KREBS CYCLE (TCA CYCLE)

It is also known as **TriCarboxylic Acid (TCA)** cycle. In **prokaryotic cells**, the citric acid cycle occurs in the cytoplasm; in **eukaryotic cells**, the citric acid cycle takes place in the matrix of the mitochondria.

Definition. The sequence of reactions by which most living cells generate energy during the process of aerobic respiration. It takes place in the mitochondria, using up oxygen and producing carbon dioxide and water as waste products, and ADP is converted to energy-rich ATP.

- The cycle was first elucidated by scientist "**Sir Hans Adolf Krebs**" (1900 to 1981). He shared the Nobel Prize for physiology and Medicine in 1953 with Fritz Albert Lipmann, the father of ATP cycle.

The process oxidises glucose derivatives, fatty acids and amino acids to carbon dioxide (CO2) through a series of enzyme controlled steps. The purpose of the Krebs Cycle is to collect (eight) high-energy electrons from these fuels by oxidising them, which are transported by activated carriers NADH and FADH2 to the electron transport chain. The Krebs Cycle is also the source for the precursors of many other molecules, and is therefore an amphibolic pathway (meaning it is both anabolic and catabolic).

Introduction

In the presence of oxygen organisms are capable of using the Kreb's Cycle. The reason oxygen is required is because the NADH and [$FADH_2$] produced in the Kreb's Cycle are able to be oxydized in the electron transport chain (ETC) thus replenishing the supply of NAD^+ and [FAD].

Steps

In order for pyruvate from glycolysis to enter the Kreb's Cycle it must first be converted into acetyl-CoA by the pyruvate dehydrogenase complex which is an oxidative process wherein NADH and CO_2 are formed. Another source of acetyl-CoA is beta oxidation of fatty acids.

Step 1. In the first step of the citric acid cycle, acetyl CoA joins with a four-carbon molecule, oxaloacetate, releasing the CoA group and forming a six-carbon molecule called citrate.

Step 2. In the second step, citrate is converted into its isomer, isocitrate. This is actually a two-step process, involving first the removal and then the addition of a water molecule, which is why the citric acid cycle is sometimes described as having nine steps—rather than the eight listed here.

Step 3. In the third step, isocitrate is oxidized and releases a molecule of carbon dioxide, leaving behind a five-carbon molecule—α-ketoglutarate. During this step, NAD+ is reduced to form NADH .The enzyme catalyzing this step, **isocitrate dehydrogenase**, is important in regulating the speed of the citric acid cycle.

Step 4. The fourth step is similar to the third. In this case, it's α-ketoglutarate that's oxidized, reducing NAD+ to NADH and releasing a molecule of carbon dioxide in the process. The remaining four-carbon molecule picks up Coenzyme A, forming the unstable compound succinyl CoAs. The enzyme catalyzing this step, **α-ketoglutarate dehydrogenase**, is also important in regulation of the citric acid cycle.

Step 5. In step five, the CoA of succinyl CoA is replaced by a phosphate group, which is then transferred to ADP to make ATP. In some cells, GDP—guanosine diphosphate—is used instead of ADP, forming GTP guanosine triphosphate—as a product. The four-carbon molecule produced in this step is called succinate.

Step 6. In step six, succinate is oxidized, forming another four-carbon molecule called fumarate. In this reaction, two hydrogen atoms—with their electrons—are transferred to FAD, producing FADH2. The enzyme that carries out this step is embedded in the inner membrane of the mitochondrion, so FADH2can transfer its electrons directly into the electron transport chain.

Step 7. In step seven, water is added to the four-carbon molecule fumarate, converting it into another four-carbon molecule called malate.

Step 8. In the last step of the citric acid cycle, oxaloacetate—the starting four-carbon compound—is regenerated by oxidation of malate. Another molecule of NAD+ is reduced to NADH in the process.

