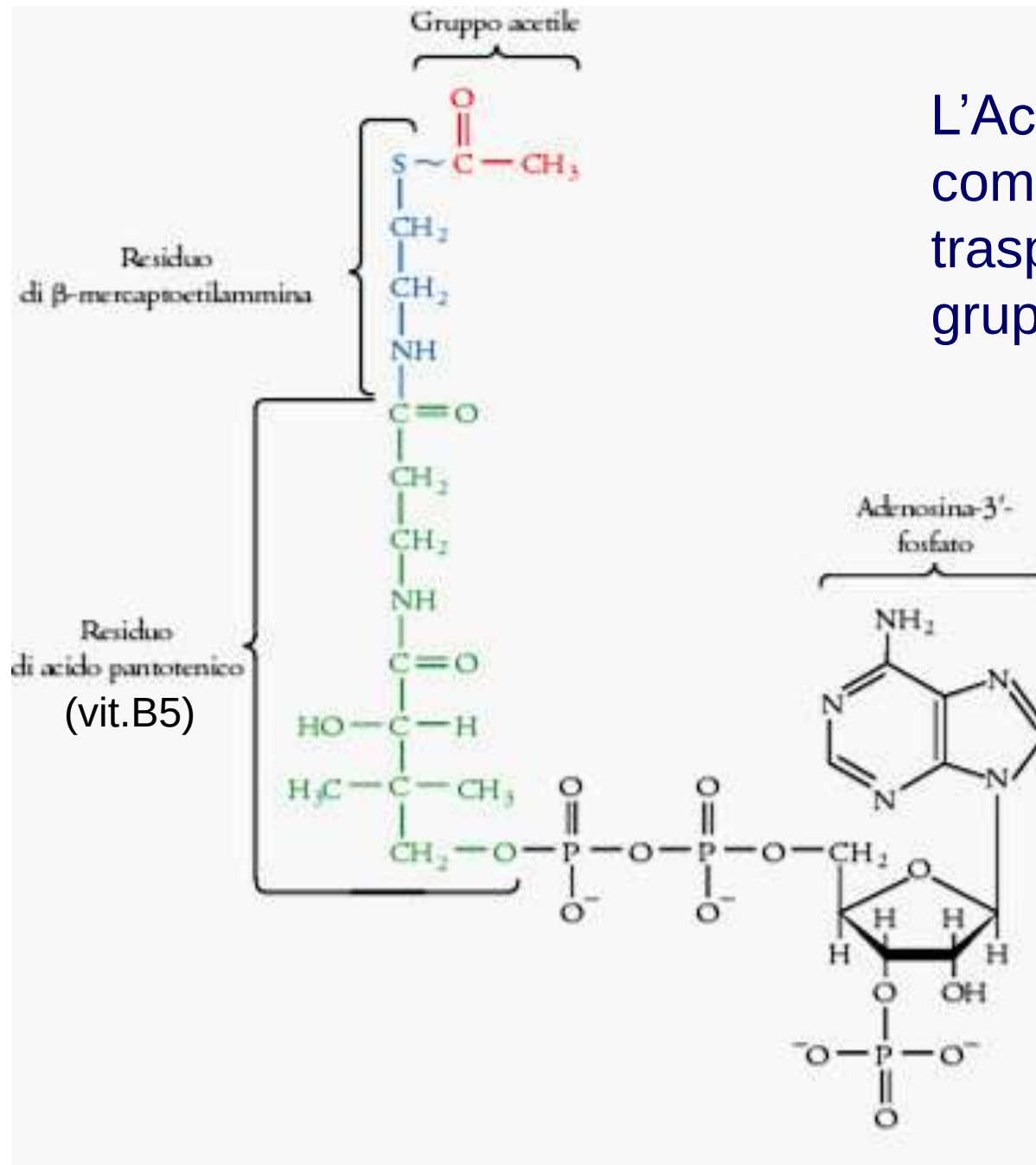


Biosintesi degli acidi grassi

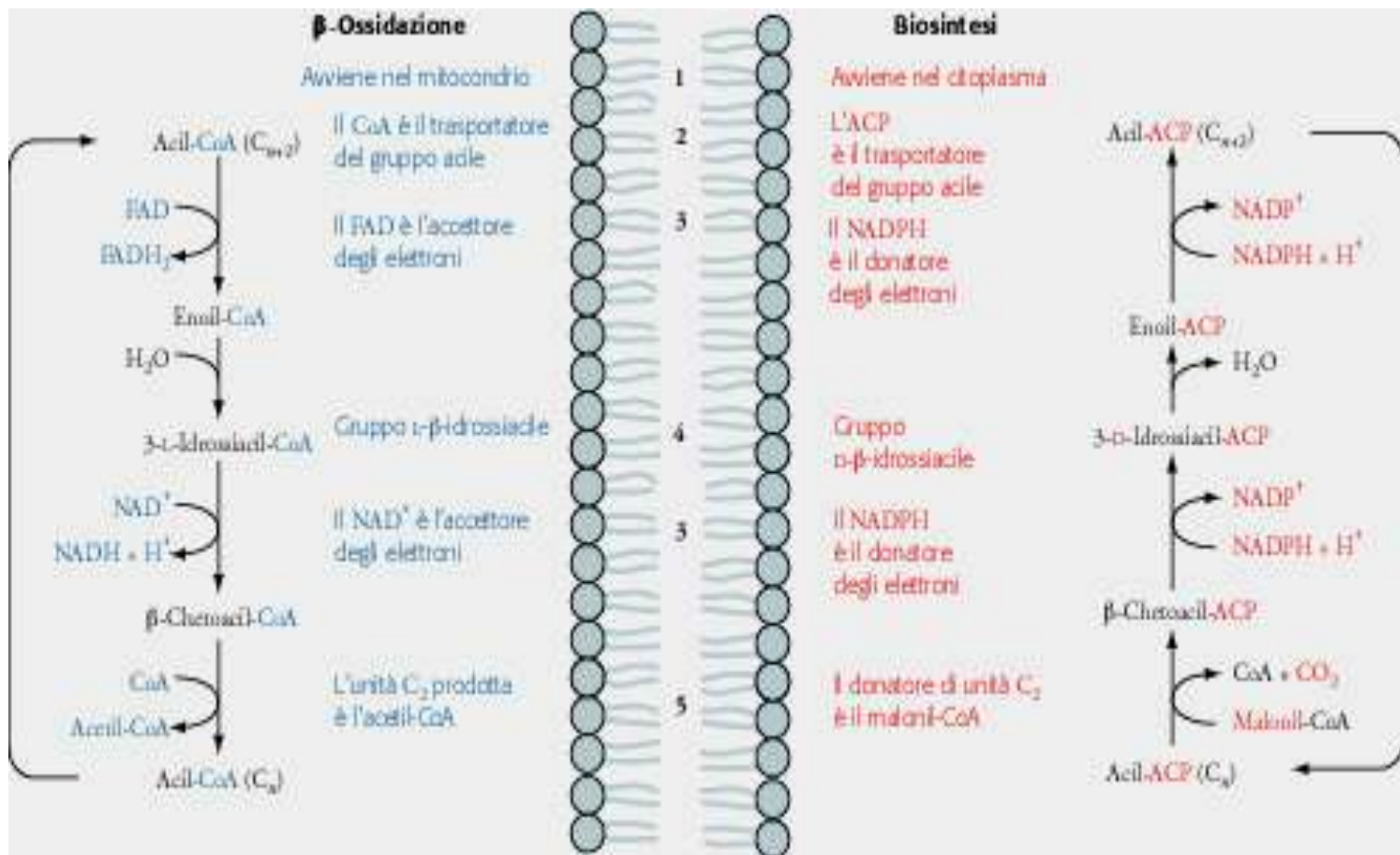
Gli acidi grassi provengono per la maggior parte dalla dieta. Tuttavia, se presenti in **eccesso**, **carboidrati e proteine possono venire convertiti ad acidi grassi**. Questi vengono poi immagazzinati sotto forma di trigliceridi.

Nei mammiferi la sintesi di acidi grassi avviene principalmente nel **fegato** (ma anche nelle ghiandole mammarie in lattazione e negli adipociti).

- La biosintesi degli acidi grassi avviene tramite la condensazione di unità C_2 , un processo inverso rispetto alla beta-ossidazione.
- In entrambi i casi viene utilizzato AcetilCoA
- Tuttavia, la via di sintesi è diversa da quella di ossidazione

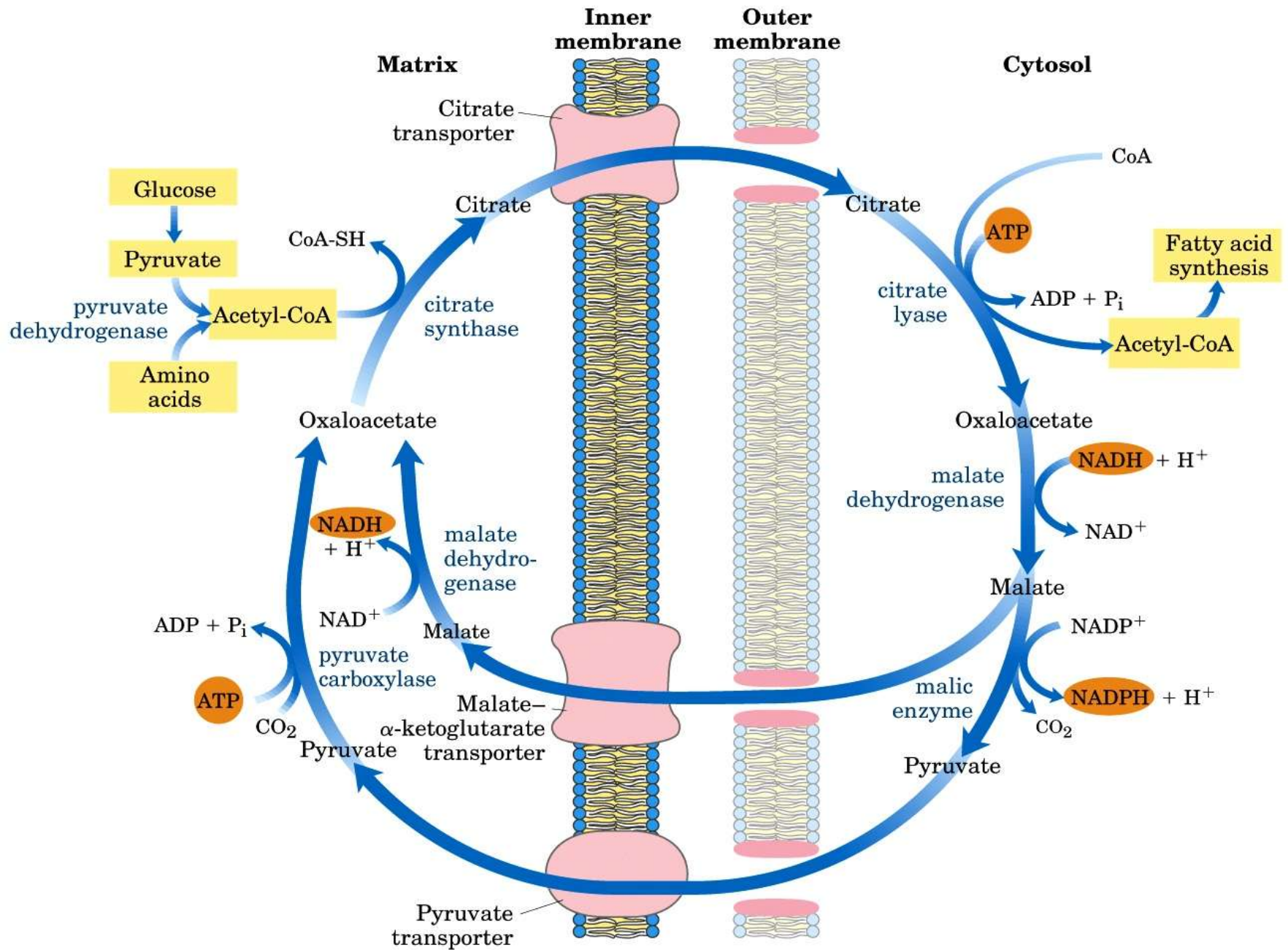


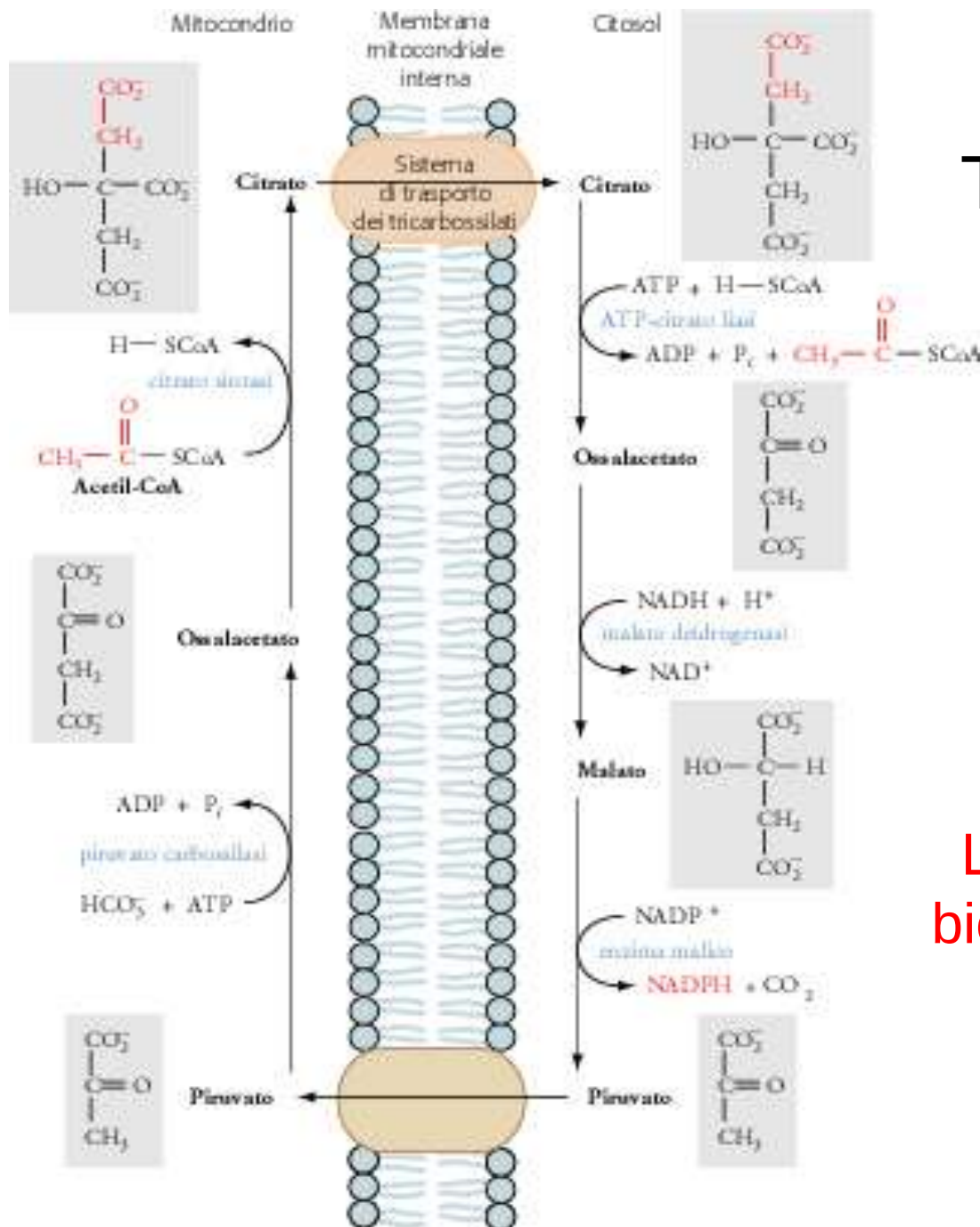
L'Acetil-CoA si comporta da trasportatore di gruppi acetili e acili



ACP = proteina trasportatrice di acili

1° tappa : trasferimento di una **unità di acetile**
dall'acetylCoA mitocondriale al citosol
mediante trasporto del citrato
(il CoA non può attraversare la membrana mitocondriale)

