Module 17 / TCA Cycle

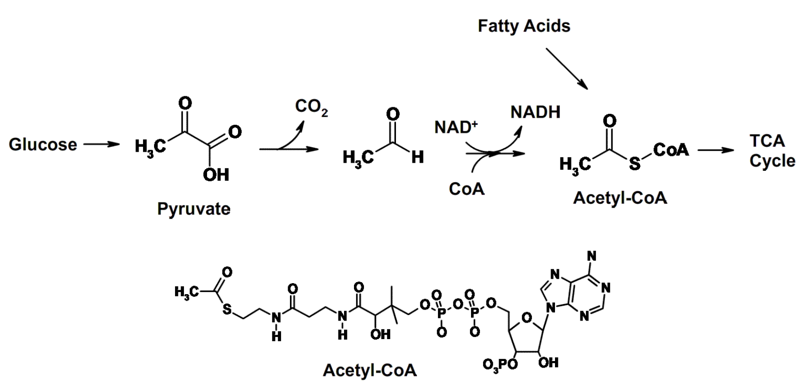
- Describe how glycolysis connects to the TCA cycle and where the TCA cycle occurs.
- Explain where CO_2 is released.
- Expound on where, and in what form, the energy released by the TCA cycle is stored.
- Describe how intermediates in the TCA cycle are used to synthesize a wide range of compounds.

Catabolic Process of the TCA Cycle

The tricarboxylic acid (TCA) cycle, also known as the Krebs cycle or the citric acid cycle, is a central pathway in the metabolism of all organisms. Not only is this pathway the next step for the oxidation of glucose and fatty acids, it also plays a key role in amino acid metabolism. All carbons that enter the TCA cycle, regardless of their source, are fully oxidized to carbon dioxide. The electrons that are released from these oxidations are stored on NADH and $FADH_2$ for subsequent processing by the electron transport chain.

Entry of **carbohydrates** into the TCA cycle occurs by the transport of pyruvate from the cytoplasm into the mitochondrial matrix. There, the pyruvate undergoes a process called **oxidative decarboxylation** to produce a key intermediate in metabolism, **acetyl-CoA**, which enters the TCA cycle.

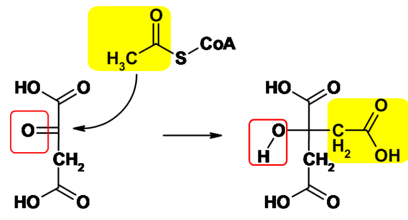
Entry of **fatty acids** into the TCA occurs directly into acetyl-CoA. During the process of fatty acid oxidation (beta-oxidation) which also occurs in the mitochondrial matrix, two-carbon fragments are progressively released from fatty acids and incorporated into acetyl-CoA.



Entry of carbohydrates and fats into the TCA cycle. Oxidative decarboxylation of pyruvate produces acetyl-CoA, releasing one CO^2 and NADH. Fatty acid oxidation yields acetyl-CoA directly. Acetyl-CoA is a high-energy thioester that enters the citric acid cycle.

The **first** step of the TCA cycle utilizes the high-energy thioester in acetyl-CoA to drive the addition of an

The **first** step of the TCA cycle utilizes the high-energy thioester in acetyl-CoA to drive the addition of an acetate group to oxaloacetic acid to produce citrate.



Oxaloacetate Citrate

In the first step of the TCA cycle acetyl-CoA donates an acetate group to oxaloacetate, forming citrate. Note that the ketone group on oxalacetate has become an alcohol in citrate.

The remaining steps in the TCA cycle convert citrate back to oxaloacetate. This process produces:

- 2 CO_2, from oxidative decarboxylations.
- 3 NADH, all from oxidation of alcohols to ketones.
- 1 $FADH_2$, from the oxidation of an alkane to an alkene
- 1 GTP, from the hydrolysis of a thio-ester.

Given the above information, your task is to deduce the series of reactions that convert citrate back to oxaloacetate using the following learn-by-doing activity.

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Anabolic Role of the TCA Cycle.

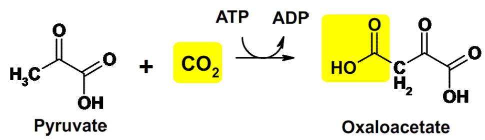
Intermediates of the TCA cycle are utilized in the following synthetic pathways:

- Fatty acids and steroids from acetyl-CoA.
- Amino acids aspartate, asparagine, lysine, isoleucine, methionine from oxaloacetate.
- Amino acids glutamate, glutamine, proline, arginine from alpha-ketoglutaric acid
- Porphyrin, a precursor to heme, from Succinyl-CoA

What major metabolite is missing from this list? Carbohydrates! It is not possible for mammals to use carbon

What major metabolite is missing from this list? Carbohydrates! It is not possible for mammals to use carbon atoms derived from the TCA cycle to synthesize glucose. How glucose is synthesized from pyruvate will be discussed in the module on integrated metabolism.

If compounds in the TCA cycle are used to synthesize other compounds, such as amino acids, the TCA cycle will eventually halt due to depletion of oxaloacetate. Consequently it is necessary to "fill up" the TCA cycle with an **"anaplerotic"** reaction. In this case, pyruvate is converted to oxaloacetate by the enzyme pyruvate carboxylase:



Anaplerotic reaction that generates oxaloacetate from pyruvate. This reaction replenishes the carbons in the TCA cycle, allowing it to continue to operate under anabolic conditions.

did I get this

In cellular respiration, the majority of the carbon dioxide production takes place in

- converting pyruvate to Acetyl-CoA
- fermentation
- glycolysis
- the citric acid cycle

NEXT »

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