CITRIC ACID CYCLE

TIG

Introduction:

In order for ATP to be produced through oxidative phosphorylation, electrons are required so that they can pass down the electron transport chain. These electrons come from electron carriers such as NADH and $FADH_2$, which are produced by the Tricarboxylic Acid Cycle (TCA cycle, aka Kreb's/Citric Acid cycle).

Site: Mitochondria.

Link Reaction:

Prior to the TCA cycle, glycolysis has occurred. This has generated molecules including pyruvate, ATP and NADH.

Pyruvate is then decarboxylated to form acetyl-coA by the pyruvate decarboxylase complex. Acetyl-coA is the intermediate that enters the TCA cycle.

The TCA Cycle:

The TCA cycle is a central pathway that provides a unifying point for many metabolites, which feed in at various points. It takes place over eight different steps:

Step 1: Acetyl CoA (two carbon molecule) joins with oxaloacetate (4 carbon molecule) to form citrate (6 carbon molecule).

Step 2: Citrate is converted to isocitrate (an isomer of citrate)

Step 3: Isocitrate is oxidised to alpha-ketoglutarate (a five carbon molecule) which results in the release of carbon dioxide. One NADH molecule is formed.

The enzyme responsible for catalysing this step is isocitrate dehydrogenase. This is a rate limiting step as isocitrate dehydrogenase is an allosterically controlled enzyme.

Step 4: Alpha-ketoglutarate is oxidised to form a 4 carbon molecule. This binds to coenzyme A forming succinyl CoA. A second molecule of NADH is produced, alongside a second molecule of carbon dioxide.

Step 5: Succinyl CoA is then converted to succinate (4 carbon molecule) and one GTP molecule is produced.

Step 6: Succinate is converted into fumarate (4 carbon molecule) and a molecule of $FADH_2$ is produced.

Step 7: Fumarate is converted to malate (another 4 carbon molecule).

Step 8: Malate is then converted into oxaloacetate. The third molecule of NADH is produced.

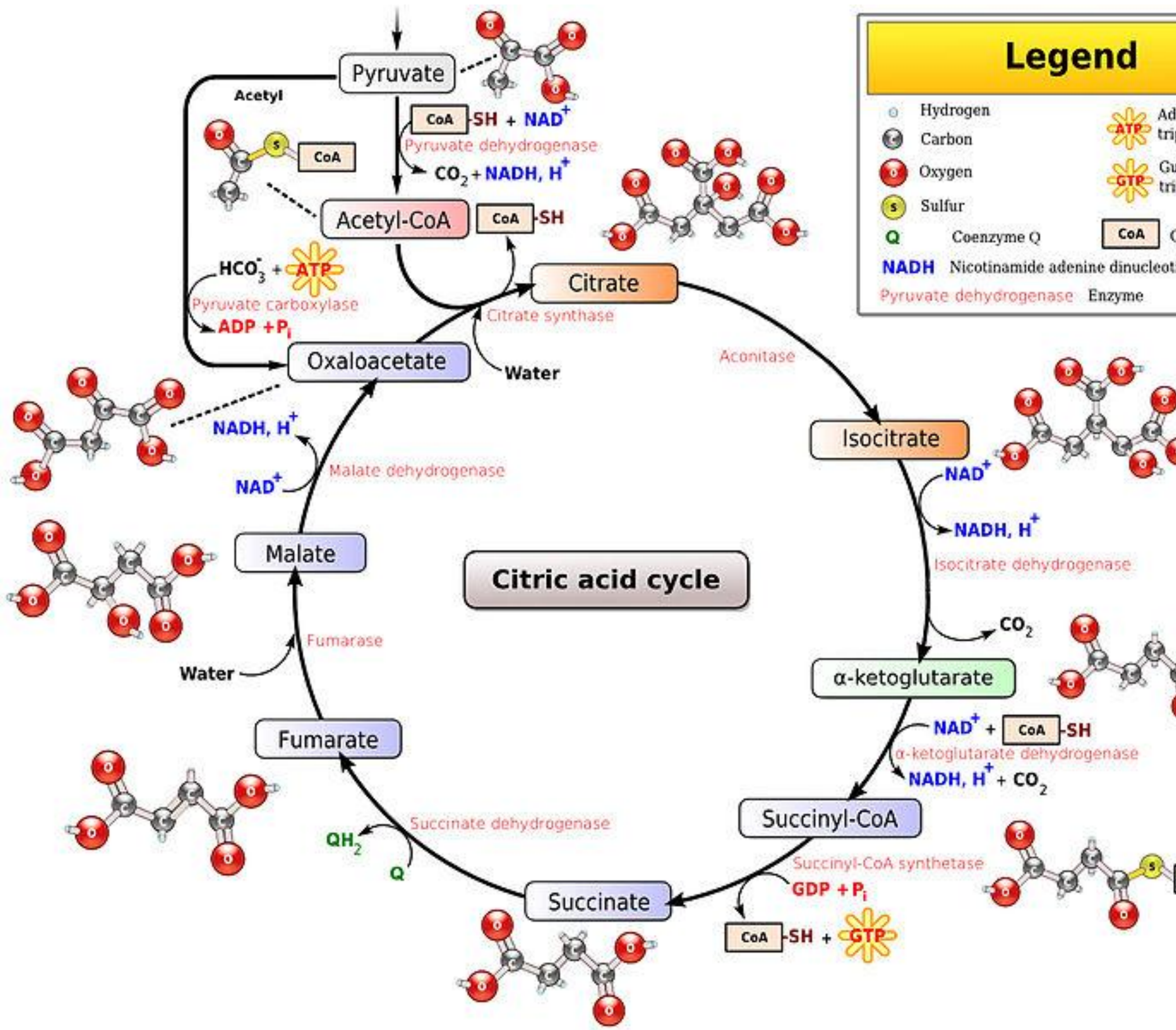

Fig 1 – Diagram showing the steps of the TCA cycle.

Amphibolic pathway:

It is important to be aware that whilst the primary role of the TCA cycle is production of NADH and $FADH_2$, it also produces molecules that supply various biosynthetic processes. These enter or exit the cycle at various points depending on demand. For example, alpha-ketoglutarate can leave the cycle to be converted into amino acids, and succinate can be converted to haem.

Net Output:

Each cycle produces:

Two molecules of carbon dioxide.

Three molecules of NADH.

Three hydrogen ions.

One molecule of $FADH_2$

One molecule of GTP.

Each molecule of glucose produces two molecules of pyruvate, which in turn produce two molecules of acetyl-coA. Therefore, each molecule of glucose produces double this.

Regulation of the TCA Cycle:

The TCA Cycle is regulated in a variety of ways including:

Metabolites: The products of the cycle provide negative feedback on the enzymes that catalyse it. For example, NADH inhibits the majority of the enzymes found in the TCA cycle.

Citrate: Inhibits phosphofructokinase, a key enzyme in glycolysis. This reduces the rate of production of pyruvate and therefore of acetyl-coA.

Calcium: Calcium accelerates the TCA cycle by stimulating the link reaction.