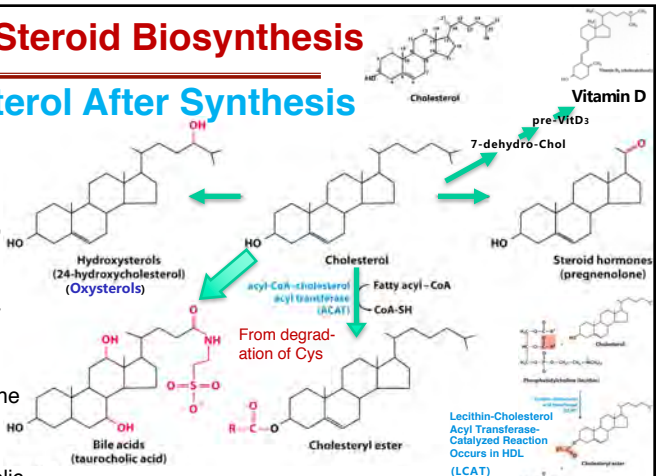


Cholesterol and Steroid Biosynthesis

Fates of Cholesterol After Synthesis

- In vertebrates, most cholesterol is synthesized in the liver, then exported.
  - –They are exported as bile acids, biliary cholesterol, or cholesteryl esters.
  - –Bile is stored in the gall bladder and secreted into the small intestine after fatty meal.
  - –Bile acids such as taurocholic acid emulsify fats.
  - –They surround droplets of fat, increasing surface area for attack by lipases.
- Other tissues convert cholesterol into steroid hormones and Vitamin D

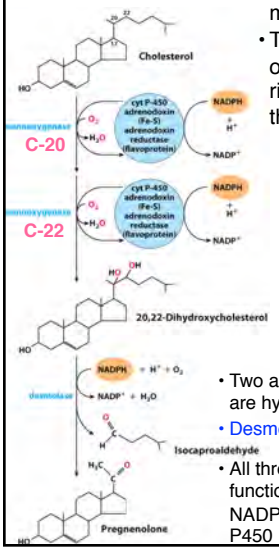


- Adrenal gland-synthesized steroids:
  - – mineralcorticoids
    - control electrolyte balance, reabsorption of Na^+, Cl^-, HCO_3^- from kidney
  - – glucocorticoids
    - regulate gluconeogenesis, reduce inflammation
- Gonad-synthesized steroids:
  - – progesterone, testosterone, estrogens

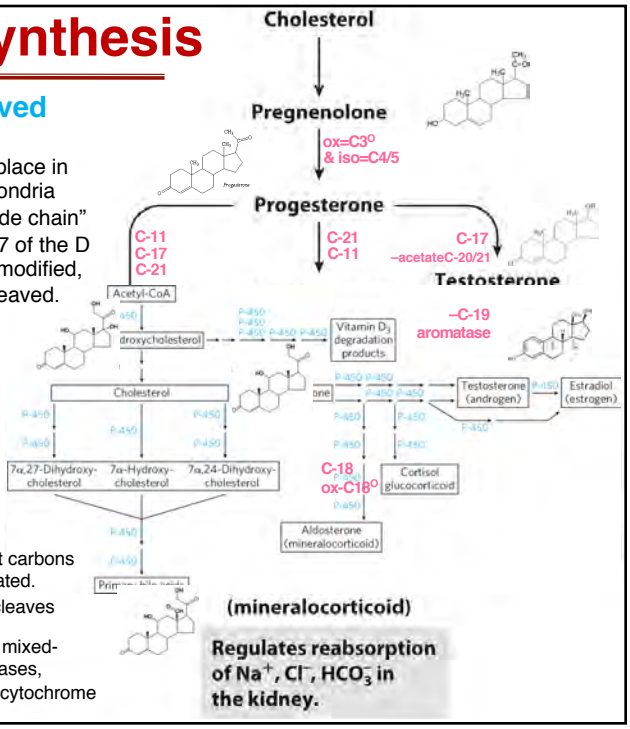
Steroid Biosynthesis

Steroid Hormones Derived from Cholesterol

- Takes place in mitochondria
- The "side chain" on C-17 of the D ring is modified, then cleaved.



