بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 7

Degradation of F.A. pt.2 + F.A. synthesis pt.1

Written by : DST

Reviewed by : NST

وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الطاهر من كل عيب، المنزّه المبرّأ من كل شر ونقص، لأنه موصوف بصفات الجلال والكمال.

الورود: ورد مرتين في القرآن الكريم.

الشاهد: ﴿ ٱلْمَلِكِ ٱلْقُدُّوسِ ٱلْعَزِيزِ ٱلْحَكِيمِ ﴾ [الجمعة:١] .

٢٢

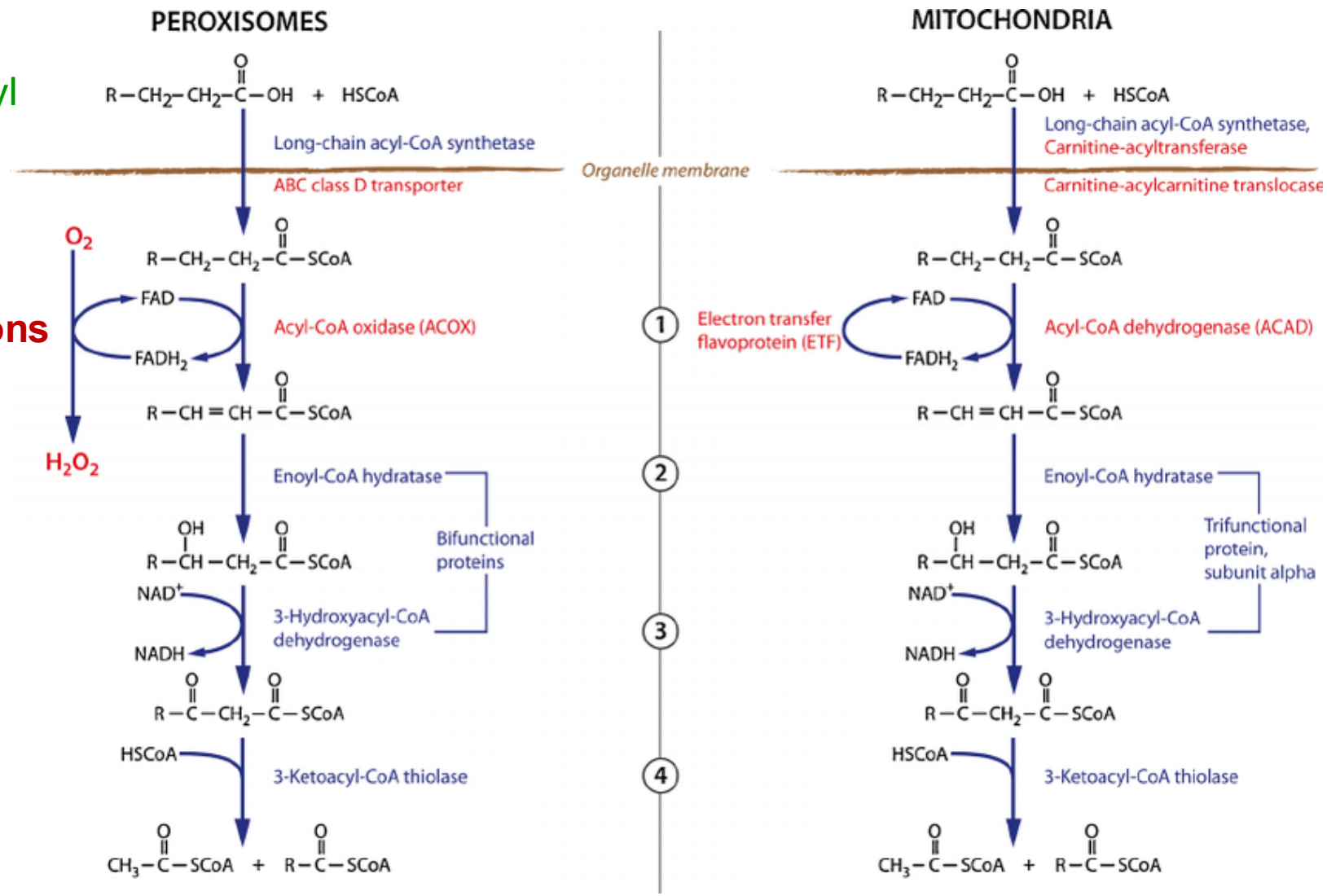
اضغط هنا لشرحٍ أكثر تفصيلًا

Peroxisomal β-oxidation

VLCFA ≥22

FAD Containing acyl CoA Oxidase

Loss of electrons



Peroxisomal β-oxidation / 1

Beta oxidation in the mitochondria can metabolize short- , medium- , and long-chain fatty acids. However, **very long-chain fatty acids (VLCFAs)** undergo beta oxidation in peroxisomes rather than mitochondria due to differences in their transport and enzymatic systems.

- **Transport of VLCFAs into Peroxisomes**

- VLCFAs cross the peroxisomal membrane through a specialized transport system distinct from that of mitochondria. In peroxisomes , the **ABC class D transporter** facilitates the entry of VLCFAs in an inactive form , accompanied by **CoA (coenzyme A)**. Activation of VLCFAs through CoA addition occurs inside the peroxisome.
- In general, fatty acids must be linked to CoA to participate in metabolic reactions, as this activates the acyl chains for subsequent processing.

- **Beta Oxidation in Peroxisomes**

Once activated, the beta oxidation pathway in peroxisomes proceeds similarly to that in mitochondria but with key differences :

1) Oxidation :

- In mitochondria , acyl-CoA dehydrogenase catalyzes the first oxidation step, reducing FAD to $FADH_2$, which enters the electron transport chain to produce energy.
- In peroxisomes , the enzyme acyl-CoA oxidase performs this step. Instead of contributing $FADH_2$ to the electron transport chain , $FADH_2$ is re-oxidized to FAD, reducing oxygen to hydrogen peroxide (H_2O_2) , a reactive oxygen species.
- This distinction results in less energy production during beta oxidation in peroxisomes compared to mitochondria.

Peroxisomal β-oxidation / 2

2) Hydration :
The enzyme enoyl-CoA hydratase creates an alcohol group .

3) Second Oxidation :
3-Hydroxyacyl-CoA dehydrogenase catalyzes the oxidation of the alcohol group , reducing NAD to NADH. This step is similar to the process in mitochondria.

4) Cleavage :
3-Ketoacyl-CoA thiolase cleaves the fatty acid chain, adding another CoA molecule and producing a shortened fatty acyl-CoA chain.

- **Structural and Functional Differences between mitochondrial and peroxisomal oxidation**

- Transport Process
- The hydratase and 3-hydroxacyle dehydrogenase enzymes in peroxisomes are bifunctional proteins , whereas in the mitochondria they are trifunctional proteins.
- The overall process is less energy-efficient in peroxisomes due to the generation of hydrogen peroxide instead of ATP from $FADH_2$.

Diseases Associated with Peroxisomal Beta Oxidation

- **Zellweger syndrome : a peroxisomal biogenesis disorder**

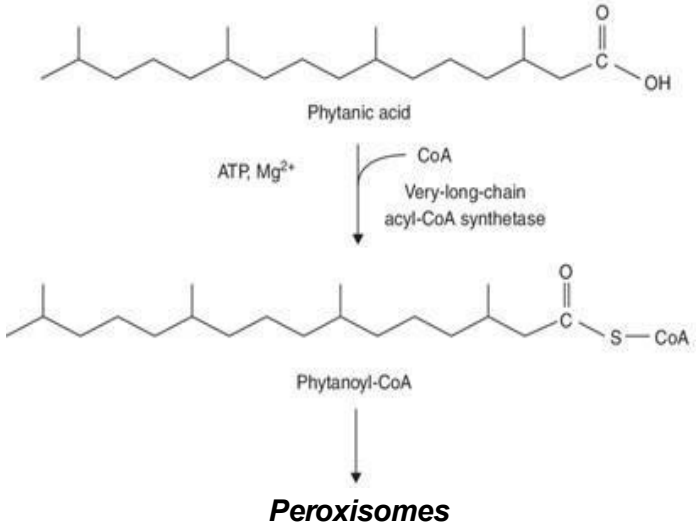
A disorder caused by defective peroxisome (which is a dynamic organelle) biogenesis. As a result, peroxisomal functions , including beta oxidation and detoxification of oxidative stress, are impaired.

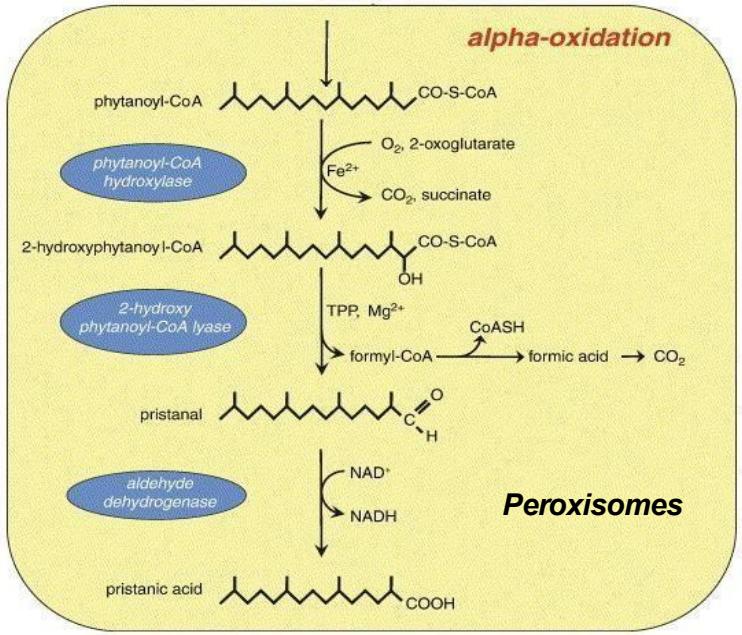
- **X-linked adrenoleukodystrophy: dysfunctional transport VLCFA across the peroxisomal membrane (Accumulation of VLCFAs)**

A genetic condition characterized by impaired transport of VLCFAs into peroxisomes due to defective ABC class D transporters. This leads to the accumulation of VLCFAs , causing cellular damage and neurological dysfunction.

Peroxisomal α-oxidation of branched chain FAs

- Phytanic acid is a breakdown product of Chlorophyll.
- It is activated by CoA , transported into peroxisome , hydroxylated by phytanoyl CoA α-hydroxylase (PhyH) and carbon 1 is released as CO2 (unlike beta oxidation) .
- When fully degraded , it generates formyl-CoA , propionyl-CoA , acetyl-CoA , and 2-methyl-propionyl- CoA.





Refsum disease is an autosomal recessive disorder caused by a deficiency of peroxisomal PhyH.

PLEASE SEE NEXT SLIDE

Peroxisomal α-oxidation of branched chain FAs

This pathway is used for branched-chain fatty acids like phytanic acid , which is a product of chlorophyll breakdown. Although phytanic acid is saturated , it contains branches that make it unsuitable for beta-oxidation.

- **Activation:**

Initially , very-long-chain acyl-CoA synthetase activates phytanic acid outside the peroxisome by attaching a CoA group , forming phytanoyl-CoA , which is now active and ready for peroxisomal metabolism.