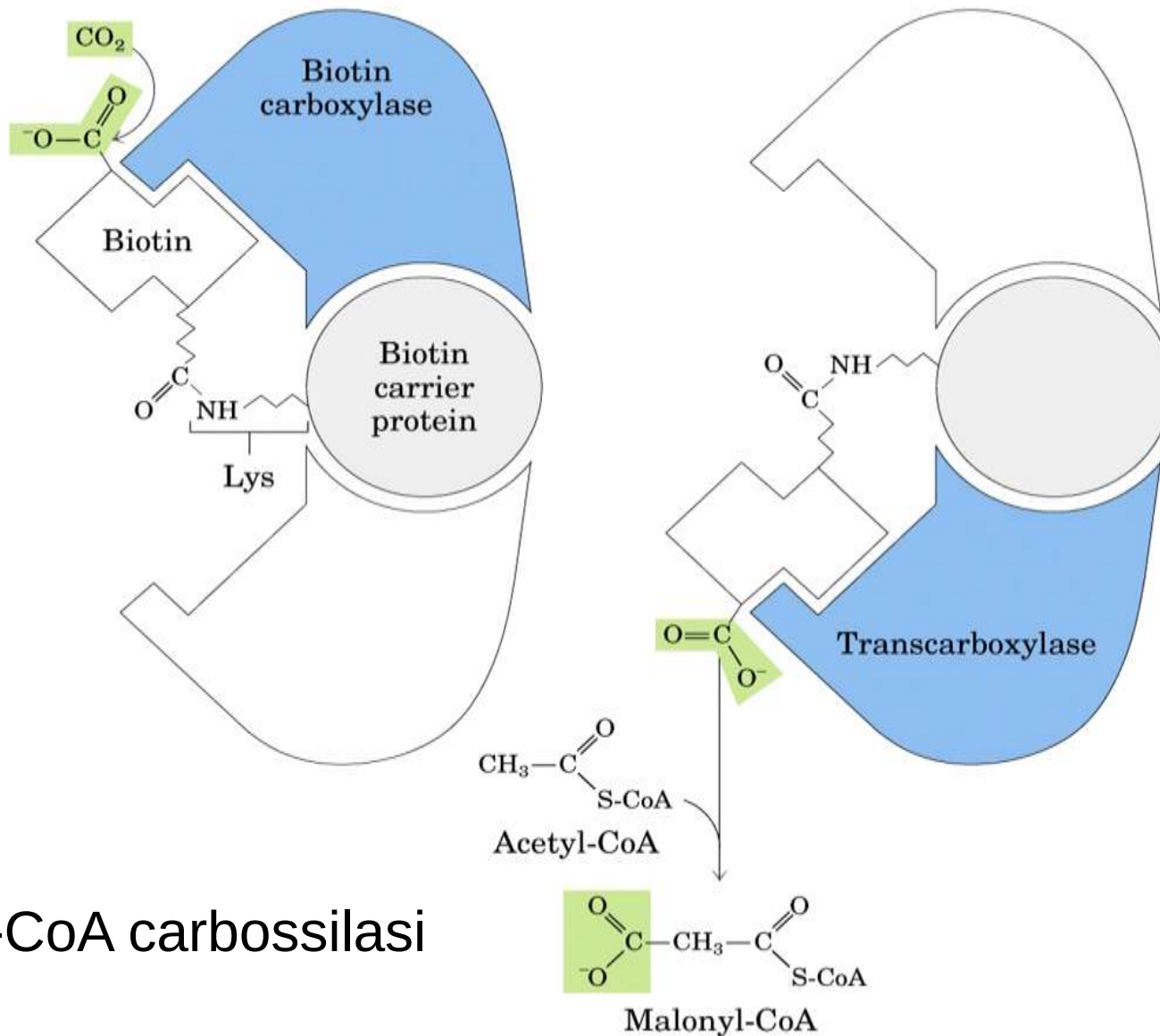




Trasporto nel citosol dell'acetil-CoA mitocondriale

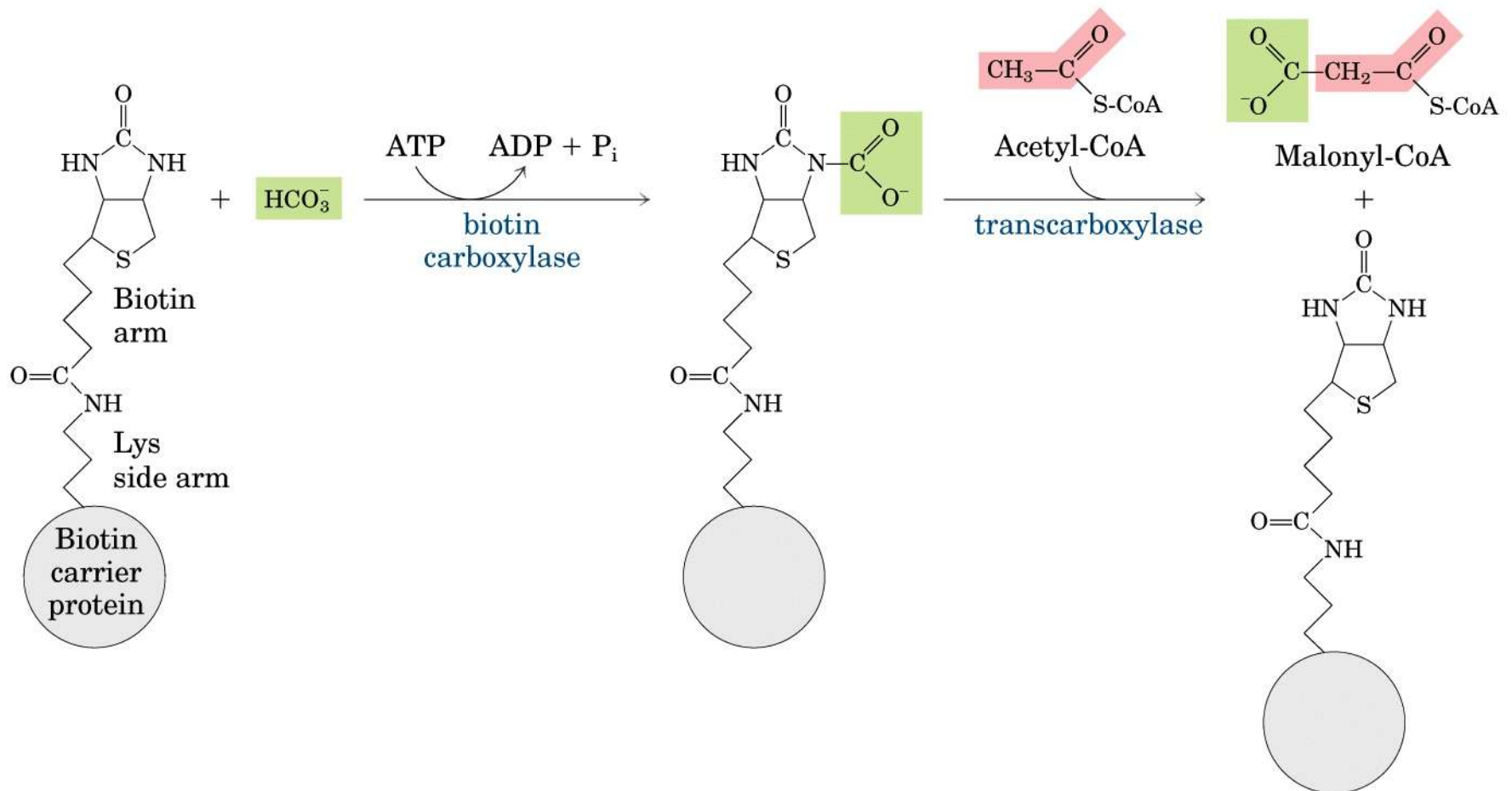
L'acetyl-CoA usato per la biosintesi degli acidi grassi non deriva dal loro catabolismo!

2° tappa : carbossilazione dall'acetilCoA a malonil-CoA



Acetil-CoA carbossilasi

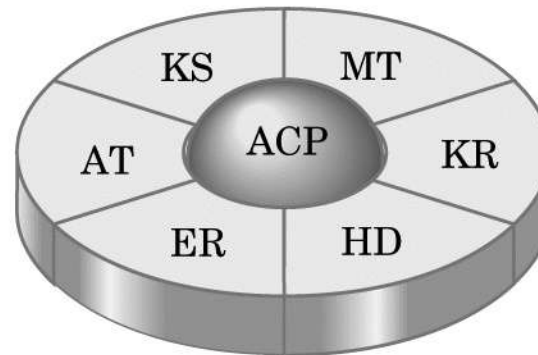
Acetil-CoA carbossilasi



Gli acidi grassi vengono sintetizzati
mediante una sequenza di reazioni
ripetute, realizzate dal **complesso** dell'
acido grasso sintetasi

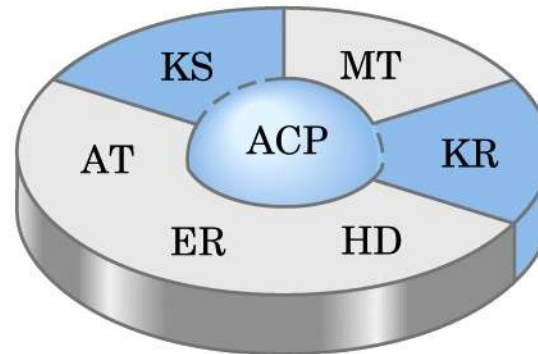
Bacteria, Plants

Seven activities
in seven separate
polypeptides



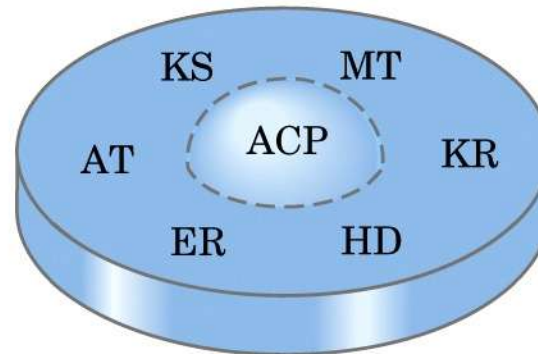
Yeast

Seven activities
in two separate
polypeptides



Vertebrates

Seven activities
in one large
polypeptide



Proteins of the Fatty Acid Synthase Complex of *E. coli*

Protein

Role

Acyl carrier protein (ACP)

Carries acyl groups in thioester linkage

Acetyl-CoA-ACP transacetylase (AT)

Transfers acyl group from CoA to Cys residue of KS

β -Ketoacyl-ACP synthase (KS)

Condenses acyl and malonyl groups
(there are at least three isozymes of KS)

Malonyl-CoA-ACP transferase (MT)

Transfers malonyl group from CoA to ACP

β -Ketoacyl-ACP reductase (KR)

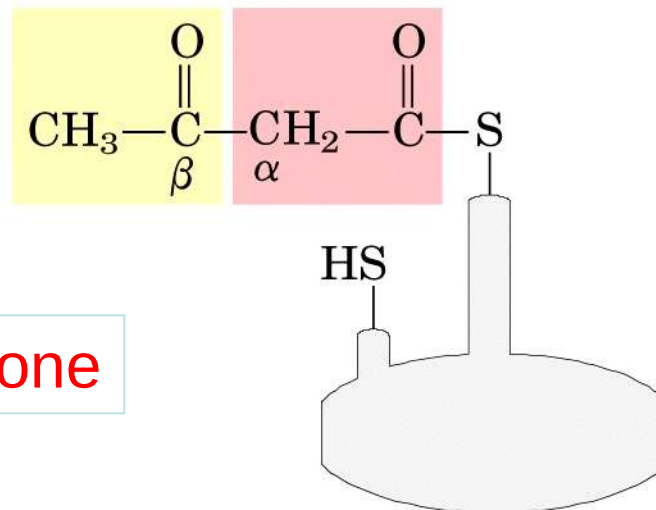
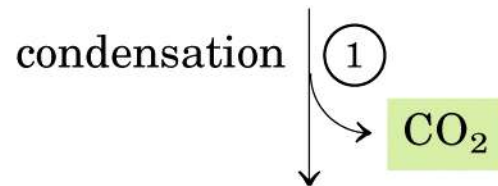
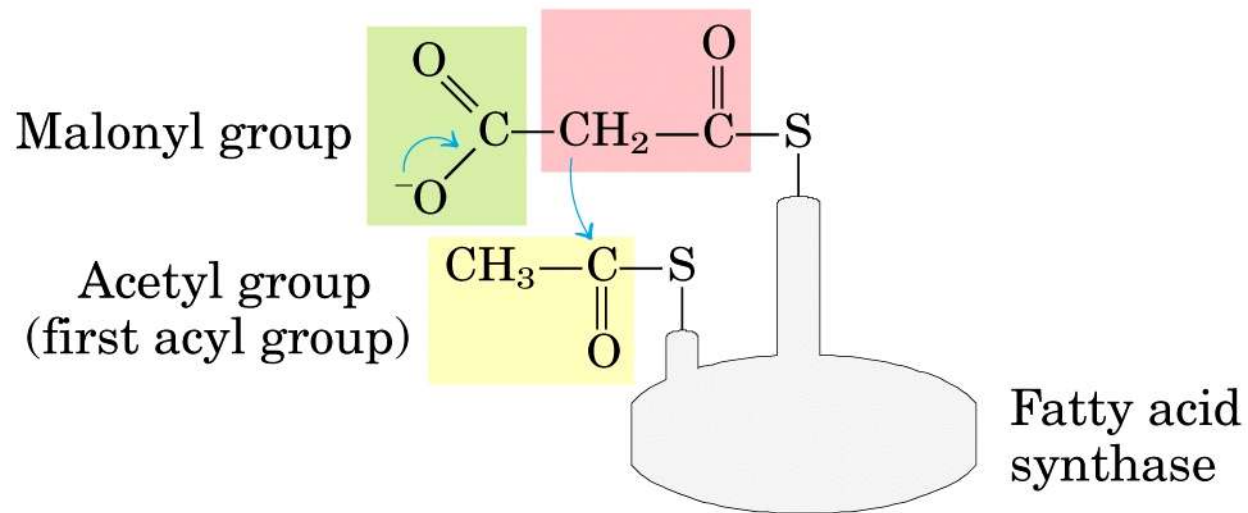
Reduces β -keto group to β -hydroxy group

β -Hydroxyacyl-ACP dehydratase (HD)

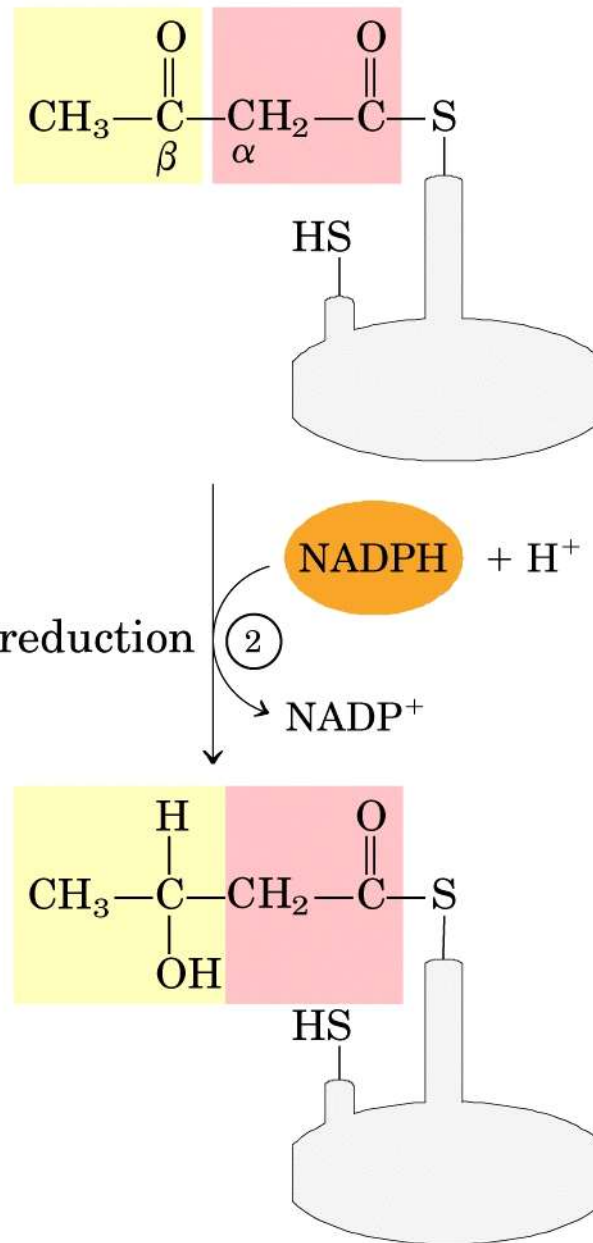
Removes H₂O from β -hydroxyacyl-ACP, creating double bond

Enoyl-ACP reductase (ER)

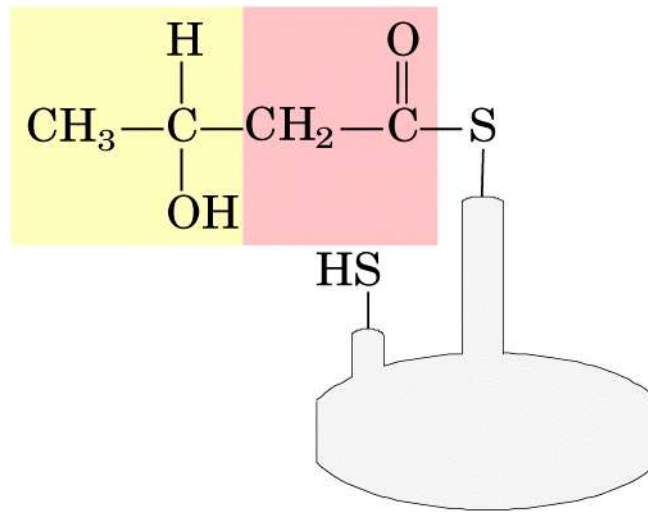
Reduces double bond, forming saturated acyl-ACP



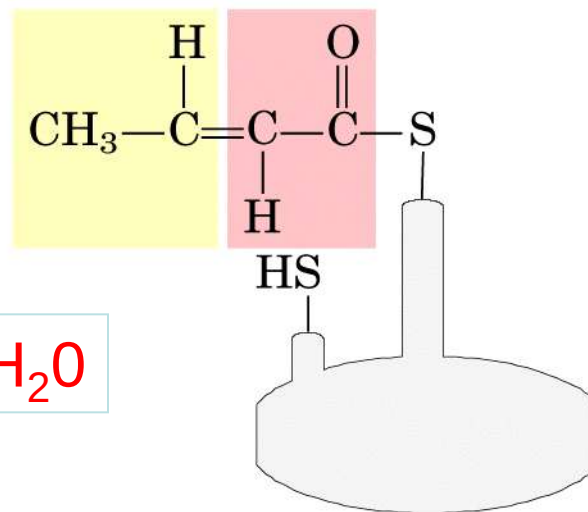
1. condensazione



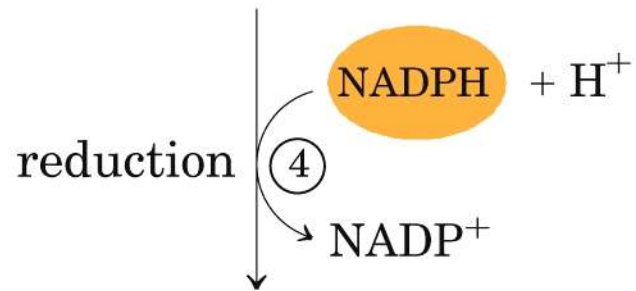
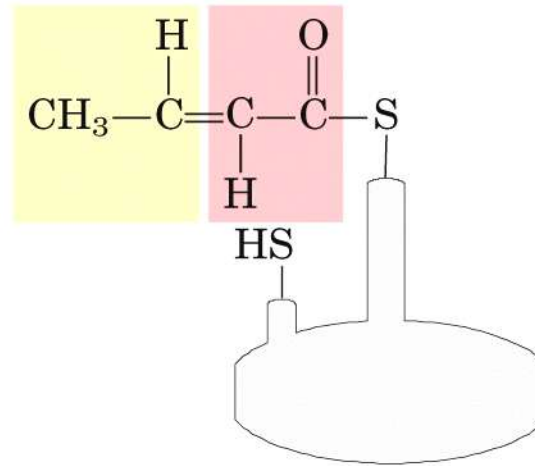
2. riduzione



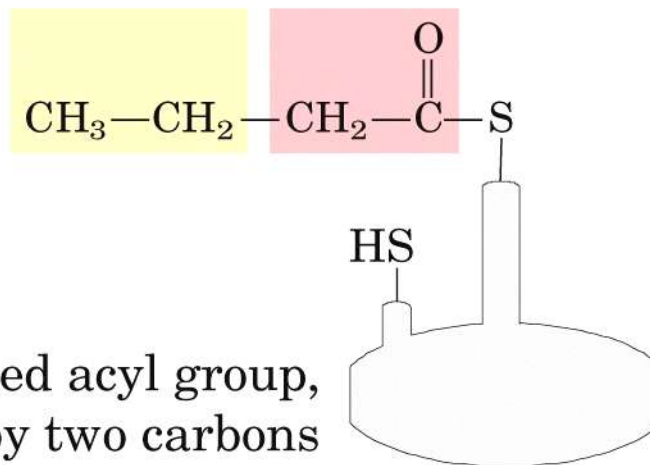
dehydration $\text{\textcircled{3}}$
 $\downarrow$ $\rightarrow \text{H}_2\text{O}$



