

Biochemistry IN PERSPECTIVE

The Evolutionary History of the Citric Acid Cycle

How and why did the citric acid cycle originate?

Biological evolution is, in general, a conservative process: metabolites and enzymes that perform vital functions are retained. Over time, as environmental conditions change, organisms often recruit preexisting components for new functions. The citric acid cycle provides an interesting example. As a result of

the genomic and biochemical analysis of a vast number of prokaryotic and eukaryotic species, life scientists have begun to piece together the origins of the cycle. A major feature of this work has been the examination of organisms that use fragments of the cycle, use it in reverse, or do not use it at all.

It is almost certainly true that the citric acid cycle, the hub of metabolic processes in most modern organisms, did not emerge in

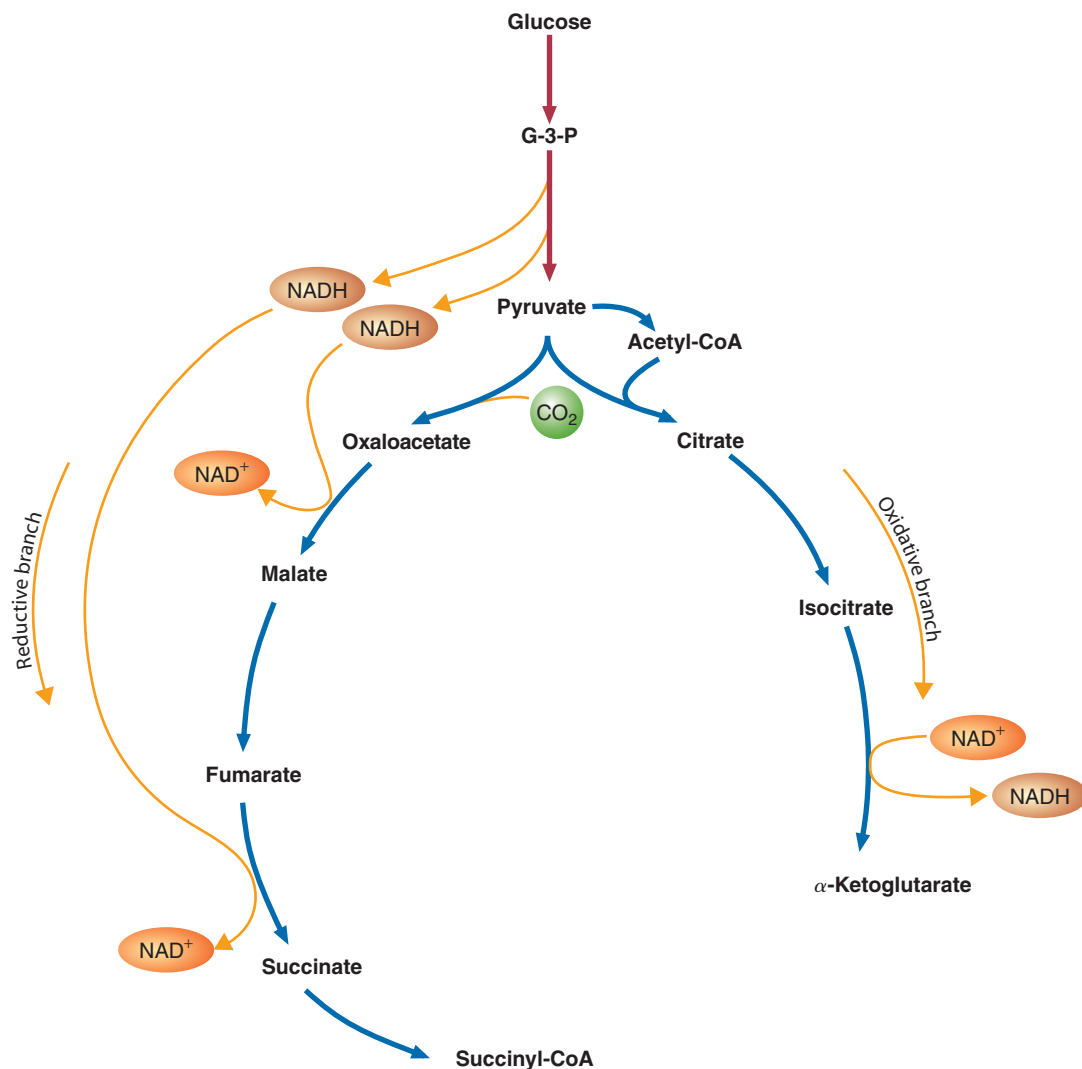


FIGURE 9A

The Incomplete Citric Acid Cycle

Under the anaerobic conditions, primitive prokaryotes developed two branches of what would eventually become the modern citric acid cycle. In the reductive branch (pyruvate → succinate or, in this illustration, succinyl-CoA), a portion of the NADH molecules generated from hexose molecules were reoxidized so that glycolysis could continue to function, thus sparing pyruvate for use in biosynthetic reactions. The oxidative branch (pyruvate → α-ketoglutarate, in this illustration, or succinyl-CoA) was used to generate NADH to be used to generate energy (probably using sulfur or sulfur compounds as electron acceptors) and biosynthetic precursor molecules.



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its modern form as soon as O_2 began to accumulate in Earth's atmosphere. There is significant evidence to suggest that the citric acid cycle originally evolved in anaerobic prokaryotes as two separate pathways: a reductive branch (oxaloacetate \rightarrow succinate or succinyl-CoA) and an oxidative branch (oxaloacetate \rightarrow α -ketoglutarate or succinyl-CoA) (Figure 9A).

The reductive branch solved several problems of primordial organisms. Among these are providing a source of electron acceptors and biosynthetic precursors. Recall that the continued function of the glycolytic pathway requires that pyruvate molecules be reduced so that NADH can be reoxidized. This "redox balance," however, prevents the use of pyruvate molecules as metabolic