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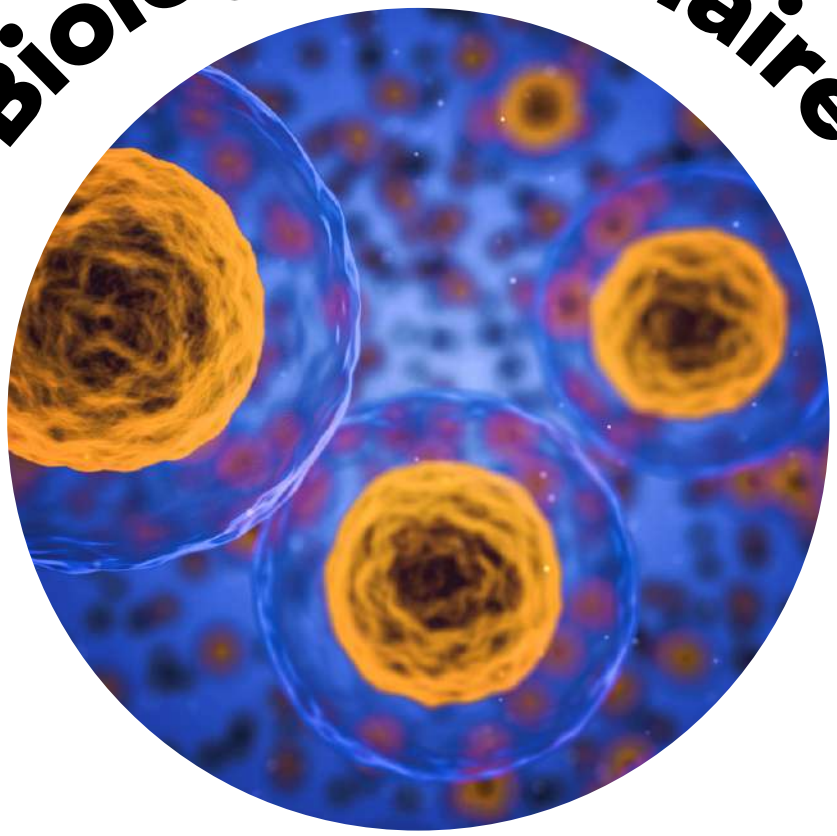
Biologie Cellulaire



SCIENCES DE LA VIE ET DE LA TERRE

Krebs cycle

Josef Fontana

EC - 46

Overview of the seminar

- Krebs cycle (KC)
  - The importance of the KC for the cell - amphibolic character
  - The overall equation and the individual reactions of the KC
  - Anaplerotic reactions of the KC and the linking of the KC to with the other metabolic pathways in the cells
  - Regulation of the KC

Sir Hans Adolf Krebs
(25.8.1900 - 22.11.1981

Was a German-born British physician and biochemist.

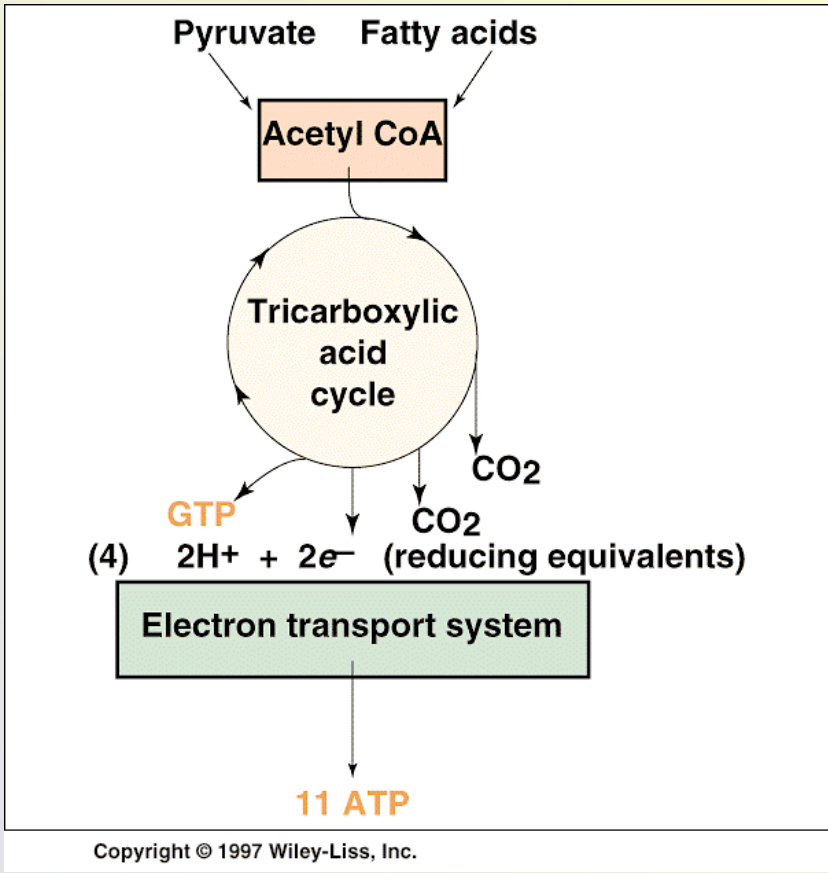
The Nobel Prize in Physiology or Medicine in 1953 for his discovery of the citric acid cycle.

