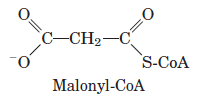
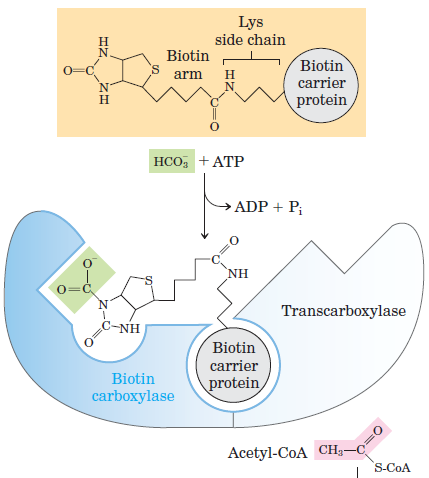
**Chapter 21** **Lipid Biosynthesis**

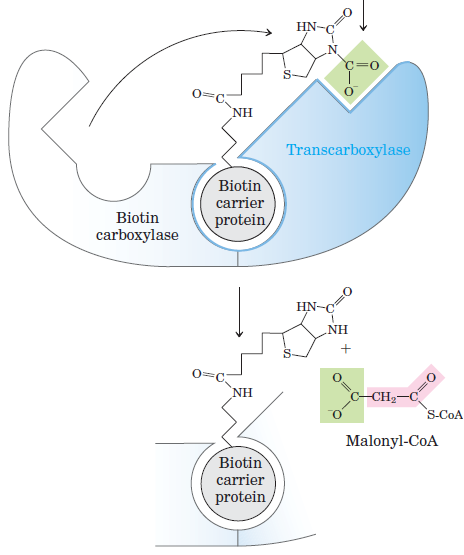
* Lipids are the principal form of stored energy in most organisms and major constituents of cellular membranes.
* Specialized lipids serve as
  + pigments (retinal, carotene),
  + cofactors (vitamin K),
  + detergents (bile salts),
  + transporters (dolichols),
  + hormones (vitamin D derivatives, sex hormones),
  + extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives),
  + anchors for membrane proteins (covalently attached fatty acids, prenyl groups, and phosphatidylinositol).
  1. **Biosynthesis of Fatty Acids**
* Fatty acid biosynthesis and breakdown occur by different pathways, are catalyzed by different sets of enzymes, and take place in different parts of the cell.
* Biosynthesis requires the participation of a three-carbon intermediate, **malonyl-CoA**, that is not involved in fatty acid breakdown.

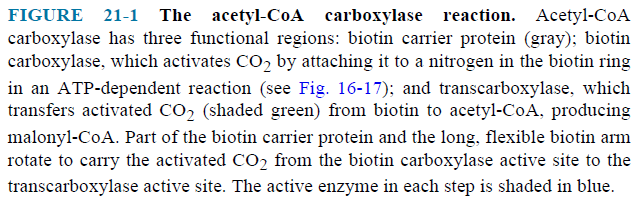


**Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate**

* The formation of malonyl-CoA from acetyl-CoA is an irreversible process, catalyzed by **acetyl-CoA carboxylase (Fig. 21–1)**.