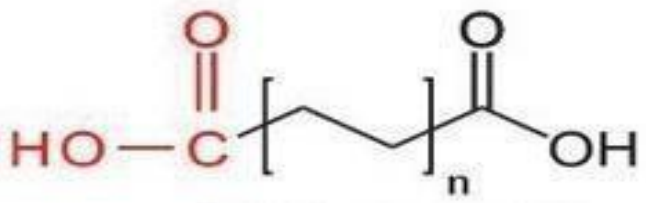
- **Alpha-Oxidation Process in Peroxisomes :**

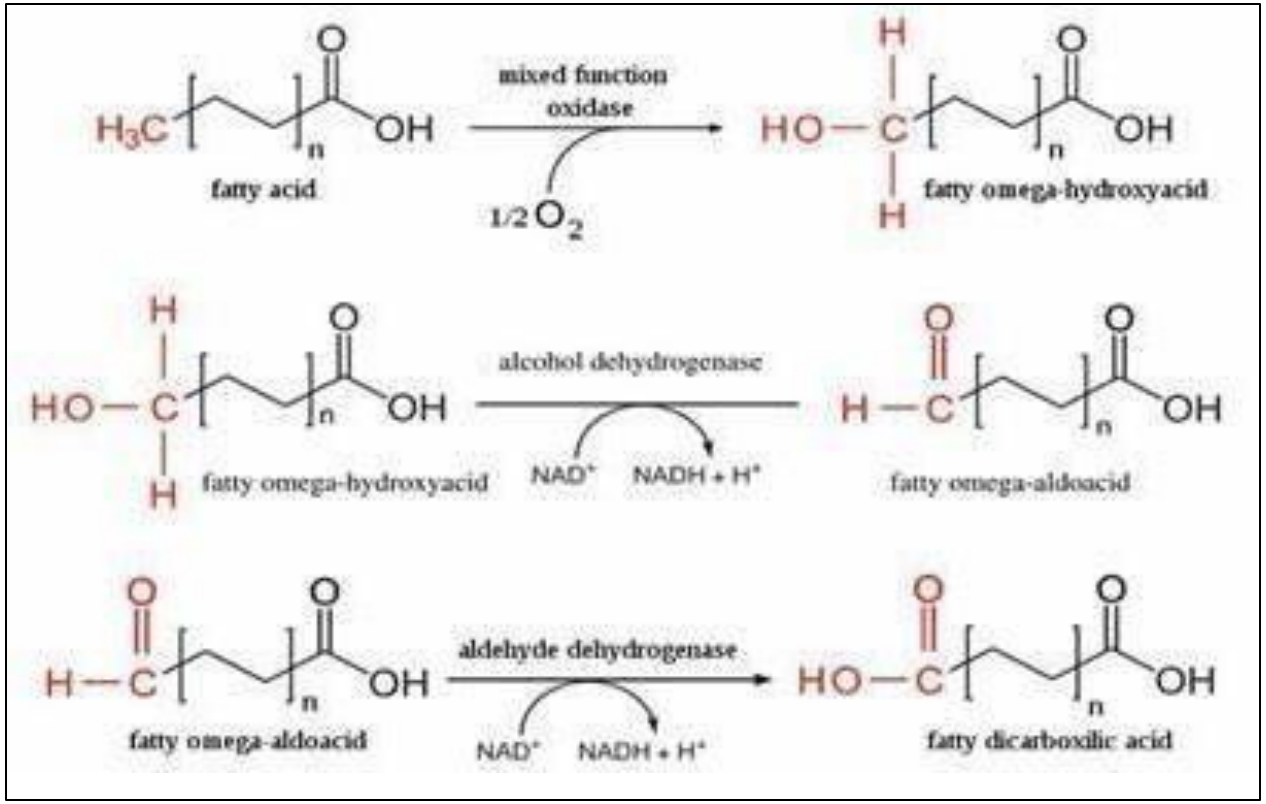
- Phytanoyl-CoA hydroxylase introduces a hydroxyl (-OH) group on the alpha-carbon
- This facilitates the cleavage of the carbonyl group with CoA by **2-hydroxy phytanoyl-CoA lyase** , releasing it as formyl-CoA , which is further broken down (by removing CoA) to formic acid and then CO_2.
- The remaining hydroxyl group is oxidized to form an aldehyde via **2-hydroxy phytanoyl-CoA lyase** , resulting
- in the production of pristanal.
- Pristanal undergoes further oxidation to a carboxyl group using **aldehyde dehydrogenase** , with NAD^+ reduced to NADH , forming pristanic acid.

- The cycle repeats until the fatty acid is completely metabolized. However, due to the branches , subsequent cycles may produce varying products , including formyl-CoA , acetyl-CoA , propionyl-CoA , or methyl- propionyl-CoA , depending on the structure of the acid.

ω-Oxidation

- ω-Oxidation is a minor pathway of the SER (smooth endoplasmic reticulum)
- It generates dicarboxylic acids.
- It is upregulated in certain conditions such as MCAD (medium-chain acyl-CoA dehydrogenase) deficiency.



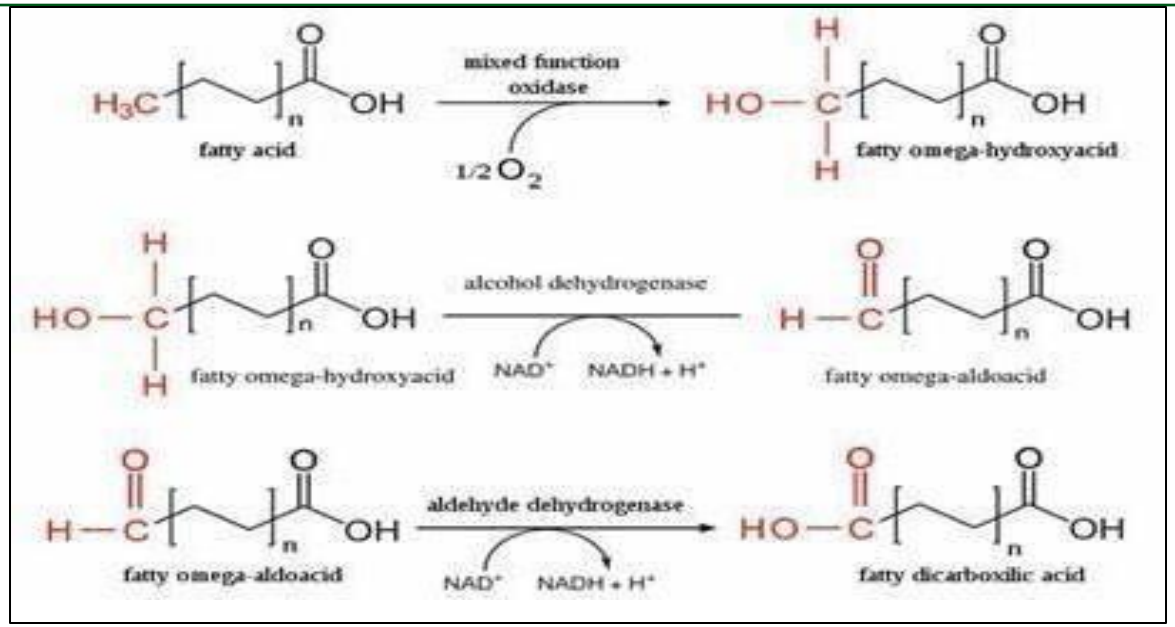


ω-Oxidation

- This minor oxidation pathway targets the omega (last) carbons of the fatty acid chain , opposite the carboxyl group. It typically occurs in the SER as a minor pathway but becomes significant under certain conditions , such as (MCAD) deficiency.

- An **oxidase** introduces a hydroxyl (-OH) group at the omega carbon , converting it into an alcohol.
- **Alcohol dehydrogenase** oxidizes the alcohol to an aldehyde , producing NADH.
- **Aldehyde dehydrogenase** oxidizes the aldehyde to a carboxyl group , producing NADH .

- Once the omega carbon is converted into a carboxyl group, the fatty acid is ready for cleavage from the omega side. The process repeats multiple times .



Lipids and energy

- TAGs are the body's major fuel storage reserve.
- The complete oxidation of fatty acids to CO2 and H2O generates 9 kcal/g of fat (as compared to 4 kcal/g protein or carbohydrate). Why?

	carbohydrates	lipids
Stored as...?	Starch - plants Glycogen - animals	Fats & oils (plants Fat (animals)
Long/short term storage?	Starch: long-term Gylcogen: short-term	Long term
Ease of digestion/ release of energy?	Easy to release energy	Harder to release energy (needs more oxygen)
Energy per gram?	17kJ/g	38kJ/g
Solubility in water? (and consequence)	Soluble	Not soluble
Use of oxygen in metabolism? (and consequence)	Needs less oxygen, useful for high-demand activity	Needs more oxygen, less efficient to release energy

Lipids and energy

- Lipids : Each gram of lipids provides approximately 9 kcal (38 kJ) , making them energy-dense. However, lipid oxidation is a slower and more complex process , involving hormonal regulation and the release of fatty acids from adipocytes.
- Carbohydrates : Provide 4 kcal (17 kJ) per gram but serve as the body's first source of energy because their metabolism is faster and more efficient.
- Lipid oxidation during fasting is limited due to the diversion of oxaloacetate for gluconeogenesis. As a result , some acetyl-CoA from fatty acid oxidation is used for energy , while the rest contributes to ketogenesis.
- NOTE: some tissues produce fatty acids but for other purposes not for energy production, so all tissues uptake fatty acids from bloodstream for energy production

	carbohydrates	lipids
Stored as...?	Starch - plants Glycogen - animals	Fats & oils (plants Fat (animals)
Long/short term storage?	Starch: long-term Gylcogen: short-term	Long term
Ease of digestion/ release of energy?	Easy to release energy	Harder to release energy (needs more oxygen)
Energy per gram?	17kJ/g	38kJ/g
Solubility in water? (and consequence)	Soluble	Not soluble
Use of oxygen in metabolism? (and consequence)	Needs less oxygen, useful for high-demand activity	Needs more oxygen, less efficient to release energy