3. Eliminazione H_2O

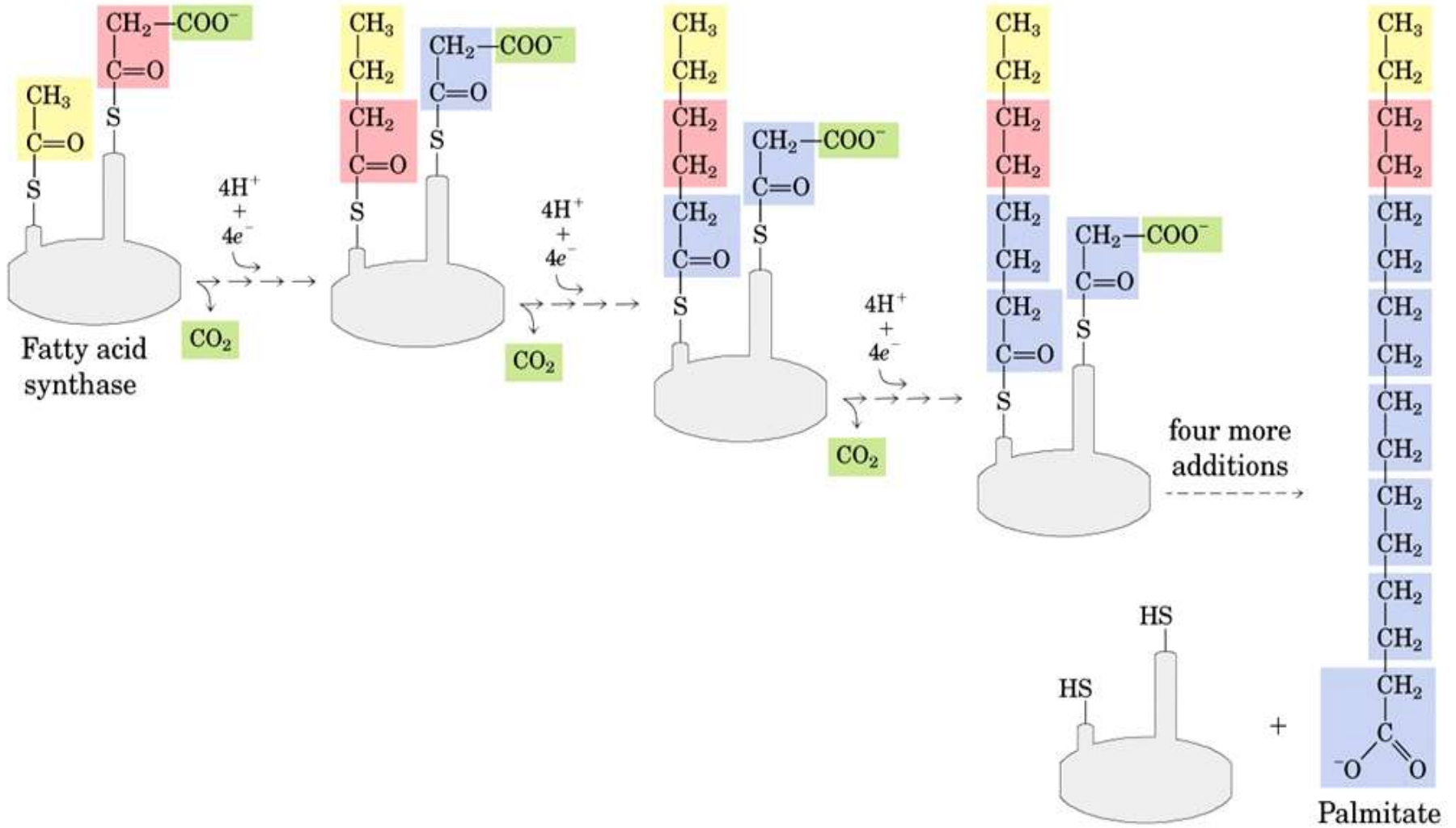


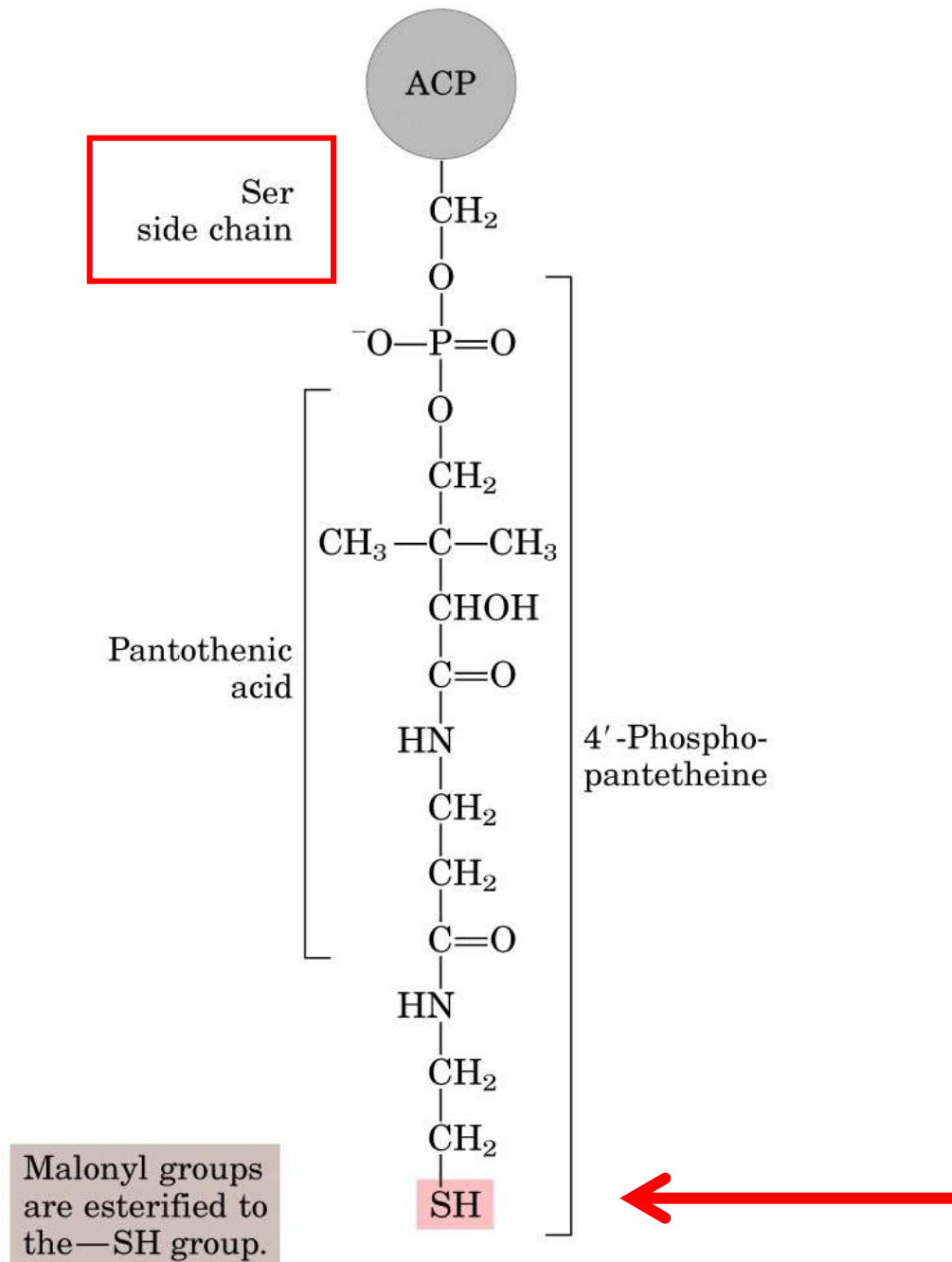
4. riduzione

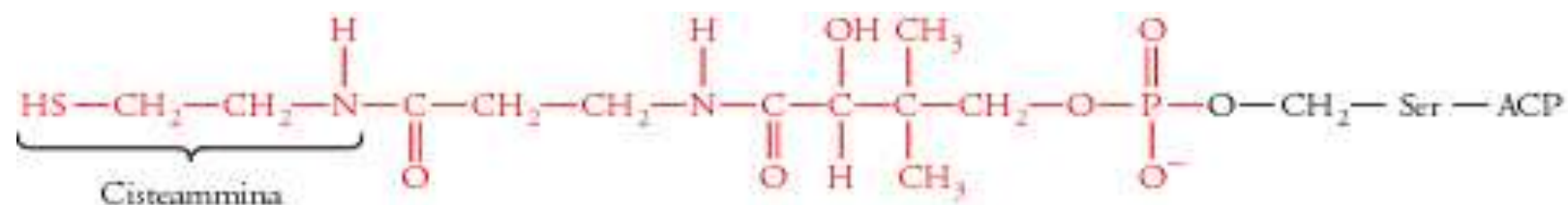


Saturated acyl group,
lengthened by two carbons

La sintesi del palmitato



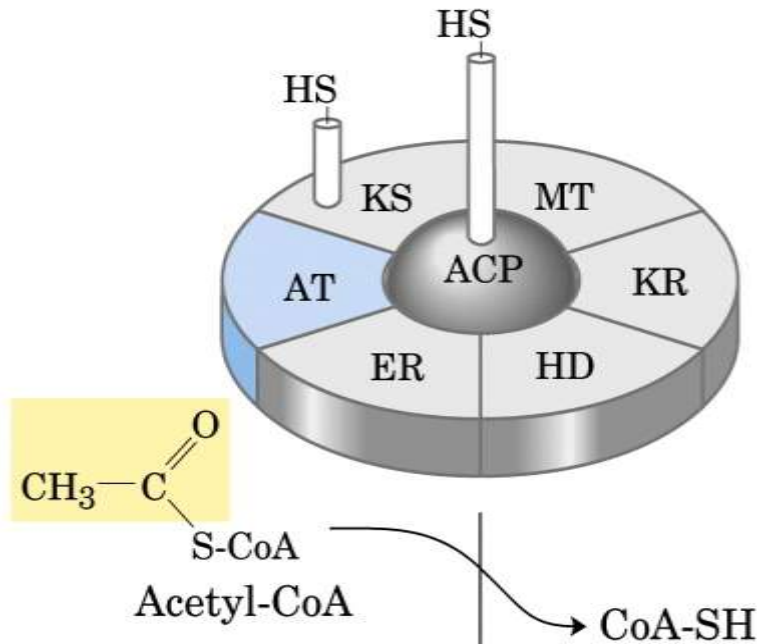




Gruppo prostetico fosfopanteteina dell'ACP

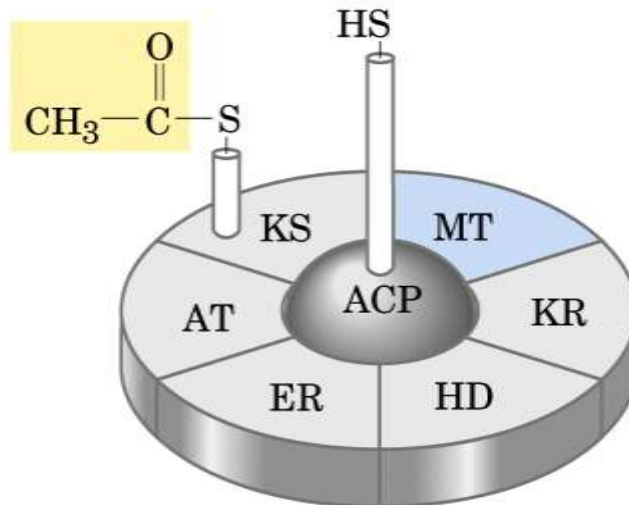


Gruppo fosfopanteteina del CoA



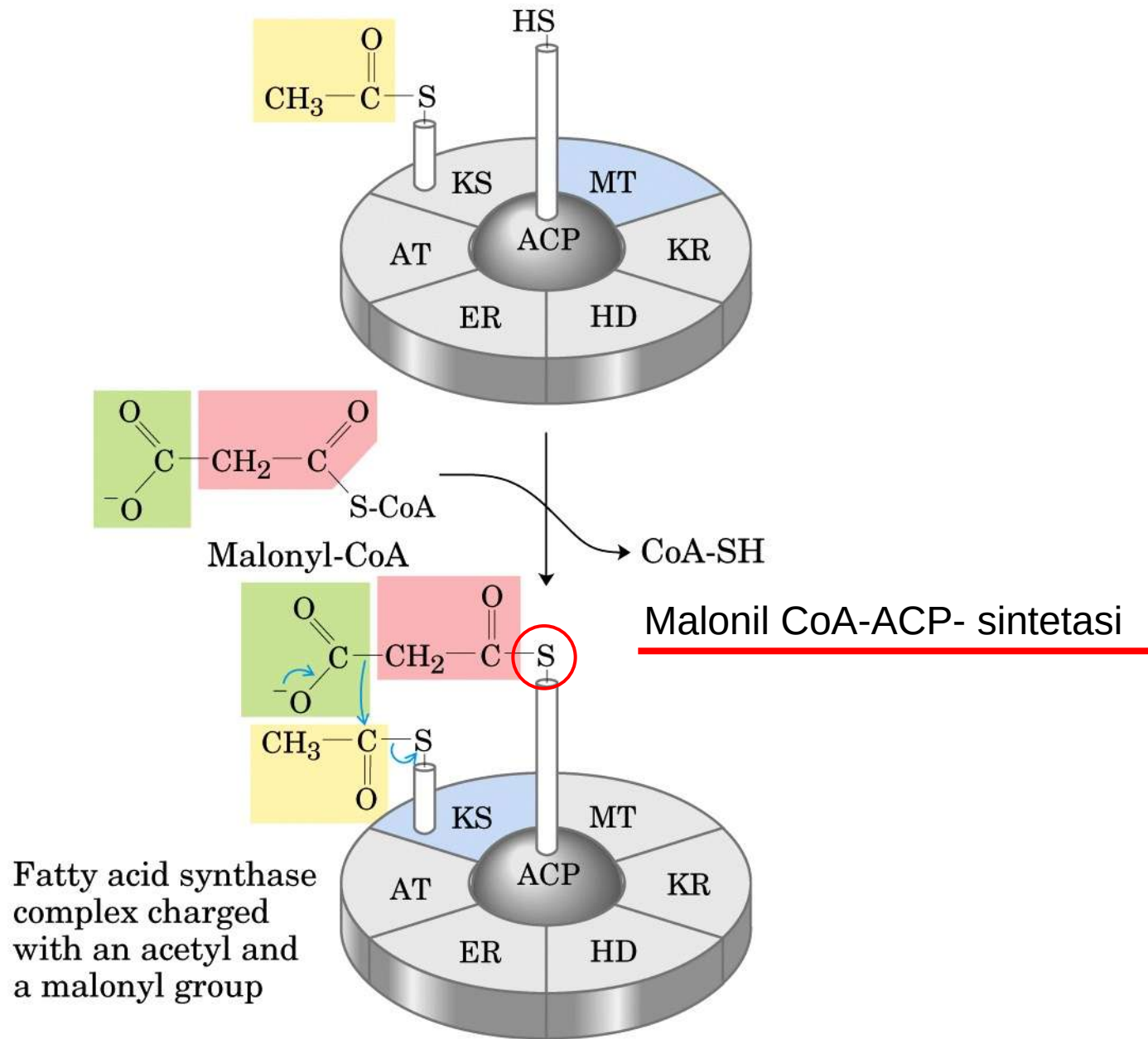
AT

Acetil-CoA-ACP-transacetilasi

