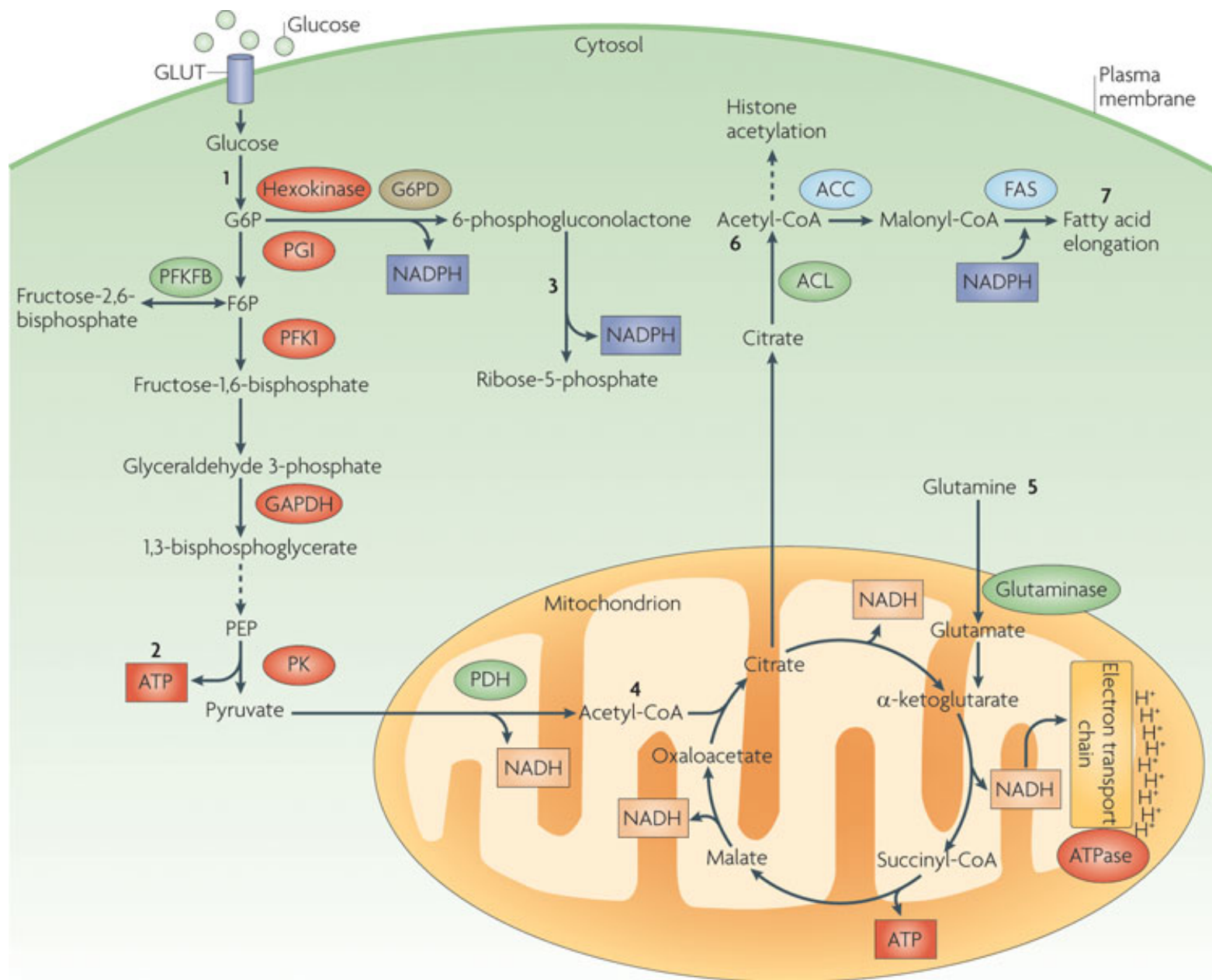
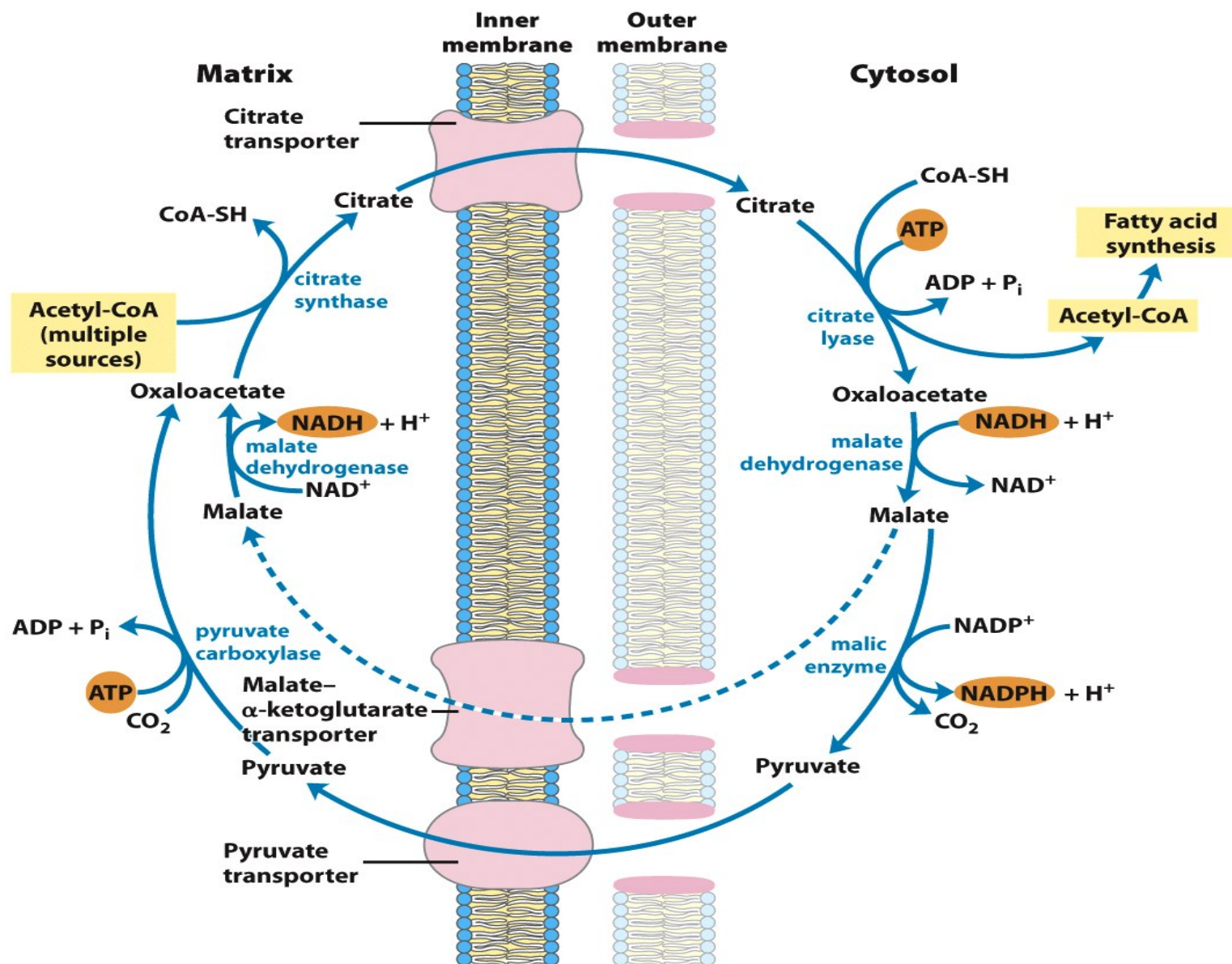