Products of the citric acid cycle

In a single turn of the cycle,

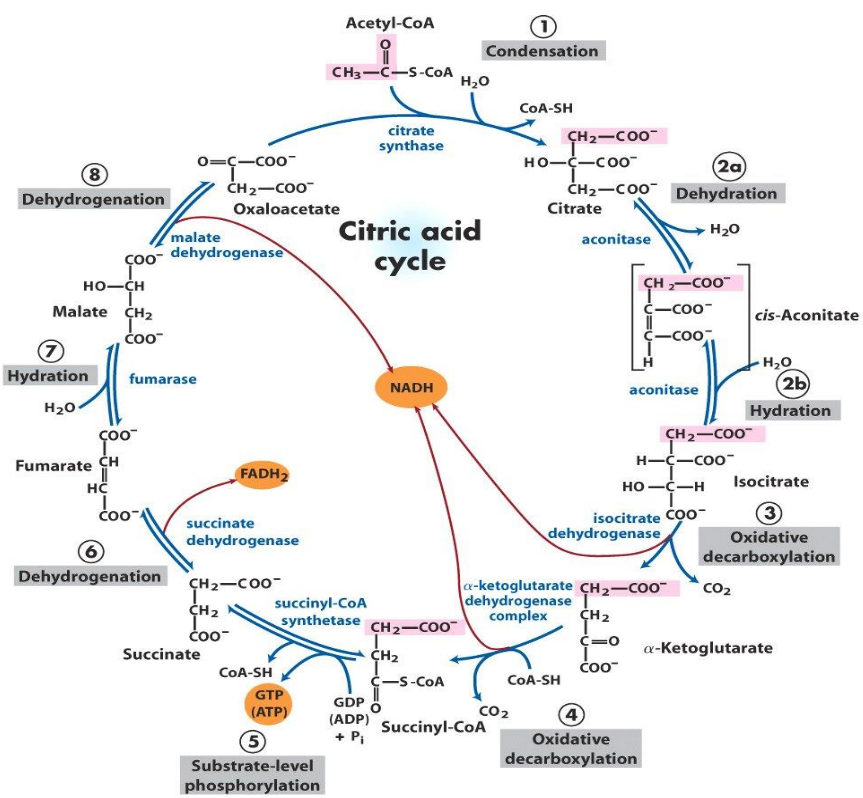
- two carbons enter from acetyl CoA and two molecules of carbon dioxide are released;
- three molecules of NADH and one molecule of FADH2 are generated; and
- one molecule of ATP or GTP is produced.

These figures are for one turn of the cycle, corresponding to one molecule of acetyl CoA. Each glucose produces two acetyl CoA molecules, so we need to multiply these numbers by 2 if we want the per-glucose yield.

Where's all the ATP?

You may be thinking that the ATP output of the citric acid cycle seems pretty unimpressive. All that work for just one ATP or GTP?

It's true that the citric acid cycle doesn't produce much directly. However, it can make a lot of ATP *indirectly*, by way of the NADH and FADH2 it generates. These electron carriers will connect with the last portion of cellular respiration, depositing their electrons into the electron transport chain to drive synthesis of ATP molecules through [oxidative phosphorylation].