Krebs cycle

The importance of the KC for the cell - amphibolic character

Citric acid cycle (CAC)

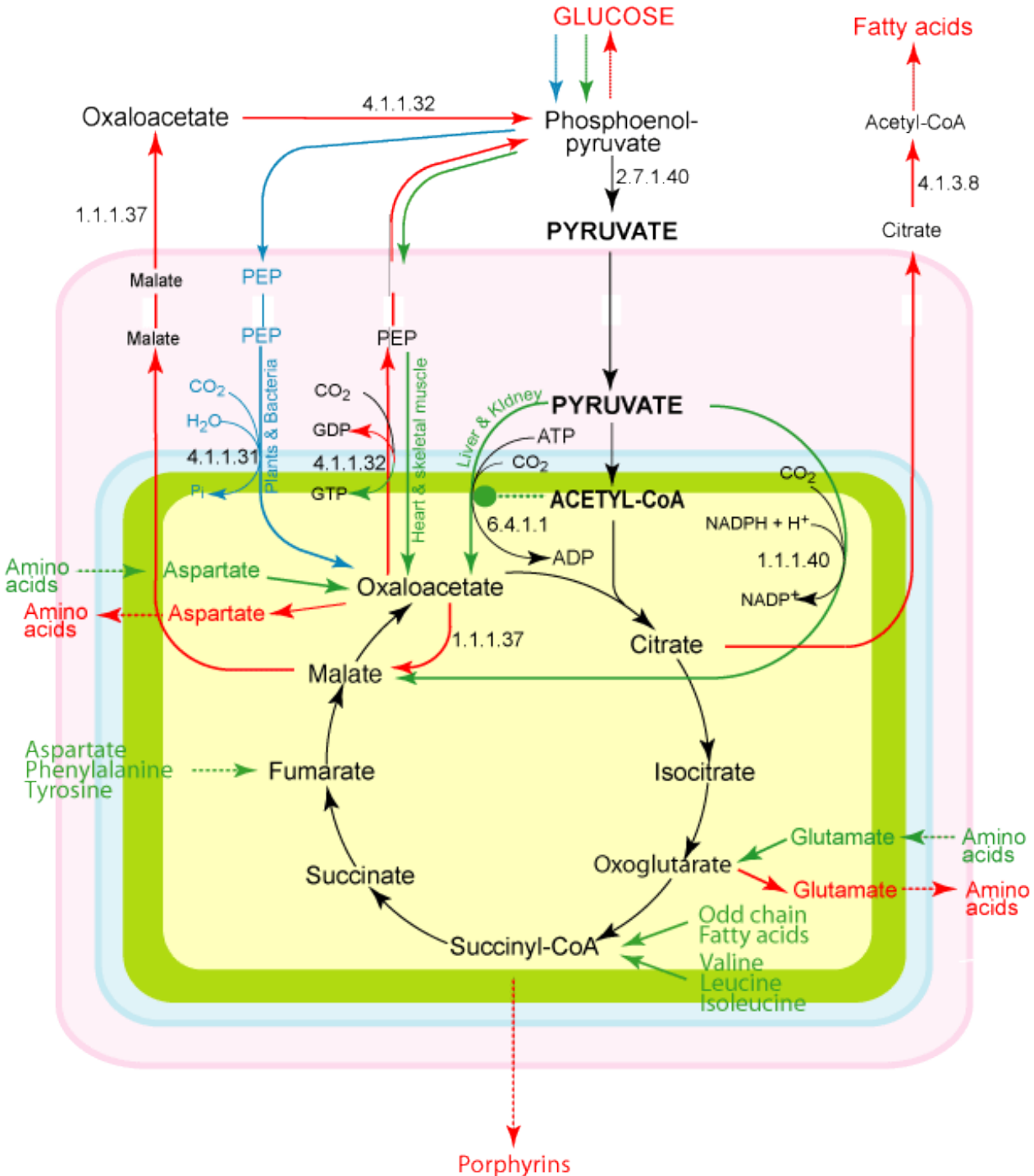
- CAC takes place in the MIT matrix (not in erythrocytes) and only under aerobic conditions.
- It is the ultimate path of oxidation.
- Substrate is **Acetyl~CoA**, which is oxidised to $2CO_2$ with simultaneous reduction of cofactors (**3NAD+** and **1FAD**). They are then reoxidised in RC.
- We get 1GTP directly (= ATP).
- CAC plays a key role in futher metabolic reactions (i. e. gluconeogenesis, transamination, deamination or lipogenesis).



The figure is adopted from the book: Devlin, T. M. (editor): Textbook of Biochemistry with Clinical Correlations, 4th ed. Wiley–Liss, Inc., New York, 1997. ISBN 0–471–15451–2

Amphibolic character

- It is not only catabolic pathway, but its intermediates create many biologically important compounds.
- E.g.:
  - From α-ketoglutarate via transamination → AA glutamate, which is the most abundant excitatory neurotransmitter in the brain.
  - From Suc ~ CoA → tetrapyroles (Heme).
- Therefore has KC also amphibolic function.


