FATTY ACID SYNTHESIS (PART 2)

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Medical Editor: Uta Hüning

OUTLINE

I) RECAPITULATION

- Glucose → Pyruvate → Acetyl-CoA
- Acetyl-CoA → Krebs cycle → ECT → ATP
  → High ATP → no need to produce more ATP
  → Build-up of citrate
  → Citrate leaves mitochondria via transporter
  → In cytoplasm citrate is cut into OAA + Acetyl-CoA
  - By: citrate lyase
- OAA → Malate → Pyruvate → Gluconeogenesis
  - Malate → Pyruvate by Malic enzyme, yields NADPH
- Acetyl-CoA → Malonyl-CoA
  - By: **acetyl-CoA carboxylase**
  - Inhibitors: glucagon, NE, E, LCFA
  - Stimulators: insulin, citrate

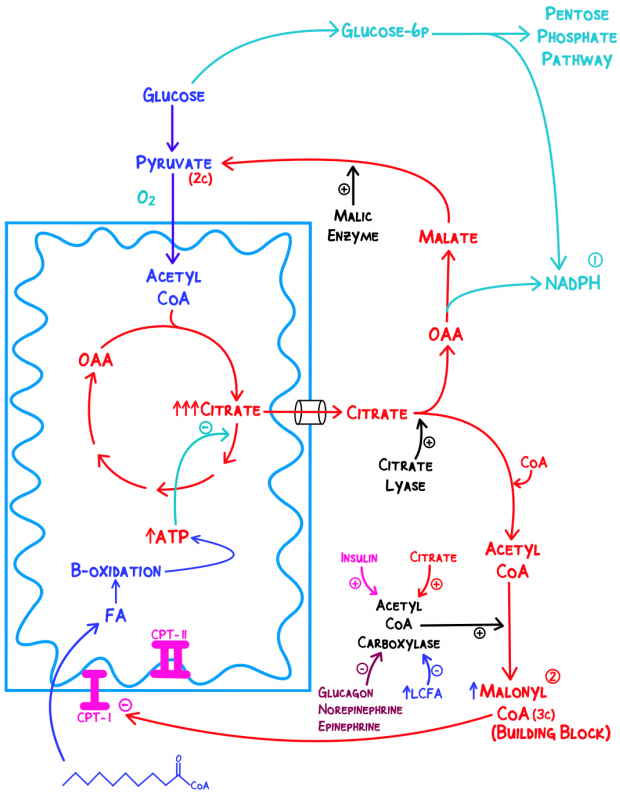


Figure 1: Generating the substrates for FA synthesis, NADPH and malonyl-CoA

(1) Substrates for FA synthesis

- NADPH
- Malonyl-CoA
- FAS-1 enzyme
- Acetyl-CoA

(2) About the substrates

- **NADPH** source:
  - Malic enzyme
  - Pentose phosphate pathway (oxidative phase)
- **Malonyl-CoA** source:
  - Citrate build up
  - Citrate split into OAA + Acetyl-CoA by citrate lyase
  - Acetyl-CoA → by ACC → Malonyl-COA

Remember:
- **NADPH** = **reducing agent** for FA synthesis
- **Malonyl-CoA** = **precursor** of FA synthesis

- Malonyl-CoA also **inhibits FA oxidation** (degradation)
  - CAT transporter on mitochondrial membrane (carnitine-acyltransferase)
    - Type 1 (outer membrane)
    - Type 2 (inner membrane)
  - CAT-1 transports FA into mitochondria for oxidation
  - Malonyl-CoA **inhibits CAT-1** → favors FA synthesis

II) FAS – FATTY ACID SYNTHASE

- **FAS 1**: in **animals**, fungi
- FAS 2: in bacteria, archaea, plants [Zhao W. (2008)]

(1) FAS-1 Structure

- Large enzyme complex with different catalytic subunits
- On one end: **Cysteine-SH**
- On other end: **ACP** (acyl-carrier-protein) (with 4'-phosphopantetheine group which also has **SH**)
  - ACP will be carrying the growing fatty acyl-chain

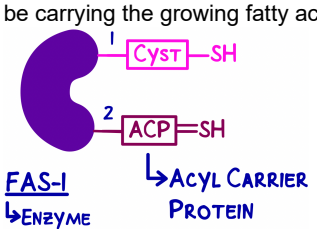
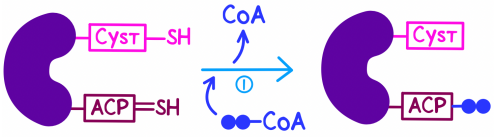