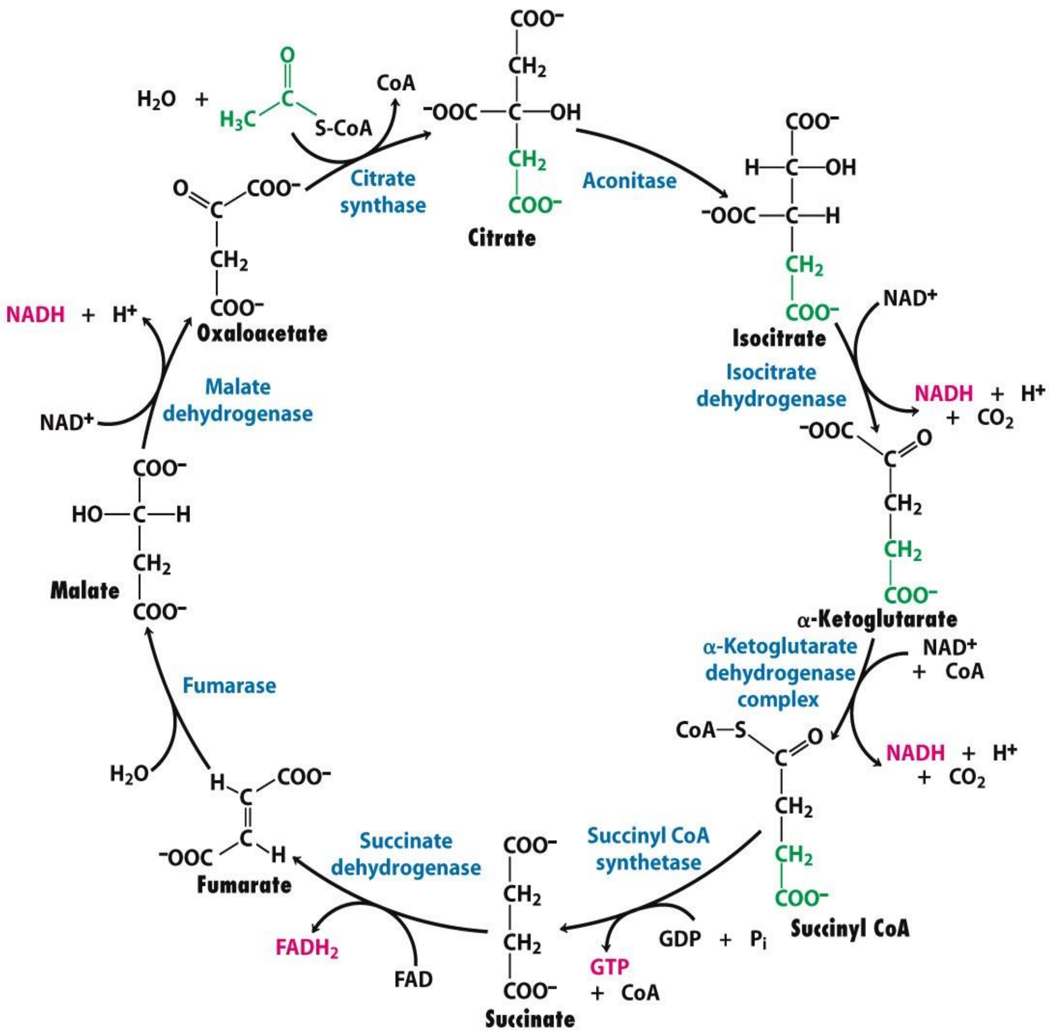


Figure 17.15
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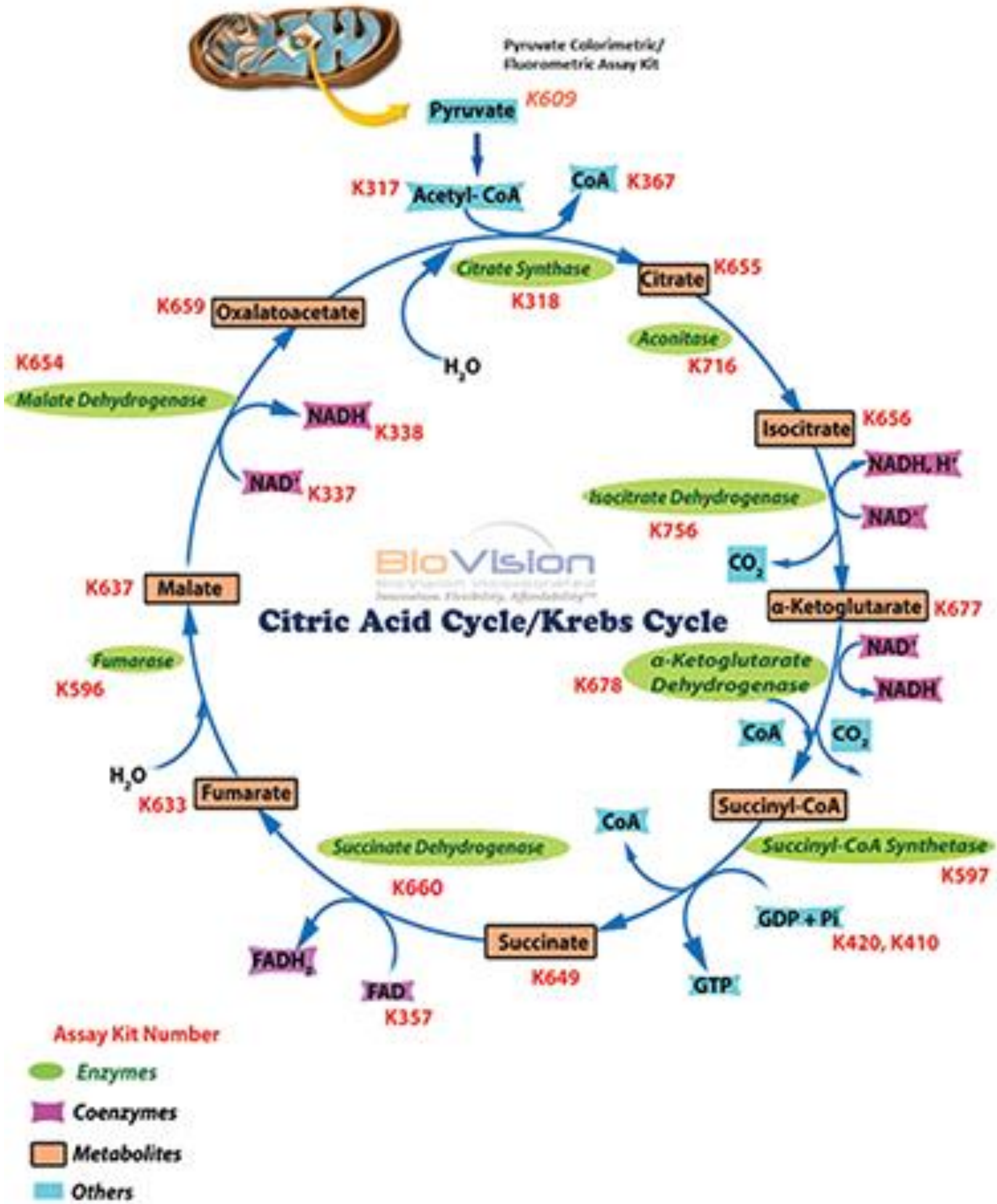

Pyruvate Colorimetric/
Fluorometric Assay Kit
Pyruvate
K609
K317
Acetyl- CoA
CoA
K367
Citrate Synthase
K318
Citrate
K655
K659
Oxalatoacetate
H_2O
Aconitase
K716
K654
Malate Dehydrogenase
NADH
K338
Isocitrate
K656
NADH, H^+
NAD^+
K337
Isocitrate Dehydrogenase
NAD^+
K756
CO_2
BioVision
K637
Malate
α-Ketoglutarate
K677
Citric Acid Cycle/Krebs Cycle
NAD^+
Fumarase
α-Ketoglutarate
Dehydrogenase
K678
NADH
K596
CoA
CO_2
H_2O
Fumarate
K633
Succinyl-CoA
CoA
Succinate Dehydrogenase
Succinyl-CoA Synthetase
K597
K660
GDP + Pi
K420, K410
$FADH_2$
Succinate
K649
GTP
FAD
K357
Assay Kit Number
Enzymes
Coenzymes
Metabolites
Others