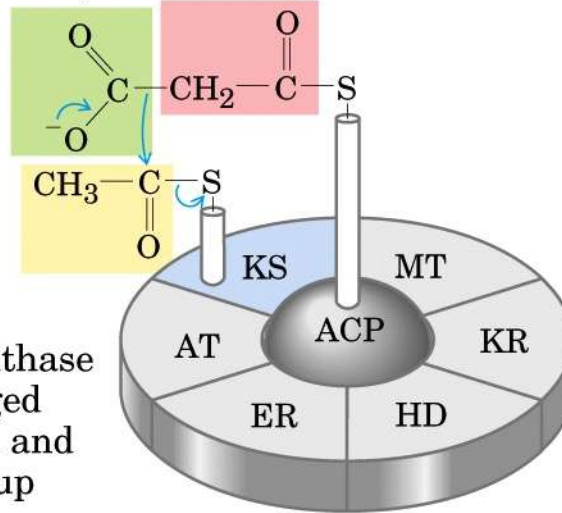


KS

Ketoacyl-sintasi

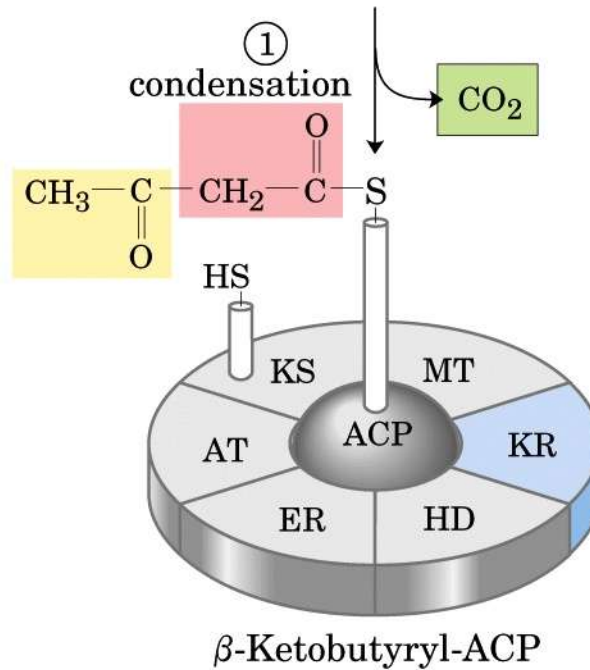


Malonyl-CoA

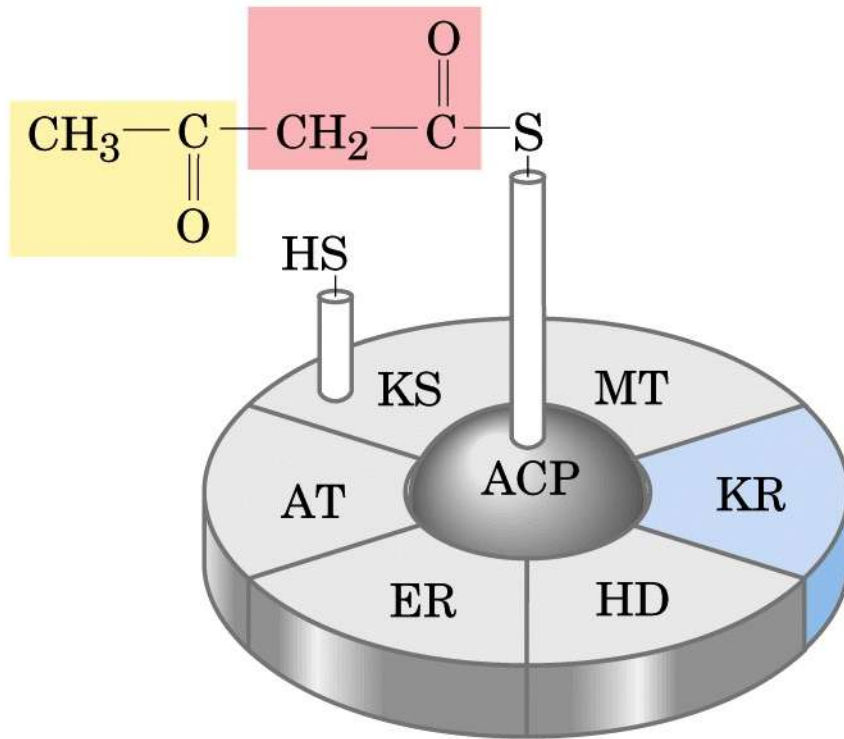


Fatty acid synthase complex charged with an acetyl and a malonyl group

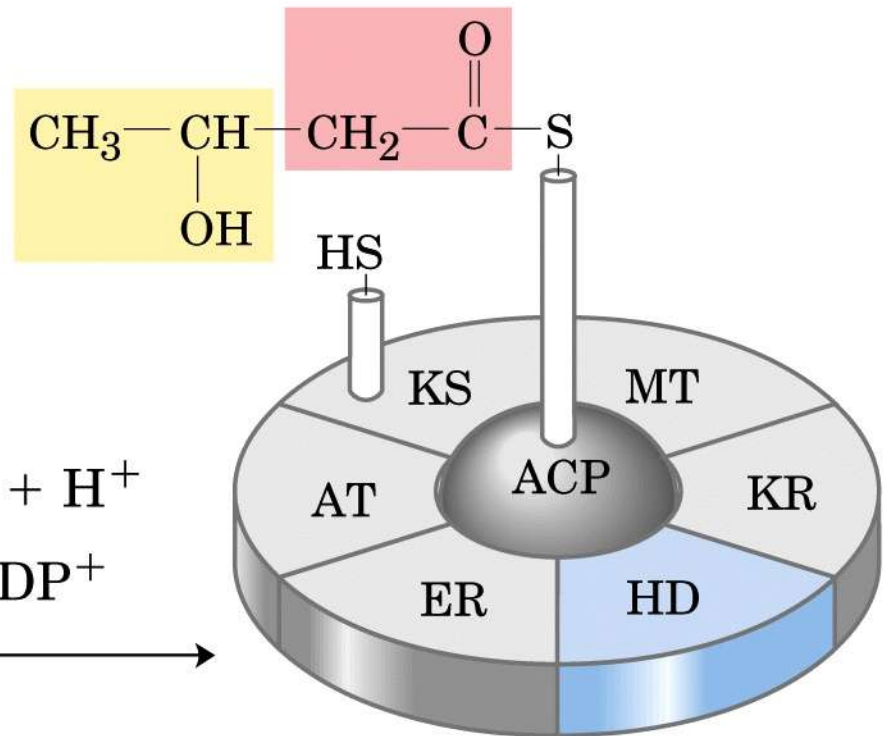
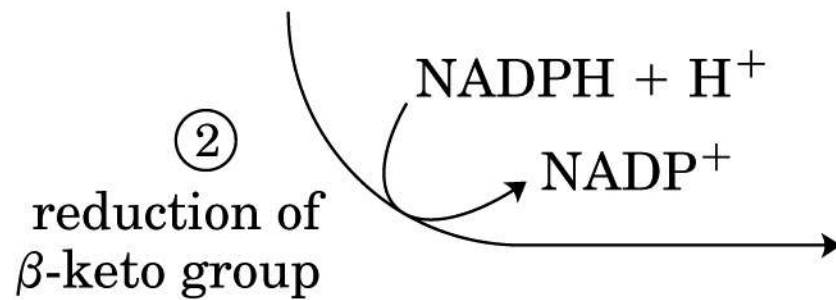
Beta-ketoacyl-ACPsintetasi



Beta-chetoacil-ACP-reduttasi

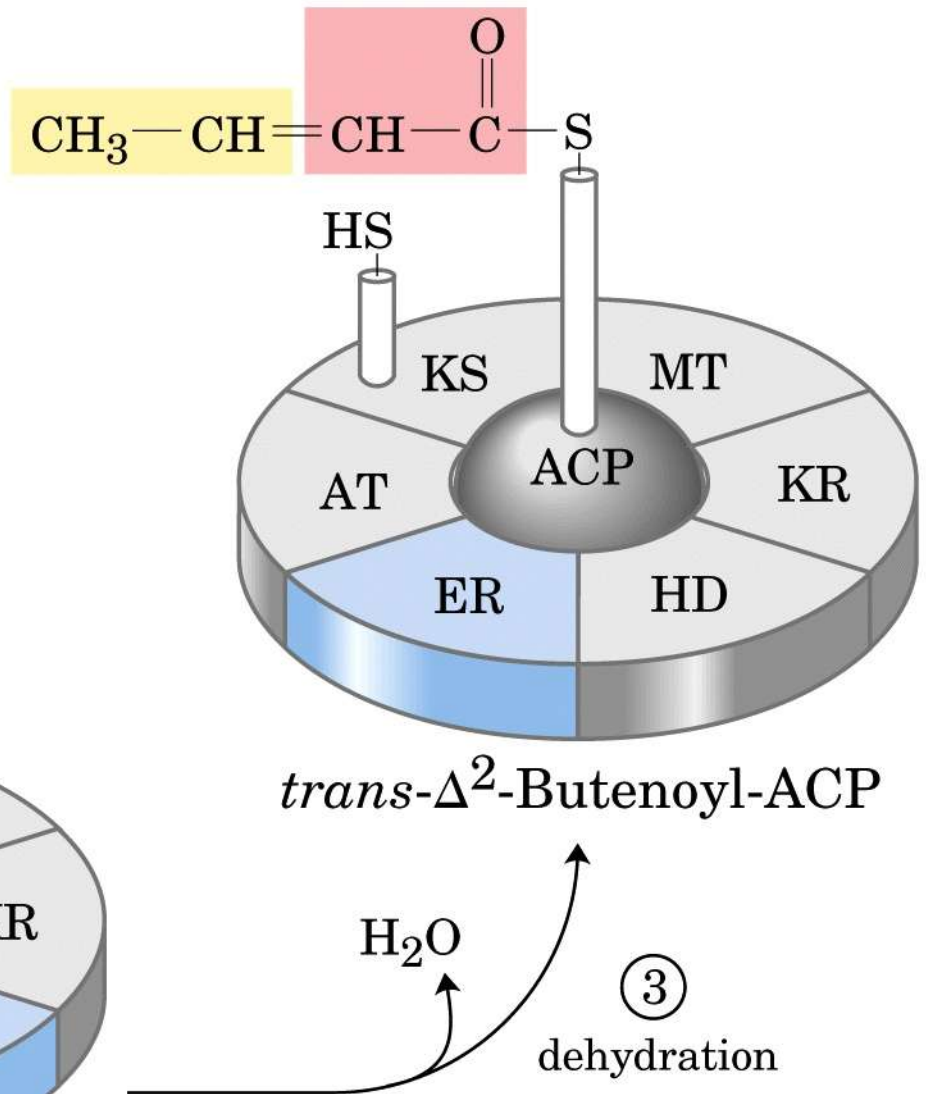
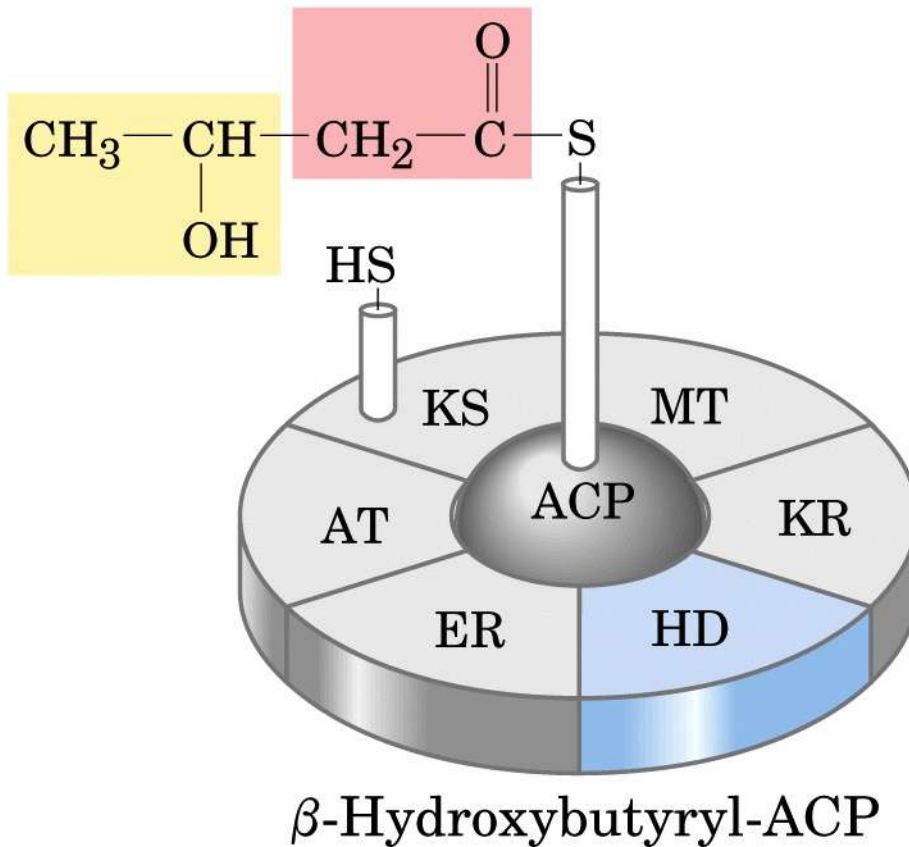