# FATTY ACID SYNTHESIS





- **Malonyl-CoA inhibits Carnitine Palmitoyl Transferase I.** Malonyl-CoA is a precursor for fatty acid synthesis. Malonyl-CoA is produced from acetyl-CoA by the enzyme **Acetyl-CoA Carboxylase**. **AMP-Activated Kinase**, a sensor of cellular energy levels, catalyzes phosphorylation of **Acetyl-CoA Carboxylase** under conditions of high AMP (when ATP is low). Phosphorylation inhibits Acetyl-CoA Carboxylase, thereby **decreasing malonyl-CoA production**. The decrease in malonyl-CoA concentration releases **Carnitine Palmitoyl Transferase I** from inhibition. The resulting increase in fatty acid oxidation generates acetyl-CoA for entry into Krebs cycle, with associated production of ATP. (See FA Oxidation).

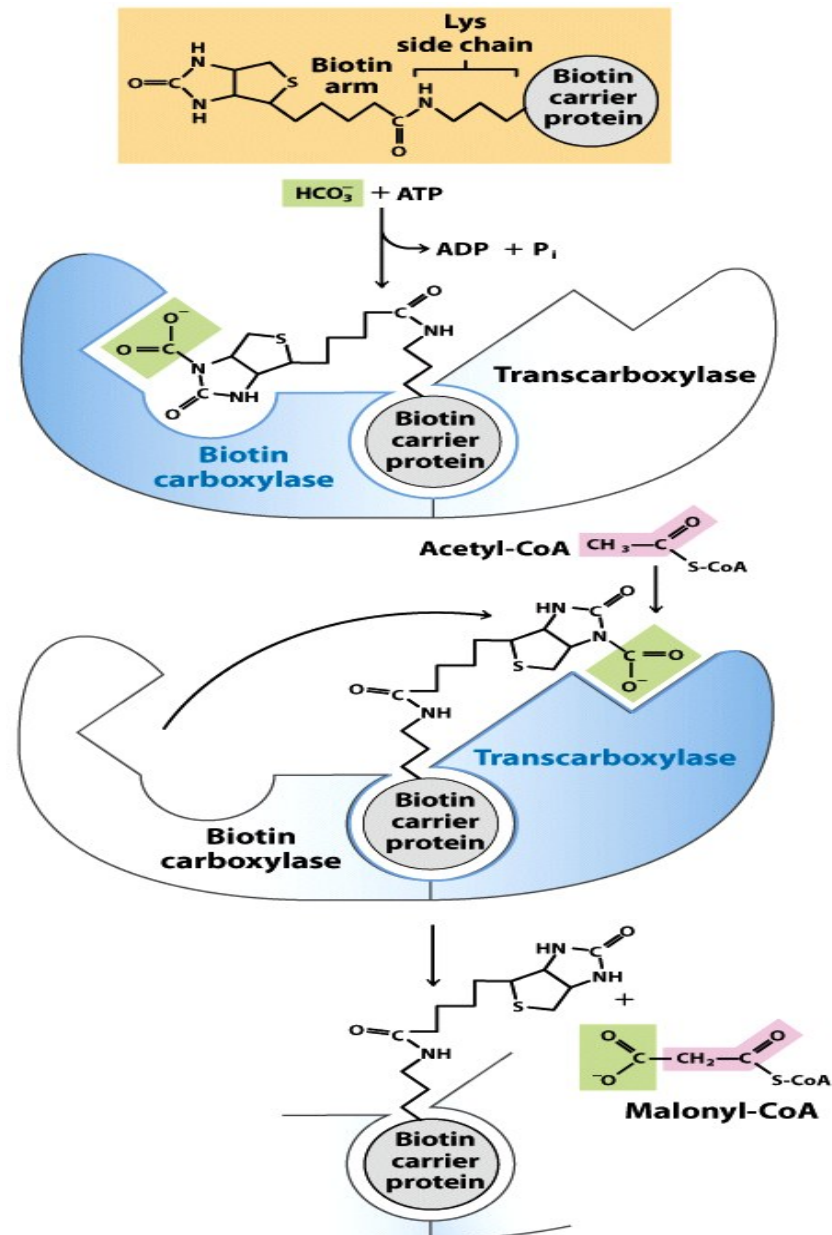
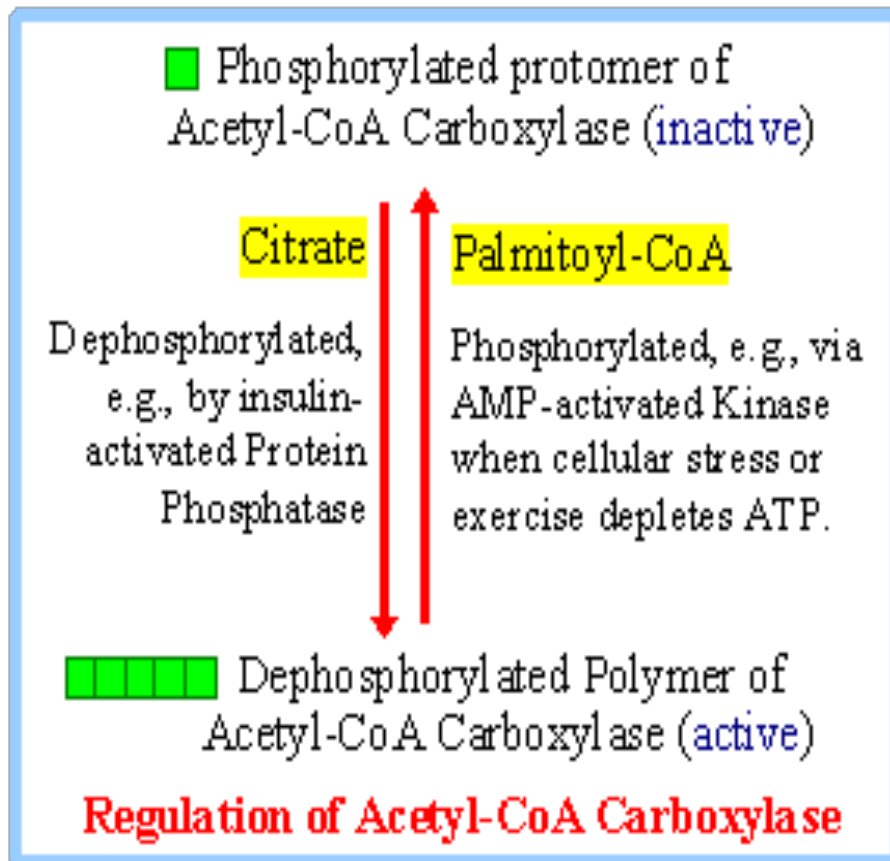


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- **Acetyl-CoA Carboxylase (ACC).** It catalyzes the 2-step reaction by which acetyl-CoA is carboxylated to form **malonyl-CoA**. As with other carboxylation reactions (e.g., **pyruvate carboxylase**), the enzyme prosthetic group is **biotin**. ATP-dependent carboxylation of the biotin, is carried out at one active site, is followed by transfer of the carboxyl group to acetyl-CoA at a second active site . The overall reaction may be summarized as;
 
$$\text{HCO}_3^- + \text{ATP} + \text{acetyl-CoA} \longrightarrow \text{ADP} + \text{Pi} + \text{malonyl-CoA}$$
- **Biotin** is linked to the enzyme by an amide bond between the terminal carboxyl of the biotin side chain and the e-amino group of a **lysine** residue. The combined biotin and lysine side chains act as a **long flexible arm** that allows the biotin ring to translocate between the 2 active sites.
- **The AAC reaction.** ACC has three functional regions: biotin carrier protein (gray); biotin carboxylase, which activates  $\text{CO}_2$  by attaching it to a nitrogen in the biotin ring in an ATP-dependent reaction; and transcarboxylase, which transfers activated  $\text{CO}_2$  (shaded green) from biotin to acetyl-CoA, producing malonyl-CoA. The long, flexible biotin arm carries the activated  $\text{CO}_2$  from the biotin carboxylase region to the transcarboxylase active site. The active enzyme in each step is shaded blue.



- Citrate activates AAC**, by promoting activation and enzyme polymerization. **[Citrate]** is high when there is adequate **acetyl-CoA** entering **TCA Cycle**. Under these conditions, excess acetyl-CoA is converted to fatty acids for storage.