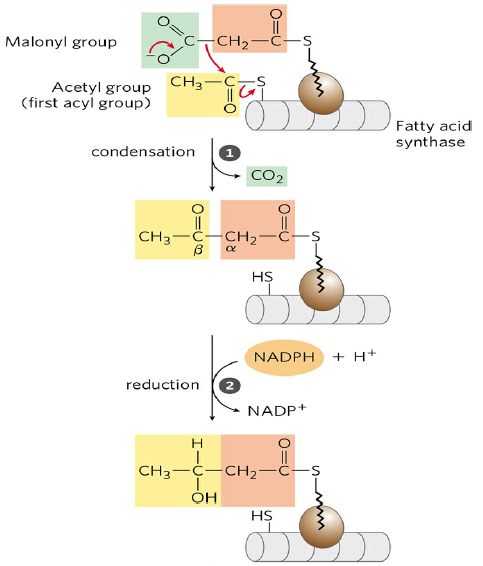


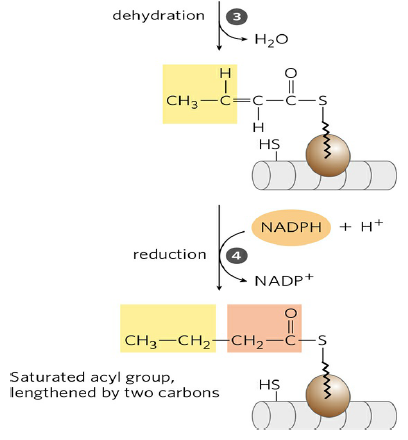


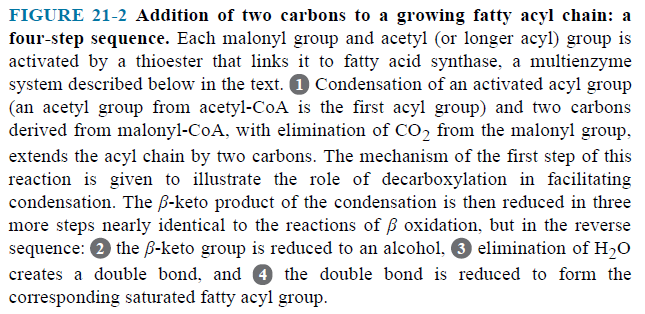


**Fatty Acid Synthesis Proceeds in a Repeating Reaction Sequence**

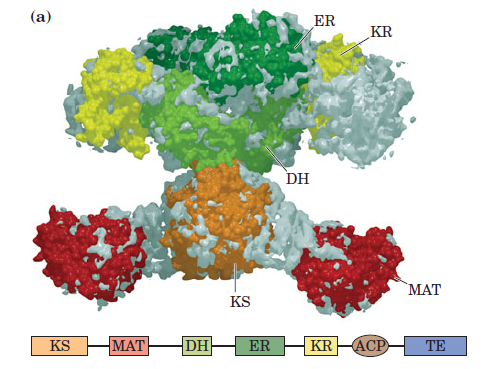
* In all organisms, the long carbon chains of fatty acids are assembled in a repeating four-step sequence, catalyzed by a system collectively referred to as **fatty acid synthase (Fig. 21–2)**.



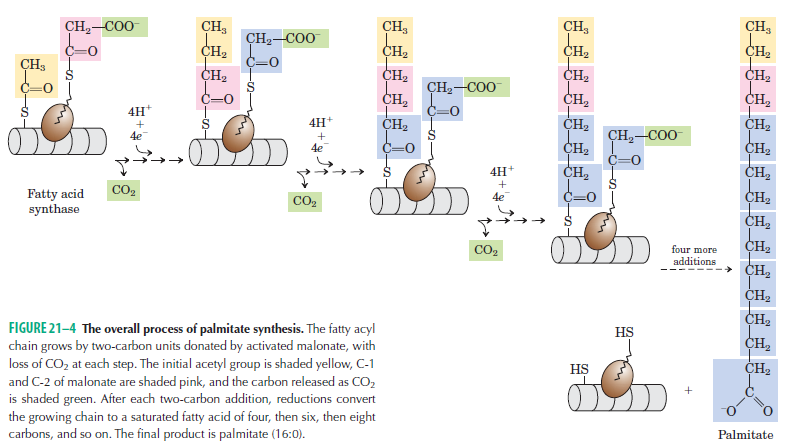




* A saturated acyl group produced by each four-step series of reactions becomes the substrate for subsequent condensation with an activated malonyl group.
* With each passage through the cycle, the fatty acyl chain is extended by two carbons.
* There are two major variants of fatty acid synthase:
* Fatty acid synthase I (FAS I), found in vertebrates and fungi,
* Fatty acid synthase II (FAS II), found in plants and bacteria.
* Seven active sites for different reactions lie in separate domains of a single polypeptide chain **(Fig. 21–3a)**.