β -Ketobutyryl-ACP

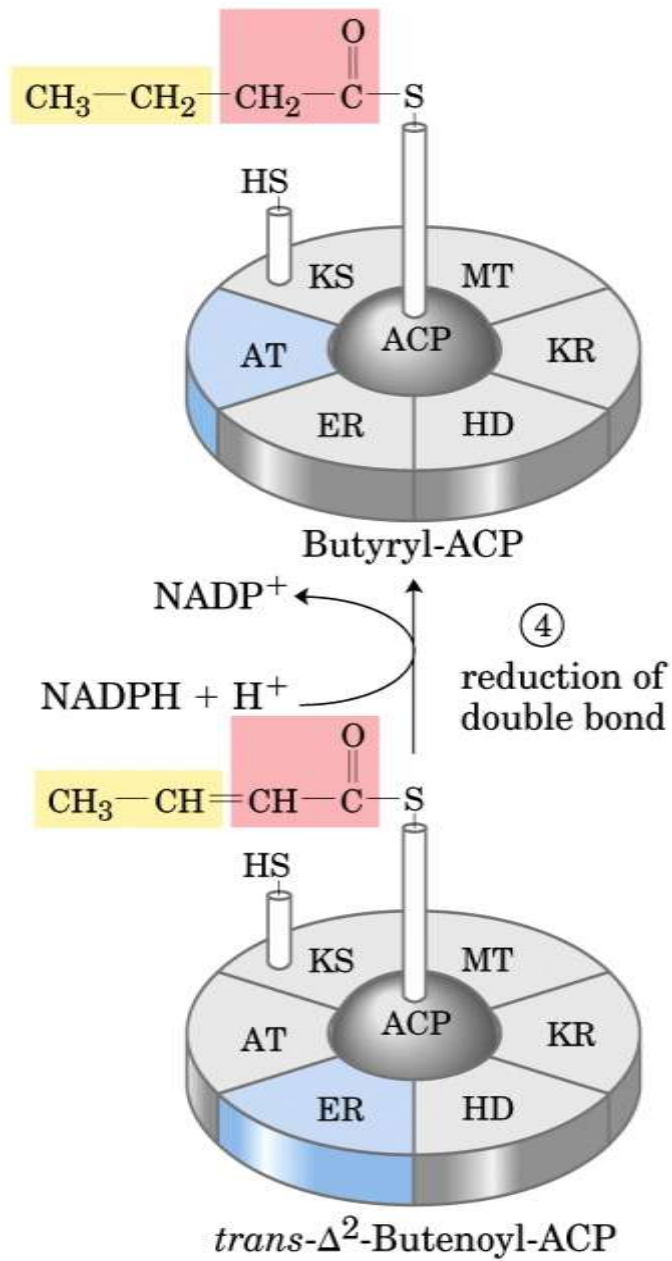


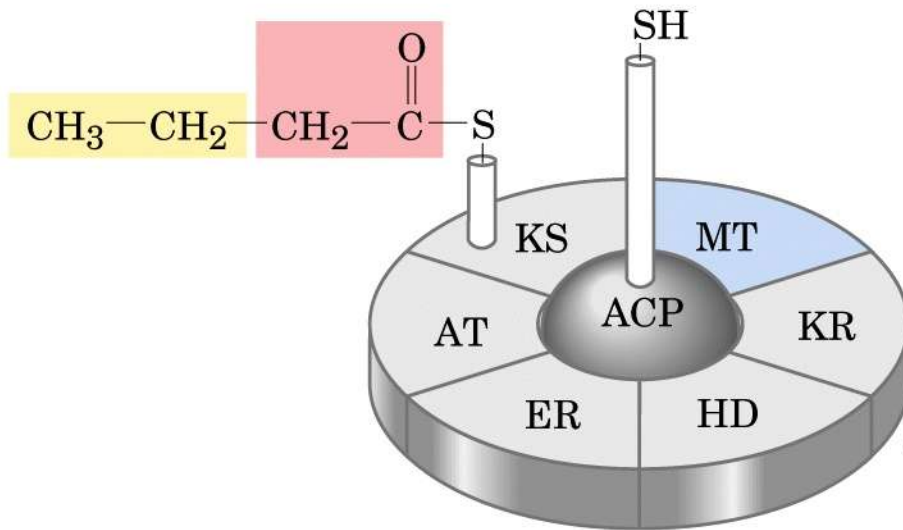
β -Hydroxybutyryl-ACP

Beta-idrossiacil-ACP -deidratasi

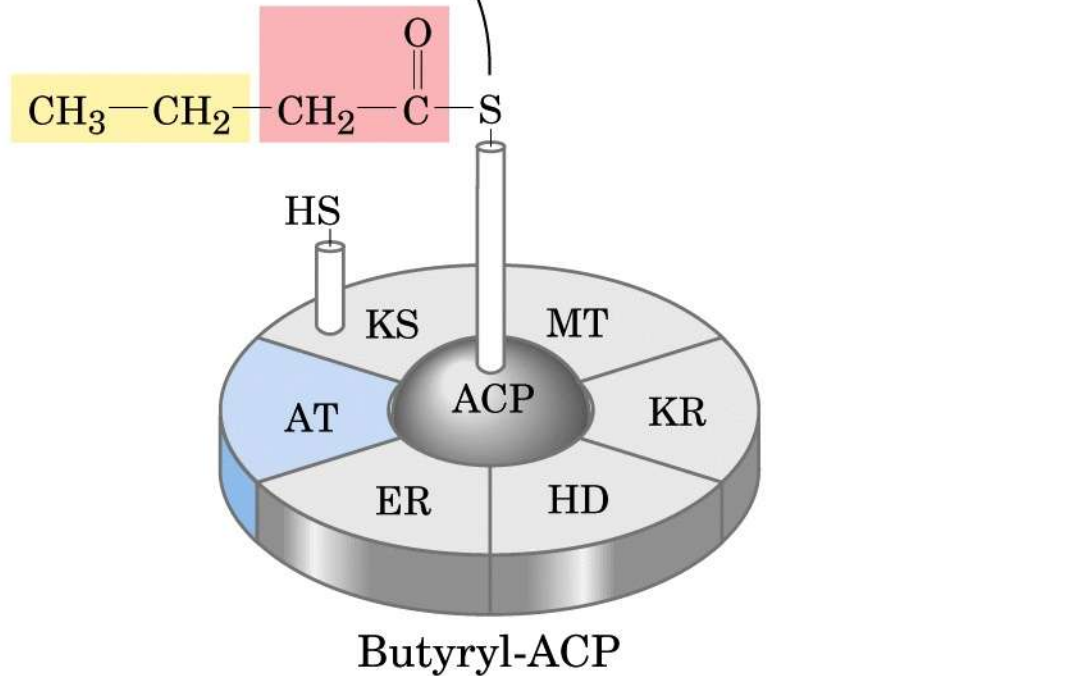


Enoil-ACP reduttasi

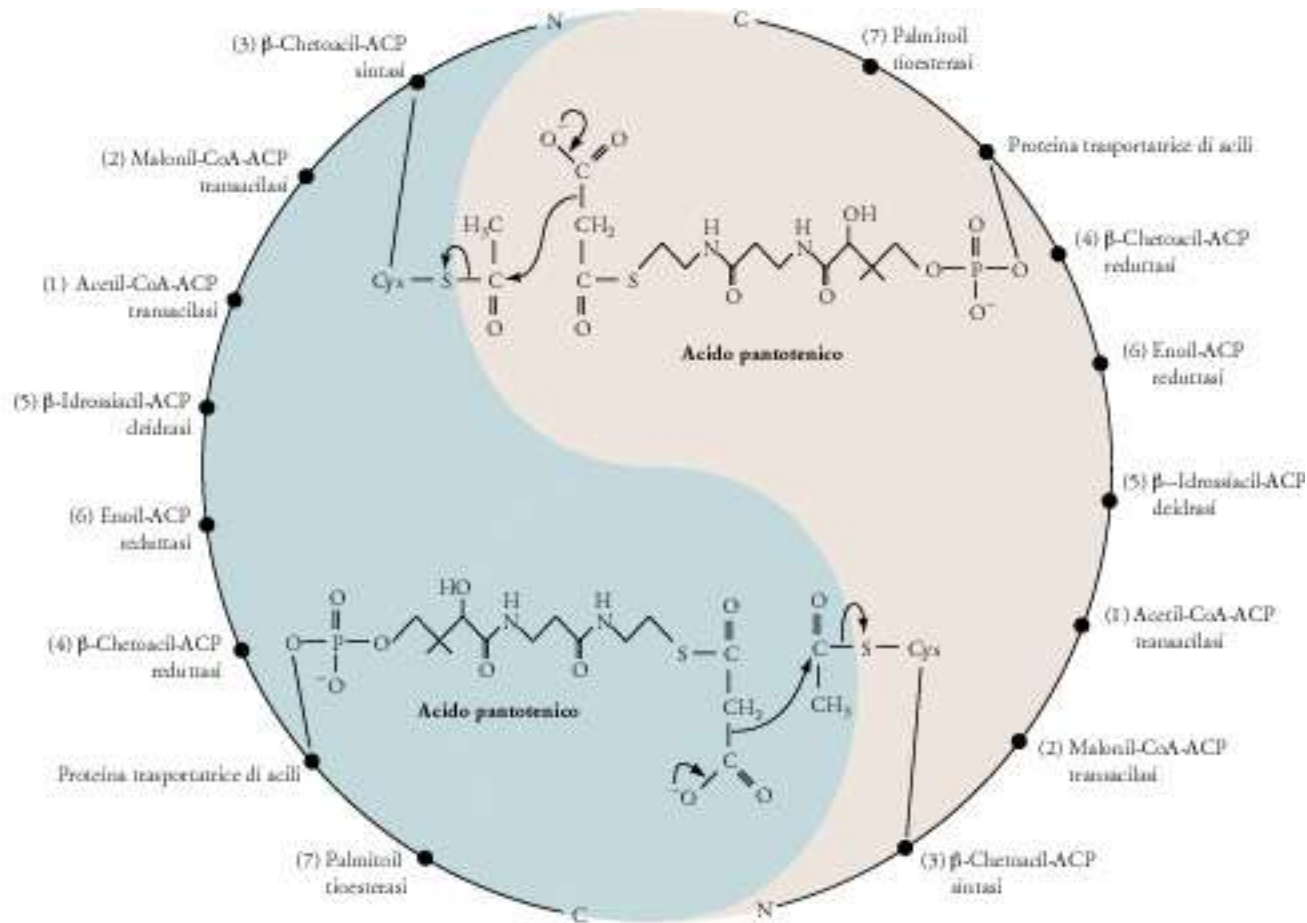




Acetil-CoA-ACP-transacetilasi



Acido grasso sintetasi animale

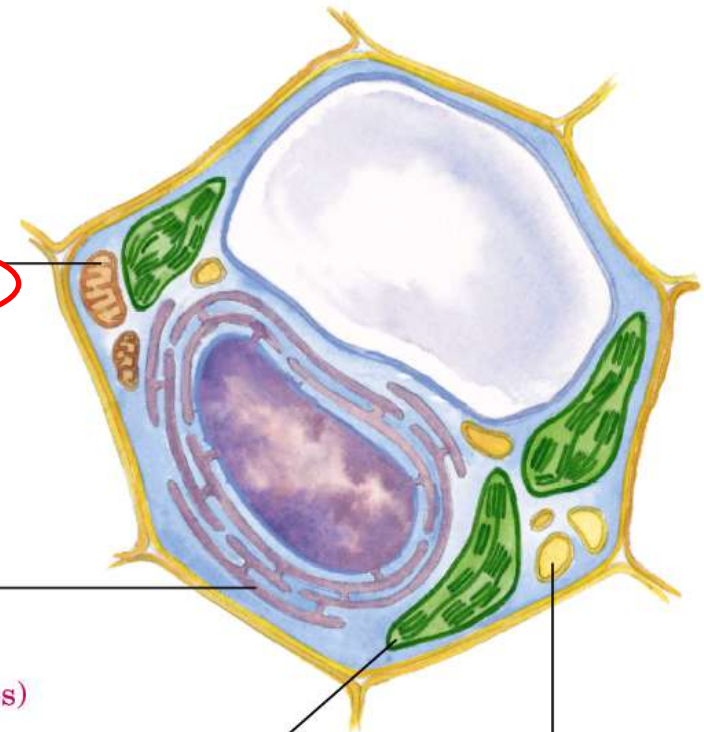
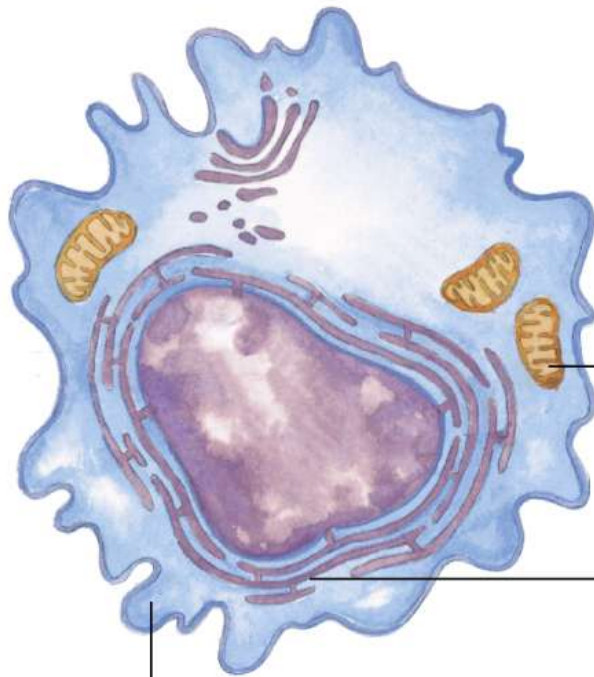


2 subunità identiche e simmetriche

- $7 \text{ AcetylCoA} + 7\text{CO}_2 + 7\text{ATP} \rightarrow 7 \text{ malonil CoA} + 7 \text{ ADP} + 7 \text{ Pi} + 7\text{H}^+$
- $\text{AcetylCoA} + 7 \text{ Malonil CoA} + 14 \text{ NADPH} + 14 \text{ H}^+ \rightarrow \text{palmitato} + 7\text{CO}_2 + 14 \text{ NADP} + 8 \text{ CoA} + 6\text{H}_2\text{O}$
- **$8 \text{ Acetil CoA} + 14\text{NADPH} + 7\text{ATP} + 7\text{H}^+ \rightarrow \text{Palmitato} + 14 \text{ NADP} + 7 \text{ ADP} + 8 \text{ CoA} + 6 \text{ H}_2\text{O} + 7 \text{ Pi}$**

Animal cells, yeast cells

Plant cells



Mitochondria

- No fatty acid oxidation

- Fatty acid oxidation
- Acetyl-CoA production
- Ketone body synthesis
- Fatty acid elongation

Endoplasmic reticulum

- Phospholipid synthesis
- Sterol synthesis (late stages)
- Fatty acid elongation
- Fatty acid desaturation

Cytosol

- NADPH production (pentose phosphate pathway; malic enzyme)
- [NADPH]/[NADP⁺] high
- Isoprenoid and sterol synthesis (early stages)
- Fatty acid synthesis

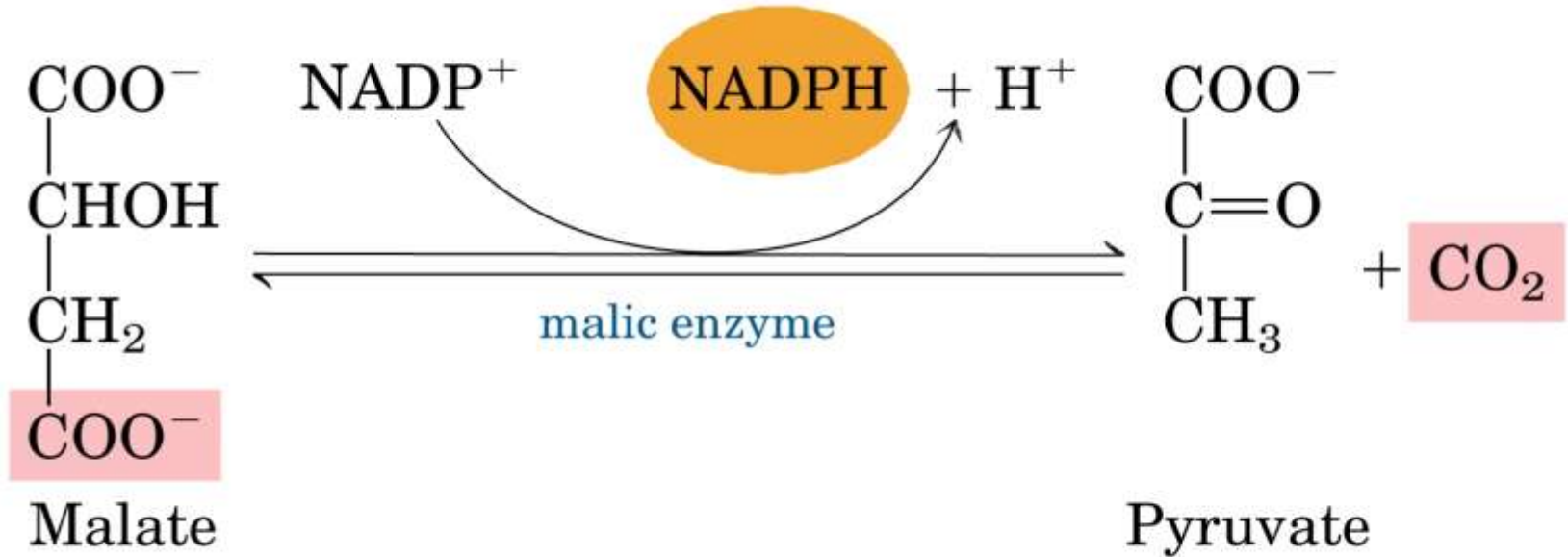
Chloroplasts

- NADPH, ATP production
- [NADPH]/[NADP⁺] high
- Fatty acid synthesis

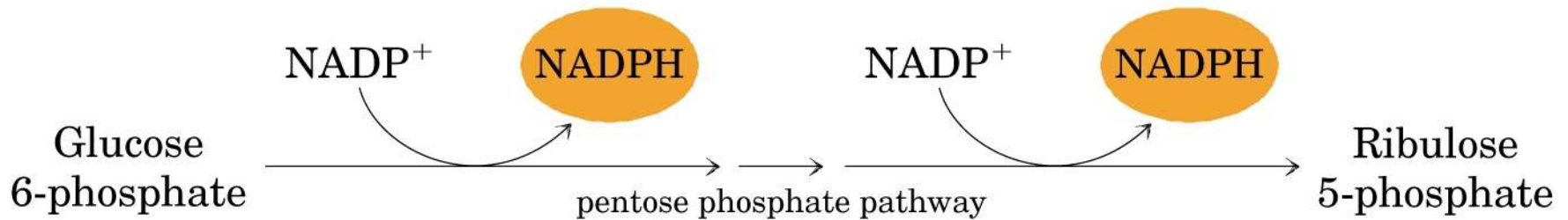
Peroxisomes

- Fatty acid oxidation
($\longrightarrow$ H₂O₂)
- Catalase, peroxidase:
H₂O₂ $\longrightarrow$ H₂O

Come è prodotto il NADPH necessario per la sintesi di acidi grassi ?

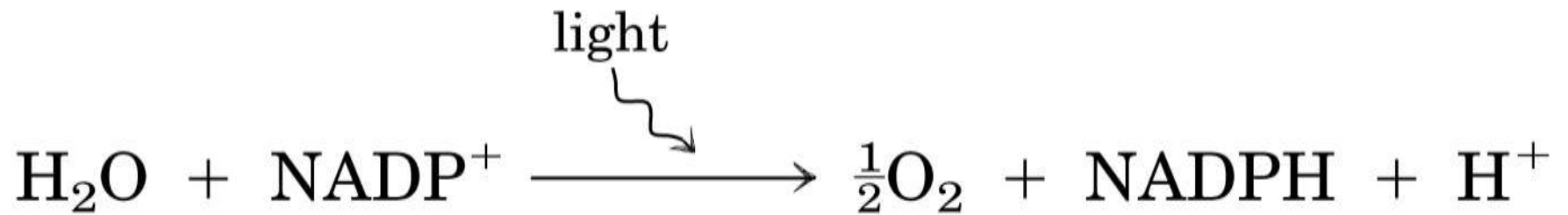


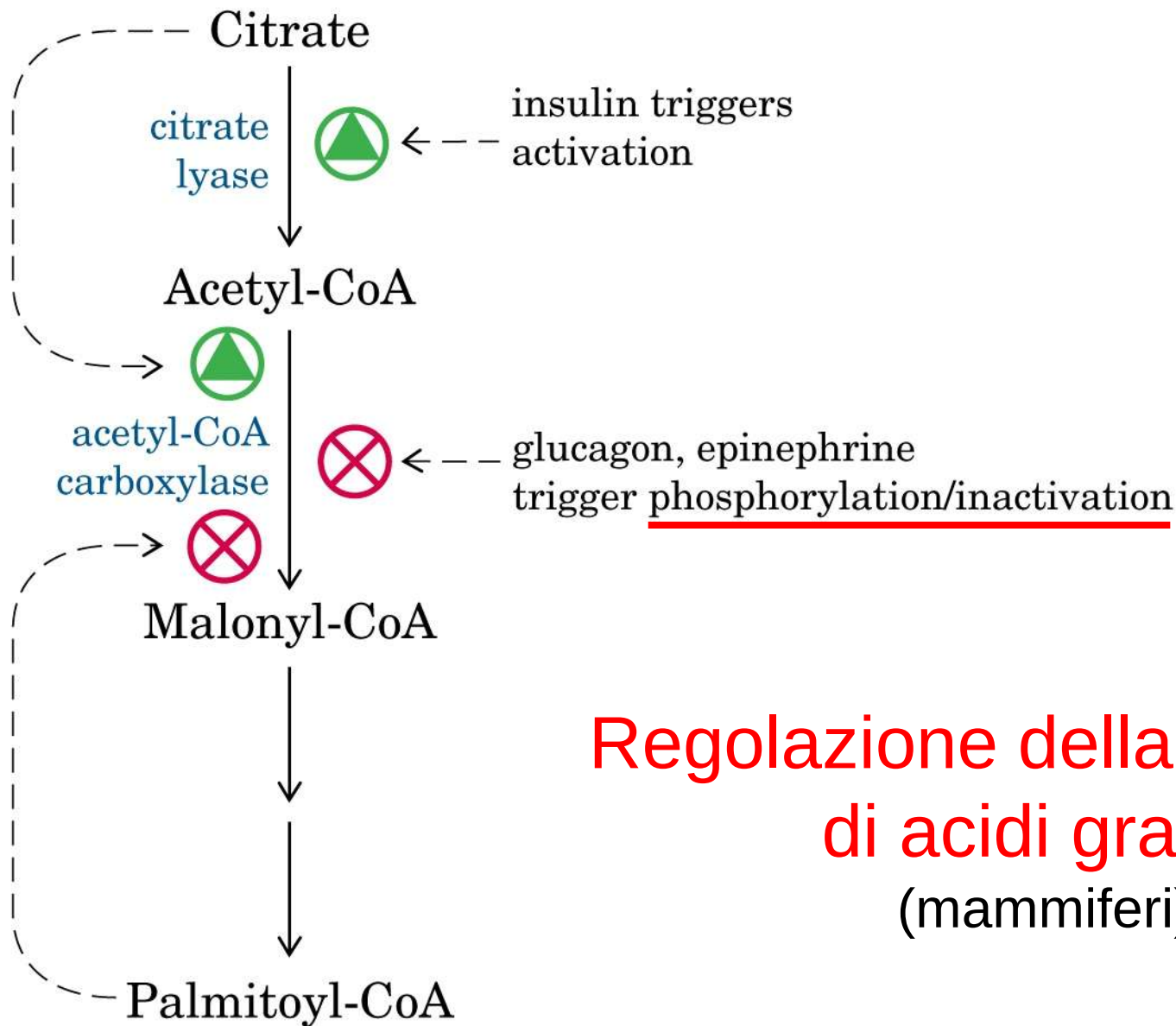
(a)



(b)

Negli organismi fotosintetici





**Regolazione della biosintesi
di acidi grassi
(mammiferi)**

(a)

Regolazione della biosintesi di acidi grassi

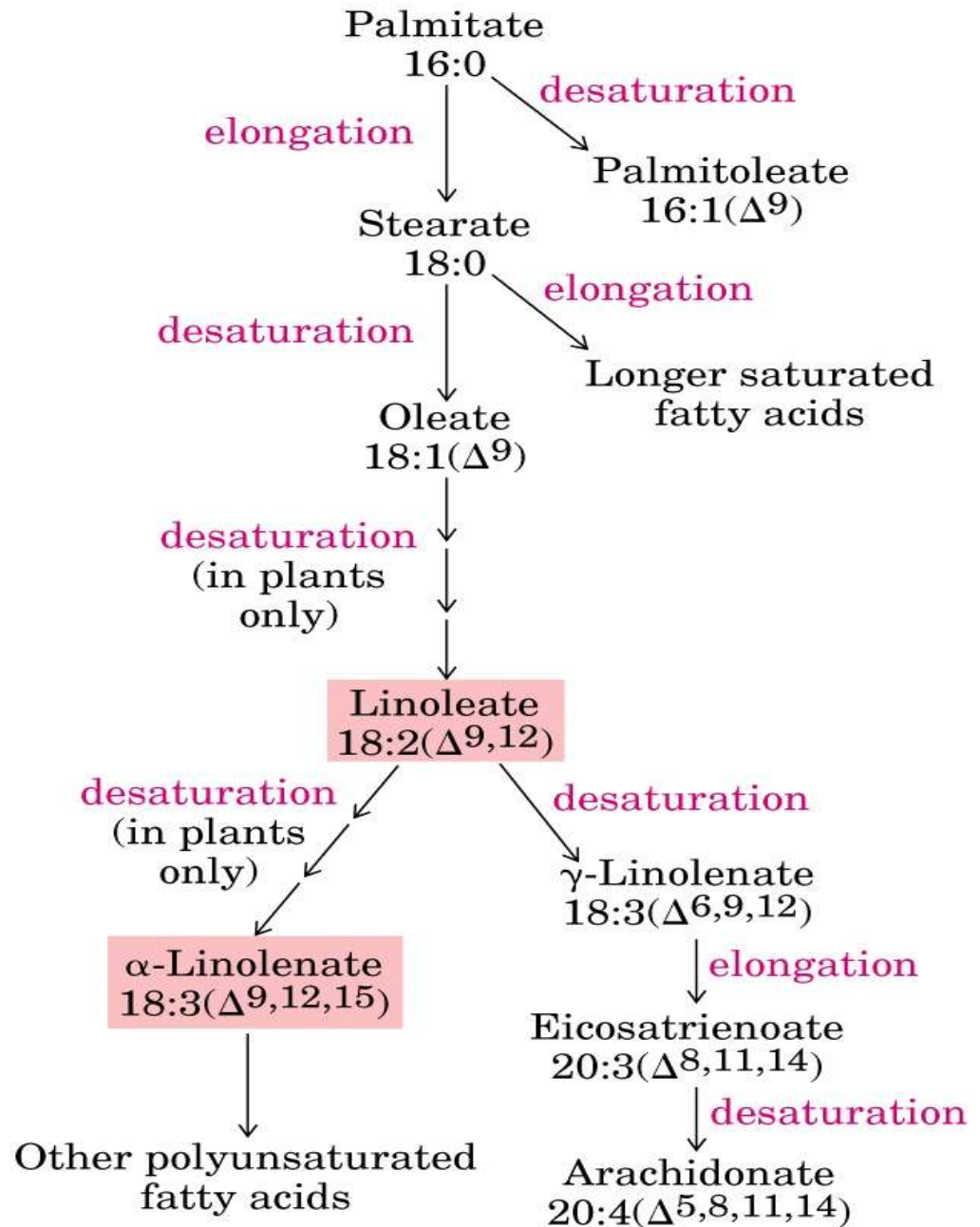
L'acetil CoA carbossilasi è presente come dimero inattivo.