Figure 2: Structure of FAS-1

(2) FAS-1 Action

(i) 1. step:

- Bring acetyl-CoA
- Release CoA (this process yields energy)
- Add **acetyl to ACP** (this process uses this energy)
- By: acetyl-transacylase
- Counting carbons:
  - Cysteine end: 0C
  - ACP end: 2C



Acetyl Transacylase

Figure 3: First step of FA synthesis

(ii) 2. step:

- **Transfer acetyl** group temporarily **to cysteine**
- Counting carbons:
  - Cysteine end: 2C
  - ACP end: 0C

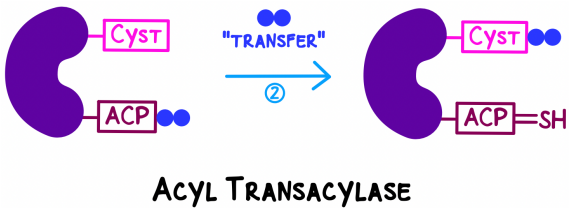


Figure 4: Second step of FA synthesis

(iii) 3. step:

- Bring malonyl-CoA
- Release CoA (this process yields energy)
- Add **malonyl to free ACP** (this process uses this energy)
- By: malonyl-transacylase
- Counting carbons:
  - Cysteine end: 2C
  - ACP end: 3C

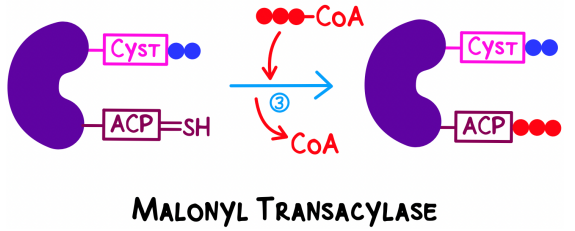


Figure 5: Third step of FA synthesis

(iv) 4. step:

- **Decarboxylation**: release 1C from malonyl-end as CO_2
- **Condensation**: add acetyl to remaining 2C at ACP
- By: acyl-malonyl-ACP-condensing enzyme (3/beta-ketoacyl-ACP-**synthase**)
- Counting carbons:
  - Cysteine end: 0C
  - ACP end: 4C Butyl group (has keto group C=O)

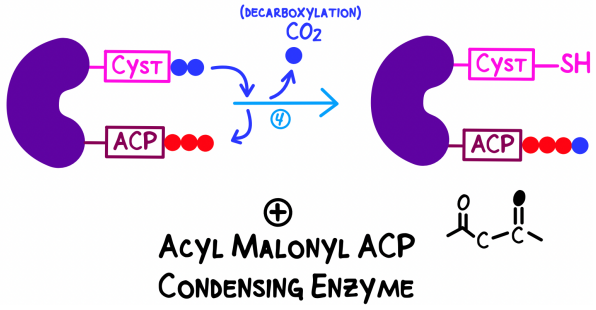


Figure 6: Fourth step of FA synthesis

(v) 5. step:

- **Reduction** with 1 NADPH → $NADP^+$
- Convert keto group (C=O) into hydroxyl group (C-OH) by adding H_2
- By: 3/beta-ketoacyl-ACP-**reductase**
- Counting carbons:
  - Cysteine end: 4C (has hydroxyl group C-OH)
  - ACP end: 0C

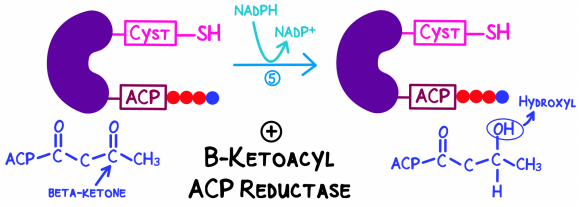


Figure 7: Fifth step of FA synthesis

(vi) 6. step:

- Convert alcohol group (C=O) into enoyl group (C-OH) by releasing H_20
- By: 3/beta-hydroxyacyl-ACP-**dehydratase**
- Counting carbons:
  - Cysteine end: 0C
  - ACP end: 4C (has double bond C=C)

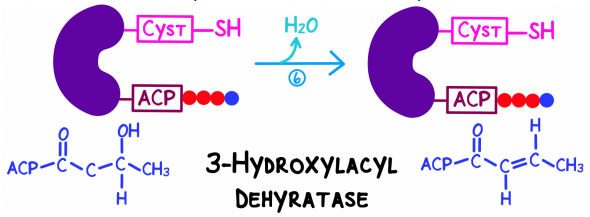


Figure 8: Sixth step of FA synthesis

(vii) 7. step:

- **Reduction** with 1 NADPH → $NADP^+$
- Convert enoyl group (C=C) into single bonds (C-H_2) by adding H from NADPH
- By: enoyl-CoA-ACP-**reductase**
- Counting carbons:
  - Cysteine end: 0C
  - ACP end: 4C (has single bonds C-H_2)

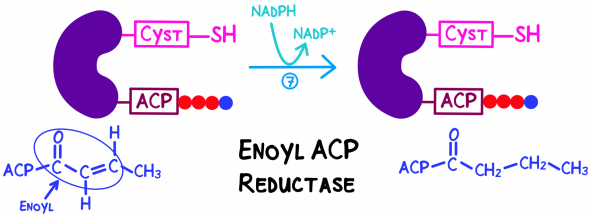


Figure 9: Seventh step of FA synthesis

(viii) 8. step = 2. step:

- See step 2: transfer of acyl chain from ACP to cysteine
- Counting carbons:
  - Cysteine end: 4C
  - ACP end: 0C

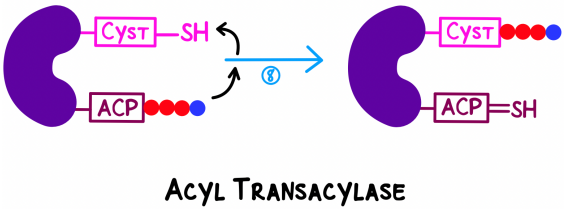


Figure 10: Repeat of second step of FA synthesis

(ix) 9. step = 3. step:

- See step 3: add malonyl to free ACP
- Counting carbons:
  - Cysteine end: 4C
  - ACP end: 3C (has a keto group C=O)

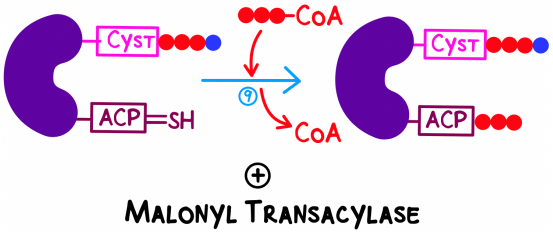


Figure 11: Repeat of third step of FA synthesis

(x) 10. step = 4. step:

- See step 4: decarboxylase 1C, acyl chain condenses with remaining 2C on ACP end
- Counting carbons:
  - Cysteine end: 0C
  - ACP end: 6C (has a keto group C=O)

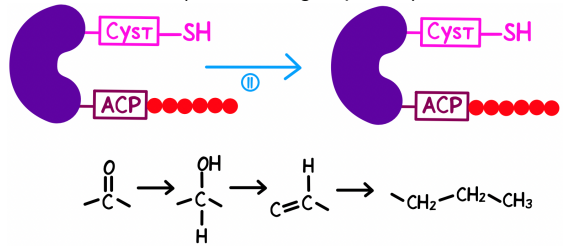


Figure 12: Repeat of fourth step of FA synthesis

- Repeat to add 2C with each round until **palmitate (16C)** or longer FA is formed
- Then cleave FA from ACP
- By: thioesterase

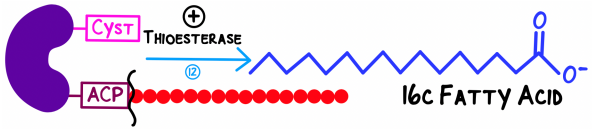


Figure 13: Final product 16C palmitic fatty acid

Remember:
- How many rounds of FA synthesis do we need to form a 16C FA?
- First round adds 4C, every next round adds 2C
- 16-4=12 → 12C remaining, 1st + 6 = **7 rounds total**

III) SUMMARY

(1) Add Acetyl

- 2C added to ACP

(2) Transfer Acetyl

- 2C added to cysteine

(3) Add Malonyl

- 3C added to ACP

(4) Decarboxylation & Condensation

- Malonyl loses 1C
- 2C acetyl fuses to 2C malonyl-residue on ACP
- Keto group exists C=O (now 4C)

(5) Reduction

- NADPH gives H
- Changes keto group into hydroxy group C-OH (4C)

(6) Dehydration

- H_2O pulled out
- Changes alcohol group into double bond C=C (4C)