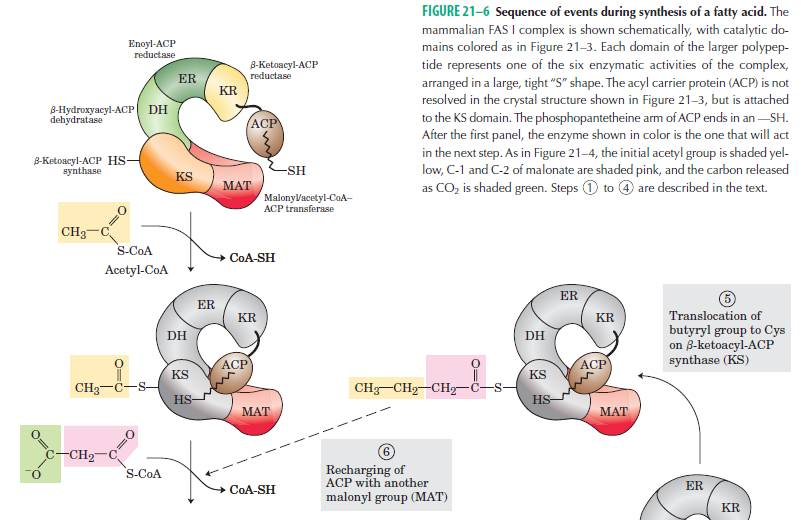
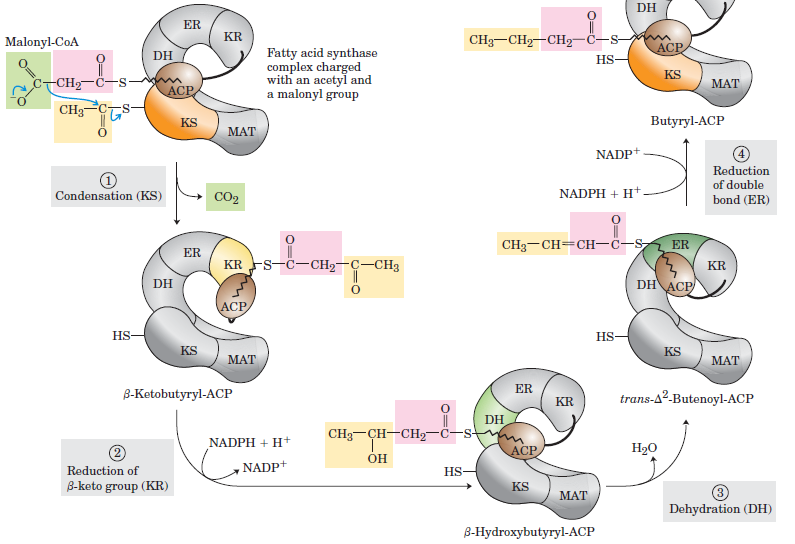


* **-ketoacyl-ACP synthase (KS),
* malonyl/acetyl-CoA–ACP transferase (MAT),
* **-hydroxyacyl-ACP dehydratase (DH),
* enoyl-ACP reductase (ER),
* **-ketoacyl-ACP reductase (KR).
* acyl carrier protein (ACP).
* thioesterase (TE)
* When the chain length reaches 16 carbons, that product (palmitate, 16:0) leaves the cycle **(Fig. 21–4)**.
* The mammalian polypeptide functions as a homodimer.
* The subunits appear to function independently.



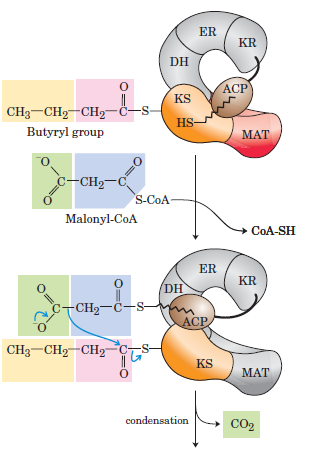
**Fatty Acid Synthase Receives the Acetyl and Malonyl Groups**