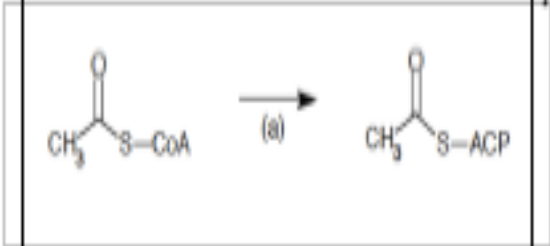
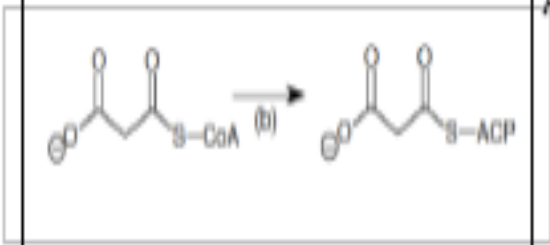
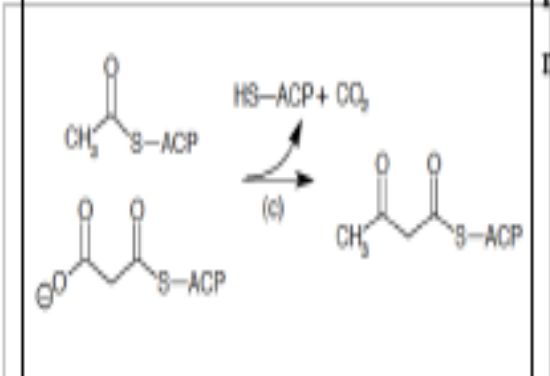


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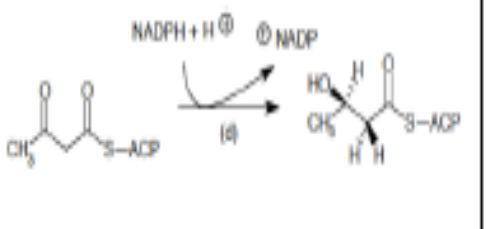
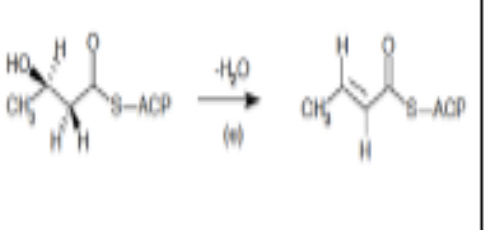
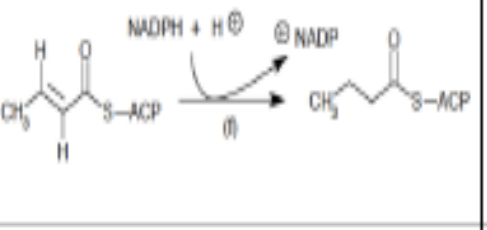
- In **bacteria** are catalyzed by six different enzymes plus a separate acyl carrier protein.
- In **mammals** are catalyzed by individual domains of a single large polypeptide that also includes an acyl-carrier protein domain. Evolution of the mammalian **Fatty Acid Synthase** apparently has involved gene fusion.

N-	Condensing Enzyme (Cys)	Malonyl/acetyl-CoA Transacylase (Ser)	Dehydratase	Enoyl Reductase	$\beta$ -Ketoacyl Reductase	ACP (Pant)	Thioesterase	-C
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Order of domains in primary structure of mammalian Fatty Acid Synthase

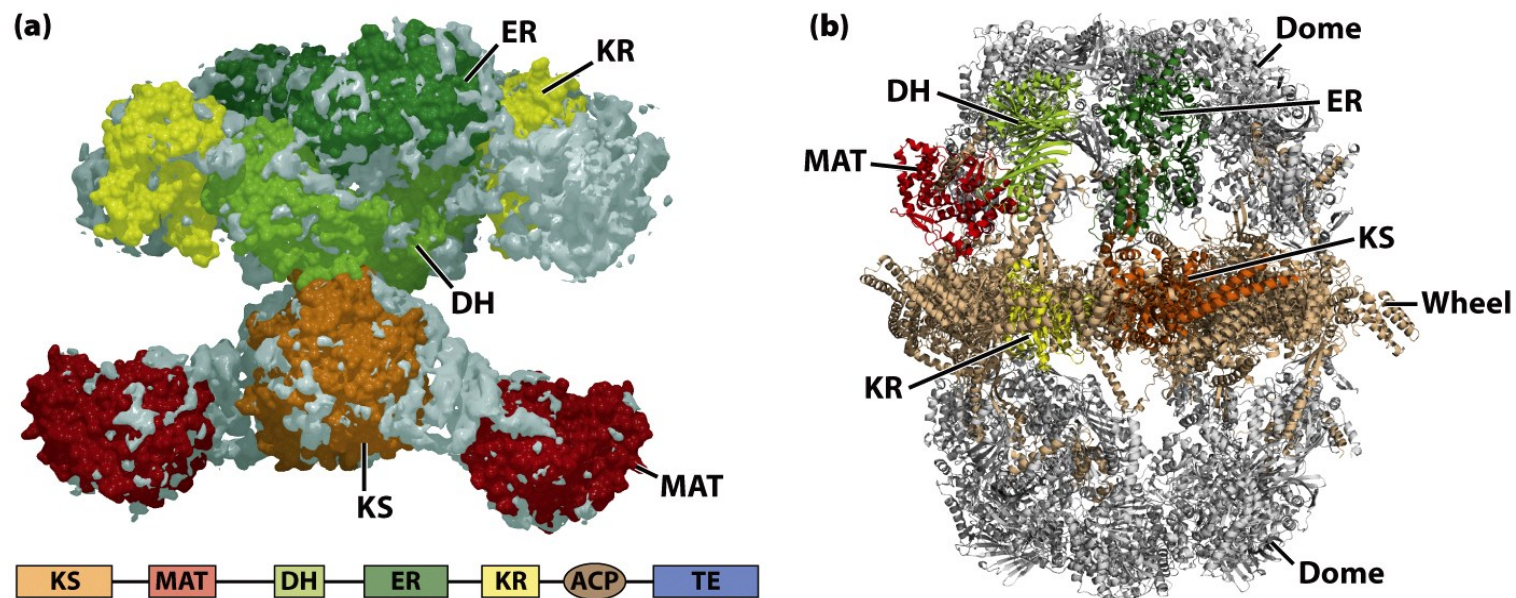
Step	Enzyme	Reaction	Description
(a)	Acetyl CoA:ACP transacylase		Activates acetyl CoA for reaction with malonyl-ACP
(b)	Malonyl CoA:ACP transacylase		Activates malonyl CoA for reaction with acetyl-ACP
(c)	3-ketoacyl-ACP synthetase		Reacts priming acetyl-ACP with chain-extending malonyl-ACP.