- Two adjacent carbons are hydroxylated.
- Desmolase cleaves
- All three use mixed-function oxidases, NADPH and cytochrome P450



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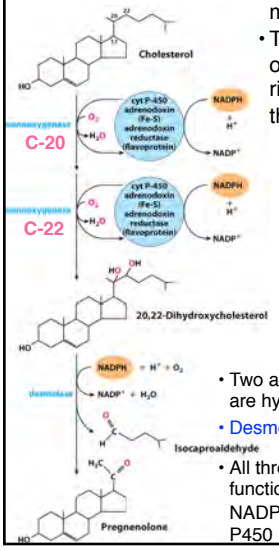

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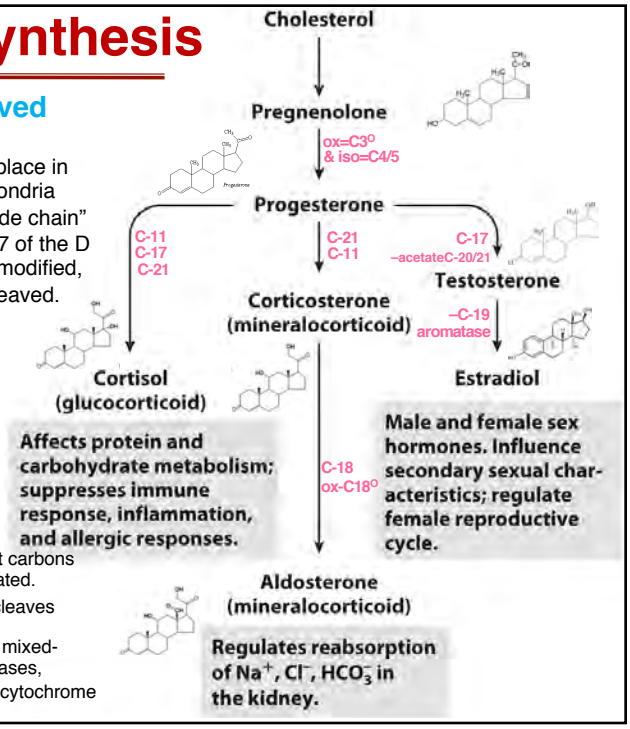


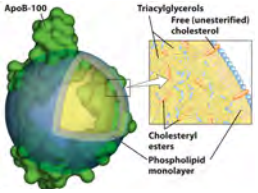
Cholesterol and Steroid Biosynthesis

TABLE 21-1 Major Classes of Human Plasma Lipoproteins: Some Properties

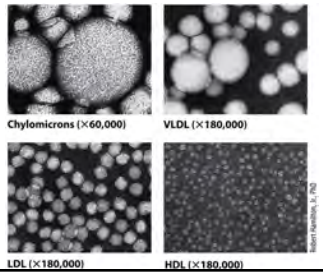
Lipoprotein	Density (g/ml)	Composition (wt %)				
		Protein	PL	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2 (ApoB-48,-E,-CII)	9	1	3	85
VLDL	0.95–1.006	10 (ApoC-I,CII)	18	7	12	50
LDL	1.006–1.063	23 (ApoB-100)	20	8	37	10
HDL	1.063–1.210	55 (ApoA-I,-II)	24	2	15	4

Source: Data from D. Kritchevsky, *Nutr. Int.* 2:290, 1986.

- Lipids are carried through the plasma on spherical particles.
  - –surface is made of protein (called apolipoprotein*) and a phospholipid monolayer
  - –interior contains cholesterol, TAGs, and cholesteryl esters, which are more nonpolar than cholesterol



*"apolipoprotein" refers to the protein part of a lipoprotein particle.



- Named based on position of sedimentation (density) in centrifuge
- Composition varies between class of lipoprotein
- Includes four major classes shown in Table

Cholesterol and Steroid Biosynthesis

Biological Roles and Characteristics of Lipoproteins

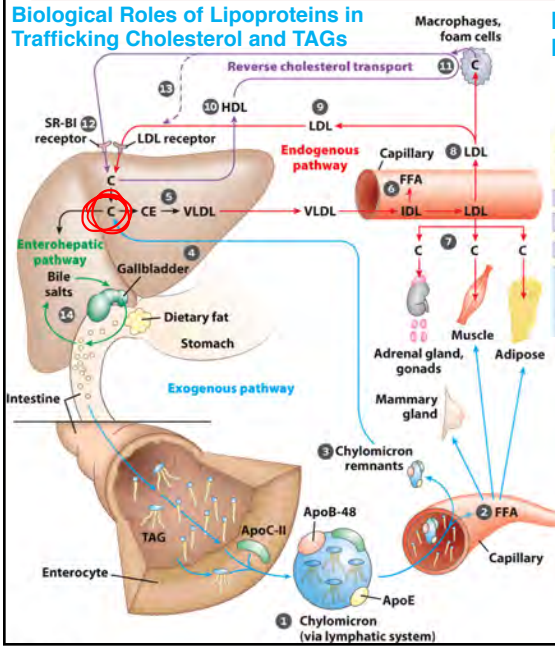
TABLE 21-2 Apolipoproteins of the Human Plasma Lipoproteins