GLUCOSE
Fatty acids
Oxaloacetate
4.1.1.32
Phosphoenol-pyruvate
Acetyl-CoA
2.7.1.40
4.1.3.8
1.1.1.37
PYRUVATE
Citrate
Malate
PEP
Malate
PEP
PEP
Plants & Bacteria
Heart & skeletal muscle
Liver & Kidney
CO_2
H_2O
4.1.1.31
P_i
CO_2
GDP
4.1.1.32
GTP
PYRUVATE
ATP
CO_2
ACETYL-CoA
6.4.1.1
ADP
CO_2
NADPH + H^+
1.1.1.40
$NADP^+$
Amino acids
Aspartate
Oxaloacetate
Amino acids
Aspartate
1.1.1.37
Citrate
Malate
Aspartate
Phenylalanine
Tyrosine
Fumarate
Isocitrate
Glutamate
Amino acids
Oxoglutarate
Glutamate
Amino acids
Succinate
Odd chain Fatty acids
Valine
Leucine
Isoleucine
Succinyl-CoA
Porphyrins

Krebs cycle

The overall equation and the individual reactions of the KC

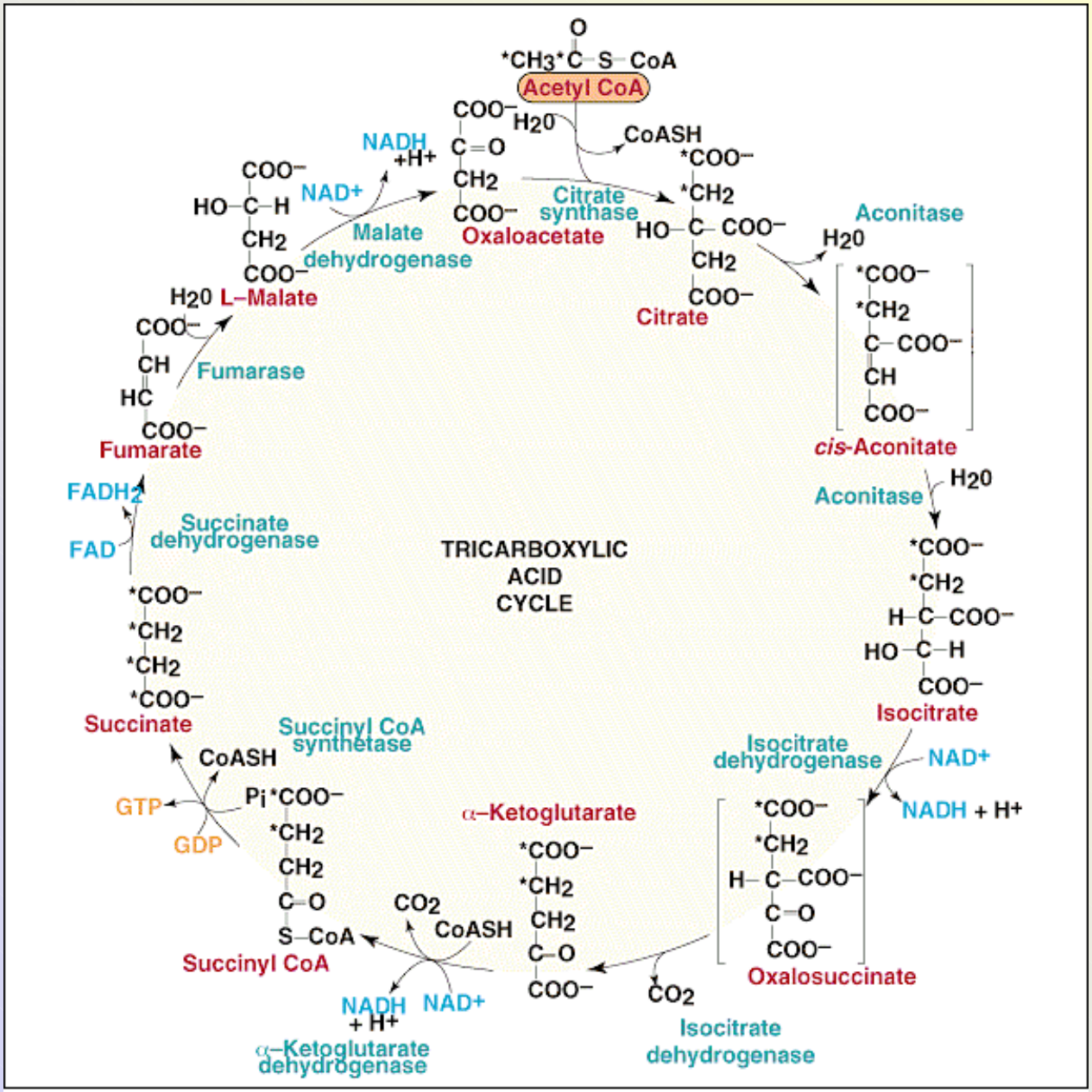
Overall equation

$CH_3\text{-}CO\text{-}COOH + 4\ NAD^+ + FAD + ADP + P_i + 2\ H_2O \rightarrow 3\ CO_2 + 4\ NADH + 4\ H^+ + FADH_2 + ATP$