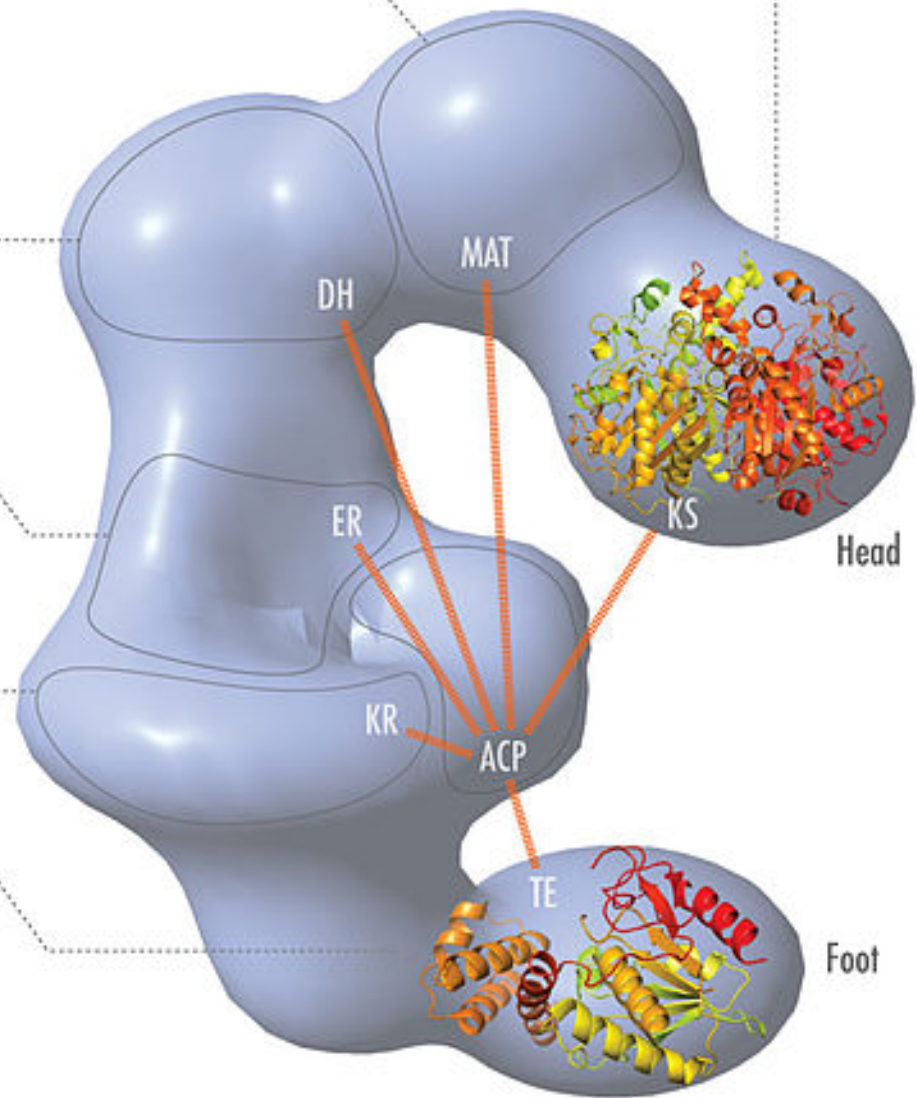
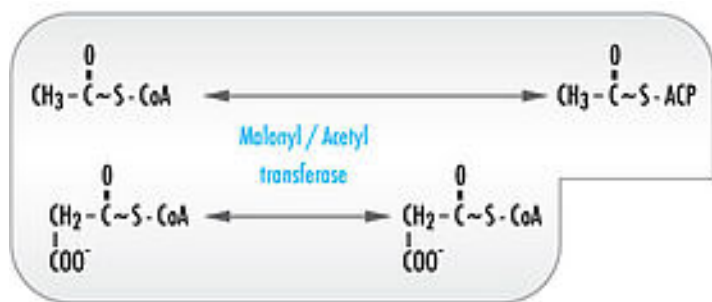
(d)	3-ketoacyl-ACP reductase		Reduces the carbon 3 ketone to a hydroxyl group
(e)	3-Hydroxyacyl ACP dehydrase		Removes water
(f)	Enoyl-ACP reductase		Reduces the C3-C4 double bond.