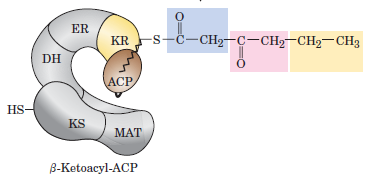
* The acetyl group of acetyl-CoA is transferred to ACP by the **malonyl /acetyl-CoA–ACP transferase** (MAT). The acetyl group is then transferred to the Cys —SH group of the ****-ketoacyl-ACP synthase** (KS) **(Fig. 21–6)**.
* Transfer of the malonyl group from malonyl-CoA to the —SH group of ACP, is also catalyzed by MAT.
* Acetyl and malonyl groups are combined to form **acetoacetyl-ACP** by KS**.**
* The acetoacetyl-ACP undergoes reduction to form -hydroxybutyryl-ACP by **-ketoacyl-ACP reductase** (KR).
* Water is removed from -hydroxybutyryl-ACP to yield trans-2-butenoyl-ACP by **-hydroxyacyl-ACP** dehydratase (DH).
* Trans-2-butenoyl-ACP is reduced (saturated) to form butyryl-ACP by **enoyl-ACP reductase** (ER).

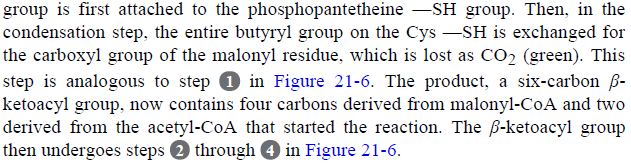
 

**The Fatty Acid Synthase Reactions Are Repeated to Form Palmitate**

* The butyryl group is transferred from the —SH group of ACP to the —SH group of **-ketoacyl-ACP synthase**.
* To start the next cycle of four reactions that lengthens the chain by two more carbons, another malonyl group is linked to the —SH group of ACP by **MAT (Fig. 21–7)**.
* After condensation, the product is a six-carbon acyl group.
* Seven cycles of condensation and reduction produce the 16-carbon saturated palmitoyl group, still bound to ACP.
* Free palmitate is released from the ACP by **thioesterase** (TE) in the multifunctional protein.





* The overall reaction for the synthesis of palmitate from acetyl-CoA is in two parts.
* The formation of seven malonyl-CoA molecules:

7 Acetyl-CoA + 7 CO2 + 7 ATPS  7 malonyl-CoA + 7 ADP + 7 Pi

* The seven cycles of condensation and reduction:

Acetyl-CoA + 7 malonyl-CoA + 14 NADPH +14 H+

palmitate + 7 CO2 + 8 CoA + 14 NADP+ + 6 H2O

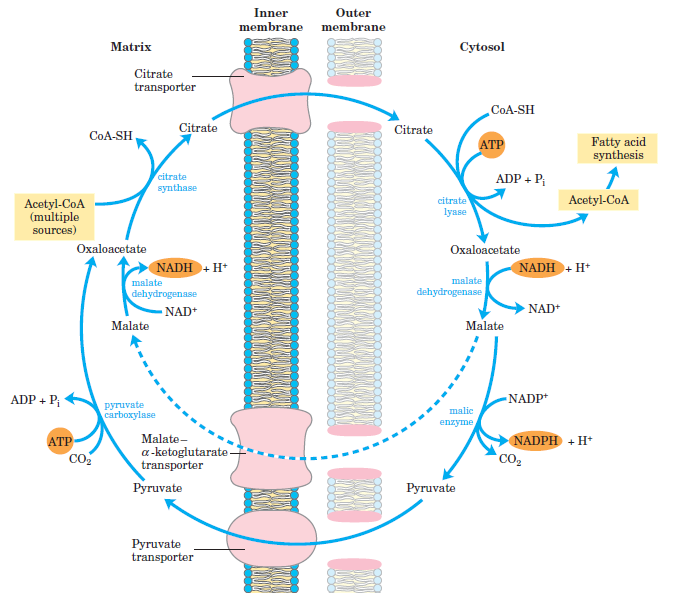
* Only six net water molecules are produced, because one is used to hydrolyze the thioester linking the palmitate product.
* The overall process is