La conversione a polimero attivo è regolata allostericamente :

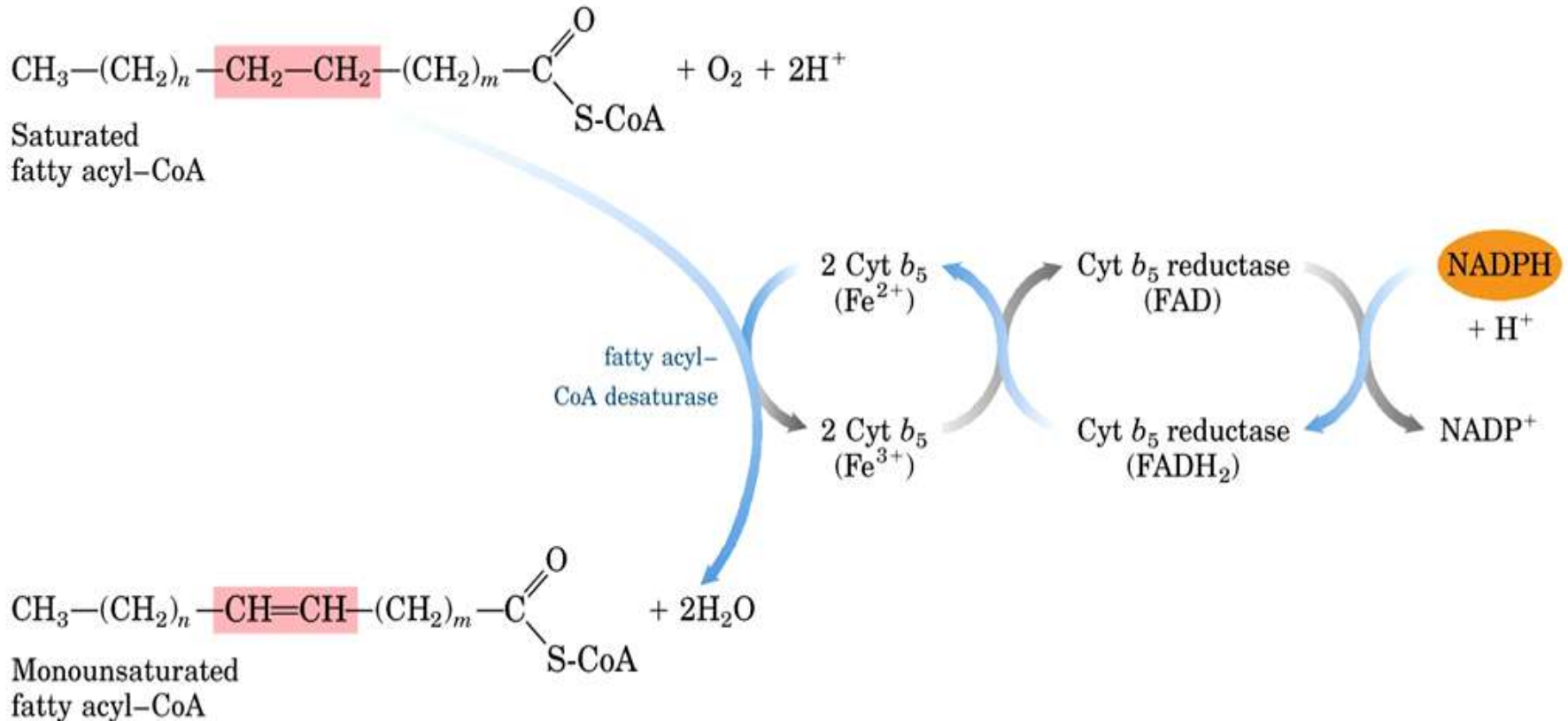
attivata da citrato

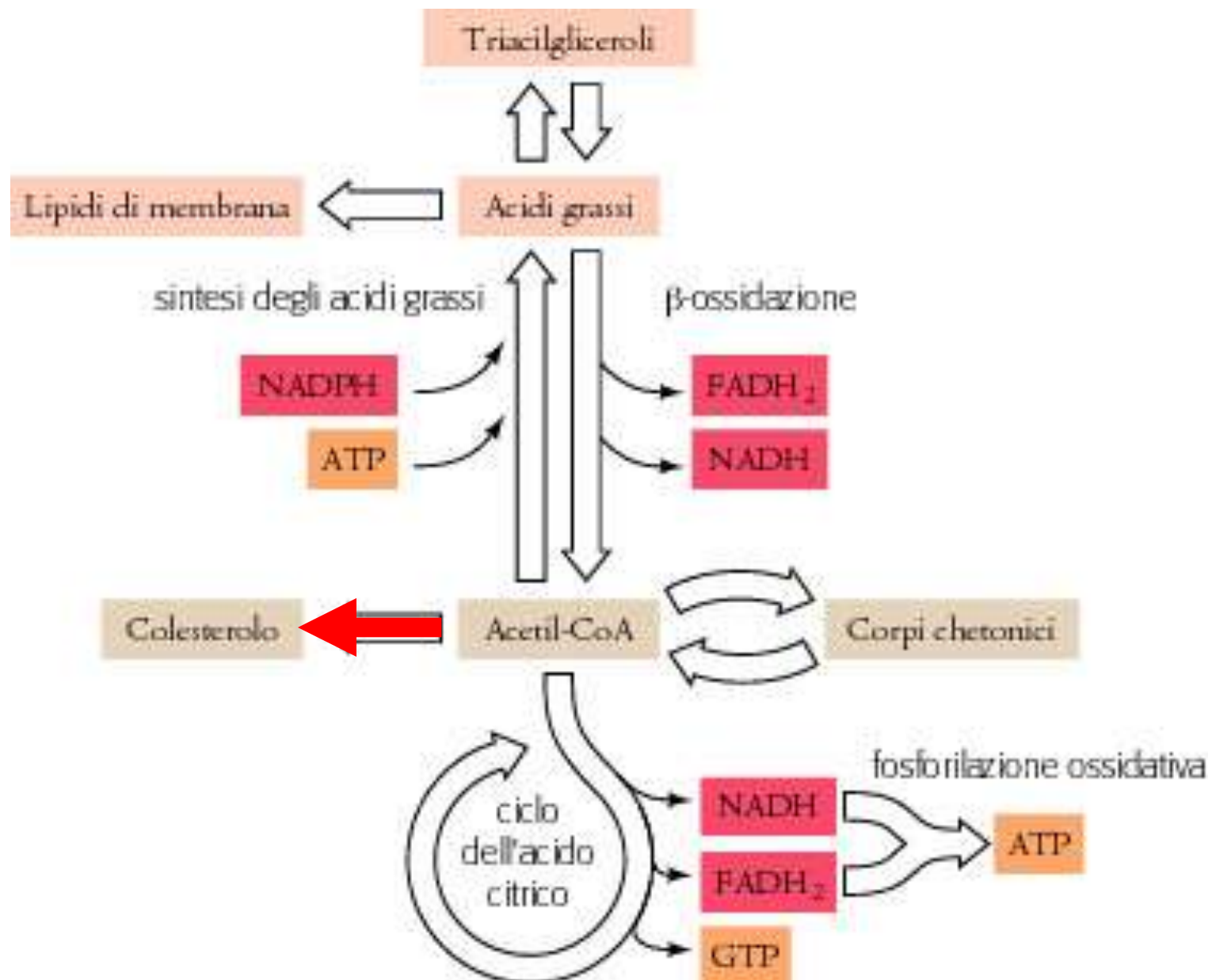
inattivata da AcilCoA

Sintesi degli acidi grassi insaturi

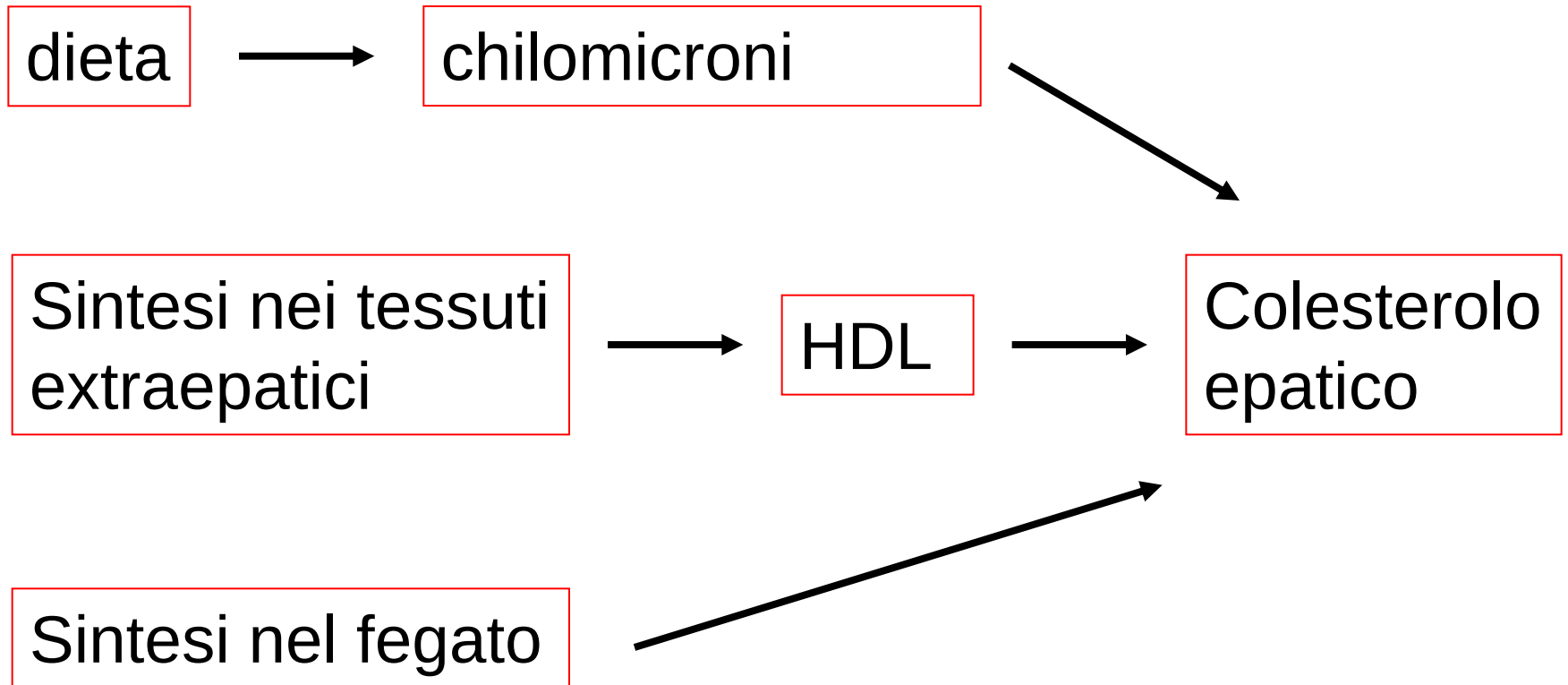


I **doppi** legami vengono introdotti da **desaturasi**



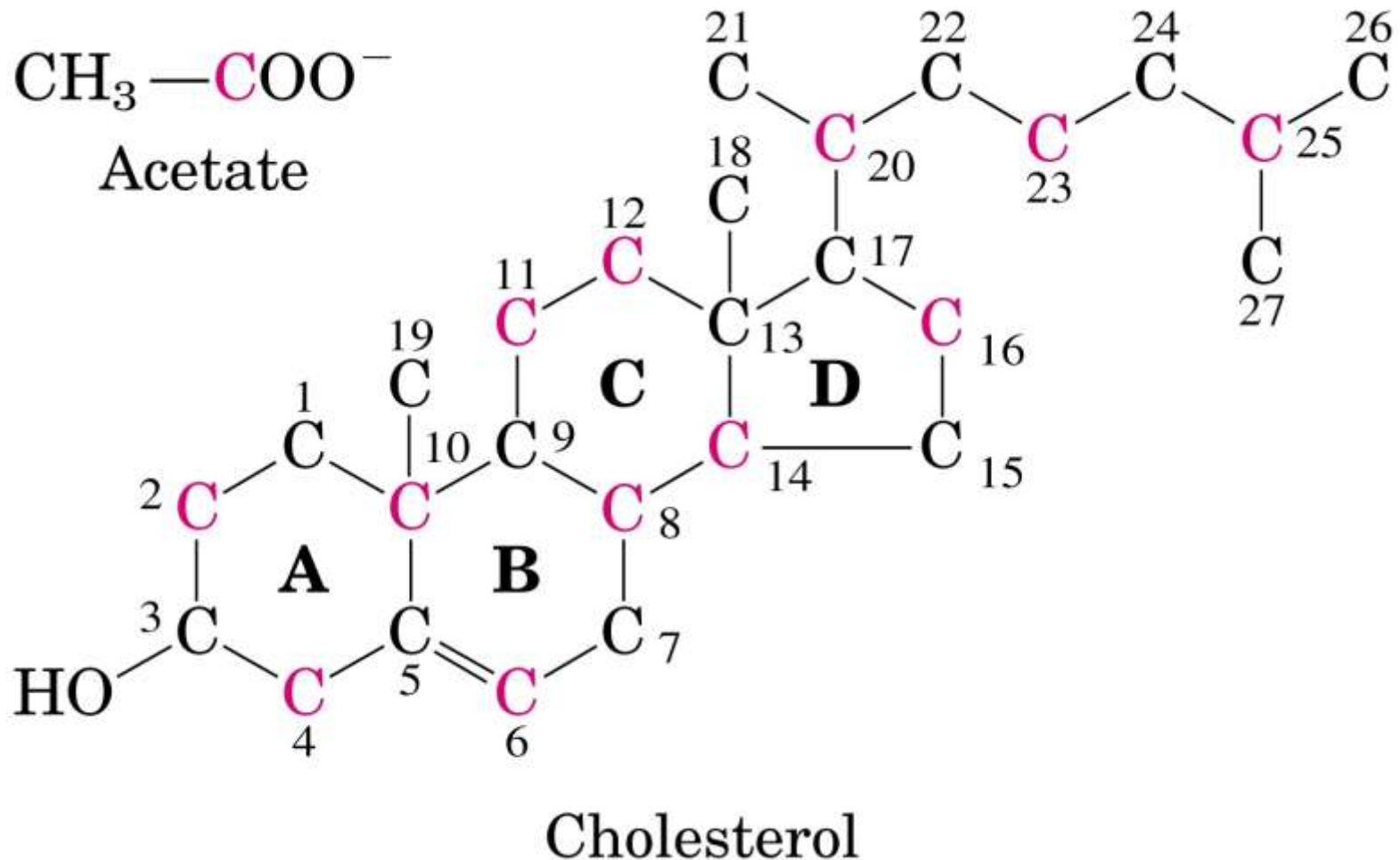


Biosintesi del **colesterolo**



L'uomo produce per biosintesi autonoma la maggior parte del colesterolo necessario (negli adulti 1-2 grammi al giorno).
Solo una piccola parte (0,1 - 0,5 grammi) viene assunta con l'alimentazione

Come per gli acidi grassi, tutti gli atomi C derivano unità **acetile** e l'NADPH fornisce equivalenti riducenti



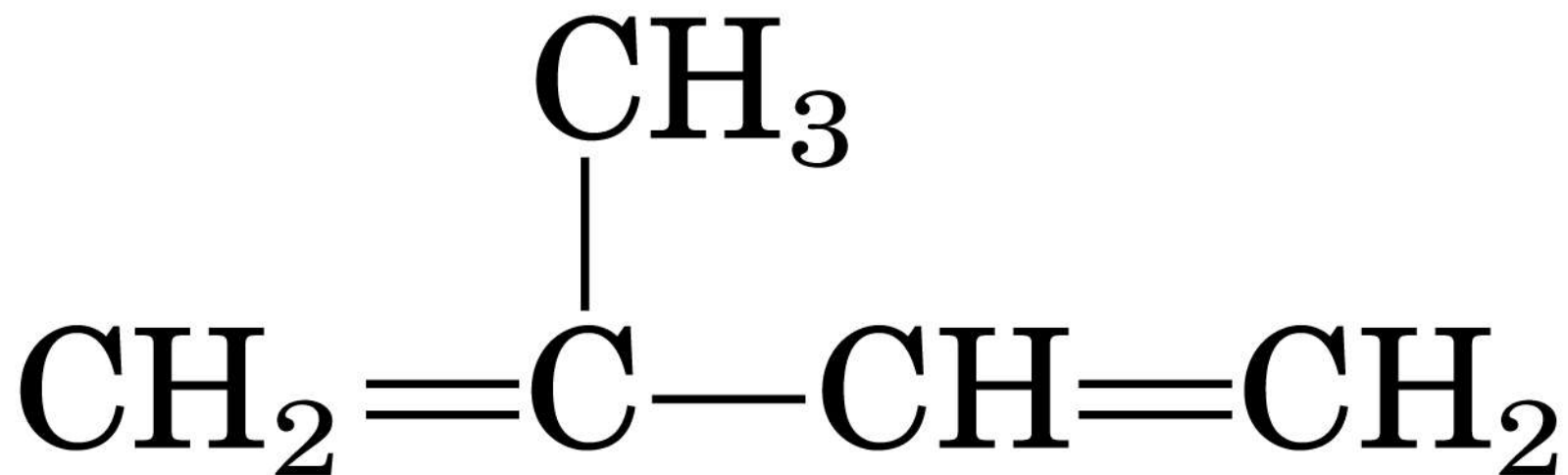
Le tappe della biosintesi del colesterolo:

1. conversione dell'**acetil-CoA** in **mevalonato**. È suddivisa in tre sotto-tappe : le prime due tappe sono reversibili mentre la terza è una tappa **obbligata** che **determina** la velocità della reazione.

2. formazione di unità **isopreniche** attivate (tre gruppi fosfato vengono aggiunti al mevalonato per trasferimento dall'**ATP**). Si forma il Δ^3 -isopentenil pirofosfato. Per **isomerizzazione** di quest'ultimo si forma il **dimetilallil pirofosfato**.

3. (in tre sotto-tappe) si forma lo **squalene** per condensazioni "testa-coda" (prime due tappe) o "testa-testa" (terza tappa) tra le unità isopreniche attivate formatesi nelle reazioni precedenti.

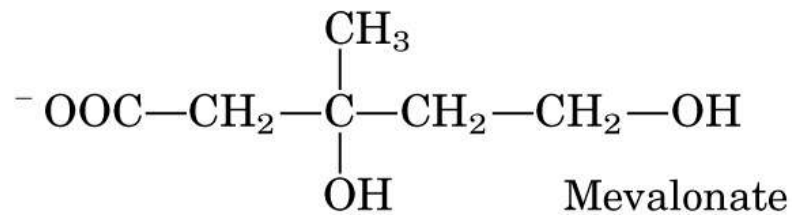
4. lo squalene, lineare, viene **ciclicizzato** e convertito in colesterolo in una serie di reazioni.