- **Pyruvate dehydrogenase reaction (oxidative decarboxylation, mitochondrial matrix) Irreversible reaction!**
- $\mathbf{CH_3\text{-}CO\text{-}COOH} + NAD^+ + HSCoA \rightarrow CO_2 + NADH + H^+ + \mathbf{CH_3\text{-}CO\sim SCoA}$

- **Krebs cycle**

  $CH_3\text{-}CO\sim SCoA + 3\ NAD^+ + FAD + GDP + P_i + 2\ H_2O \rightarrow 2\ CO_2 + 3\ NADH + 3\ H^+ + FADH_2 + GTP$



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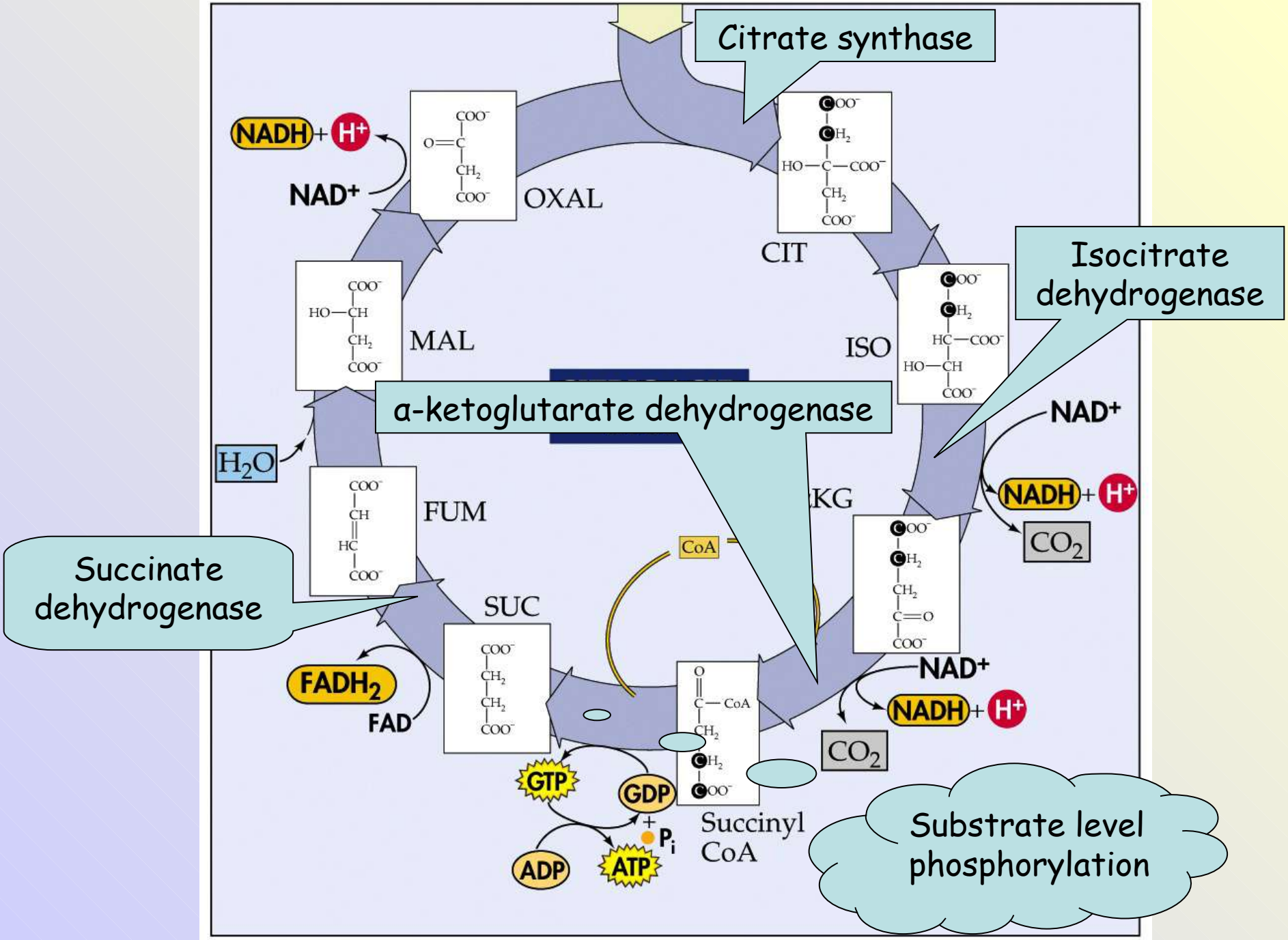


Substrate level phosphorylation in KC

- In the KC, there is one substrate level - **thioester bond in Suc~CoA decays with water to form succinate and HSCoA**.
- This reaction releases so much energy that it can be coupled with the phosphorylation of GDP to GTP (exchanged for ATP).
- This reaction may also be bypassed in the degradation of ketone bodies, acetoacetate reacts with the Suc~CoA to form succinate and acetoacetyl~CoA. But we gain no GTP.

