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NAAC ACCREDITED 'A' GRADE

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Citric Acid Cycle

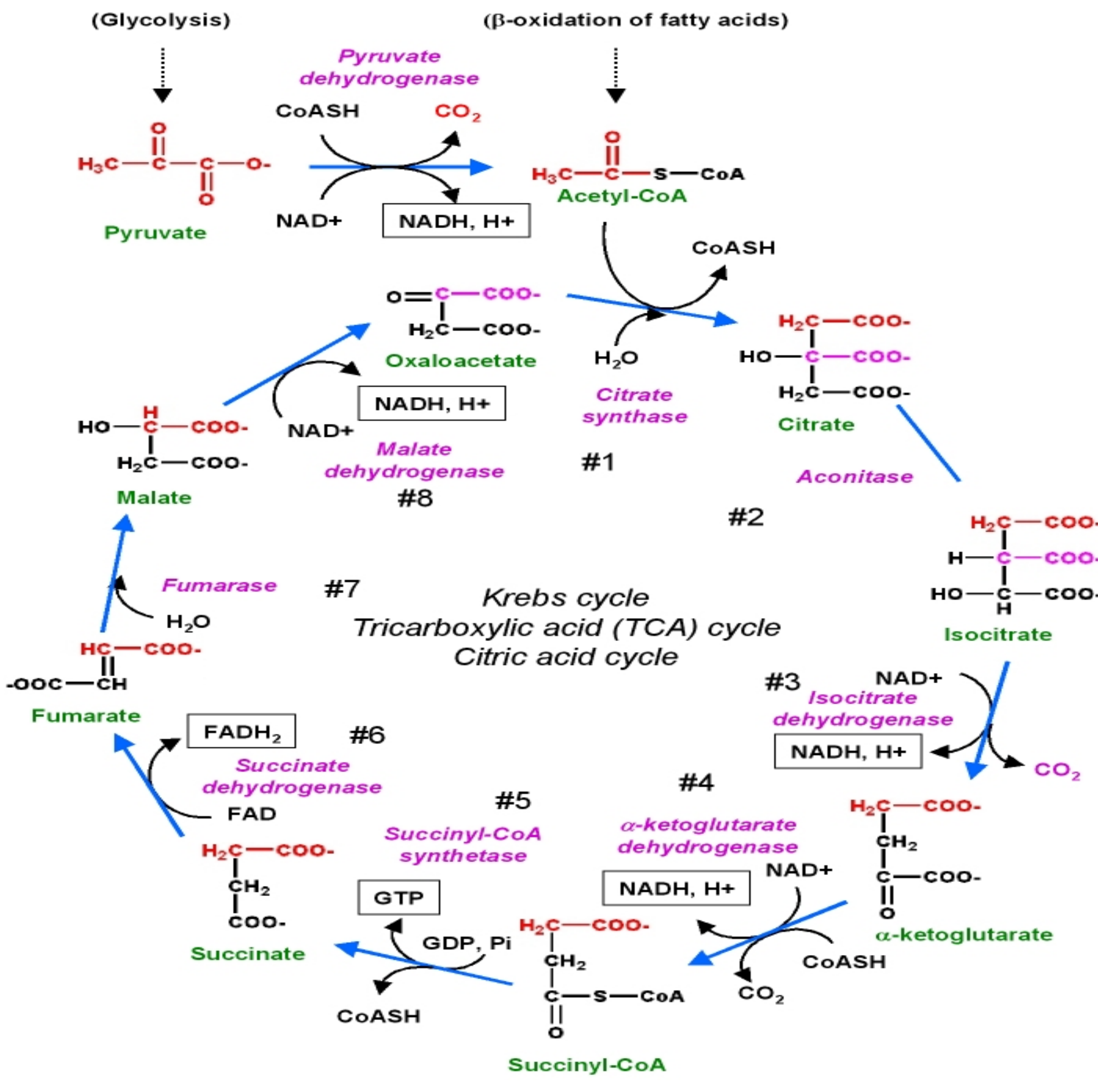
The most nearly universal pathway for aerobic metabolism is the cyclic series of reactions termed **citric acid cycle** or **Krebs cycle**. The first name has been applied because citric is the first intermediate formed in the cycle. The second name has been given in the honour of its most illustrious proponent, Sir Hans A. Krebs, who first postulated it in 1937. The **citric acid cycle** (CAC) also known as the **TCA cycle** (tricarboxylic acid cycle). is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl CoA derived from cabohydrates, fats, and proteins, into adenosine triphosphate(ATP) and carbon dioxide. Under aerobic conditions, the pyruvate generated from glucose is oxidatively decarboxylated to form acetyl CoA. In eukaryotes, the reactions of the citric acid cycle take place inside mitochondria, in contrast with those of glycolysis, which take place in the cytosol.