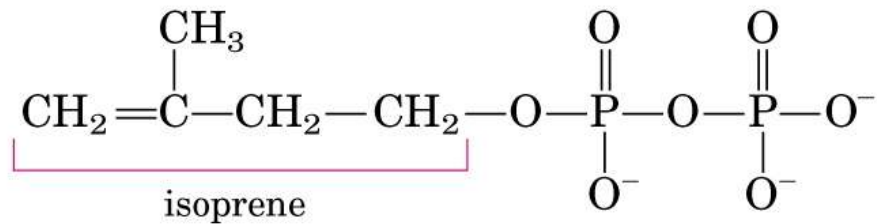
Isoprene

3 $\text{CH}_3\text{—COO}^-$ Acetate

① ↓

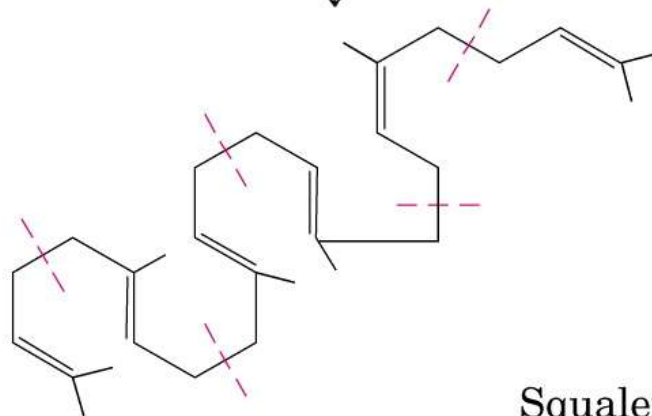


② ↓

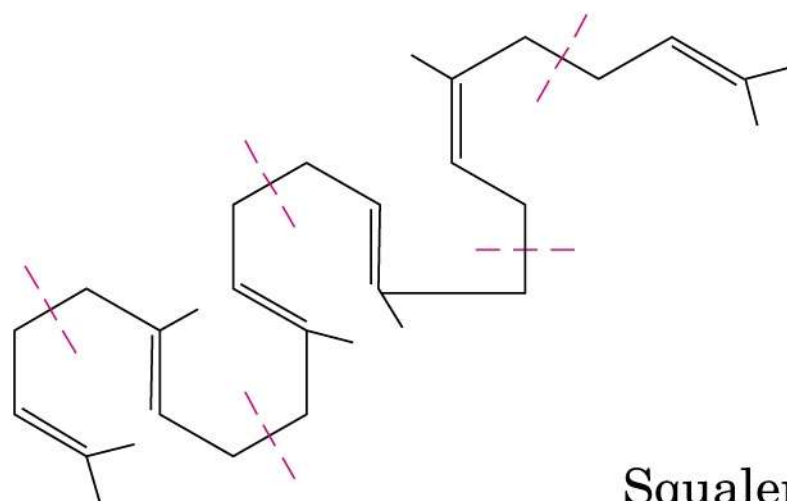


Activated isoprene

③ ↓

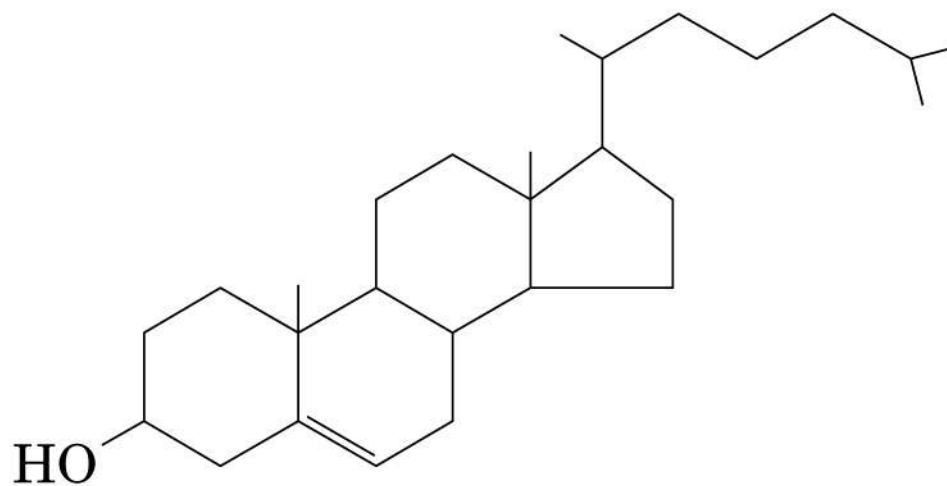


Squalene



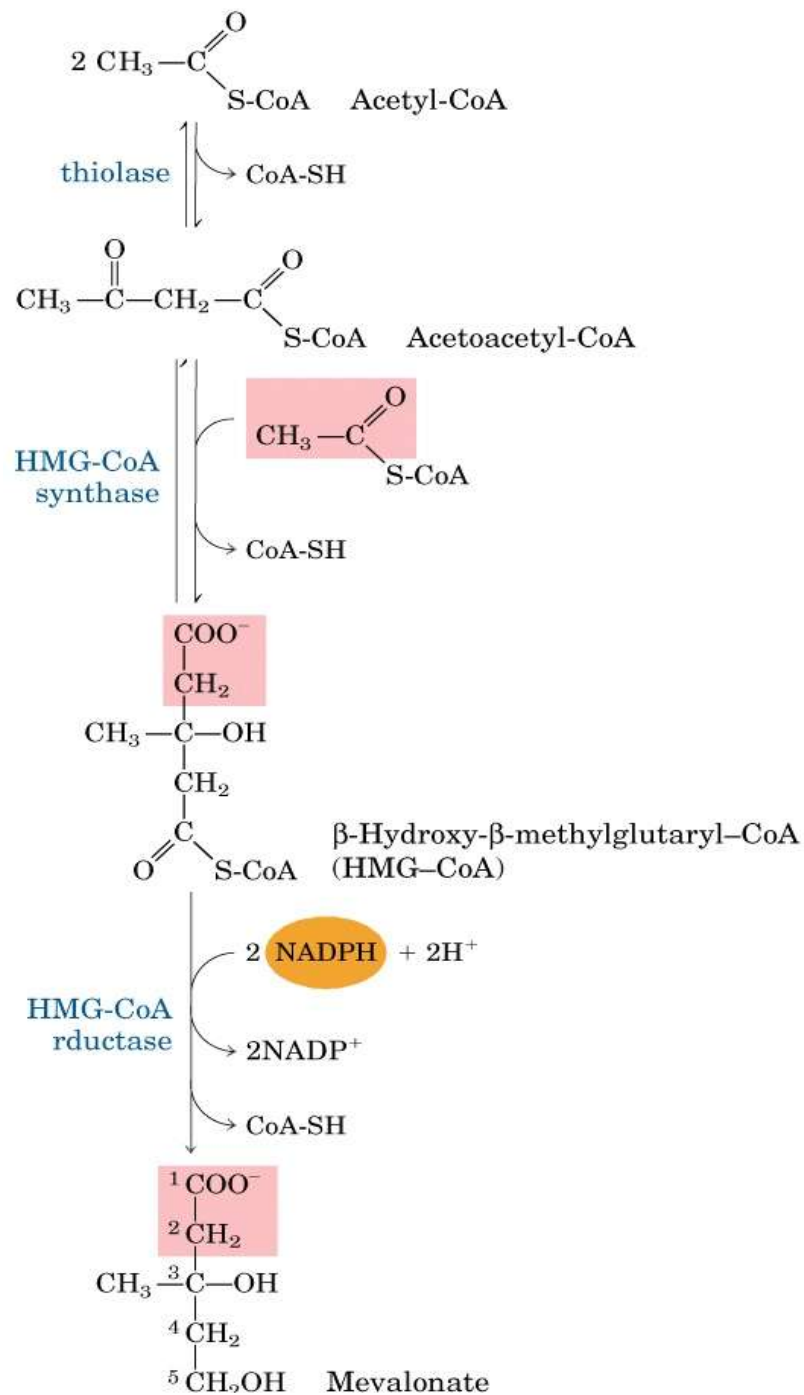
Squalene

④ ↓

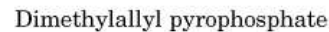


Cholesterol

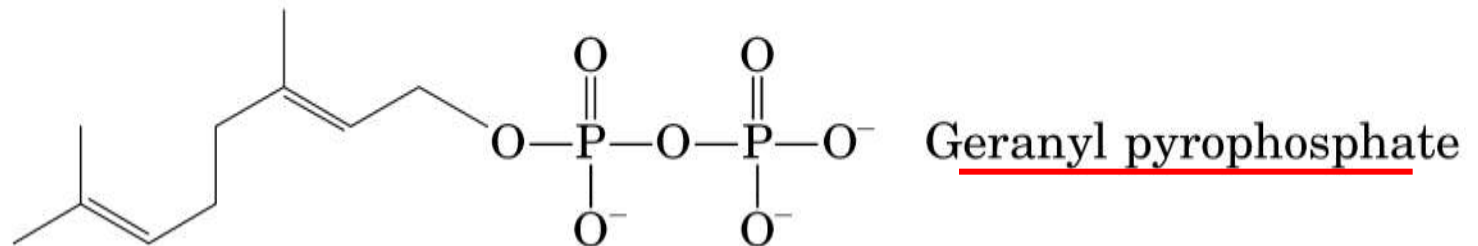
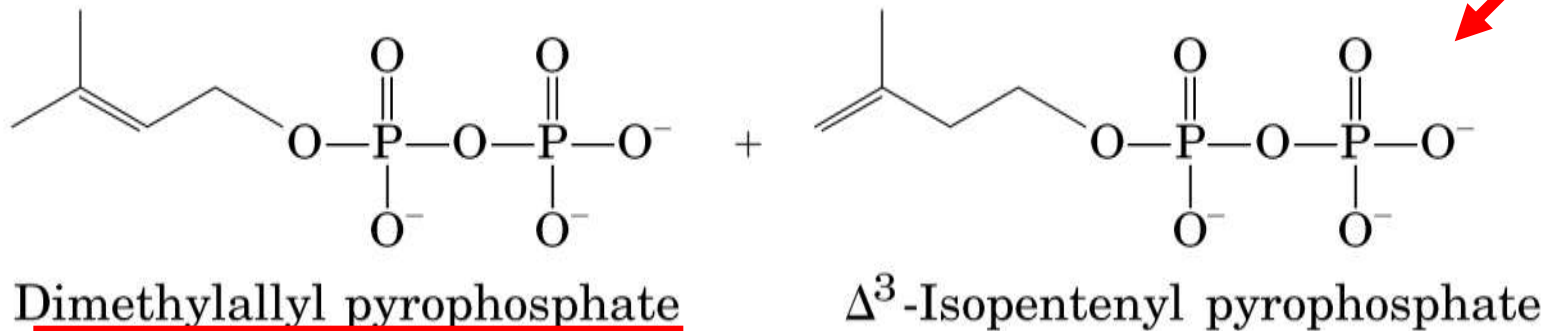
1. conversione dell'acetyl-CoA in mevalonato.

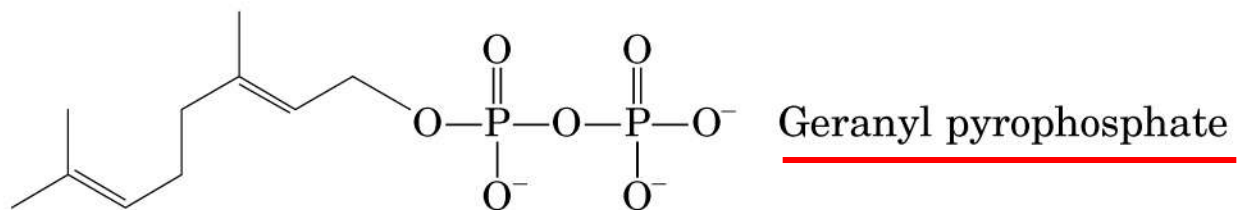


Mevalonate

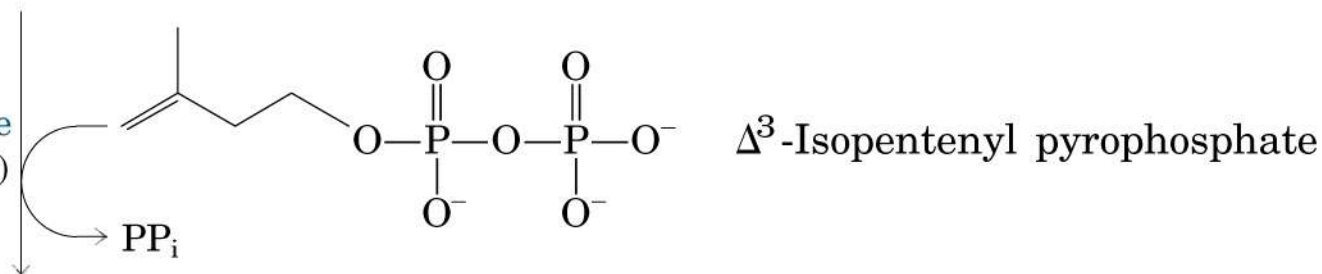


3. (in tre sotto-tappe) si forma lo **squalene**

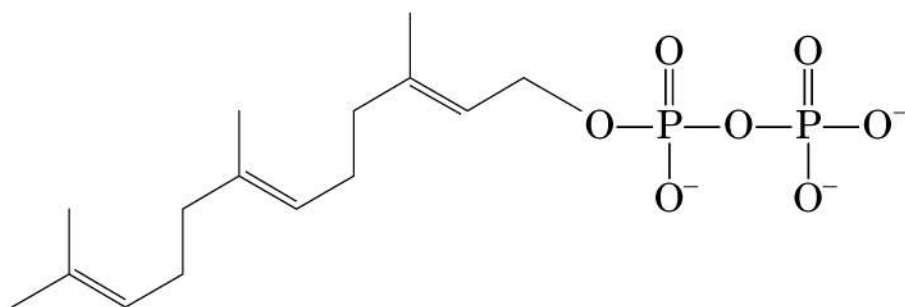


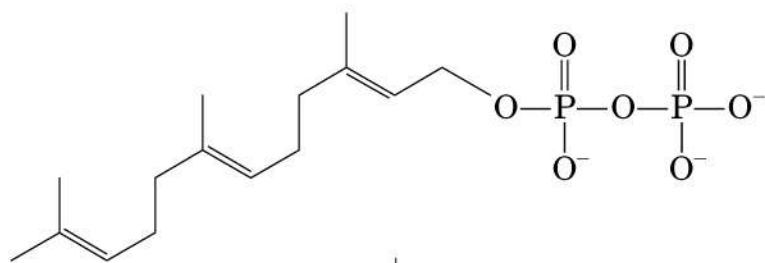


prenyl transferase
(head-to-tail)

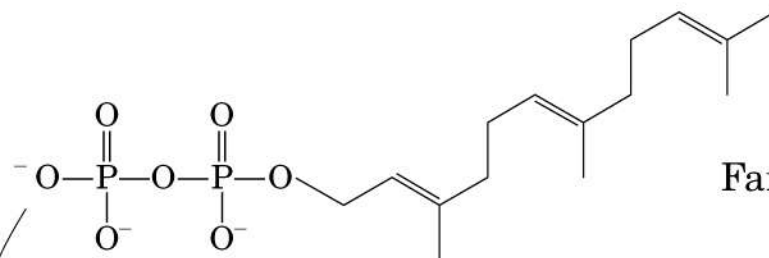


PP_i





Farnesyl pyrophosphate



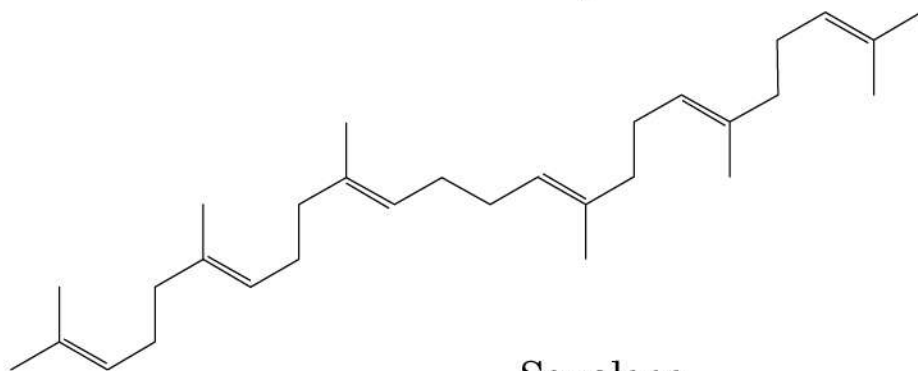
Farnesyl pyrophosphate

squalene synthase
(head-to-head)