(7) Reduction

- NADPH gives H
- Changes double bond into single bond C-C (4C)

IV) APPENDIX

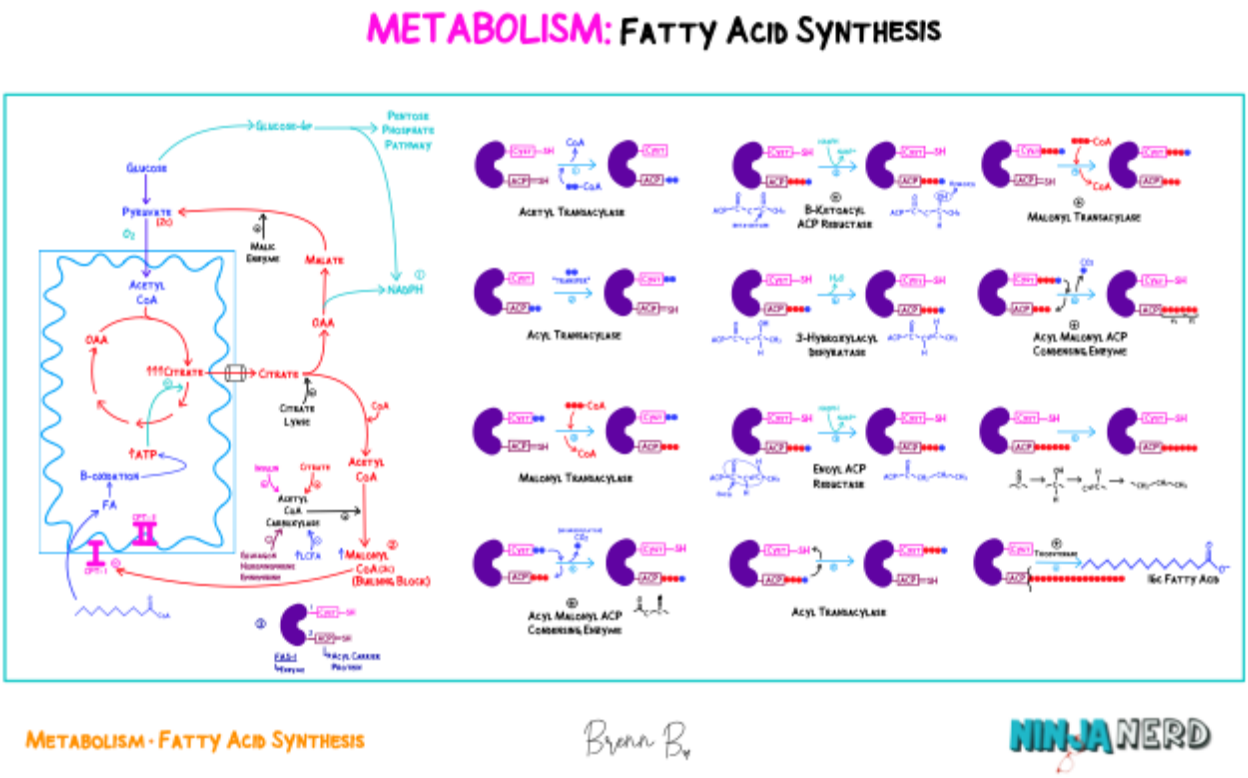


Figure 14: Overview FA synthesis

V) REVIEW QUESTIONS

1) What is the role of malonyl-CoA?
- a) Stimulation of FA synthesis and FA oxidation
- b) Stimulation of FA synthesis and inhibition of FA oxidation
- c) Inhibition of FA synthesis and FA oxidation
- d) Inhibition of FA synthesis and stimulation of FA oxidation

2) How many carbons are added with each repetition?
- a) 1
- b) 2
- c) 3
- d) 4

3) What is the minimum number of carbons before the synthesized FA is released?
- a) 10
- b) 12
- c) 14
- d) 16

4) Arrange the steps of the FAS-1 in the correct order:
- a) Reduction forming a hydroxy group
- b) Dehydration
- c) Decarboxylation, condensation
- d) Reduction removing a double bond

5) How is the final FA released from the ACP end?
- a) Automatically
- b) By thioesterase
- c) By decarboxylation
- d) By FAS-2

6) How many times do we need to repeat the steps for FA synthesis to synthesize a 16C FA?
- a) 10 times
- b) 9 times
- c) 8 times
- d) 7 times

CHECK YOUR ANSWERS