Sucinate dehydrogenase

- In the KC it catalyzes:

  $^{-}OOC\text{-}CH_2\text{-}CH_2\text{-}COO^{-} \leftrightarrow {}^{-}OOC\text{-}CH{=}CH\text{-}COO^{-}$

  succinate fumarate

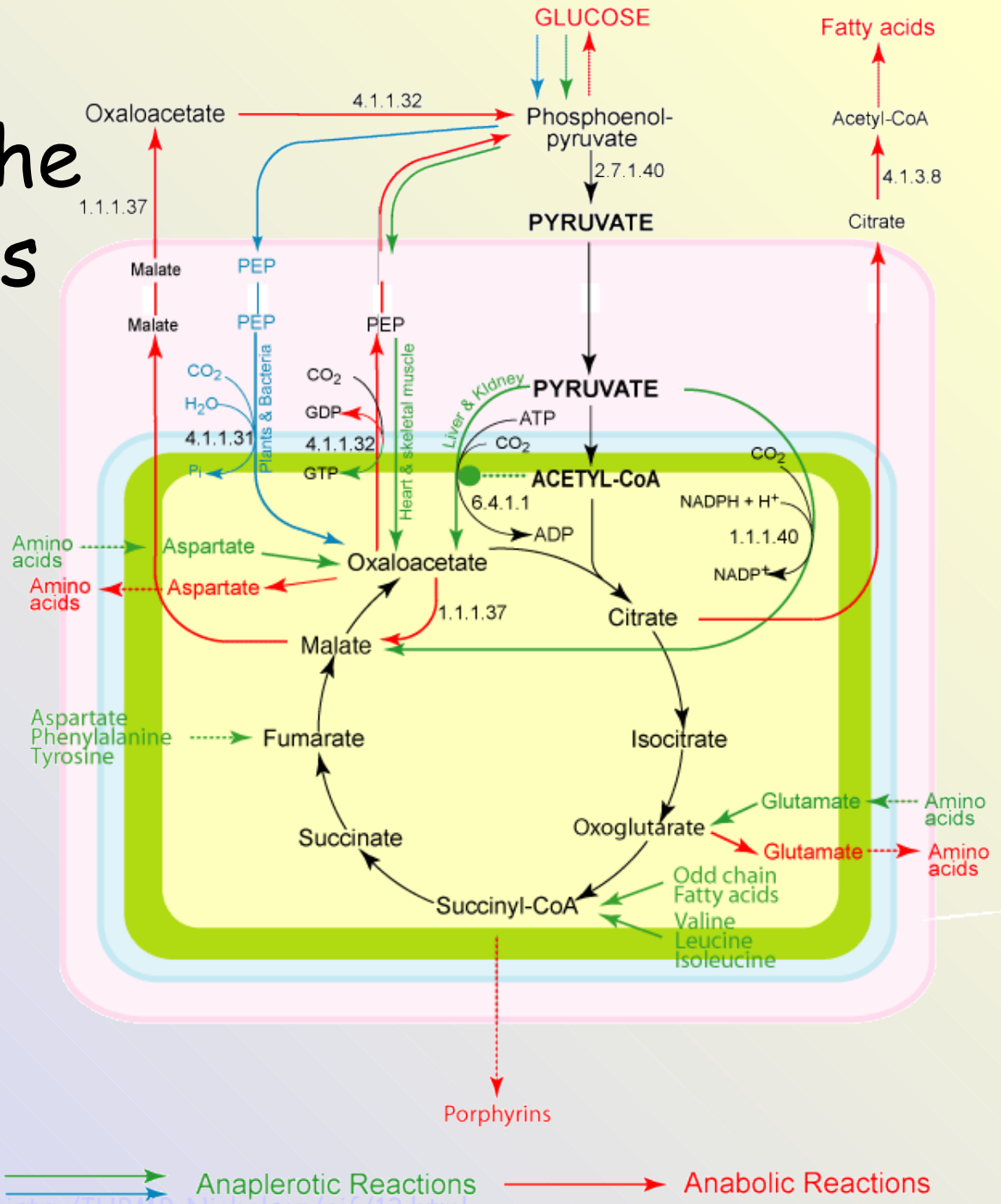
- Its prosthetic group is FAD.
- But it is also complex II in the inner mitochondrial membrane (respiratory chain). Electrons from $FADH_2$ are passed directly to complex III.