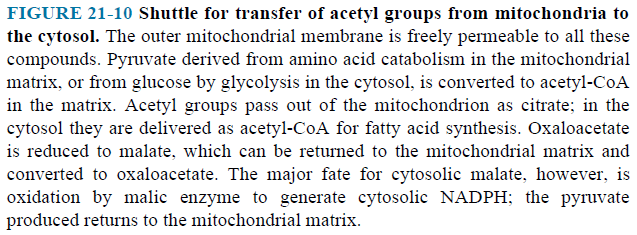
8 Acetyl-CoA + 7 ATP + 14 NADPH + 14 H+

palmitate + 8 CoA + 7 ADP + 7 Pi + 14 NADP+ + 6H2O

**Acetate Is Shuttled out of Mitochondria as Citrate**

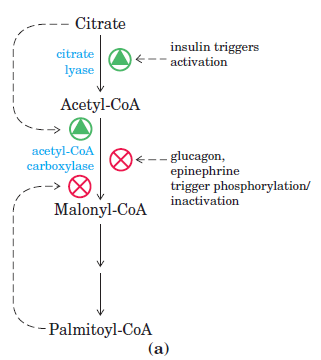
* In nonphotosynthetic eukaryotes, nearly all the acetyl-CoA used in fatty acid synthesis is formed in mitochondria from pyruvate oxidation and from the catabolism of the carbon skeletons of amino acids.
* Acetyl-CoA is generated in the mitochondria and must be transported to the cytosol.
* Mitochondrial acetyl-CoA first reacts with oxaloacetate to form citrate, in the citric acid cycle reaction catalyzed by **citrate synthase (Fig. 21–10)**.
* Citrate then passes through the inner membrane on the **citrate transporter**.
* In the cytosol, citrate cleavage by **citrate lyase** regenerates acetyl-CoA and oxaloacetate.

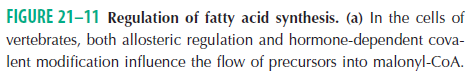




**Fatty Acid Biosynthesis Is Tightly Regulated**

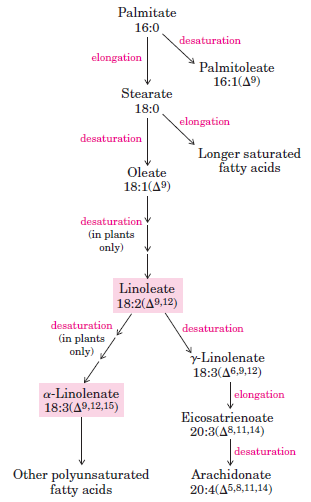
* The reaction catalyzed by acetyl-CoA carboxylase is the rate-limiting step in the biosynthesis of fatty acids, and this enzyme is an important site of regulation.
* In vertebrates,
* Palmitoyl-CoA, glucagon and epinephrine are inhibitor
* Citrate is activator **(Fig. 21–11a)**.

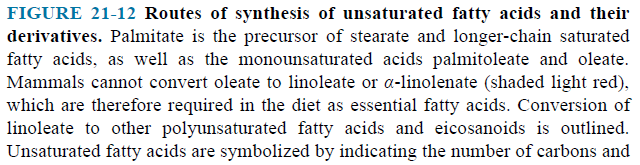




**Long-Chain Saturated Fatty Acids Are Synthesized from Palmitate**

* Palmitate (16:0) is the precursor of other long-chain fatty acids **(Fig. 21–12)**.
* Palmitoleate (16:1), stearate (18:0), oleate (18:1), linoleate (18:2) are synthesized from palmitate.
* Mammals cannot make linoleate and must obtain it from plant sources.

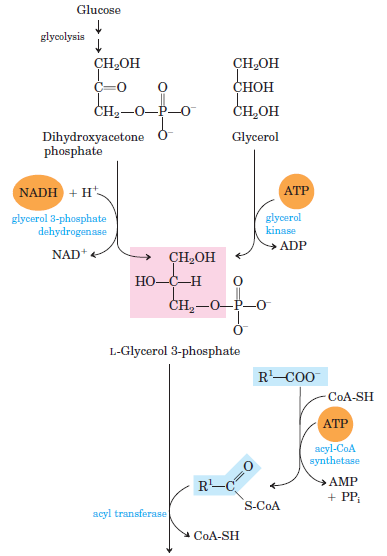




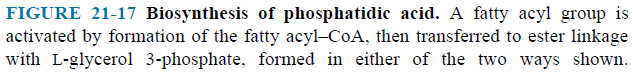
* 1. **Biosynthesis of Triacylglycerols**
* Most of the fatty acids have one of two fates:
* incorporation into triacylglycerols for the storage of metabolic energy
* incorporation into the phospholipid components of membranes.
* Both pathways begin at the same point: the formation of fatty acyl esters of glycerol.