Apolipoprotein	Polypeptide molecular weight	Lipoprotein association	Function (if known)
ApoA-I	28,100	HDL	Activates LCAT; interacts with ABC transporter
ApoA-II	17,400	HDL	Inhibits LCAT
ApoA-IV	44,500	Chylomicrons, HDL	Activates LCAT; cholesterol transport/clearance
ApoB-48	242,000	Chylomicrons	Cholesterol transport/clearance
ApoB-100	512,000	VLDL, LDL	Binds to LDL receptor
ApoC-I	7,000	VLDL, HDL	
ApoC-II	9,000	Chylomicrons, VLDL, HDL	Activates lipoprotein lipase
ApoC-III	9,000	Chylomicrons, VLDL, HDL	Inhibits lipoprotein lipase
ApoD	32,500	HDL	
ApoE	34,200	Chylomicrons, VLDL, HDL	Triggers clearance of VLDL and chylomicron remnants
ApoH	50,000	Possibly VLDL, binds cardiolipin	Roles in coagulation, lipid metabolism, apoptosis, inflammation

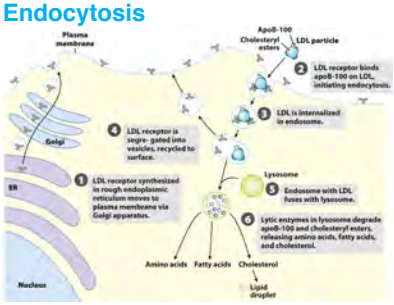
Source: Information from D. E. Vance and J. E. Vance (eds), *Biochemistry of Lipids and Membranes*, 5th edn, Elsevier Science Publishing, 2008.

Cholesterol and Steroid Biosynthesis

Biological Roles of Lipoproteins in Trafficking Cholesterol and TAGs



Receptor-Mediated Endocytosis



IN:

- **Exogenous (diet) Pathway** ❶–❹
- **HDL Pathway** ❿–⓭

OUT:

- **Endogenous Pathway** ❺–❾
- **Enteropepatic Pathway** ⓮

Cholesterol and Steroid Biosynthesis

Chylomicrons

- Least dense of lipoproteins (contains most TAG)
- Have apoB-48, apoE, and apoC-II
- ApoC-II activates lipoprotein lipase to allow free fatty acid release for fuel in adipose tissue, heart, and skeletal muscle.
- When fats are depleted, remnants go to the liver for absorption via apoE-mediated endocytosis.

VLDL

- Contains TAG and cholesteryl esters in high concentrations
- Contain apoB-100, apoC-I, apoC-II, apoC-III, and apoE
- Again, apoC-II activates lipoprotein lipase to release free fatty acids.
- Adipocytes take up the FFAs, reconvert them to TAGs, and store them in lipid droplets.
- Muscle uses the TAG for energy.

LDL

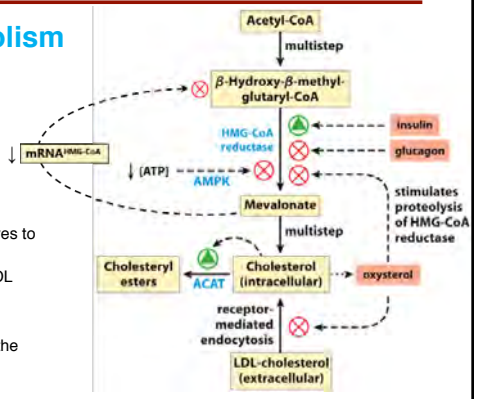
- Produced by removal of TAG from VLDL
- LDL is enriched in cholesterol/ chloesteryl esters.
- ApoB-100 is the major apolipoprotein.
- Muscle and adipose tissue have LDL receptors and recognize apoB-100.
- Myocytes and adipocytes take up cholesterol via receptor-mediated endocytosis.

