Kreb Cycle Reaction

'*Summary equation describing the Krebs cycle*:

$$CH_3\text{-}CO\sim SCoA + 3\ NAD^+ + FAD + GDP + P_i + 2\ H_{2</\ sub>O \rightarrow 2\ CO_2 + 3\ NADH + 3\ H^+ + FADH_2 + GTP$$

Most acetyl−CoA, which supplies acetyl residues to the Krebs cycle, comes from ß-oxidation of fatty acids and from pyruvate dehydrogenase reactions (processes taking place in the matrix mitochondria).

Pyruvate dehydrogenase reaction

It is an irreversible oxidative decarboxylation of pyruvate.

$$CH_3\text{-}CO\text{-}COOH + NAD^+ + HSCoA \rightarrow CO_2 + NADH + H^+ + CH_3\text{-}CO\sim SCoA$$

If we connect the pyruvate dehydrogenase reaction and the summary reaction of the Krebs cycle, we get an equation describing the complete oxidation of pyruvate.

$$CH_3\text{-}CO\text{-}COOH + 4\ NAD^+ + FAD + ADP + P_i + 2\ H_{2</\ sub>O \rightarrow 3\ CO_2 + 4\ NADH + 4\ H^+ + FADH_2 + ATP$$

Individual reactions of the Krebs cycle

Oxidation of acetyl residues takes place through several intermediate steps.

1. Acetyl residue (2C) transferred to oxaloacetate (4C)

- reaction catalyzed by the enzyme citrate synthase - ""citrate (6C)"" is formed
- irreversible - regulatory reaction

2. Isomerization of citrate to isocitrate

- via aconitate, catalyzed by the enzyme aconitate-hydratase (aconitase)
- reaction freely reversible

3. Oxidation of isocitrate to α-ketoglutarate

- catalyzed by the enzyme isocitrate dehydrogenase
- oxidative decarboxylation – oxidation of the −OH group of isocitrate to a keto group (formation of **NADH + H^+**) with simultaneous cleavage of one carboxyl group in the form of **CO_2**
- irreversible – the most important regulatory reaction

4. Oxidation of α-ketoglutarate to succinyl-CoA

- catalyzed by α-ketoglutarate dehydrogenase (multienzyme complex)
- this is oxidative decarboxylation - another molecule of 'CO_2 is split off
- formation of NADH + H^+
- irreversible and regulatory reaction

5. Conversion of succinyl-CoA to succinate and coenzyme A

- catalyzed by succinyl-CoA-ligase
- typical substrate phosphorylation
- reversible reaction
- formation of GTP, which can be converted into ATP.

In the previous reactions there was a complete oxidation of the acetyl residue to 2 CO_2 and oxaloacetate was reduced to succinate. The following three reactions regenerate oxaloacetate from succinate

6. Oxidation of succinate to fumarate

- using the enzyme succinate dehydrogenase (an integral protein in the inner mitochondrial membrane that is part of the respiratory chain – complex II)
- cofactor is FAD – $FADH_2$ is formed

7. Addition of water to the double bond in fumarate to form malate

- catalyzed by the enzyme fumarate hydratase (fumarase)

8. Oxidation of malate to oxaloacetate

- using the enzyme maltate dehydrogenase

- produces **NADH + H^+'**
- closes the Krebs cycle

Krebs cycle products

In one turn of the Krebs cycle, **2 CO_2, 3 NADH + H^+, 1 $FADH_2$ and 1 GTP are formed'** (can be exchanged for ATP).

> Carbon dioxide diffuses out of the mitochondria and is finally excreted in the lungs. Reduced cofactors (NADH + H^+, $FADH_2$) saturate the respiratory chain, which subsequently forms ATP. The energy balance of the Krebs cycle (direct formation of GTP and formation of ATP in the respiratory chain) varies between **10-12 ATP'** per one acetyl-CoA molecule. The situation is much more complicated and the exact number is problematic to determine.

Complementary (anaplerotic) reactions

Krebs cycle intermediates are found in very small amounts in mitochondria. On the one hand, anabolic pathways create the main outflow of intermediate products from the Krebs cycle - for example: succinyl-CoA → hemu synthesis, oxaloacetate → gluconeogenesis. On the other hand, during the oxidation of acetyl residues, their constant regeneration occurs, and therefore their concentrations remain relatively stable over time. Reactions that replenish these losses of Krebs cycle intermediates