Exercise and sources of energy

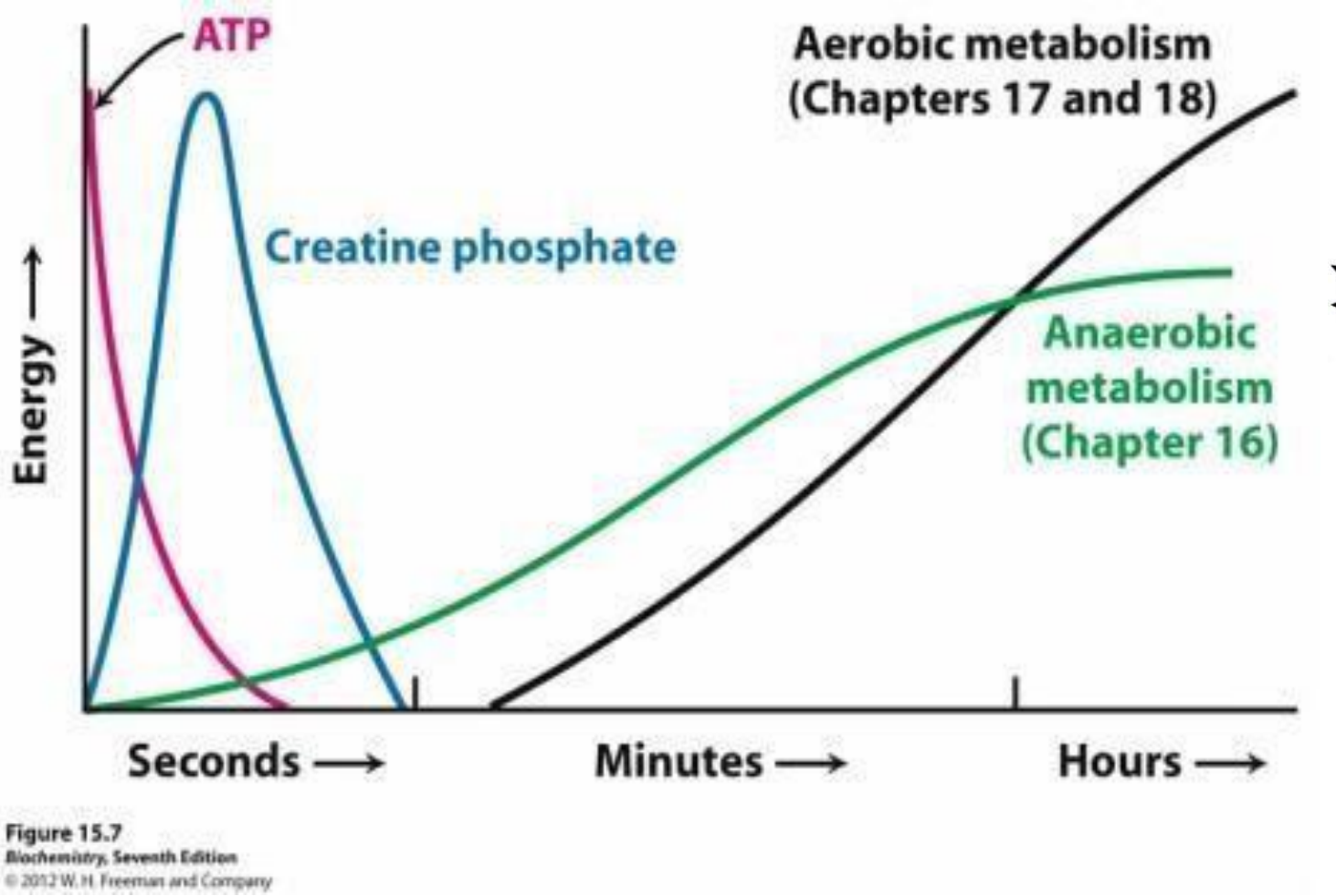
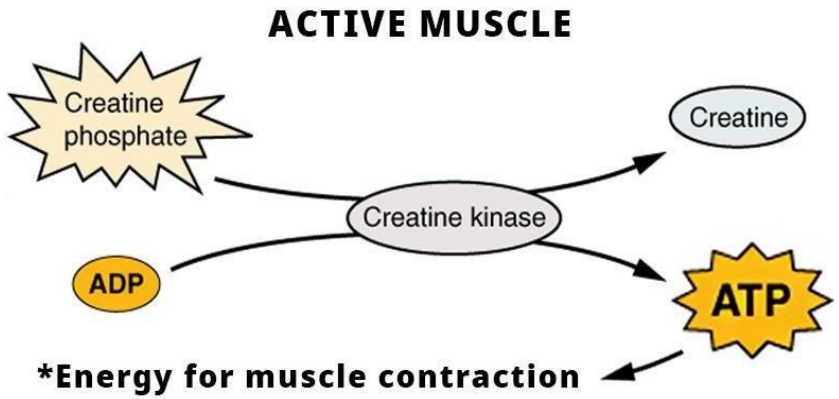


Figure 15.7
Biochemistry, Seventh Edition



Exercise and sources of energy

Muscle energy demands increase significantly during exercise . The sequence of energy utilization is as follows :

- **Immediate ATP Use :**

ATP already present in cells is consumed first , but its concentration rapidly decreases.

- **Creatine Phosphate :**

This high-energy phosphate compound provides a quick energy boost by hydrolysis , but its supply depletes rapidly within seconds.

- **Anaerobic Respiration :**

Activated before aerobic respiration , anaerobic metabolism provides a fast , albeit less efficient , energy source. This is because oxygen delivery to tissues delays as the heart and respiratory rates adjust to increased demands.

- **Aerobic Respiration :**

Once oxygen availability improves , aerobic respiration becomes the predominant energy provider. However , this shift requires time due to its dependency on oxygen delivery and transport mechanisms.

Thus , during exercise , energy initially relies on ATP , creatine phosphate , and anaerobic respiration before transitioning to the more sustainable aerobic respiration pathway.
Initially, aerobic respiration is inhibited due to the presence of high concentration of ATP

Synthesis of fatty acids

Dr. Diala Abu-Hassan

Lippincott's Biochemistry, Ch. 16

Fatty Acid Synthesis

- Excess carbohydrates and proteins in diet will be used to synthesize fatty acids and stored as TAGs.
- Occurs in liver, lactating mammary glands and adipose tissue
- Requires :
  - Carbon Source : Acetyl CoA
  - Reducing Power : NADPH
  - Energy Input : ATP

Fatty acid synthesis is an anabolic pathway that occurs in the well-fed state when energy and nutrients are abundant. It is primarily triggered by excess carbohydrates and proteins in the diet, not dietary fats. The goal is energy storage as triacylglycerols (TAGs) and incorporation into membrane lipids, not immediate energy production.

Fatty Acid Synthesis

- **Carbohydrates :**
- Excess glucose leads to increased glycolysis, generating acetyl-CoA through pyruvate oxidation.
- Acetyl-CoA enters the Krebs cycle, where high levels of citrate signal energy sufficiency. Citrate exits the
- mitochondria and contributes to fatty acid synthesis.
- The synthesized fatty acids are stored as triacylglycerols in adipocytes.
- Can be used to produce glycerol.

- **Proteins :**
- Amino acids from dietary proteins cannot be stored directly. They are either used for protein synthesis , converted into nitrogen-containing compounds , or catabolized for energy.
- Excess amino acids can be converted into acetyl-CoA (via specific pathways) , fueling fatty acid synthesis and
- subsequent storage as triacylglycerols.

- **Major Sites of Fatty Acid Synthesis**
- Adipocytes : Serve as primary storage sites for triacylglycerols.
- Liver : Synthesizes fatty acids for lipoproteins (e.g., LDL, cholesterol esters) and other metabolic needs.
- Lactating Mammary Glands : Under the influence of prolactin , fatty acid synthesis is upregulated to produce the short- and medium-chain fatty acids essential for breast milk.

- The raw material to be used is Acetyl-CoA. Since the degenerative pathway involves oxidation , the corresponding biosynthetic pathway is expected to follow a reductive process. In this pathway , the main substrate undergoes reduction , while the coenzyme NADPH is oxidized to NADP+. Conversely , during the degenerative pathway , NAD+ is reduced to NADH , or FAD is reduced to FADH2.

Why Energy ?

Fatty Acid	Acetyl CoA	Acetyl CoA + n(ATP)
↓	↓	↓
↓	↓	↓
↓	↓	↓
↓	↓	↓
Acetyl CoA	Fatty Acid	Fatty Acid + n(ADP)
ΔG^{o} : -ve	ΔG^{o} : +ve	ΔG^{o} : -ve

- Energy is required in this process, as it is an anabolic pathway. In contrast, during fatty acid degradation, Acetyl-CoA is produced , and energy is not extensively consumed , except in a single step : the activation step , where CoA is added. This step requires 1 ATP , which is hydrolyzed to AMP (effectively breaking two phosphate bonds) . Overall, when summing the ΔG values of the degradation pathway , the reactions are negative , making it an energy-producing pathway.

- On the other hand , the reverse process starts with Acetyl-CoA and leads to fatty acid synthesis. This is expected to have a positive ΔG , requiring energy input. To drive the reaction forward , coupling with ATP hydrolysis is necessary to make the overall ΔG negative , allowing the reaction to proceed efficiently.

Overview of fatty acid synthesis

- **The fatty acids are synthesized by:**

1. Production of malonyl CoA
2. Binding of acetyl CoA and malonyl CoA to the fatty acid synthase
3. Condensation of acetyl CoA and malonyl CoA
4. Elongation of the acyl CoA by 2 carbons per round (spiral pathway)
   - Reduction, dehydration, reduction
5. Binding of malonyl CoA
6. Repeat steps 3 (acyl CoA), 4, and 5
7. Release of the hydrocarbon chain by a thioesterase (TE)

Which is a three carbon molecule

Complex enzyme

One carbon will be removed as CO_2 by decarboxylation

The extra carbonyl group is removed

Don't worry if you don't understand this slide , it will be clearer when the entire pathway is explained

FA Degradation and Synthesis

Acyl CoA $_{(n)}$

↓ Oxidation

↓ Hydration

↓ Oxidation

↓ Thyolysis

Acyl CoA $_{(n-2)}$ + Acetyl CoA

Acyl CoA $_{(n+2)}$

↑ reduction

↑ dehydration

↑ reduction

↑ condensation

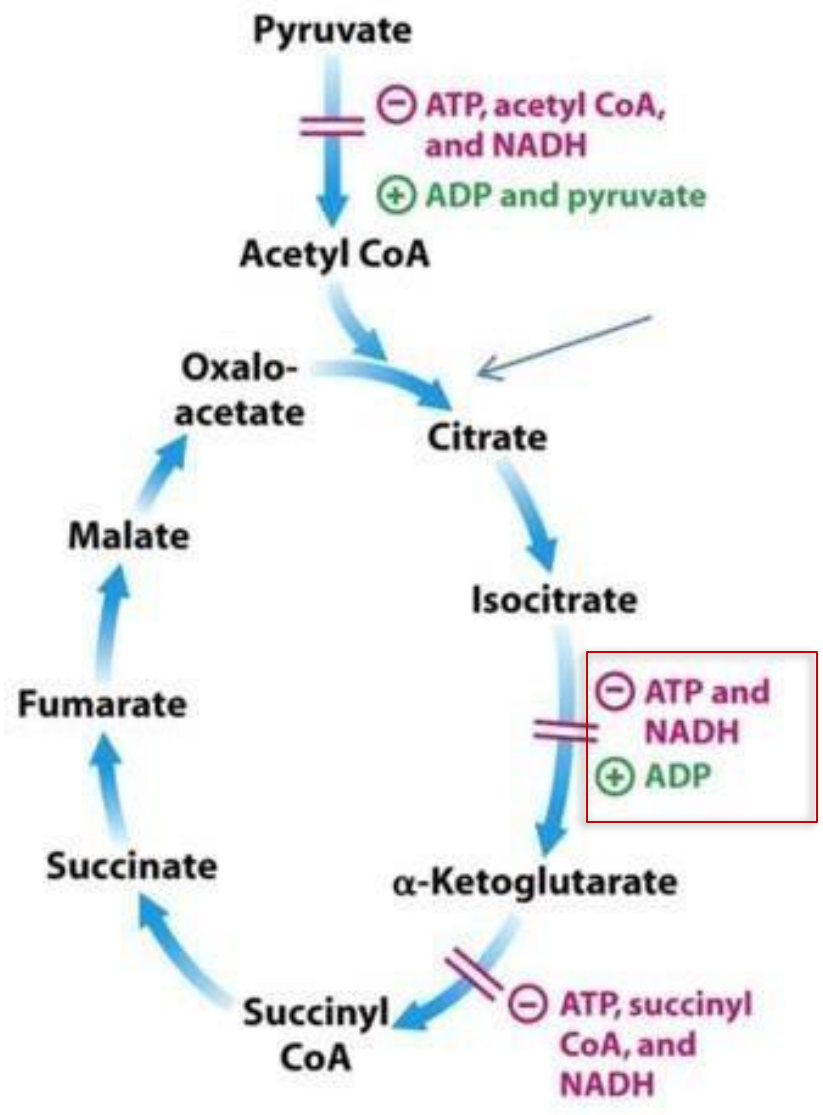
Acyl CoA$_{(n)}$ + Malonyl CoA

FA Degradation and Synthesis

	Degradation	Synthesis
Starting substrate	**Acyl CoA $_{(n)}$**	**Acetyl CoA $_{(n)}$ + Malonyl CoA**
First step	**Oxidation : Formation a double bond**	**Condensation : Combining acetyl group with malonyl group followed by malonyl CoA binding**
Second step	**Hydration : Converting double bond to an alcohol**	**Reduction : Removal of oxygen and double bond**
Third step	**Oxidation : Converting alcohol to a carbonyl**	**Dehydration : Eliminating oxygen**
Fourth step	**Thyolysis : cleavage of acetyl CoA and reformating an acyl CoA $_{(n-2)}$**	**Reduction : Formation of Acyl CoA group (fatty acid)**
Products	**Acyle CoA (n-2) + Acetyl CoA**	**Acyl CoA $_{(n+2)}$**

Fatty acid synthesis and degradation are excellent examples of spiral metabolic pathways, characterized by repeated cycles of similar reactions. These processes are highly regulated to ensure metabolic efficiency and adaptability to physiological conditions, such as energy demand or nutrient availability.