NADPH + H⁺

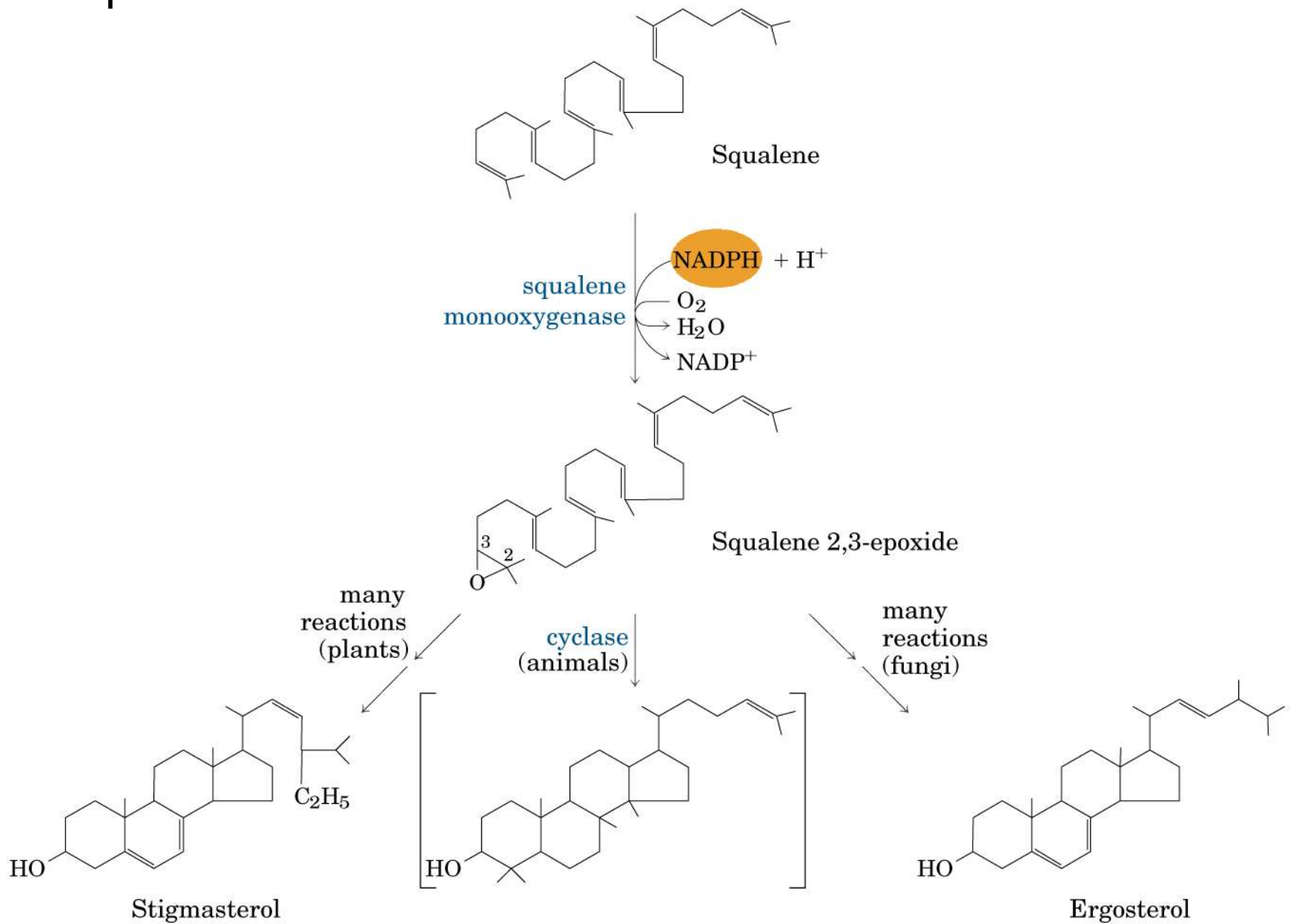
NADP⁺

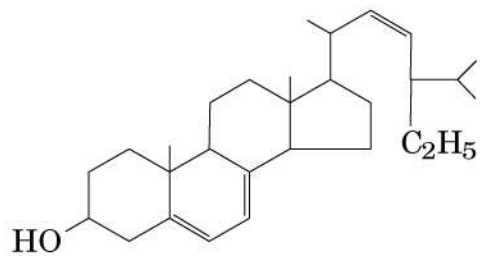
2 PP_i



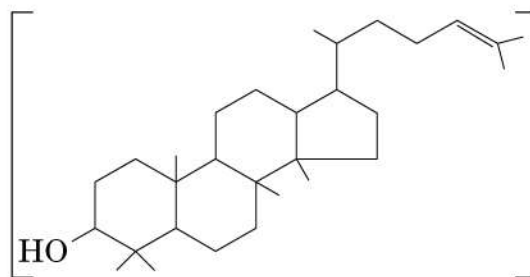
Squalene

4. lo squalene viene **ciclicizzato**

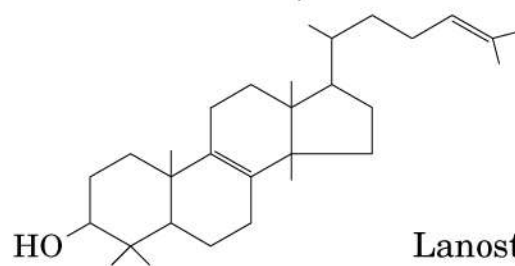




Stigmasterol

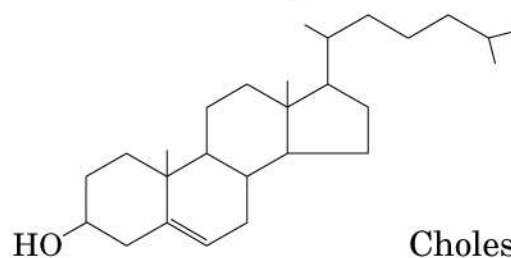


cyclase

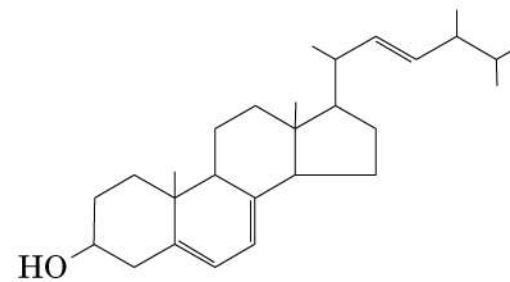


Lanosterol

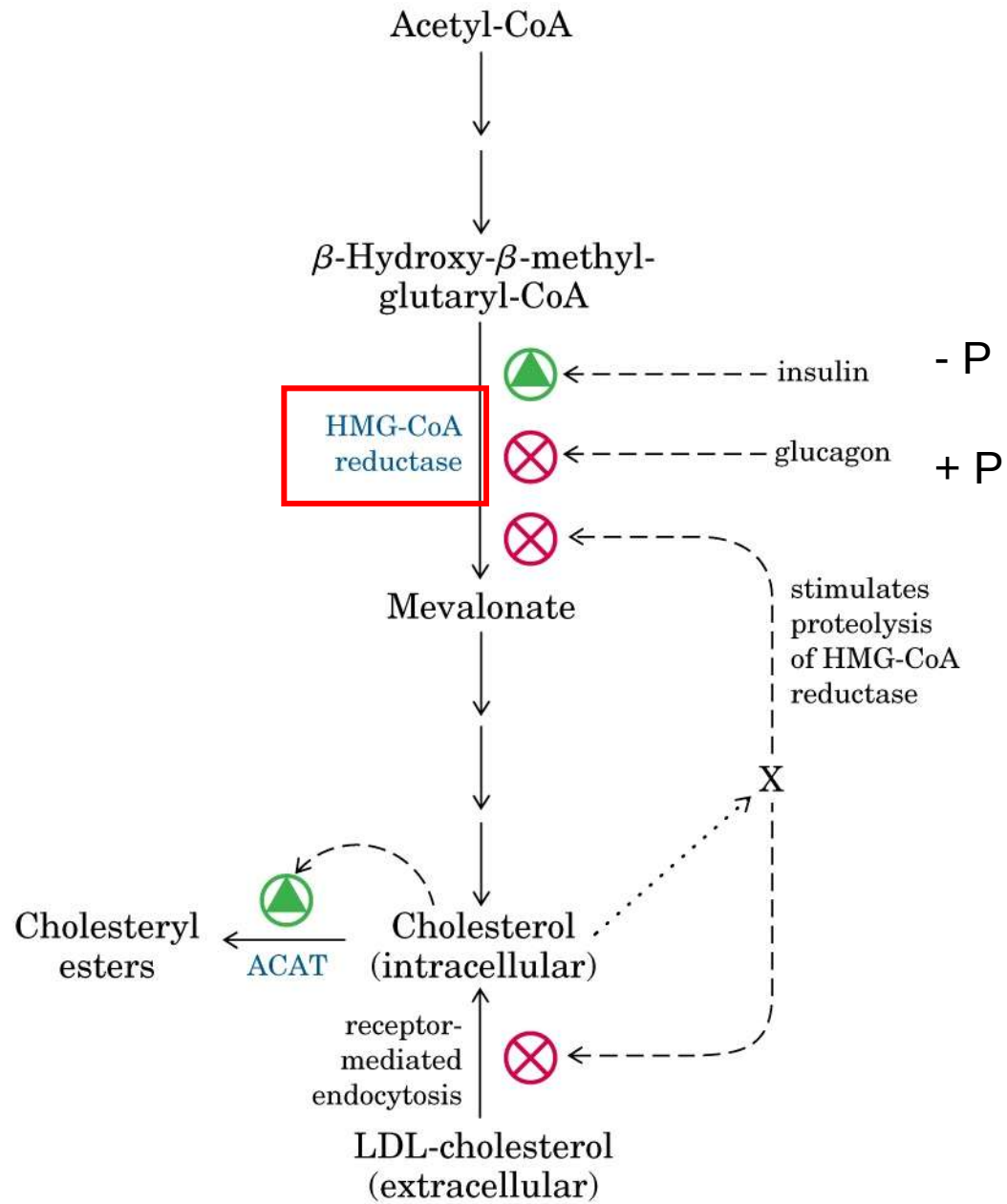
many
reactions

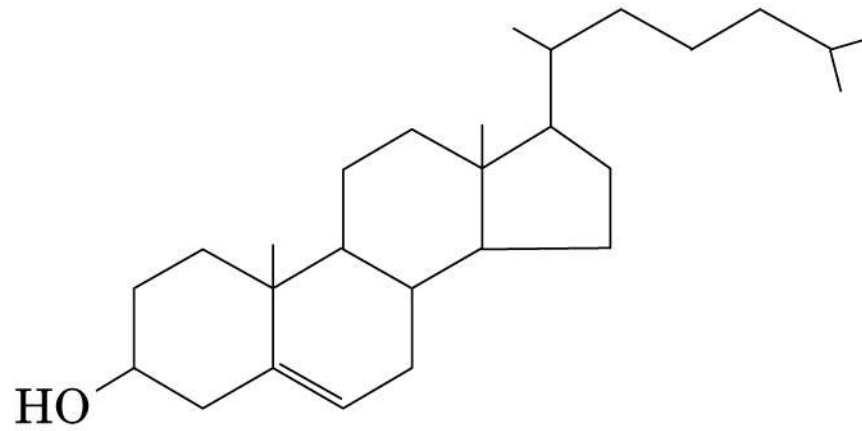


Cholesterol

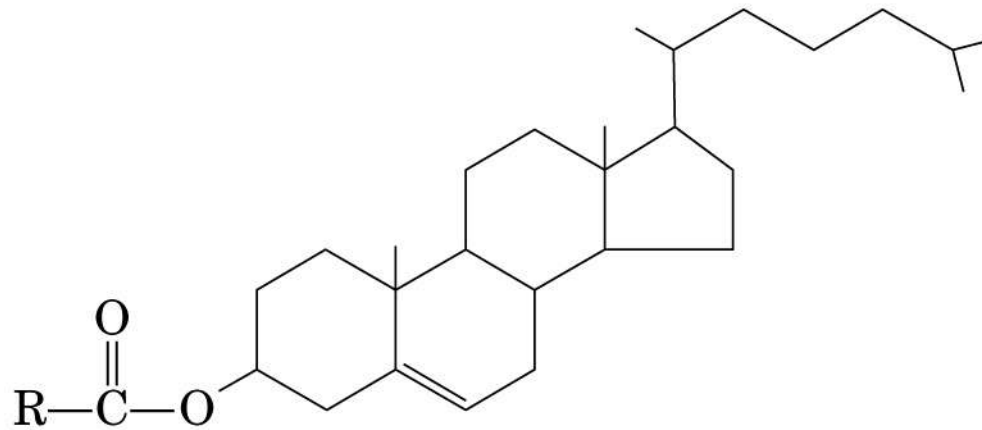
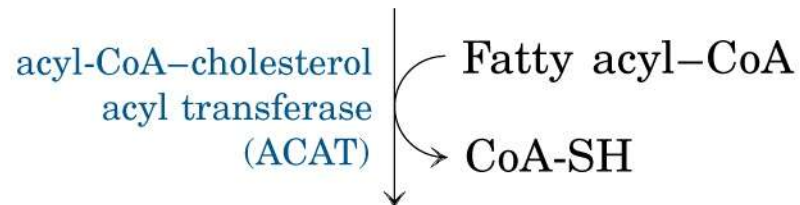


Ergosterol

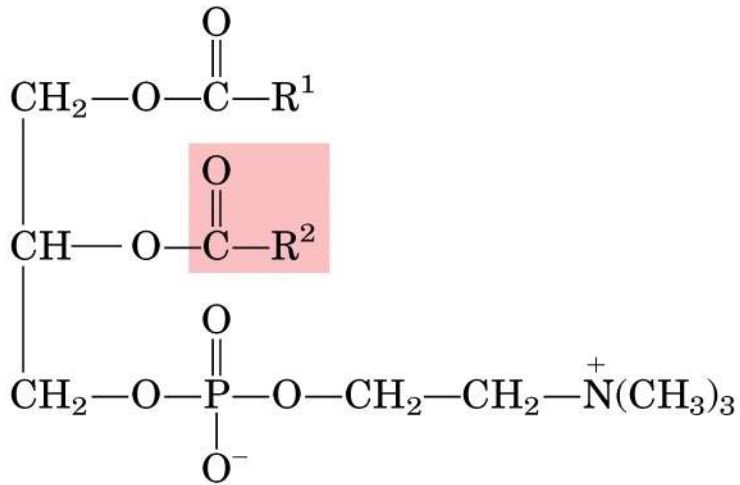




Cholesterol

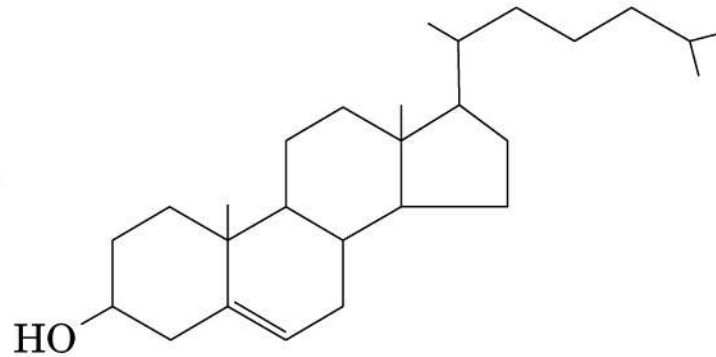


Cholesteryl ester



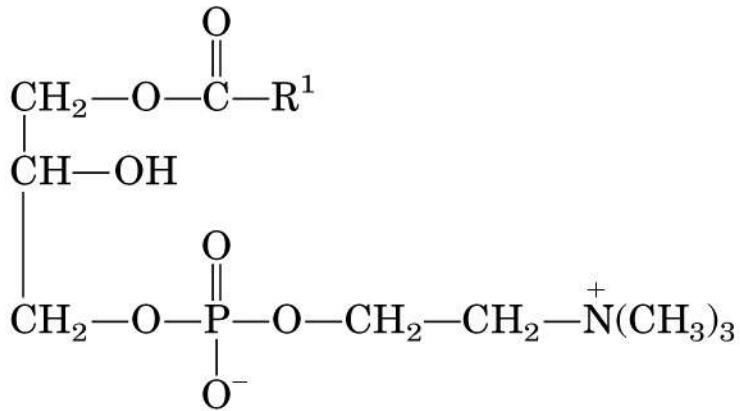
Phosphatidylcholine (lecithin)

+



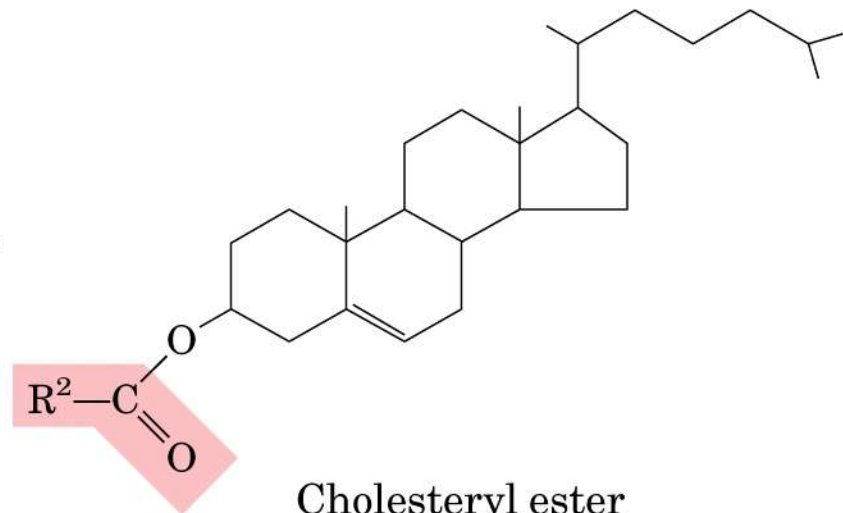
Cholesterol

lecithin-cholesterol
acyl transferase
(LCAT)

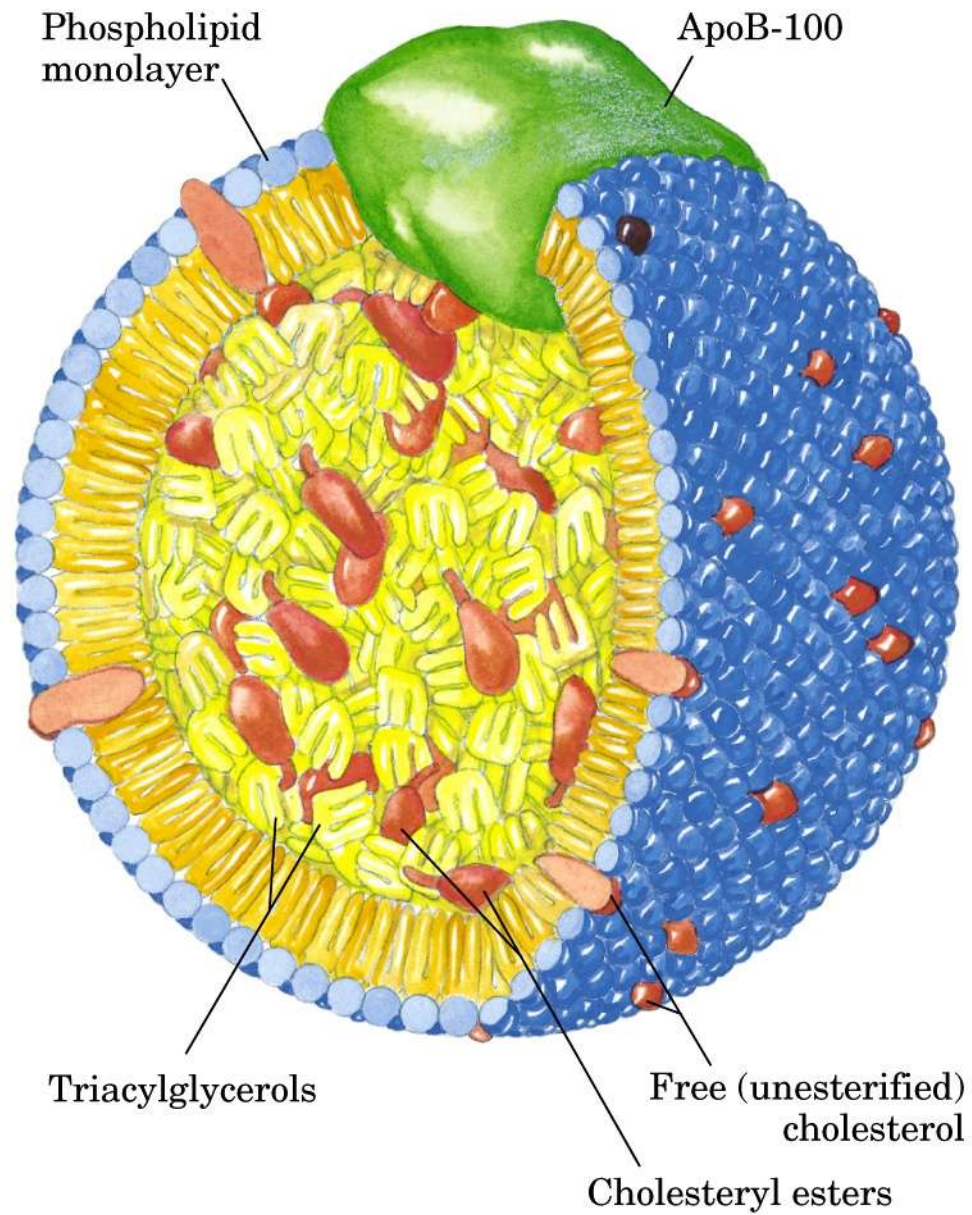


Lysolecithin

+



Cholesteryl ester



(a)

table 21-2

Major Classes of Human Plasma Lipoproteins: Some Properties

Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4



