Citric Acid Cycle / Tricarboxylic Acid Cycle {TCA} / Krebs Cycle

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2ND LECTURE

● The cycle is a sequence of reactions taking place in the mitochondria in which the acetyl moiety of **Acetyl-CoA** (derived from carbohydrates , lipids & proteins) is oxidized to CO_2 & H_2O and in which **reduced coenzymes** are produced . The reduced coenzymes are then re-oxidized in the electron transport chain to generate ATP .

Reactions of TCA cycle :

1 . Condensation of acetyl-CoA with oxaloacetate forming **Citrate** catalyzed by the enzyme **citrate synthase** .

2 . Isomerization of **Citrate** to **Isocitrate** .

3 . Isocitrate undergo oxidative decarboxylation to **α-ketoglutarate** by the enzyme **isocitrate dehydrogenase** which is NAD^+-linked . One molecule of NADH is produced and one molecule of CO_2 is released .

4 . Second oxidative decarboxylation converts α-Ketoglutarate to high-energy compound **succinyl-CoA** . One molecule of CO_2 is released and **one molecule** of **NADH** is produced .

5 . Succinyl-CoA is converted to **Succinate** by the enzyme **Succinate thiokinase** . GDP is phosphorylated to GTP . GTP is equivalent to ATP .

6 . Succinate is oxidized to **Fumarate** by FAD-linked **Succinate dehydrogenase** . One molecule of **$FADH_2$** is formed .

7 . Fumarate is hydrated by the enzyme Fumarase to form **L–malate** .

8 . **Regeneration of oxaloacetate** : the cycle is completed by the oxidation of malate to Oxaloacetate by NAD^+-linked **malate dehydrogenase** . One molecule of NADH is produced .

Energy production by the TCA cycle

*Number of ATP molecules generated by TCA Cycle per molecule of Glucose :

	Enzyme/step	Source	Number of ATP gained or used
3.	Isocitrate dehydrogenase	2 NADH	6 ATP (gained)
4.	α- Ketoglutarate dehydrogenase	2 NADH	6 ATP (gained)
5.	Succinate thiokinase	2 GTP	2 ATP (gained)
6.	Succinate dehydrogenase	2 $FADH_2$	4 ATP (gained)
8.	Malate dehydrogenase	2 NADH	6 ATP (gained)

Total = 24 ATP generated per molecule of glucose

ATP formation in the aerobic metabolism of glucose

1. **Glycolysis reactions to Pyruvate = 8 molecules of ATP gained**

2. **Pyruvate Dehydrogenase step :**
   Two molecules of NADH produced = 6 molecules of ATP generated

3. **Citric Acid Cycle = 24 molecules of ATP generated**

Total ATP per molecule of glucose under aerobic condition = 8+6+24 = 38 ATP

Metabolic Purposes (Importance) of TCA cycle

1. **Citric acid cycle is the major energy-producing pathway in the body . The cycle is the common pathway for the aerobic oxidation of carbohydrates , lipids , and proteins to generate energy (ATP) .**

2. **The citric acid cycle is amphibolic in nature ; it functions in both oxidative pathway (catabolism) and synthetic pathway (anabolism) ; TCA cycle acts as link between catabolic and anabolic pathways .**

   Catabolic function

   ■ **Glucose and fatty acids are metabolized to acetyl-CoA which enters the cycle** and oxidized .

- ■ Amino acids are metabolized to acetyl-CoA or to intermediates of the cycle .

<u>Anabolic function</u>

- ■ Some of the intermediates of the cycle act as the starting point for the synthesis of the compounds needed by the living cells . Ex: Synthesis of :
  Heme from succinyl-CoA ,

3. Reactions of the TCA cycle are utilized in the fasting state for the production of glucose from non – carbohydrate sources (Gluconeogenesis) .

4. Reactions of TCA cycle are also used to synthesize amino acids or to convert one amino acid to another ; ex:

<u>Regulation of citric acid cycle</u>

The cycle is regulated by the need of the cell for ATP :

- **When the concentration of ATP is high (when the cell has an adequate energy supply) , the electron transport chain slows down and NADH builds up . NADH & ATP inhibit all the enzymes catalyzing the reactions of the cycle that generate NADH (specially isocitrate dehydrogenase) resulting in slowing of the cycle .**