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ORIGIN OF LIFE

Cycling citrate *sans* enzymes

> With just two inorganic catalysts we can replicate a series of catabolic reactions that look very much like the core network structure that operates in central metabolism

Central to aerobic life, the Krebs cycle provides precursors for amino-acid biosynthesis and releases energy from carbohydrates, enabling cells to store it in the form of ATP. It was long thought that this combination of chemical reactions could only have arisen from Darwinian selection — a post-genetic origin. But herein lies a chicken-and-egg type problem: how could the many complex enzymes that control the cycle have come into existence if the enzymes themselves are made from the metabolic products of the cycle? One possible explanation is that at least some of the key reactions can be catalysed by simple inorganic species. Now, Markus Ralser and co-workers have discovered that 24 equilibrium reactions that are found in the Krebs cycle can be catalysed by sulfate radicals generated from peroxydisulfate.

"A few years ago, we stumbled on reactions that replicate the features of glycolysis and the pentose phosphate pathway," says Ralser, "and were able to show that the reactions were catalysed by iron(II) — something that would have been widely available on the early Earth before an oxygen-rich atmosphere developed." These reactions, along with the Krebs cycle, are known as the central metabolic pathways — they provide the precursor metabolites for all other pathways — and identifying a species that can catalyse these interconversions would be an important step in connecting our knowledge of prebiotic molecules with extant life. However, the origin of glucose and carbohydrate phosphate intermediates in these networks is unknown, prompting Ralser and co-workers to instead study the Krebs cycle itself. Several of the intermediates in the Krebs cycle are known to have occurred in prebiotic environments.

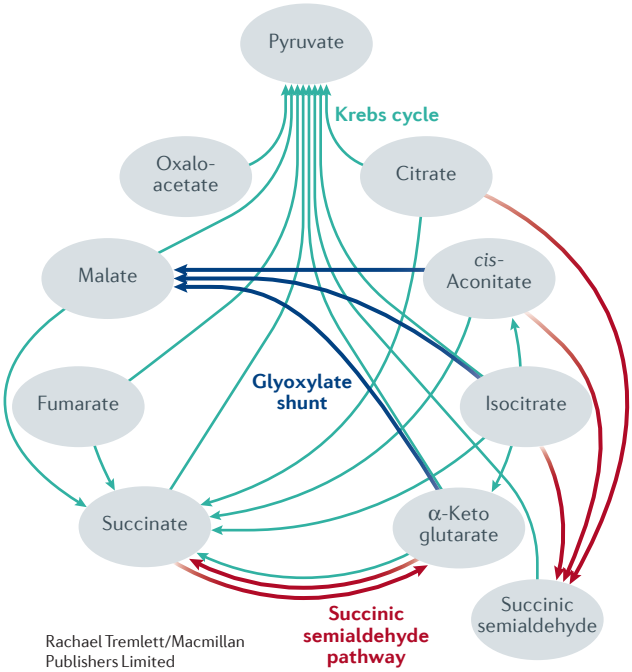
Ralser and colleagues used a liquid chromatography multiple reaction monitoring method to study interconversions of intermediates in the Krebs cycle, which were heated in water under a low-oxygen atmosphere. With the exception of oxaloacetate, which underwent decarboxylation to pyruvate, no spontaneous reactions occurred. When a mixture of transition metal salts that mimic typical Archaean sediments was present, interconversions of isocitrate, succinate, pyruvate and α-ketoglutarate were observed. These reactions were shown to be dependent on iron(II) but alone were insufficient to enable even parts of a non-enzymatic Krebs cycle.

Significant missing pieces of the puzzle were identified to be the conversions of citrate to isocitrate and succinate to fumarate. The enzymes that typically catalyse these reactions contain iron–sulfur clusters; therefore, Ralser and co-workers ran a systematic screen, combining seven iron sources, ten sulfur compounds and five intermediates from the Krebs cycle. Peroxydisulfate was identified as a possible precatalyst and was most effective in combination with iron(II) sulfide. Oxidation and isomerization reactions that closely resemble those in the Krebs cycle, along with the glyoxylate shunt and the succinic semialdehyde pathway all occurred with high efficiency.

It was hypothesized that the reactions were catalysed by sulfate radicals. To support this theory, Ralser and co-workers showed that several reactions were also enabled by hydrogen peroxide — albeit far less efficiently — and were inhibited by the radical scavenger 2-propanol. "With just two inorganic catalysts we can replicate a series of catabolic reactions that look very much like the core network structure that operates in central metabolism," notes Ralser.

"There are two non-trivial problems to solve in order to arrive at a more complete theory for prebiotic metabolism," says Ralser. "First, we need to understand how catabolism and anabolism — the breakdown and build-up of the very same molecules — can occur in parallel so that metabolism can escape equilibrium in a cell. Second, we need to identify a metabolism-like scenario that can fix carbon from CO_2, or at least find a plausible explanation for the formation of the large sugar–phosphates that are so central for metabolism and also form the backbones of RNA and DNA."

Stephen G. Davey



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ORIGINAL ARTICLE Keller, M. A. *et al.* Sulfate radicals enable a non-enzymatic Krebs cycle precursor. *Nat. Ecol. Evol.* **1**, 0083 (2017)
FURTHER READING Sutherland, J. D. Studies on the origin of life — the end of the beginning. *Nat. Rev. Chem.* **1**, 0012 (2017)