Transport of acetyl-CoA from mitochondria



Glucose can be converted to fat, but fat cannot be converted to glucose.

When ATP increases:

↓

ATP inhibits isocitrate dehydrogenase

↓

Citrate is transported into the cytosol

↓

Citrate is cleaved into oxaloacetate and acetyl CoA by ATP citrate lyase

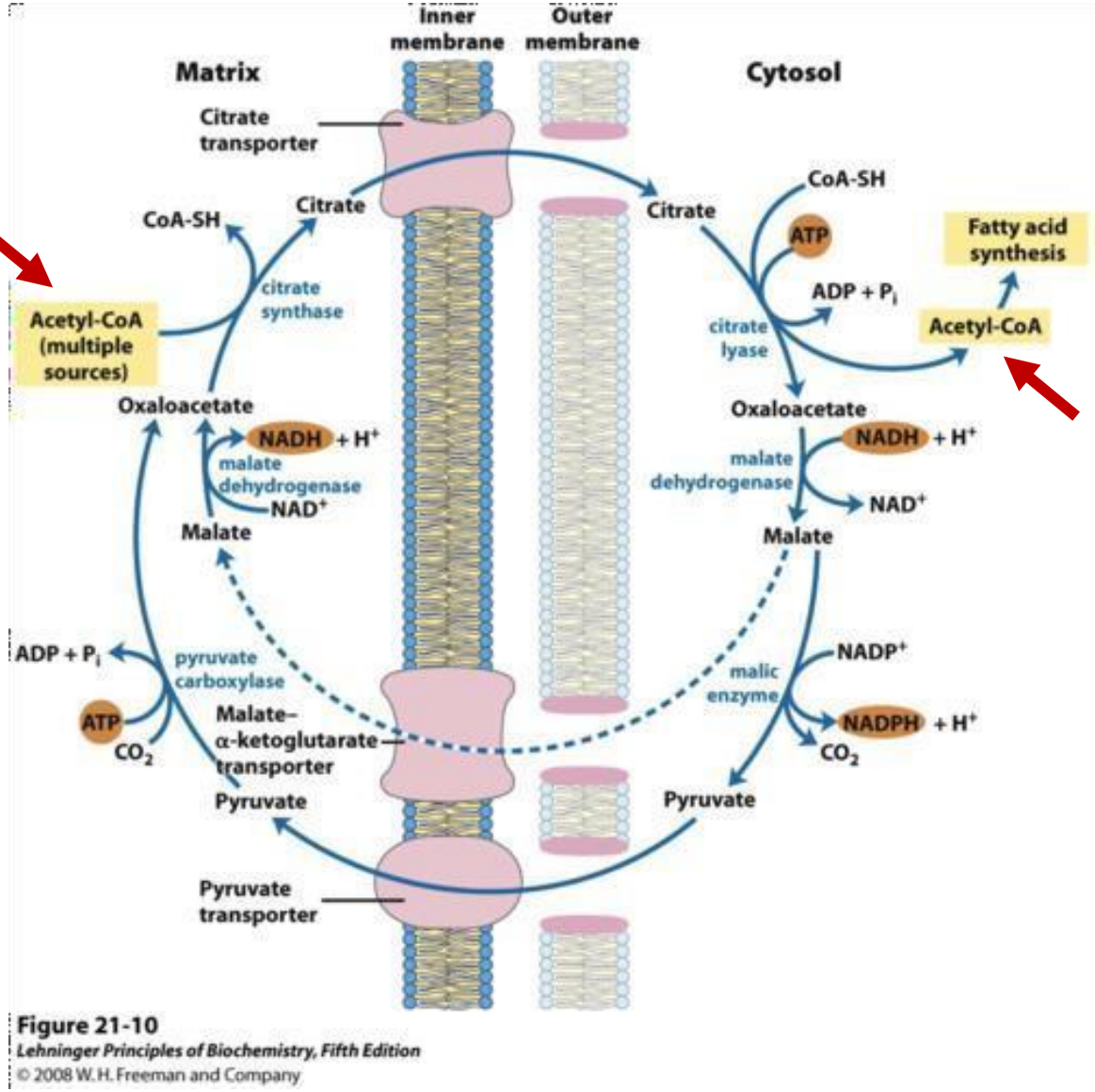


Figure 21-10
Lehninger Principles of Biochemistry, Fifth Edition

Transport of acetyl-CoA from mitochondria to cytoplasm

- **Cytosolic Acetyl-CoA Formation :**
- Isocitrate dehydrogenase undergoes inhibition, resulting in Isocitrate accumulation, and the isomerase enzyme responsible for converting citrate to isocitrate will work in the reverse direction as it's a reversible enzyme leading to citrate accumulation.
- In the well-fed state , high glucose levels increase pyruvate and acetyl-CoA production.
- Citrate , generated in the Krebs cycle , exits the mitochondria via its specific transporter.
- In the cytosol , citrate is cleaved by citrate lyase into acetyl-CoA and oxaloacetate , utilizing ATP and CoA.

- **Oxaloacetate Recycling :**
- Oxaloacetate is reduced to malate via malate dehydrogenase.
- Malate re-enters the mitochondria to participate in the Krebs cycle.

- **Acetyl CoA now is available for fatty acids synthesis**

1. High ATP in well-fed state inhibits isocitrate dehydrogenase in Krebs cycle.
2. Isocitrate accumulates, and via reversible aconitase reaction, citrate accumulates.
3. Citrate exits to cytosol via citrate transporter.
4. ATP-citrate lyase cleaves citrate to oxaloacetate (OAA) + acetyl-CoA.

5. OAA recycling:

OAA → malate (by cytosolic malate dehydrogenase, uses NADH).
Malate can re-enter mitochondria OR be converted to pyruvate + NADPH by malic enzyme (extra NADPH source).

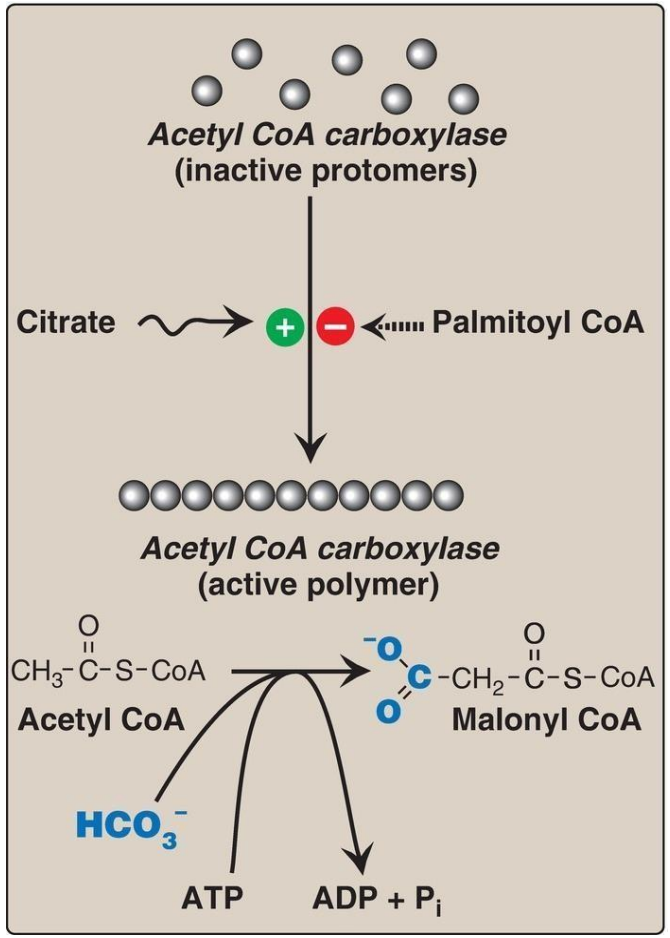
6. Acetyl-CoA is now available for synthesis.

Synthesis of malonyl-CoA

- Acetyl CoA carboxylase (ACC) transfers a carbon from CO2 (as a bicarbonate) via biotin (vitamin B7), which is covalently bound to ACC.

  - ATP is needed.
  - The reaction is the rate-limiting reaction.
  - ACC is an allosteric enzyme.

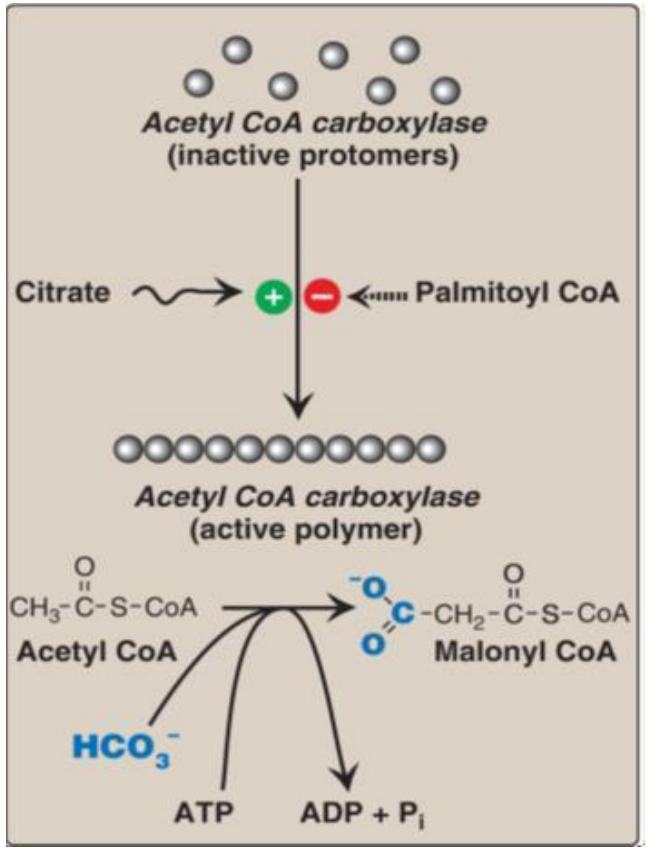
ACC exists in two physical states: Inactive protomers (separate subunits). Active polymer (filamentous form). Citrate promotes polymerization → activation. Palmitoyl-CoA prevents polymerization → inhibition (feedback).

