Krebs cycle

Krebs cycle (also known as the citric acid cycle or tricarboxylic acid cycle) was discovered by H. A. Kreb, German born British Biochemist who received the Nobel prize in 1953. This cycle occurs in the matrix of mitochondria (cytosol in prokaryotes). The whole cycle is explained in the following figure. The net result of Kreb cycle is that for each acetyl group entering the cycle as Acetyl-CoA, two molecules of CO_2 are produced.

Step 1 : The citric acid cycle begins with the condensation of an oxaloacetate (four carbons unit), and the acetyl group of acetyl CoA (two-carbon unit). Oxaloacetate reacts with acetyl-CoA and H_2O to yield citrate and CoA. This reaction, which is an aldol condensation followed by a hydrolysis, is catalyzed by *citrate synthase*.

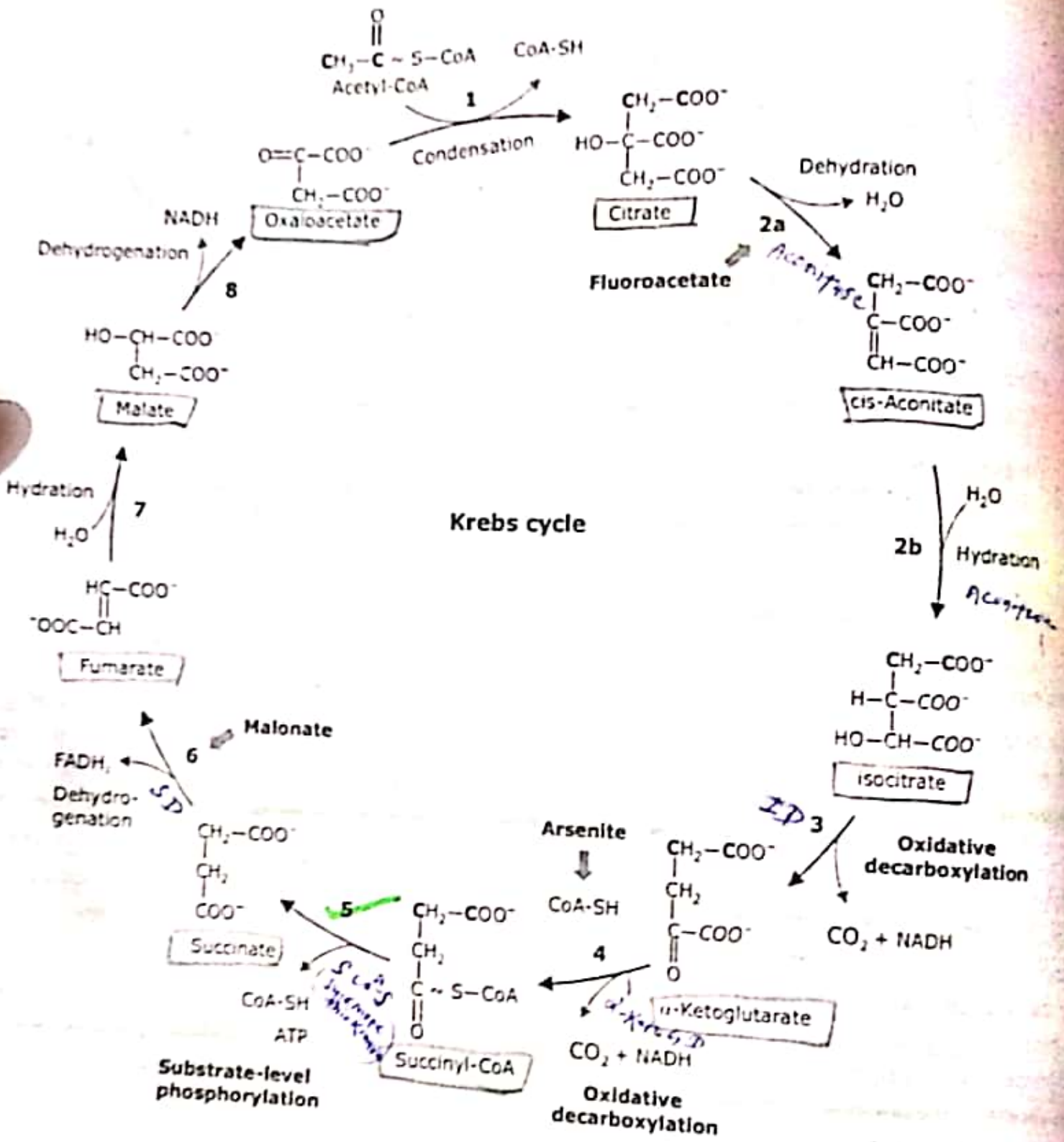
Step 2a and 2b : An isomerization reaction, in which water is first removed and then added back, moves the hydroxyl group from one carbon atom to its neighbour. The enzyme catalyzing this step, aconitase (nonheme iron protein), is the target site for the toxic compound **fluoroacetate** (used as a pesticide). Fluoroacetate blocks the citric acid cycle by its metabolic conversion of *fluorocitrate*, which is a potent inhibitor of aconitase.