precursors. This problem was apparently solved by two reactions in the reductive branch of the pathway that reoxidize NADH. The first is the conversion of oxaloacetate to malate. This reaction is catalyzed by malate dehydrogenase, an enzyme that is believed to have originated from a duplication of the lactate dehydrogenase gene. An extension of the reductive branch was made possible by the addition of fumarase and fumarate reductase, which catalyze the reversible conversion of malate to fumarate, and the reduction of fumarate to form succinate, respectively. Organisms that developed this mechanism for reoxidizing NADH would have had a selective advantage because of

increased biosynthetic potential. In addition to using some pyruvate molecules as biosynthetic precursors (e.g., certain amino acids and acetyl-CoA), these organisms were also able to exploit the intermediates in the reductive branch for biosynthesis. Examples include the synthesis of aspartate from oxaloacetate and porphyrins from succinyl-CoA.

The oxidative branch of an incomplete citric acid cycle generates α -ketoglutarate (or possibly succinyl-CoA) from citrate, the product of the reaction of oxaloacetate and acetyl-CoA. Both citrate and α -ketoglutarate are biosynthetic precursor molecules (e.g., fatty acids and glutamate, respectively). The maintenance of redox balance of these reactions required a terminal electron acceptor for the NADH produced by the oxidation of isocitrate to form α -ketoglutarate. In primitive anaerobic organisms, sulfur is believed to have served this function.

As atmospheric oxygen levels rose, the exploitation of O_2 as an electron acceptor was made possible by a complete citric acid cycle. Two possible mechanisms have been proposed. In one scenario, the two branches (pyruvate \rightarrow α -ketoglutarate and pyruvate \rightarrow succinyl-CoA) were linked by α -ketoglutarate dehydrogenase, the product of the duplication of the pyruvate dehydrogenase gene. Alternatively, succinyl-CoA synthetase was the enzyme used to link the branches (pyruvate \rightarrow succinyl-CoA and pyruvate \rightarrow succinate), thus completing the cycle.

SUMMARY: The citric acid cycle probably developed in primordial cells as two separate pathways: the reductive branch, which provided a means of reoxidizing NADH, generated in glycolysis, and an oxidative branch, which produced the biosynthetic precursor molecules citrate and α -ketoglutarate.