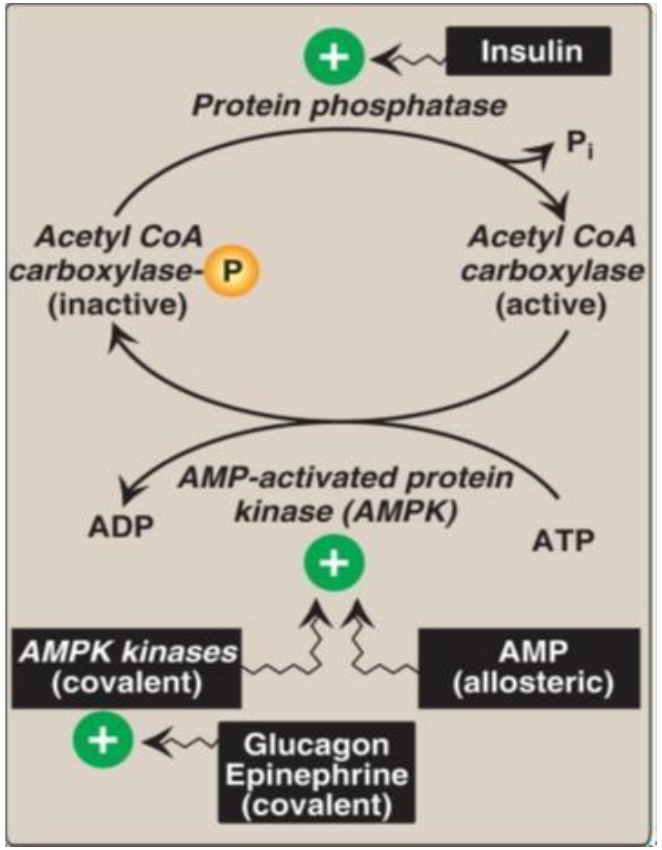


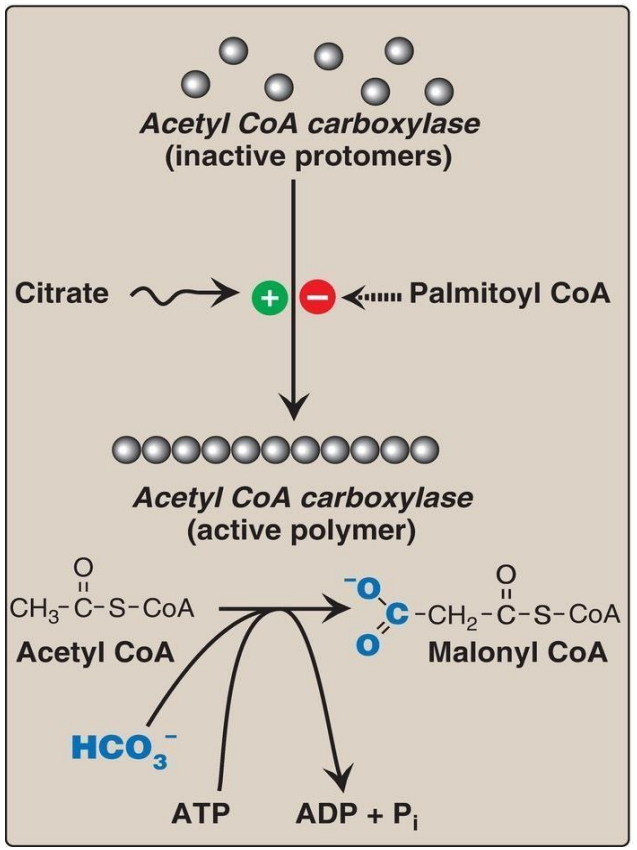
PLEASE SEE SLIDE 34

Regulation of ACC

- ACC is inactivated by :
  - Palmitoyl-CoA
  - Phosphorylation by AMPK, which is activated by glucagon and epinephrine.







PLEASE SEE SLIDE 34

Regulation of ACC / 1

- **Synthesis of Malonyl-CoA :**
- Acetyl-CoA is converted to malonyl-CoA by acetyl-CoA carboxylase (ACC).
- This carboxylation reaction requires ATP , biotin , and bicarbonate (HCO_3^-).
- Malonyl-CoA serves as a critical intermediate for chain elongation during fatty acid synthesis.

- **Reduction Reactions :**
- The synthesis pathway involves repeated reduction reactions , using NADPH as the reducing agent.
- Energy is provided by ATP hydrolysis to drive these thermodynamically unfavorable reactions.

- **Rate-Limiting Step :**
- Acetyl-CoA carboxylase (ACC) is the primary regulatory enzyme.
- It is regulated by allosteric interactions , covalent modifications , and hormonal signals.

- **Allosteric Regulation :**
- High citrate levels activate ACC by promoting its polymerization from inactive protomers (allosteric activator)
- Palmitoyl-CoA (a product of fatty acid synthesis) acts as a feedback inhibitor.

Regulation of ACC / 2

- **Phosphorylation (covalent modification) and Hormonal Control :**

This process involves an enzyme called AMPK (AMP-Activated Protein Kinase) , which phosphorylates acetyl-CoA carboxylase (ACC) , leading to its inhibition. As a result , fatty acid synthesis is suppressed.

- **Fasting State :**

- AMPK is activated under fasting conditions.
- This activation is mediated indirectly by glucagon and epinephrine through signaling pathways , including protein kinase A (PKA).
- PKA activates AMPK kinases , which phosphorylate and activate AMPK.
- Active AMPK then phosphorylates ACC , rendering it inactive and inhibiting fatty acid synthesis.

- **Well-Fed State :**

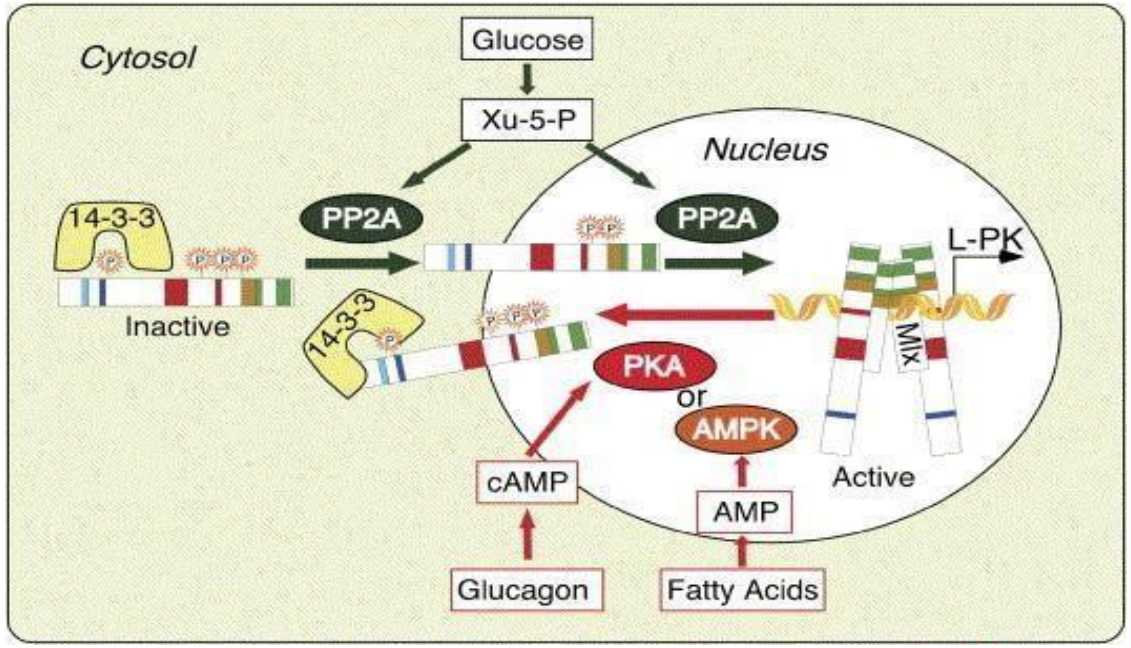
- In the presence of insulin , protein phosphatases are activated.
- These phosphatases remove the phosphate group from ACC , reactivating it and promoting fatty acid synthesis.

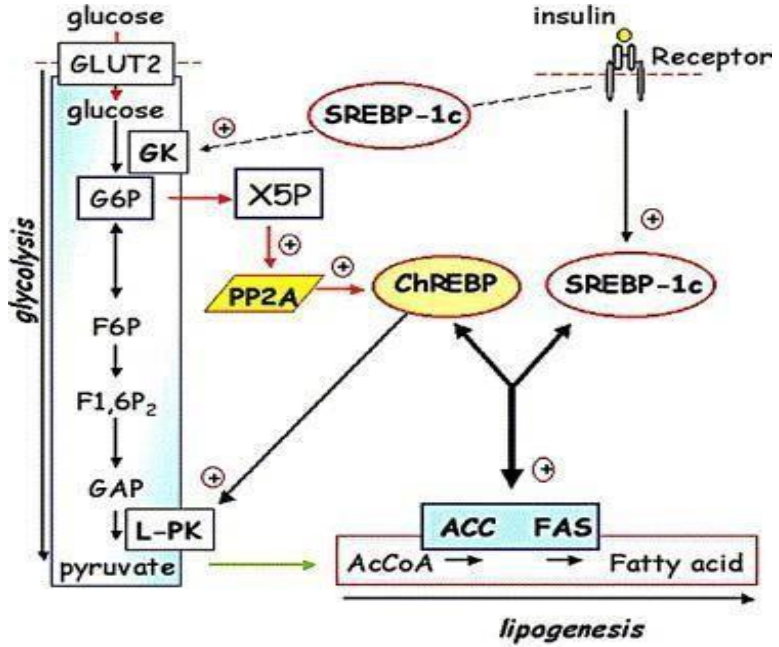
- This regulatory mechanism ensures that fatty acid synthesis is tightly controlled , occurring primarily during the fed state and being suppressed during fasting.

- This ensures synthesis occurs only in the fed state and stops during fasting/stress.

Regulation of ACC synthesis by transcription factors

- The carbohydrate response element–binding protein (ChREBP)
  - ChREBP is inactivated by phosphorylation by PKA and AMPK preventing its nuclear localization.
  - It is dephosphorylated by excess glucose.
- The sterol regulatory element–binding protein-1c (SREBP-1c)
  - SREBP-1 is activated by insulin.





Regulation of ACC synthesis by transcription factors / 1

Fatty acid synthesis begins with the production of malonyl-CoA , a three-carbon molecule formed from acetyl- CoA through the action of the enzyme acetyl-CoA carboxylase (ACC). This step represents the rate-limiting stage of fatty acid synthesis and is subject to multiple levels of regulation.

- **Regulation of Acetyl-CoA Carboxylase (ACC)**

Another key regulatory mechanism involves controlling the synthesis of ACC itself. By modulating the concentration of the enzyme , the reaction rate and the Vmax can be altered. This regulation is achieved through
the activity of transcription factors that influence the expression of ACC. Two major transcription factors involved are ChREBP (Carbohydrate Response Element Binding Protein) and SREBP-1c (Sterol Regulatory Element Binding Protein 1c).

ChREBP (Carbohydrate Response Element Binding Protein)

- Inactivation by AMP Kinase (AMPK) :

Under fasting conditions , ChREBP is phosphorylated and inactivated by AMPK. This phosphorylation prevents ChREBP from increasing ACC synthesis , thereby reducing fatty acid synthesis.

- Activation by Insulin :

In the well-fed state , insulin activates phosphatases that dephosphorylate ChREBP , restoring its active form. Active CHREBP can then enter the nucleus and stimulate the expression of ACC.