Krebs cycle

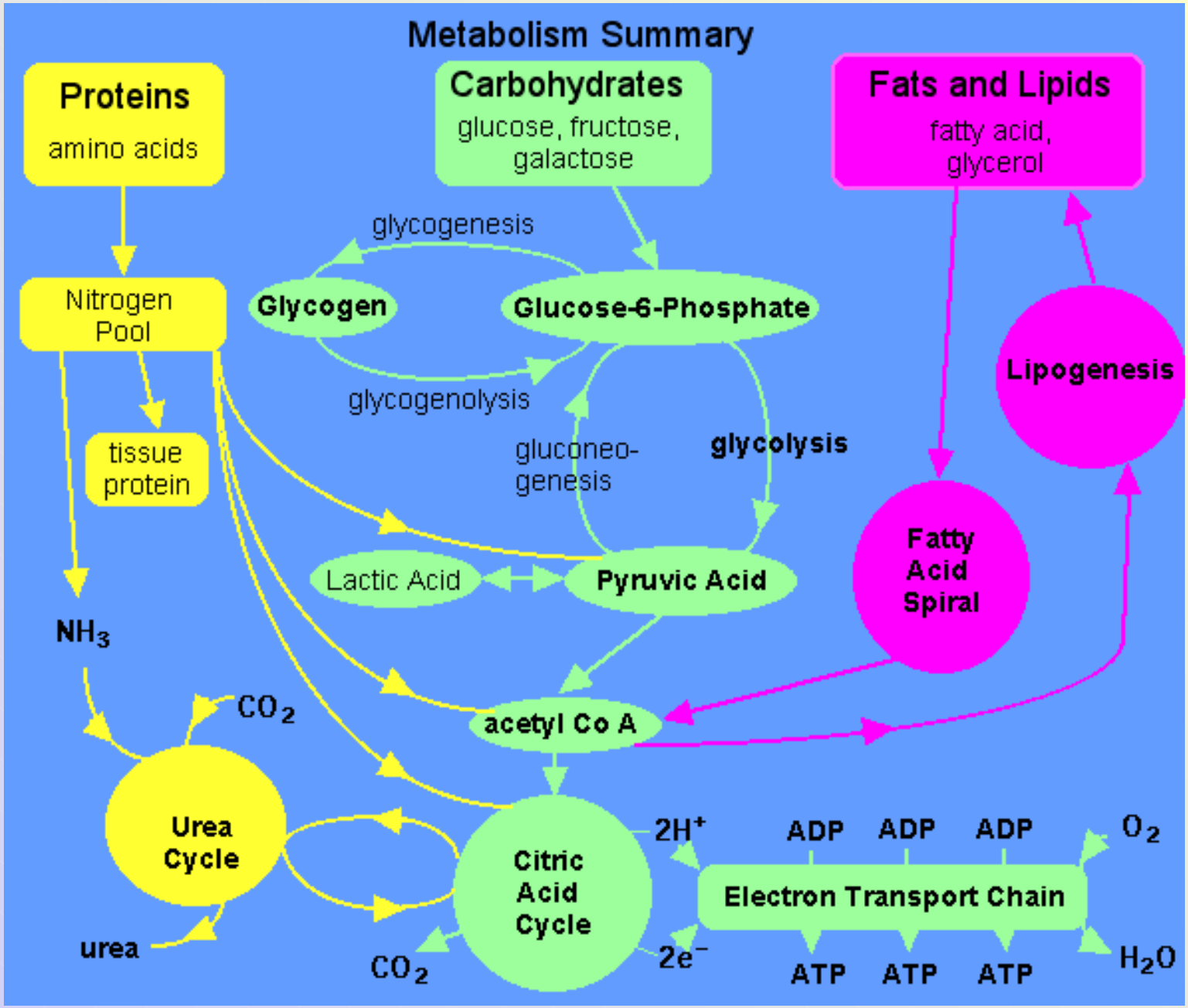
Anaplerotic reactions of the KC and the linking of the KC to with the other metabolic pathways in the cells

Connection to the other pathways

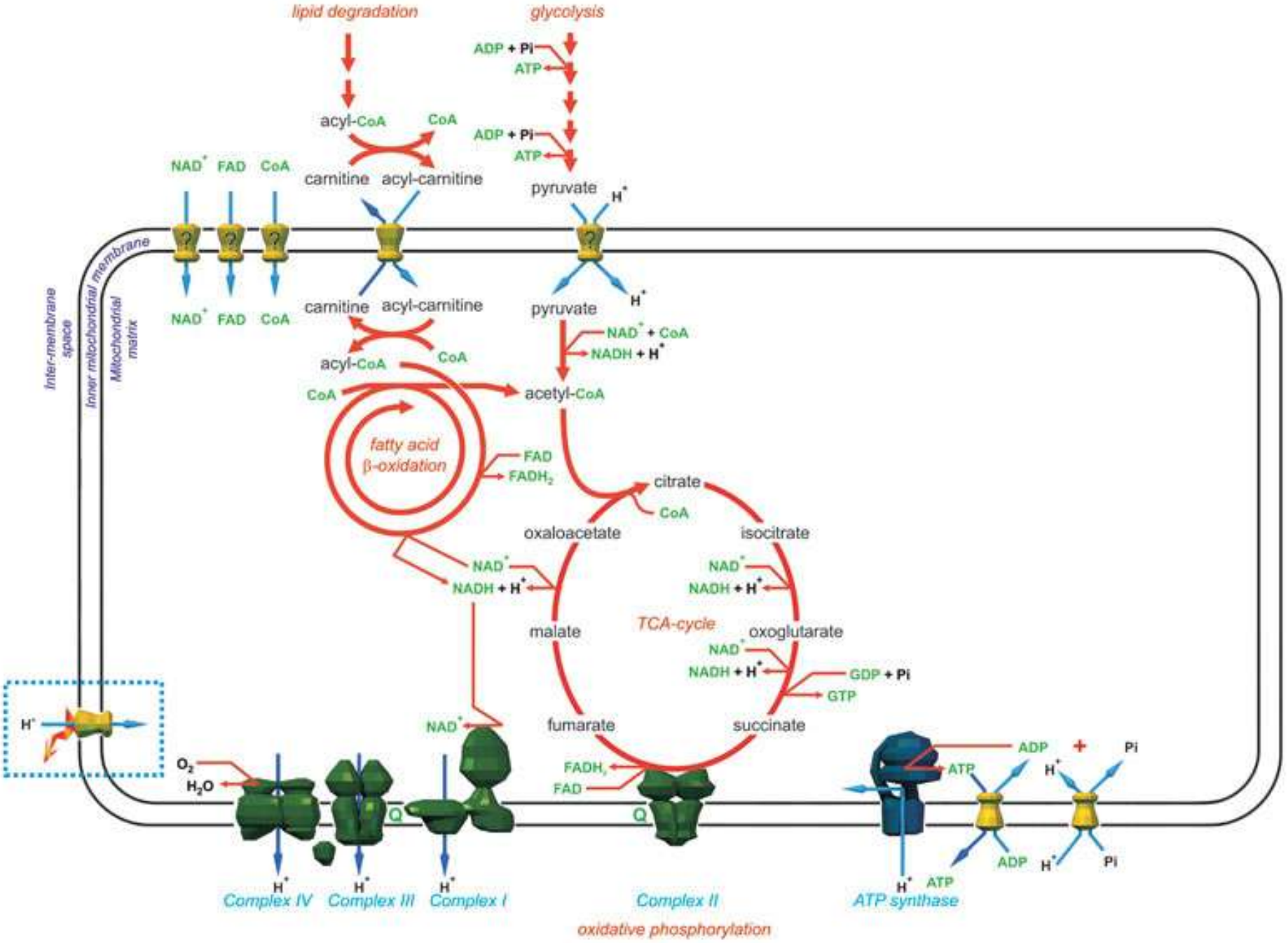
- Respiratory chain
- Metabolism of amino acids
- Urea cycle
- Synthesis of heme
- Gluconeogenesis
- FA synthesis
- Citrate cycle as a source of substrates used in a synthesis of other molecules.