In eukaryotic cells, the citric acid cycle occurs in the matrix of the mitochondria. In prokaryotic cells, such as bacteria, which lack mitochondria, the citric acid cycle reaction sequence is performed in the cytosol with the proton gradient for ATP production being across the cell's surface (plasma membrane) rather than the inner membrane of the mitochondrion. The overall yield of energy-containing compounds from the TCA cycle is three NADH, one $FADH_2$, and one GTP.

Two **fundamental differences** exists between glycolysis and citric acid cycle:

- ✓ Glycolysis takes place by a linear sequence of 10 enzyme-catalysed reactions. In contrast, citric acid cycle proceeds in a cyclic way by 8-enzyme catalysed reactions.
- ✓ The reactions of glycolysis occur in the cytosol in contrast with those of citric acid cycle which occur inside mitochondria.

The overall reactions of the Citric Acid Cycle



Enzymes of the Citric Acid Cycle

	Substrates	Products	Enzyme	Reaction type
1	Oxaloacetate + Acetyl CoA + H_2O	Citrate + CoA-SH	Citrate synthase	Aldol codensation (irreversible)
2	Citrate	*cis*-Aconitate + H_2O	Aconitase	Dehydration (reversible isomerisation)
3	*cis*-Aconitate + H_2O	Isocitrate	Aconitase	Hydration (reversible)
4	Isocitrate + NAD^+	α-Ketoglutarate + CO_2	Isocitrate dehydrogenase	Oxidation decarboxylation (irreversible stage)
5	α-Ketoglutarate + NAD^+ + CoA-SH	Succinyl-CoA + NADH + H^+ + CO_2	α-Ketoglutarate dehydrogenase	Oxidative decarboxylation (irreversible stage)
6	Succinyl-CoA + GDP + P_i	Succinate + CoA-SH + GTP	Succinyl-CoA synthetase	substrate-level phosphorylation (reversible)
7	Succinate + ubiquinone (Q)	Fumarate + ubiquinol (QH_2)	Succinate dehydrogenase	Oxidation (reversible)
8	Fumarate + H_2O	*L*-Malate	Fumarase	Hydration (reversible)
9	L-Malate + NAD^+	Oxaloacetate + NADH + H^+	Malate dehydrogenase	Oxidation (reversible)
10	Oxaloacetate + Acetyl CoA + H_2O	Citrate + CoA-SH	Citrate synthase	Aldol condensation (irreversible)

Steps

Reaction 1: Formation of Citrate

- The first reaction of the cycle is the condensation of **acetyl-CoA** with **oxaloacetate** to form **citrate**, catalyzed by **citrate synthase**.
- Once oxaloacetate is joined with acetyl-CoA, a water molecule attacks the acetyl leading to the release of coenzyme A from the complex.