- Role of AMPK :

AMPK plays a dual role by phosphorylating and inhibiting both CREBP and ACC directly . This inhibition occurs during fasting or energy-deprived states when glucagon levels are elevated.

Regulation of ACC synthesis by transcription factors / 2

SREBP-1c (Sterol Regulatory Element Binding Protein 1c)

Activation by Insulin :

In the well-fed state , elevated insulin levels activate receptor tyrosine kinases , leading to the activation of SREBP-1c.

Active SREBP-1c promotes the transcription of ACC . This , in turn , leads to higher enzyme concentrations and enhanced fatty acid synthesis.

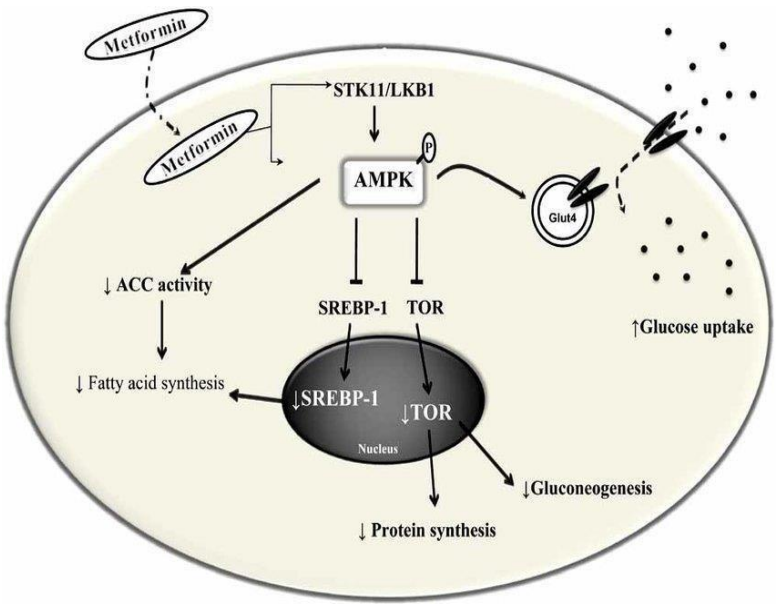
- **Hormonal Regulation**
- Insulin :
- Directly activates SREBP-1c , increasing ACC expression.
- Indirectly activates ChREBP by dephosphorylation via phosphatases.

- Glucagon:
- Activates AMPK , which inhibits ChREBP and ACC activity , reducing fatty acid synthesis.

- In summary , both ChREBP and SREBP-1c enhance the expression of acetyl-CoA carboxylase , but their activity is regulated by distinct hormonal and metabolic signals. Insulin promotes ACC expression through both transcription factors , while glucagon and energy deprivation inhibit fatty acid synthesis via AMPK activation.

Application : Metformin

- Metformin lowers plasma TAG by :
  - Activation of AMPK, resulting in inhibition of ACC activity (by phosphorylation) and inhibition of ACC and fatty acid synthase expression (by decreasing ChREBP and SREBP-1c).
- It lowers blood glucose by increasing AMPK-mediated glucose uptake by muscle.



Application : Metformin

One application related to fatty acid synthesis involves the medication metformin , commonly known by Glucophage. While metformin is widely used for the treatment of diabetes , some individuals misuse it as a weight-loss aid , despite its potential for severe and even fatal side effects. Therefore , its use should always be carefully supervised and not taken haphazardly.

Metformin primarily acts by **activating AMPK** (AMP-activated protein kinase) , mimicking fasting conditions in the body. This activation leads to the phosphorylation of several proteins , resulting in significant metabolic effects. For example :

- **Inhibition of fatty acid synthesis and storage :** AMPK phosphorylates binding proteins (ChREBP and SREBP 1c) and enzymes like acetyl-CoA carboxylase (ACC) , inhibiting their activity. By reducing the synthesis of fatty acids , the formation of triacylglycerols , which are stored in adipocytes, is also minimized.

- **Reduction in blood glucose levels :** Metformin lowers blood glucose levels through AMPK-mediated mechanisms. It enhances glucose uptake into cells , reducing its presence in the bloodstream. This increased glucose uptake allows for its utilization in glycolysis while simultaneously inhibiting gluconeogenesis.

Overall , these mechanisms result in a reduction of fatty acid and protein synthesis , decreased gluconeogenesis , and increased glucose uptake , making metformin effective for managing blood sugar levels in diabetic patients.

Note: ACC inhibitors were researched for weight loss (ACC2 knockout mice ate without gaining weight) but failed due to efficacy, selectivity, and safety concerns. Drug development requires strict FDA approval—never use unapproved treatments.

Application : ACC2 inhibitors

- Challenges related to efficacy , selectivity and safety

Another application related to the acetyl-CoA carboxylase (ACC) enzyme dates back to earlier studies involving the development of ACC inhibitors as a potential method for weight loss. Historical reports have highlighted genetic engineering experiments in mice where ACC activity was modified , demonstrating its effects on reducing fat accumulation. Although this concept shares similarities with metformin's mechanism , the inhibitors are still under study. Despite their initial promise , no ACC inhibitors have yet been approved for clinical use due to concerns over efficacy and safety.

It is worth noting the age of some of these reports , which underscores the long-standing research interest in this area. However , until now , no ACC inhibitors have been confirmed to provide substantial benefits without significant side effects.

اكتشاف مثير ضد البدانة

لندن – قدس برس اكتشف الباحثون علاجا مثيرا وقويا ضد البدانة قد يسمح للأشخاص بتناول ما يشاؤون من الطعام دون أن يكتسبوا وزنا إضافيا، بل على العكس يمكنهم تخفيف أوزانهم الزائدة.

وقال الباحثون من كلية بايلور الطبية في تكساس، قالوا إنهم اكتشفوا إنزيما يضعف قدرة الجسم على حرق الدهون، وبالتحكم في هذا الأنزيم، فسيكون بالإمكان السماح للجسم بحرق دهون أكثر.

وقال الباحثون إن الفئران المهندسة وراثيا، التي ينقصها إنزيم «أسيتل – كو ايه كاربوكسيليز ٢» أو ما يعرف اختصارا بـ ACC2, تستطيع تناول كميات أكثر من الطعام بحوالي ٤٠ في المائة، وتزن أقل بنحو ١٥ في المائة، مقارنة مع غيرها من الحيوانات.

وسجل الدكتور صالح وكيل، كبير الباحثين، في مجلة «العلوم» الأمريكية، أن هذا الأنزيم ACC2 قد يكون هدفا لإنتاج أدوية تنظم حرق الدهون في الجسم، لذلك فقد يلعب دورا مهما في عمليات تنظيم البدانة، وعلاج السكري، وحتى في حالات استخدام وتراكم الدهون التي تزيد خطر الإصابة بتصلب الشرايين، مشيرا إلى أن الفئران التي ينقصها ذلك الجين تبدو سعيدة وحيوية وتتناسل بشكل جيد.

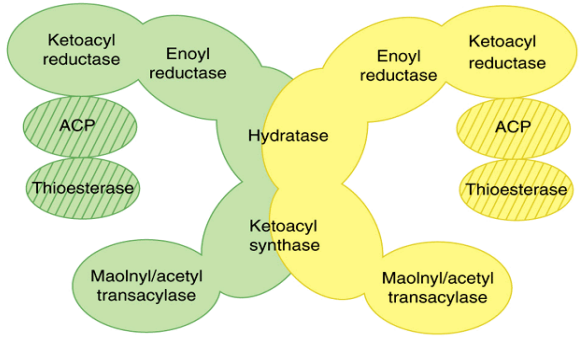
Fatty acid synthase (FAS)

- A multifunctional, homodimeric enzyme complex
- Each FAS monomer is multicatalytic with six enzymic domains and a domain for binding a phosphopantetheine-containing acyl carrier protein (ACP) domain.

The fatty acid synthesis pathway begins with the production of malonyl-CoA by the enzyme acetyl-CoA carboxylase (ACC). The next critical player in this process is fatty acid synthase (FAS) , a multifunctional enzyme complex. FAS performs seven enzymatic functions, including ketoacyl synthase , malonyl/acetyl transacylase , hydratase , enol reductase , ketoacyl reductase , acyl carrier protein (ACP) , and thioesterase. Structurally , it is a homodimer , meaning it consists of two identical subunits. Each subunit possesses all seven enzymatic functions , providing a total of 14 active sites (two identical sites for each enzymatic function)

Mammalian FAS is a single polypeptide chain with multiple enzymatic domains ("seven enzymes in one"). Two identical polypeptides form a head-to-tail homodimer. The acyl carrier protein (ACP) domain contains phosphopantetheine, derived from vitamin B5 (pantothenic acid) – the same cofactor core as in CoA. Vitamin B5 is essential for FAS function.

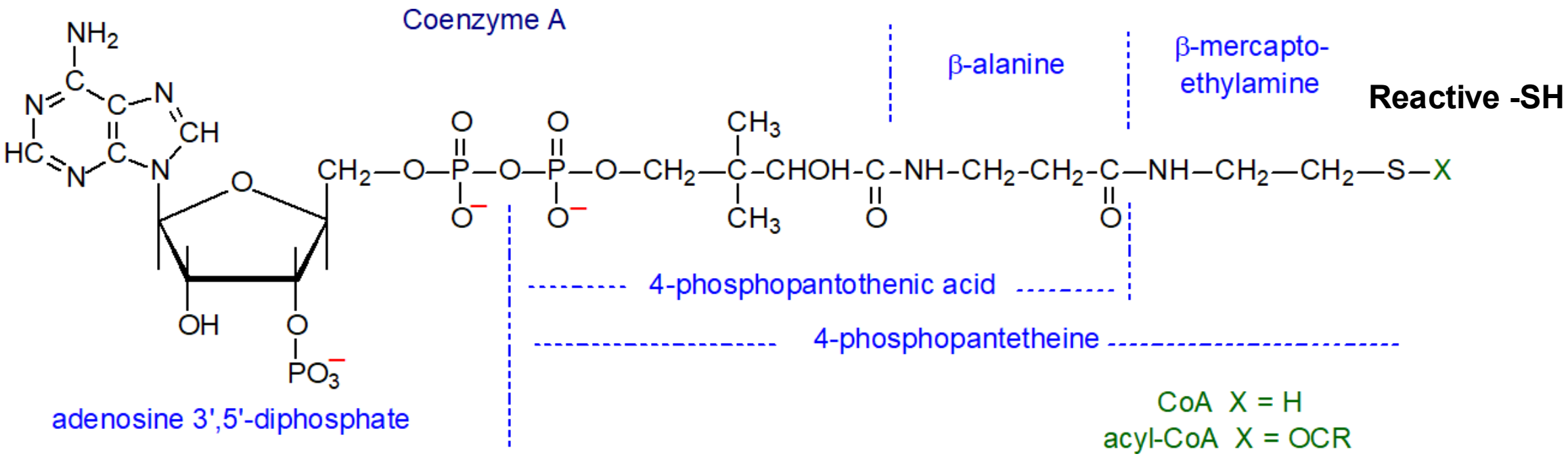
Sequence of enzyme domains in primary structure of fatty acid synthase monomer