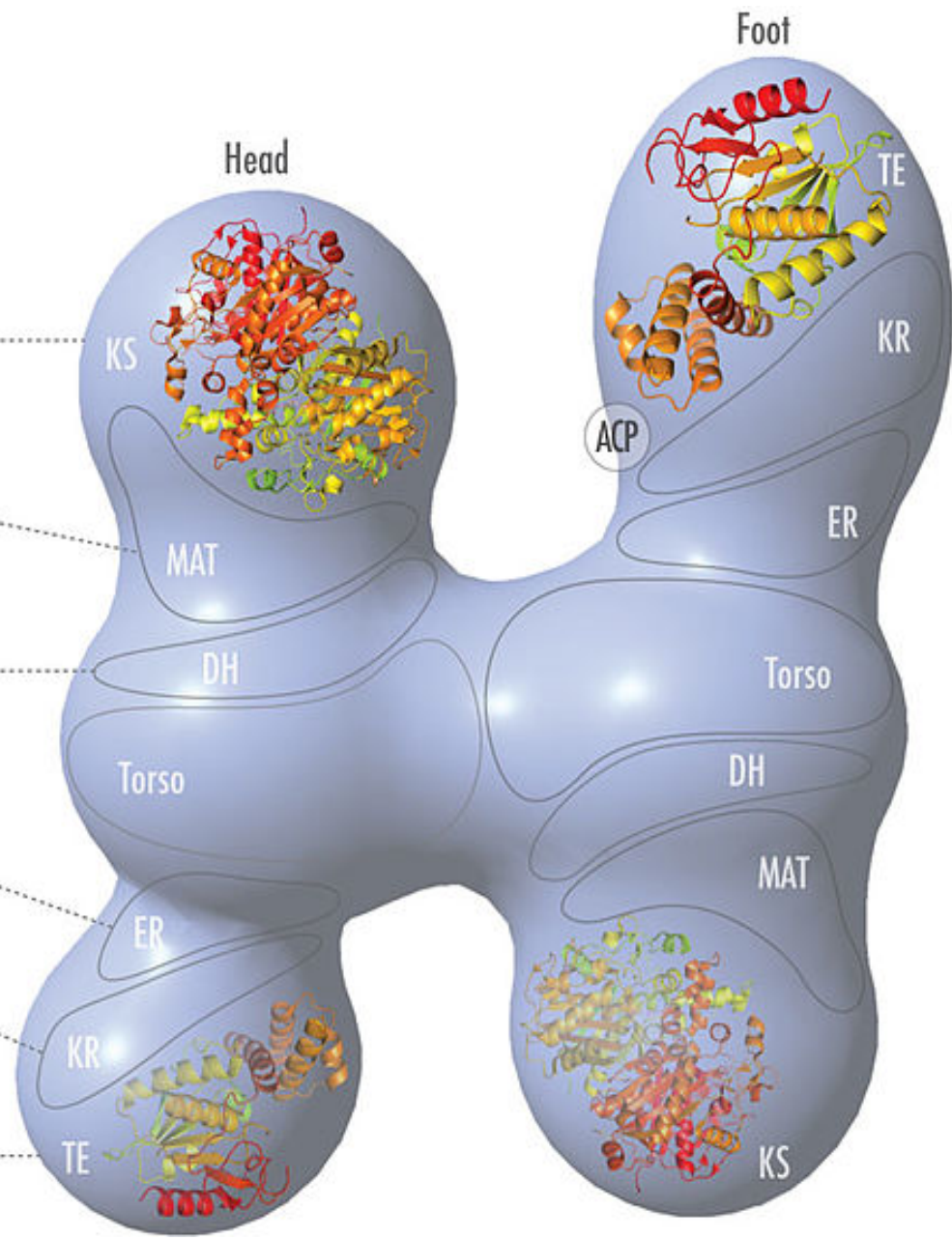
Abbreviations: ACP – Acyl carrier protein, CoA – Coenzyme A, NADP – Nicotinamide adenine dinucleotide phosphate.

**The structure of fatty acid synthase type I systems.** The low-resolution structures of **(a)** the mammalian and **(b)** fungal enzyme systems are shown. **(a)** All of the active sites in the mammalian system are located in different domains within a single large polypeptide chain. The different enzymatic activities are:  $\beta$ -ketoacyl-ACP synthase (**KS**), malonyl/acetyl-CoA—ACP transferase (**MAT**),  $\beta$ -hydroxyacyl-ACP dehydratase (**DH**), enoyl-ACP reductase (**ER**), and  $\beta$ -ketoacyl-ACP reductase (**KR**). **ACP** is the **acyl carrier protein**. The linear arrangement of the domains in the polypeptide is shown in the lower panel. The seventh domain (**TE**) is a **thioesterase** that releases the palmitate product from ACP when the synthesis is completed. The ACP and TE domains are disordered in the crystal and are therefore not shown in the structure.