The figure is found at http://www.tcd.ie/Biochemistry/IUBMB-Nicholson/gif/13.html

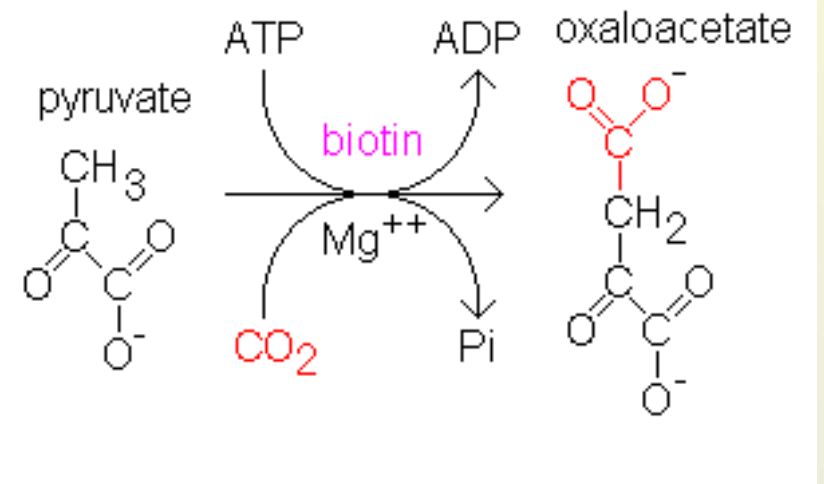


The figure is found at http://www.elmhurst.edu/~chm/vchembook/images/590metabolism.gif (December 2006)


lipid degradation
glycolysis
ADP + Pi
ATP
acyl-CoA
CoA
carnitine
acyl-carnitine
NAD+
FAD
CoA
pyruvate
H+
Inter-membrane space
Inner mitochondrial membrane
Mitochondrial matrix
NADH + H+
acetyl-CoA
fatty acid β-oxidation
FADH2
citrate
oxaloacetate
isocitrate
malate
TCA-cycle
oxoglutarate
GDP + Pi
GTP
fumarate
succinate
O2
H2O
Q
Complex IV
Complex III
Complex I
Complex II
ATP synthase
oxidative phosphorylation

Anaplerotic (support) reactions

- Because KC intermediates serve as substrates for other metabolic pathways, there are reactions to replace these losses.
- **Synthesis of OAA from Pyr** (Pyr carboxylation needs ATP) by pyruvate carboxylase.
  - This is also the first step in gluconeogenesis.
  - Biotin is a cofactor of carboxylases.



- Degradation of most amino acids gives the following intermediates of KC: OAA, α-KG, fumarate

Connecting of KC to FA formation

- Acetyl-CoA + OAA → citrate (citrate synthase in KC)
- Citrate is transferred from mitochondria into the cytoplasm, (to MIT goes malate).
- Citrate in the cytoplasm is split into acetyl-CoA and OAA (ATP-citrate lyase).

Citrate + ATP + HSCoA + H_2O → AcCoA + ADP + P_i + OAA

- AcCoA enters the synthesis of FA.
- Reduction of oxaloacetate to malate (malate dehydrogenase = consumption of NADH + H +)
- Malate returns via antiport in mitochondria or is decarboxylated to pyruvate.