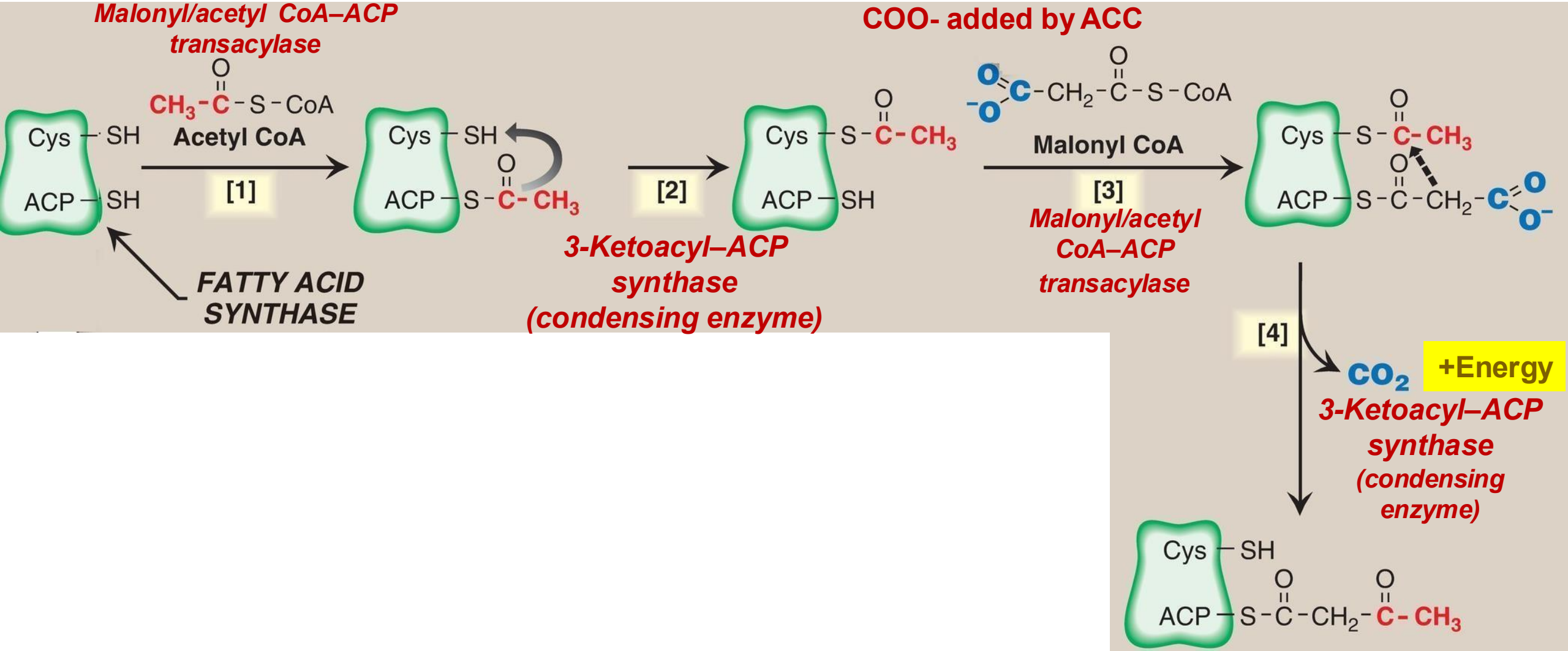
Fatty acid synthase homodimer

Fatty acid synthase (FAS)

- Phosphopantetheine, a derivative of pantothenic acid (vitamin B5), carries acyl units on its terminal thiol (–SH) group and presents them to the catalytic domains of FAS.
- It also is a component of CoA.

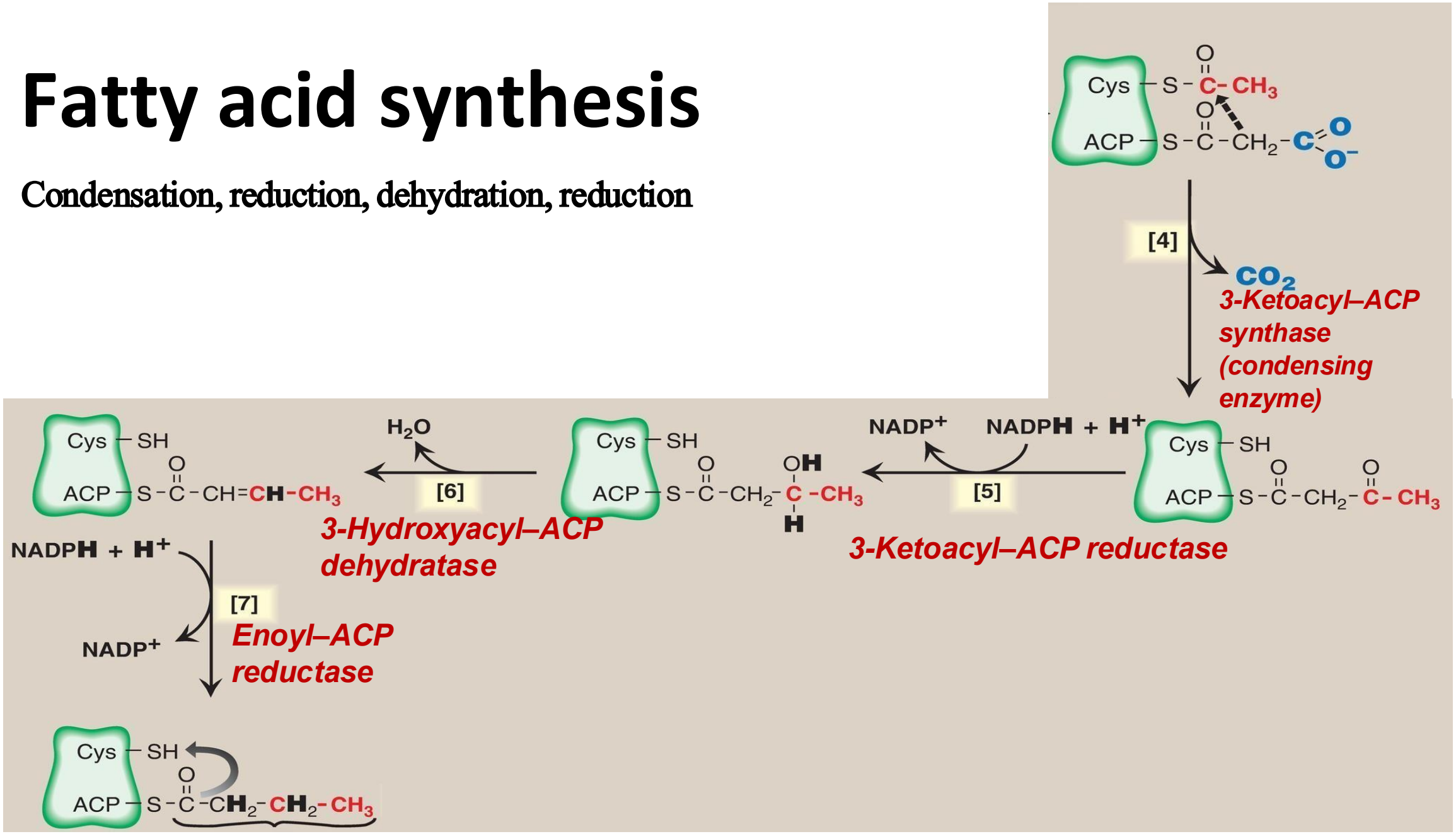


Fatty acid synthesis



Fatty acid synthesis

Condensation, reduction, dehydration, reduction



Fatty acid synthesis / 1

The synthesis pathway begins with one molecule of acetyl-CoA and one molecule of malonyl-CoA , which are processed in the following steps :

- **Attachment of Acetyl-CoA to ACP :**

Acetyl-CoA is attached to the ACP region of FAS through its reactive sulfhydryl (-SH) group . This step is catalyzed by malonyl/acetyl-CoA ACP transacylase (MAT) , which transfers the acetyl group to ACP.

- **Transfer of Acetyl Group to Cysteine :**

The acetyl group is transferred from ACP to a cysteine residue within FAS by the enzyme ketoacyl ACP synthase (KS) , leaving the ACP region available to bind malonyl-CoA.

- **Conversion of Acetyl-CoA to Malonyl-CoA**

Acetyl-CoA is carboxylated to malonyl-CoA by ACC , with the addition of a bicarbonate (HCO_3^-) group. This conversion prepares the molecule for elongation.

- **Attachment of Malonyl-CoA to ACP**

Malonyl-CoA is attached to the ACP region of FAS by malonyl/acetyl-CoA ACP transacylase, which previously attached acetyl-CoA. This creates a setup for condensation reactions.

Dr. Diala said that it is sufficient to understand the category of the enzyme (reductase, dehydratase) rather than memorizing its full name.

TO BE CONTINUED

Fatty acid synthesis / 2

- **Condensation Reaction**

A decarboxylation reaction removes the carboxyl group from malonyl-CoA , allowing the two carbons from acetyl-CoA (on the cysteine residue) to attach to the remaining two carbons of malonyl-CoA on ACP. This step is catalyzed by ketoacyl ACP synthase (KS) - the condensing enzyme , resulting in a four-carbon chain attached to ACP.

- **Reduction of the Carbonyl Group**

Fatty acids possess only a single carboxyl group , which is located at the terminal carbon (carbon number one). To achieve this , the non-terminal carbonyl group is reduced to an alcohol by the enzyme 3-ketoacyl ACP reductase. This reaction involves the oxidation of NADPH to $NADP^+$.

- **Dehydration**

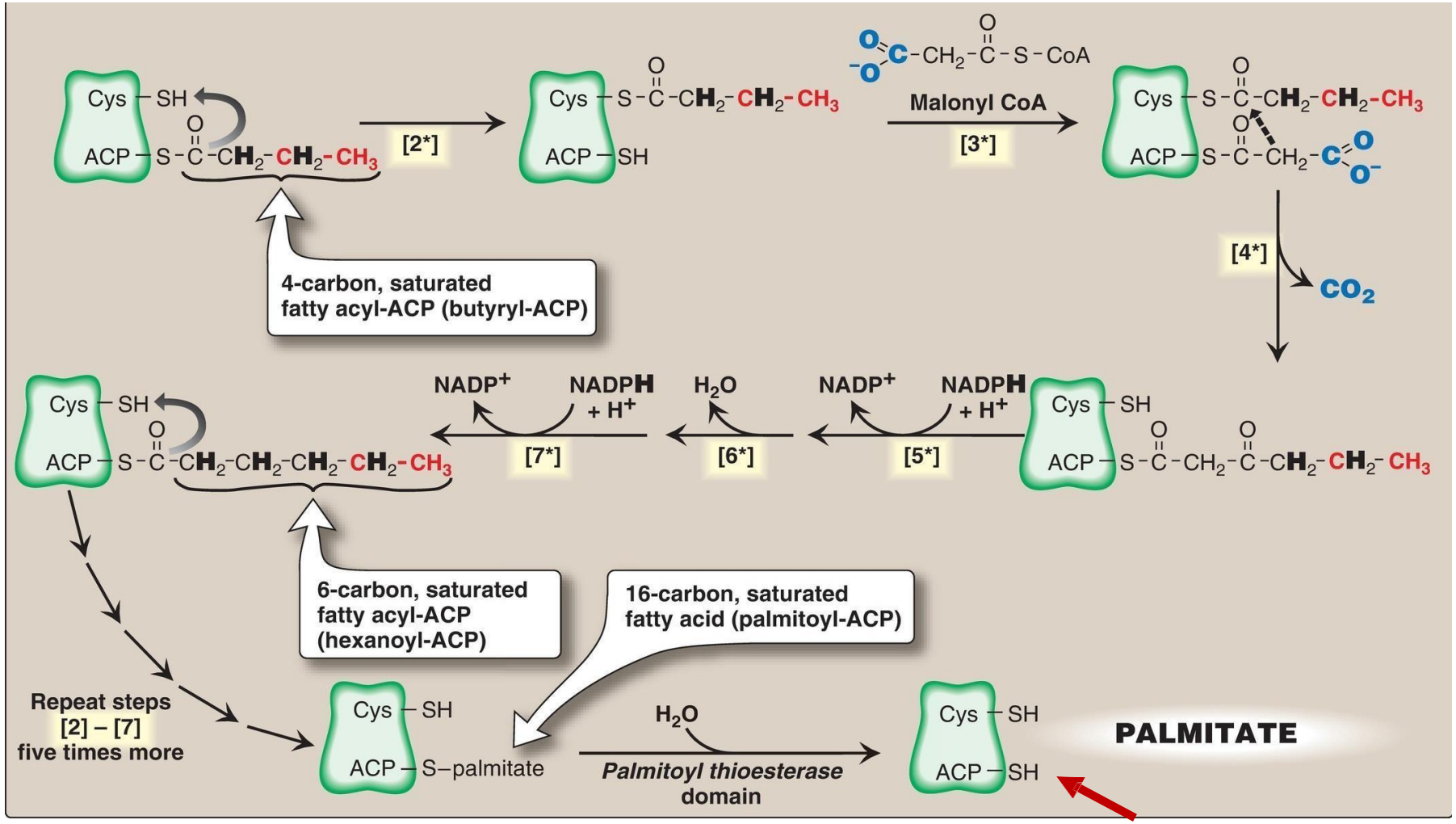
The alcohol group is removed via dehydration , resulting in the formation of a double bond. This step is catalyzed by 3-hydroxyacyl ACP dehydratase , which eliminates a water (H2O) molecule.