HDL

- Produced from enzymatic conversion of LDL and VLDL cholesterol to cholesteryl esters
- HDLs are high in protein, including apoA-I.
- HDL picks up cholesterol from the cells and returns to liver, where it can be metabolized.
- Also catalyzes conversion of remnant cholesterol of LDL and VLDL to cholesteryl esters

Cholesterol and Steroid Biosynthesis

Regulation of Cholesterol Metabolism

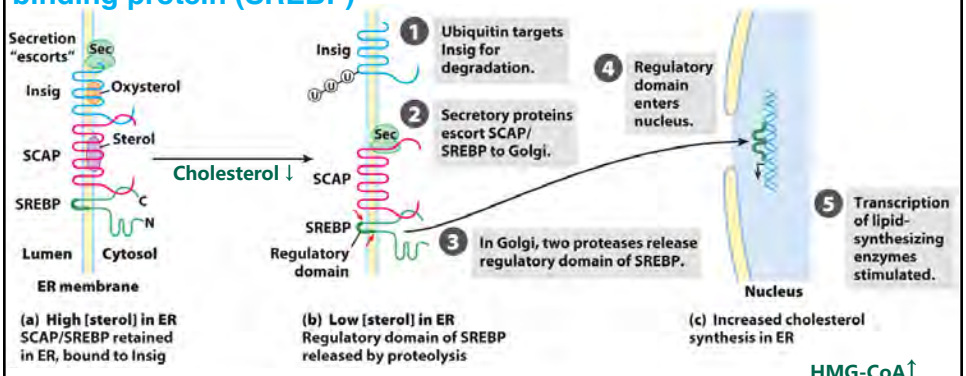


- Major regulation is by gene expression: Three levels
  - Sterol regulatory element-binding proteins (SREBPs)
    - When sterol levels are high, SREBPs are in the ER membrane with other proteins.
    - When sterol levels fall, the complex is cleaved and moves to the nucleus.
    - It activates transcription of HMG-CoA reductase and LDL receptor, as well as other genes.
  - Translational control on mRNA stability
    - Increased mevalonate and other isoprenes destabilize the HMG-CoA mRNA
  - Post-translational control
    - High cholesterol produces oxysterol, which allosterically binds HMG-CoA
    - Destabilizes by a conformational change that allows ubiquitination
    - Proteolytic degradation of HMG-CoA reductase
- Minor regulatory mechanisms: Phosphorylation/de-phosphorylation
  - Covalent modification provides short-term regulation
  - Glucagon, epinephrine
    - cascades lead to phosphorylation, ↓ activity
    - AMP-dependent protein kinase
    - also when AMP rises, kinase phosphorylates the enzyme → activity ↓, cholesterol synthesis ↓
  - Insulin: cascades lead to dephosphorylation, ↑ activity

Other effects of high cholesterol
Activation of ACAT, which increases esterification for storage
Transcriptional regulation of the LDL receptor gene activation

Cholesterol and Steroid Biosynthesis

Regulation of Cholesterol Synthesis by Sterol regulatory element-binding protein (SREBP)



HMG-CoA↑
LDL receptor↑

- Insig (***ins***ulin-***i***nduced ***g***ene ***p***rotein) senses cholesterol levels through oxysterol.
  - triggers ubiquination of HMG-CoA reductase
  - targets the enzyme for degradation by proteasomes
  - Also helps sequester SREBP in ER

Cholesterol and Steroid Biosynthesis

Summary

We learned that:

- synthesis of fatty acids is a multistep process starting from acetyl-CoA and its carboxylated product, malonyl-CoA; it uses a poly-enzyme protein
- After synthesis of palmityl-CoA, fatty acids are elongated and desaturated; PUFAs are used for prostaglandin, thromboxane, and leukotriene synthesis
- phospholipids are a precursor to TAGs
- phospholipids and TAGs are built on a glycerol backbone that can be derived from dihydroxyacetone phosphate or glycerol
- head groups are attached using one of two methods, both use CDP carrier
- pathways to the synthesis of specific head groups vary by organism and may use salvage pathways
- cholesterol is derived from isoprene units, which comes from HMG-CoA
- production of isoprene for cholesterol biosynthesis occurs via the mevalonate pathway and starts with multiple acetyl-CoA
- cholesterol can be metabolized and modified in a variety of ways
- cholesterol and TAGs are trafficked in lipoproteins; classified by density
- Regulation of lipid biosynthesis….