Reaction 2: Formation of Isocitrate

- The **citrate** is rearranged to form an isomeric form, **isocitrate** by an enzyme **acontinase.**
- In this reaction, **a water molecule is removed** from the citric acid and then put back on in another location. The overall effect of this conversion is that the –OH group is moved from the 3′ to the 4′ position on the molecule. This transformation yields the molecule **isocitrate.**

Reaction 3: Oxidation of Isocitrate to α-Ketoglutarate

- In this step, isocitrate dehydrogenase catalyzes oxidative decarboxylation of **isocitrate** to form **α-ketoglutarate.**
- In the reaction, generation of NADH from NAD is seen. The enzyme **isocitrate dehydrogenase** catalyzes the oxidation of the –OH group at the 4′ position of isocitrate to yield an intermediate which then has a carbon dioxide molecule removed from it to yield **alpha-ketoglutarate**.

Reaction 4: Oxidation of α-Ketoglutarate to Succinyl-CoA

- **Alpha-ketoglutarate** is oxidized, carbon dioxide is removed, and coenzyme A is added to form the 4-carbon compound **succinyl-CoA**.
- During this oxidation, NAD+ is reduced to NADH + H+. The enzyme that catalyzes this reaction is **alpha-ketoglutarate dehydrogenase.**

Reaction 5: Conversion of Succinyl-CoA to Succinate

- CoA is removed from **succinyl-CoA** to produce **succinate.**
- The energy released is used to make guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and Pi by substrate-level phosphorylation. GTP can then be used to make ATP. The enzyme **succinyl-CoA synthase** catalyzes this reaction of the citric acid cycle.

Reaction 6: Oxidation of Succinate to Fumarate

- **Succinate** is oxidized to **fumarate**.
- During this oxidation, FAD is reduced to FADH2. The enzyme **succinate dehydrogenase** catalyzes the removal of two hydrogens from succinate.

Reaction 7: Hydration of Fumarate to Malate

- The reversible hydration of **fumarate** to **L-malate** is catalyzed by **fumarase (fumarate hydratase).**
- **Fumarase** continues the rearrangement process by adding **Hydrogen** and **Oxygen** back into the substrate that had been previously removed.

Reaction 8: Oxidation of Malate to Oxaloacetate

- **Malate** is oxidized to produce **oxaloacetate**, the starting compound of the citric acid cycle by **malate dehydrogenase**. During this oxidation, NAD+ is reduced to NADH + H+.

Overall Balance Sheet:

$$CH_3CO\text{-}SCoA + 3NAD^+ + FAD + GDP + Pi + H_2O \rightarrow 2CO_2 + CoA\text{-}SH + 3NADH + FADH_2 + GTP + 2H^+$$

The Complete Oxidation of Glucose Yields about 30 Molecules of ATP or Stoichiometry of Glucose Oxidation

Reaction	Number of ATP or reduced coenzyme directly formed	Number of ATP ultimately formed*
Glucose ⟶ glucose 6-phosphate	−1 ATP	−1
Fructose 6-phosphate ⟶ fructose 1,6-bisphosphate	−1 ATP	−1
2 Glyceraldehyde 3-phosphate ⟶ 2 1,3-bisphosphoglycerate	2 NADH	3 or 5†
2 1,3-Bisphosphoglycerate ⟶ 2 3-phosphoglycerate	2 ATP	2
2 Phosphoenolpyruvate ⟶ 2 pyruvate	2 ATP	2
2 Pyruvate ⟶ 2 acetyl-CoA	2 NADH	5
2 Isocitrate ⟶ 2 α-ketoglutarate	2 NADH	5
2 α-Ketoglutarate ⟶ 2 succinyl-CoA	2 NADH	5
2 Succinyl-CoA ⟶ 2 succinate	2 ATP (or 2 GTP)	2
2 Succinate ⟶ 2 fumarate	2 $FADH_2$	3
2 Malate ⟶ 2 oxaloacetate	2 NADH	5
Total		30–32

*This is calculated as 2.5 ATP per NADH and 1.5 ATP per $FADH_2$. A negative value indicates consumption.

†This number is either 3 or 5, depending on the mechanism used to shuttle NADH equivalents from the cytosol to the mitochondrial matrix; see Figures 19–30 and 19–31.