- **Reduction of the Double Bond**

The double bond is reduced to form a saturated hydrocarbon chain. This reaction is catalyzed by enoyl-ACP reductase , with NADPH serving as the reducing agent and being oxidized to NADP+.

At this stage , the chain consists of four carbons , including one terminal carbonyl group and a fully saturated hydrocarbon chain. Additional elongation cycles will repeat these steps to extend the fatty acid chain until the desiresd length is achieved. Desaturation , if needed , can occur later in a separate pathway

Fatty acid synthesis



✓ *The lactating mammary gland terminates lengthening the chain EARLY.*

Fatty acid synthesis

To synthesize palmitic acid , a 16-carbon saturated fatty acid , the previously mentioned steps (resulting in a 4- carbon chain) must be repeated six additional times. Each cycle extends the fatty acyl chain by 2 carbons , as one carbon from malonyl-CoA is lost during decarboxylation.

Steps for Palmitic Acid Synthesis :

- **Initial 4-Carbon Chain Preparation**

After completing the initial steps , the fatty acyl chain (4 carbons) is attached to the ACP (acyl carrier protein) region of the fatty acid synthase (FAS).

- **Transfer of Fatty Acyl Chain to Cysteine Residue**

Using the same enzyme as before , ketoacyl ACP synthase (KS) , the fatty acyl chain is transferred from ACP to the cysteine residue of FAS , leaving ACP empty to accept a new malonyl-CoA molecule.

- **Addition of Malonyl-CoA**

A new malonyl-CoA , produced by acetyl-CoA carboxylase , is attached to the empty ACP. Following this , a decarboxylation reaction occurs , enabling the fatty acyl chain on the cysteine to combine with the 2 carbons from malonyl-CoA. This results in a 6-carbon chain attached to ACP.

TO BE CONTINUED

Fatty acid synthesis

- **Reduction , Dehydration , and Second Reduction**
- The new carbonyl group on the 6-carbon chain undergoes reduction to an alcohol by ketoacyl ACP reductase, with NADPH oxidized to NADP+.
- The alcohol group is then dehydrated by 3-hydroxyacyl ACP dehydratase , forming a double bond.
- Finally , the double bond is reduced by enoyl-ACP reductase, again using NADPH, resulting in a saturated 6- carbon chain.

- **Repetition of the Cycle**

This process (transfer , malonyl-CoA addition , decarboxylation , reduction , dehydration , and reduction) is repeated , adding 2 carbons with each cycle. After six more cycles , the chain reaches 16 carbons , forming palmitic acid.

- **Release of Palmitic Acid**

Once the 16-carbon chain is complete, palmitoyl thioesterase catalyzes the hydrolysis of the fatty acid from the
FAS complex by adding a water molecule. This releases palmitic acid.

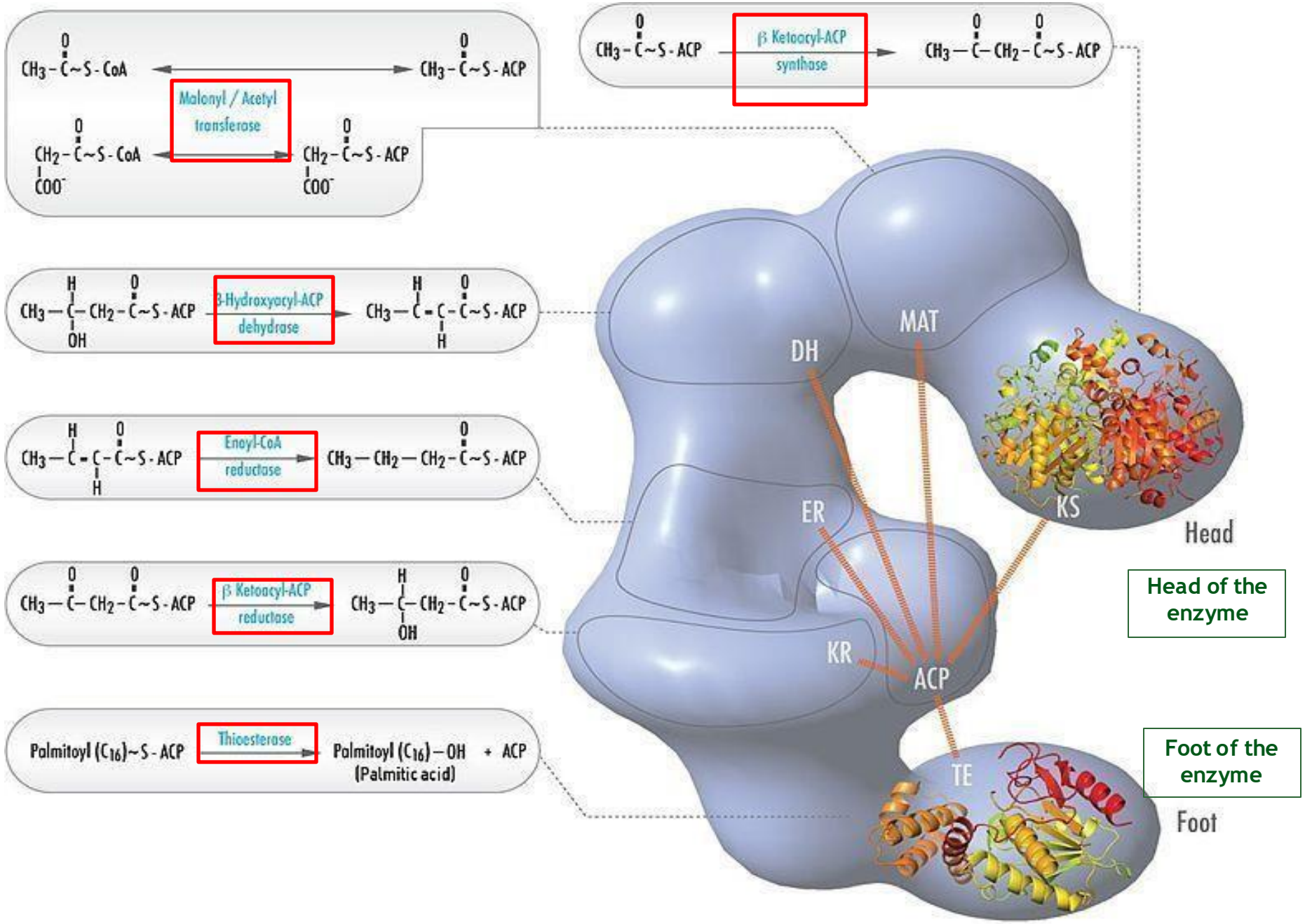
Variations in Fatty Acid Length :

In specific tissues , such as the mammary glands, the synthesis of shorter fatty acid chains (e.g. short- and medium-chain fatty acids -mainly medium-) is prioritized. This is achieved by terminating the elongation process early , after fewer cycles of the spiral pathway. These shorter chains are particularly abundant in milk fat.

- Stoichiometry for palmitate (16C):
- $8\ \text{Acetyl-CoA} + 7\ \text{ATP} + 14\ \text{NADPH} \rightarrow \text{Palmitate} + 7\ \text{ADP} + 7\ \text{Pi} + 14\ \text{NADP}^{+} + 8\ \text{CoA} + 6\ \text{H}_2\text{O}$
- *(1 acetyl-CoA as primer + 7 malonyl-CoA from 7 acetyl-CoA + 7 ATP)*

Fatty acid synthesis

This highlights how the seven functional regions of the positioned enzyme are adjacent to one another , enabling seamless transfer of intermediates between them. Each step in the process transitions the substrate to the next neighboring region of the enzyme , ensuring the reactions proceed in an efficient and coordinated manner.



Fatty acid synthesis

This slide features a video on fatty acid synthesis To watch it please

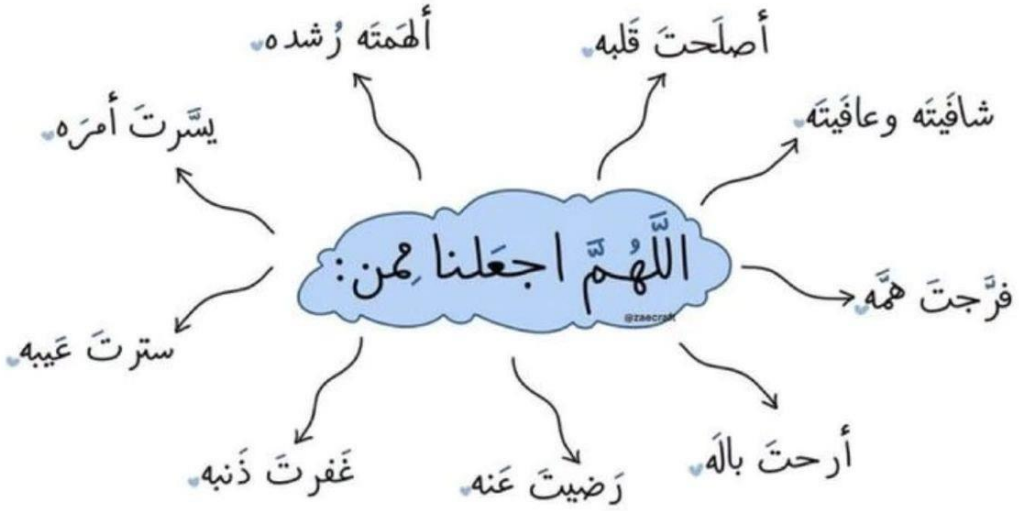
CLICK HERE

Ketoacyl synthase (KS) Malonyl/acetyltransferase (AT) Dehydrase (DH)

Enoyl reductase (ER) Ketoacyl reductase (KR) Thioesterase (TE)

Acyl carrier protein (ACP)

رسالة من الفريق العلمي:



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			