Step 3 : Isocitrate is oxidized and decarboxylated to α-ketoglutarate. In the first of four oxidation steps in the cycle, the carbon carrying the hydroxyl group is converted to a carbonyl group. The immediate product is unstable, losing CO_2 while still bound to the enzyme. The oxidative decarboxylation of isocitrate is catalyzed by *isocitrate dehydrogenase*.

Step 4 : A second oxidative decarboxylation reaction result in formation of succinyl CoA from α-ketoglutarate. α-ketoglutarate dehydrogenase catalyzes this oxidative step and produces NADH, CO_2, and a high-energy thioester bond to coenzyme A (CoA).

Step 5 : The cleavage of the thioester bond of succinyl CoA is coupled to the phosphorylation of a purine nucleoside diphosphate, usually GDP (substrate level phosphorylation). This reaction is catalyzed by *succinyl CoA synthetase* (succinate thiokinase). This is the only step in the citric acid cycle that directly yields a compound with high phosphoryl transfer potential through a substrate-level phosphorylation.

Step 6 : In the third oxidation step in the cycle, FAD removes two hydrogen atoms from succinate. The enzyme catalyzing this step, succinate dehydrogenase, is strongly inhibited by **malonate**, a structural analog of succinate and a classic example of a competitive inhibitor.



1. Citrate synthase
2a Aconitase
2b Aconitase
3. Isocitrate dehydrogenase
4. α-Ketoglutarate dehydrogenase
5. Succinate thiokinase
6. Succinate dehydrogenase
7. Fumarase
8. Malate dehydrogenase

Step 7 : The addition of water to fumarate places a hydroxyl group next to a carbonyl carbon.

Step 8 : In the last of four oxidation steps in the cycle, the carbon carrying the hydroxyl group is converted to a carbonyl group, regenerating the oxaloacetate needed for step 1.

Overall reaction:

$$\text{Acetyl CoA} + 3NAD^+ + FAD + GDP + 3H_2O \longrightarrow 2\,CO_2 + 3NADH + FADH_2 + GTP + H_2O$$

The energy yield from two pyruvate molecules when oxidized to 6 CO_2 via the pyruvate dehydrogenase complex and the citric acid cycle, and the electrons are transferred to O_2 via oxidative phosphorylation, as many as 25 ATP are obtained.

Fate of carbon in the citric acid cycle

Acetyl-CoA entering the citric acid cycle is highlighted (in bold) to show the fate of its two carbons through reaction 4. After reaction 5, the carbon atoms most recently entered are no longer highlighted, because succinate is a symmetrical molecule. Carboxyl groups that leave the cycle as CO_2 in reactions 3 and 4 are shown in *italics* letter.