Connecting of KC to FA formation

- *OAA* formed during transport of citrate into the cytosol should return back to the matrix. But the inner membrane of mitochondria is impermeable to *OAA*.
- *OAA* is therefore reduced in the presence of NADH to malate by the cytosolic malate dehydrogenase:

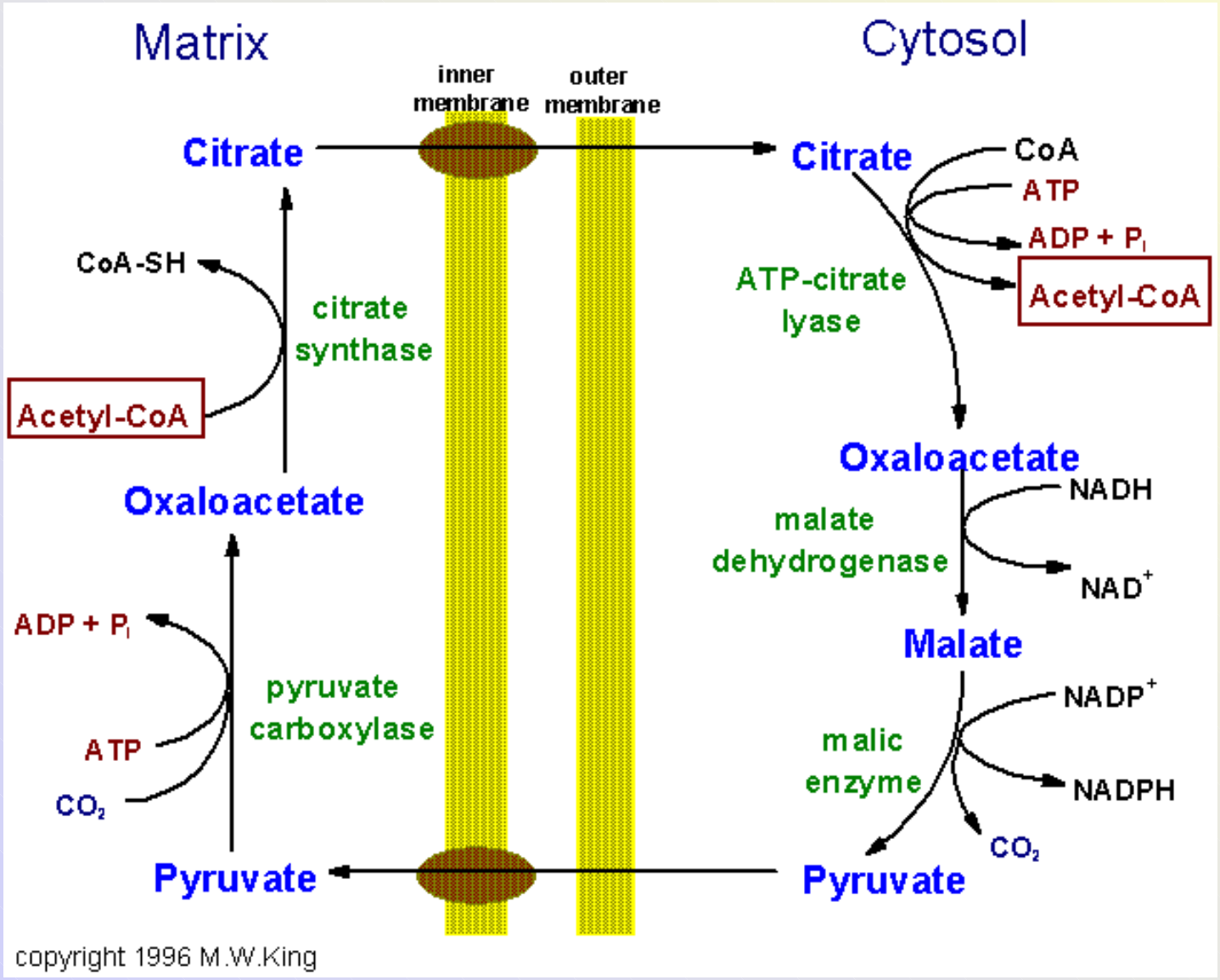
  OAA + NADH + H^+ → malate + NAD^+
- Malate is oxidatively decarboxylated by $NADP^+$- malate enzyme (malic enzyme):

  Malate + $NADP^+$ → Pyr + CO_2 + NADPH
- Finally, Pyr enters the mitochondria, where it is carboxylated by pyruvate carboxylase:

  Pyr + CO_2 + ATP + H_2O → OAA + ADP + P_i + 2 H^+
- **Summary equation:**

$NADP^+$ + NADH + ATP + H_2O → NADPH + NAD^+ + ADP + P_i + H^+

Connecting of KC to FA formation



Krebs cycle

Regulation of the KC

Regulatory enzymes

- Citrate synthase
- Isocitrate dehydrogenase
- α-ketoglutarate dehydrogenase
- The activity of *CAC* is closely linked to the availability of O_2.

Regulation of the KC

- Regulatory enzymes:
  - 1) Citrate synthase
  - 2) Izocitrate dehydrogenase
  - 3) a-ketoglutarate dehydrogenase
- Energy Control: If enough energy, enzymes 2 and 3 are inhibited - ATP is inhibitor, ADP is activator.
- Respiratory Control: KC and RC must work together. Accumulation of $NADH+H^+$ and $FADH_2$ inhibits enzymes 2, 3.
- Substrate control: Enzyme 1. Citrate synthase is mainly regulated by the availability of acetyl-CoA and oxaloacetate.

Bon courage

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