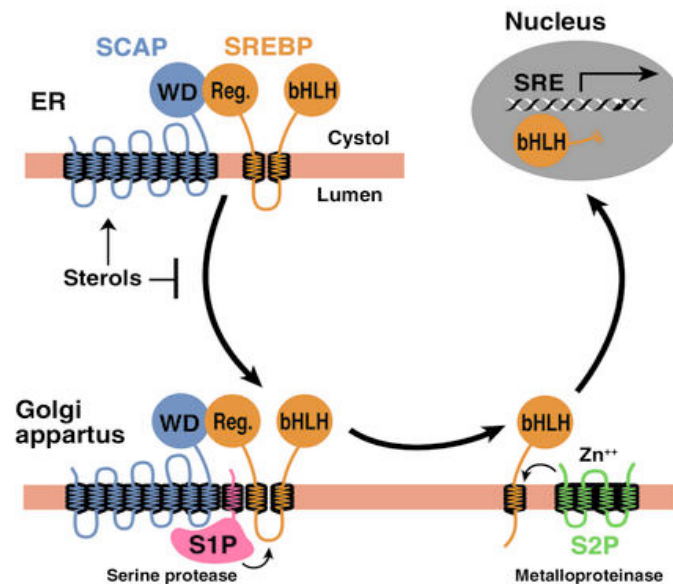
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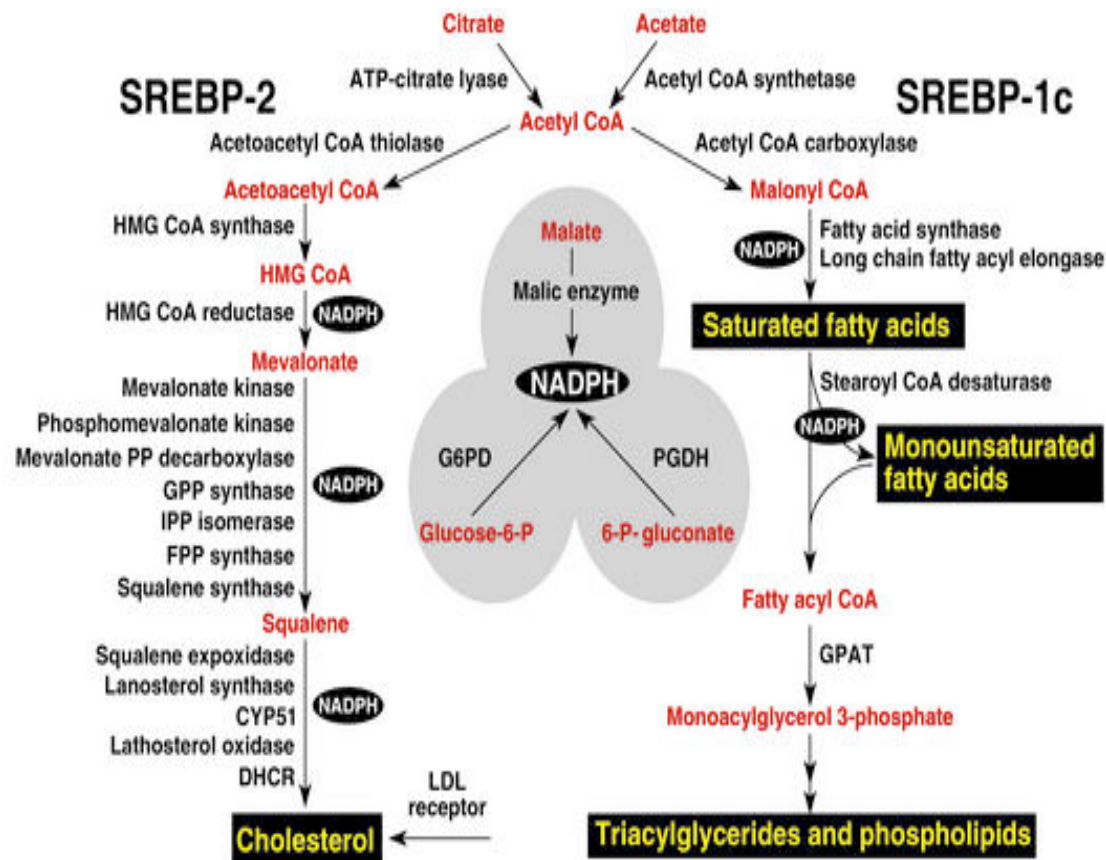
- Addition of two carbons to a growing fatty acyl chain; a four-step sequence.** Each malonyl group and acetyl (or longer acyl) group is activated by a thioester that links it to fatty acid synthase, a multienzyme system. **1.** Condensation of an activated acyl group (an acetyl group from acetyl-CoA is the first acyl group) and two carbons derived from malonyl-CoA, with elimination of  $\text{CO}_2$  from the malonyl group, extends the acyl chain by two carbons. The mechanism of the first step of this reaction is given to illustrate the role of decarboxylation in facilitating condensation. The  $\beta$ -keto product of this condensation is then reduced in three more steps nearly identical to the reactions of  $\beta$  oxidation, but in the reverse sequence: **2.** the  $\beta$ -keto group is reduced to an alcohol, **3.** elimination of  $\text{H}_2\text{O}$  creates a double bond, and **4.** the double bond is reduced to form the corresponding saturated fatty acyl group.
- Sequence of events during synthesis of a fatty acid.** The mammalian FAS I complex is shown schematically, with catalytic domains. Each domain of the larger polypeptide represents one of the six enzymatic activities of the complex, arranged in a large, tight "S" shape. The acyl carrier protein (ACP) is not resolved in the crystal structure, but is attached to the KS domain. **The phosphopantetheine arm of ACP ends in an —SH.** After the first panel, the enzyme shown in color is the one that will act in the next step. The initial acetyl group is shaded yellow, C-1 and C-2 of malonate are shaded pink, and the carbon released as  $\text{CO}_2$  is shaded green. Steps 1 to 4.



**Metabolism and homeostasis of fatty acid synthase is transcriptionally regulated by Upstream Stimulatory Factors (USF1 and USF2) and sterol regulatory element binding protein-1c (SREBP-1c) in response to feeding/insulin in living animals. Upstream stimulatory factor 1** USF-1, this gene encodes a member of the basic helix-loop-helix leucine zipper family and can function as a cellular transcription factor. The encoded protein can activate transcription through pyrimidine-rich initiator (Inr) elements and E-box motifs. This gene has been linked to familial combined hyperlipidemia (FCHL). Two transcript variants encoding distinct isoforms have been identified for this gene. **Upstream stimulatory factor 2** is a protein that in humans is encoded by the *USF2* gene. This gene encodes a member of the basic helix-loop-helix leucine zipper family, and can function as a cellular transcription factor. The encoded protein can activate transcription through pyrimidine-rich initiator (Inr) elements and E-box motifs. Two transcript variants encoding distinct isoforms have been identified for this gene. USF2 has been shown to interact with USF1 (human gene),<sup>1</sup> PPRC1 and BRCA1.