**Triacylglycerols and Glycerophospholipids Are Synthesized from the Same Precursors**

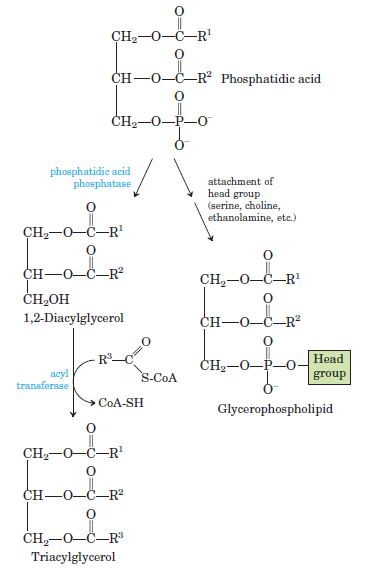
* Animals can synthesize and store large quantities of triacylglycerols, to be used later as fuel.
* Humans can store only a few hundred grams of glycogen in liver and muscle (230 g), barely enough to supply the body’s energy needs for 12 hours.
* In contrast, the total amount of stored triacylglycerol in a 70-kg man of average build is about 15 kg, enough to support basal energy needs for as long as 12 weeks.
* Triacylglycerols have the highest energy content of all stored nutrients.
* The excess of carbohydrate is converted to triacylglycerols and stored in adipose tissue.
* Glycerol 3-phosphate is derived from the dihydroxyacetone phosphate by the **glycerol 3-phosphate dehydrogenase**; a small amount of glycerol 3-phosphate is also formed from glycerol by the **glycerol kinase (Fig. 21–17)**.
* Fatty acyl–CoAs are formed from fatty acids by **acyl-CoA synthetases**.
* The first stage in the biosynthesis of triacylglycerols is the acylation of the two free hydroxyl groups of glycerol 3-phosphate by two molecules of fatty acyl–CoA to yield **diacylglycerol 3-phosphate**, more commonly called **phosphatidic acid**.







* Phosphatidic acid can be converted either to a triacylglycerol or to a glycerophospholipid **(Fig. 21–18)**.
* In the pathway to triacylglycerols, phosphatidic acid is hydrolyzed by **phosphatidic acid phosphatase** to form a 1,2-diacylglycerol.
* Diacylglycerols are then converted to triacylglycerols by transesterification with a third fatty acyl–CoA.

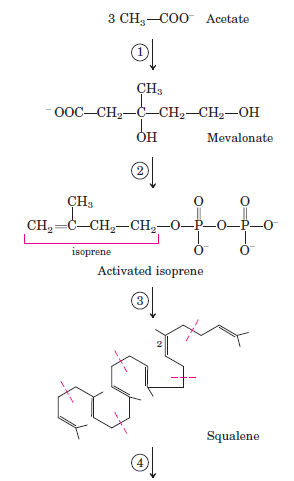


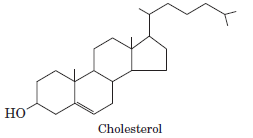


* 1. **Cholesterols Biosynthesis**
* The structure of the 27-carbon cholesterol is formed from acetyl-CoA in a complex series of reactions,
* Bile acids and steroid hormones are derived from cholesterol.

**Cholesterol Is Made from Acetyl-CoA in Four Stages**

1. Condensation of three acetate units (3 acetyl-CoA) to form a six-carbon intermediate, mevalonate **(Fig. 21–33 and 34)**.
2. Conversion of mevalonate to activated isoprene units
3. Polymerization of six 5-carbon isoprene units to form the 30-carbon linear squalene



1. Cyclization of squalene to form the four rings of the steroid nucleus, with a further series of changes (oxidations, removal or migration of methyl groups) to produce cholesterol.