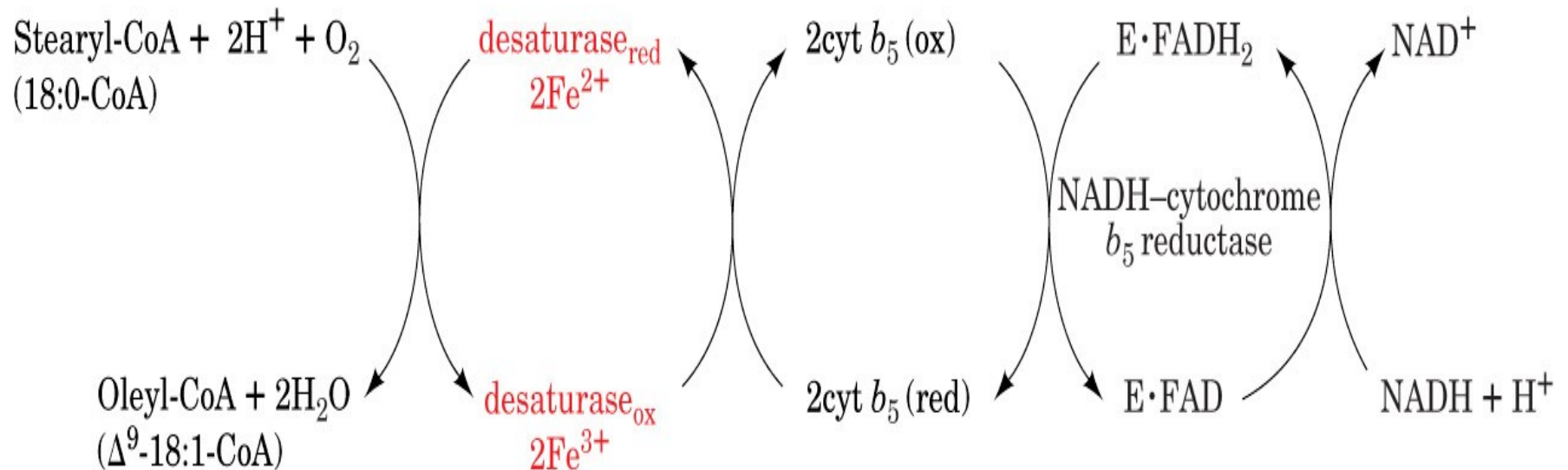


- **Sterol Regulatory Element-Binding Proteins (SREBPs)** are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Mammalian SREBPs are encoded by the genes SREBF1 and SREBF2. SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors. Unactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes. In cells with low levels of sterols, SREBPs are cleaved to a water soluble N-terminal domain that is translocated to the nucleus. These activated SREBPs then bind to specific sterol regulatory element DNA sequences, thus upregulating the synthesis of enzymes involved in sterol biosynthesis. Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feed back loop.
- **Genes regulated by SREBPs.** The diagram shows the major metabolic intermediates in the pathways for synthesis of cholesterol, fatty acids, and triglycerides. In vivo, SREBP-2 preferentially activates genes of cholesterol metabolism, whereas SREBP-1c preferentially activates genes of fatty acid and triglyceride metabolism. DHCR, 7-dehydrocholesterol reductase; FPP, farnesyl diphosphate; GPP, geranylgeranyl pyrophosphate synthase; CYP51, lanosterol 14 $\alpha$ -demethylase; G6PD, glucose-6-phosphate dehydrogenase; PGDH, 6-phosphogluconate dehydrogenase; GPAT, glycerol-3-phosphate acyltransferase.



Genes regulated by SREBPs. The diagram shows the major metabolic intermediates in the pathways for synthesis of cholesterol, fatty acids, and triglycerides. In vivo, SREBP-2 preferentially activates genes of cholesterol metabolism, whereas SREBP-1c preferentially activates genes of fatty acid and triglyceride metabolism. DHCR, 7-dehydrocholesterol reductase; FPP, farnesyl diphosphate; GPP, geranylgeranyl pyrophosphate synthase; CYP51, lanosterol 14 $\alpha$ -demethylase; G6PD, glucose-6-phosphate dehydrogenase; PGDH, 6-phosphogluconate dehydrogenase; GPAT, glycerol-3-phosphate acyltransferase.

**Desaturases** introduce **double bonds** at specific positions in a fatty acid chain. Mammalian cells are unable to produce double bonds at certain locations, e.g., D12. Thus some polyunsaturated fatty acids are dietary essentials, e.g., linoleic acid, 18:2 cis D9,12 (18 carbon atoms long, with cis double bonds at carbons 9-10 & 12-13). Formation of a double bond in a fatty acid involves the following endoplasmic reticulum membrane proteins in mammalian cells: • **NADH-cyt b5 Reductase**, a flavoprotein with **FAD** as prosthetic group. • **Cytochrome b5**, which may be a separate protein or a domain at one end of the desaturase. • **Desaturase**, with an active site that contains **two iron atoms** complexed by histidine residues. The desaturase catalyzes a **mixed function oxidation** reaction. There is a **4-electron** reduction of **O<sub>2</sub>** to form **2 H<sub>2</sub>O** as a fatty acid is oxidized to form a double bond. **Two electrons** pass from **NADH** to the desaturase via the FAD-containing reductase and cytochrome b5, the order of electron transfer being: **NADH + FAD + cyt b5 desaturase**. **Two electrons** are extracted from the **fatty acid** as the double bond is formed.



**A comparison of fatty acid  $\beta$ -oxidation and fatty acid biosynthesis.** The biosynthesis and oxidation enzymology are the same, but a reversal of each pathway. This is the major reason for the compartmentation and control mechanisms.

