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KREBS CYCLE

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Abstract

The Krebs cycle, also known as the citric acid cycle or tricarboxylic acid (TCA) cycle, is a fundamental metabolic pathway in aerobic organisms that takes place in the mitochondria. It is a key process in cellular respiration, converting carbohydrates, fats, and proteins into energy in the form of adenosine triphosphate (ATP). The cycle begins with the combination of acetyl-CoA and oxaloacetate to form citrate, followed by a series of enzyme-catalyzed reactions that release carbon dioxide, generate reducing equivalents (NADH and FADH2), and produce ATP through substrate-level phosphorylation. These reducing equivalents then transfer electrons to the electron transport chain, leading to the synthesis of the majority of cellular ATP. In addition to energy production, the Krebs cycle plays a central role in biosynthesis. Its intermediates serve as precursors for amino acids, nucleotide bases, fatty acids, and heme groups, linking energy metabolism with the synthesis of essential biomolecules. The cycle is regulated by allosteric enzymes and feedback mechanisms to maintain cellular energy balance and respond to changes in nutrient availability. Dysregulation or defects in the Krebs cycle are associated with metabolic disorders, neurodegenerative diseases, and cancer, underscoring its importance in health and disease. Studying the Krebs cycle provides insight into cellular energy metabolism, mitochondrial function, and biochemical regulation. It is essential for understanding how cells generate energy efficiently, adapt to environmental changes, and integrate metabolic signals to sustain life. Knowledge of this cycle is critical for students, researchers, and healthcare professionals in biochemistry, medicine, pharmacology, and related fields.

Keywords

Krebs cycle, citric acid cycle, TCA cycle, mitochondria, cellular respiration, ATP production, NADH, FADH2, energy metabolism, biosynthesis, acetyl-CoA, oxaloacetate, enzyme regulation, metabolic pathways, mitochondrial function, metabolic disorders

Introduction

The Krebs cycle, also known as the tricarboxylic acid (TCA) cycle or citric acid cycle, is a circular sequence of enzymatic reactions associated with the oxidation of di- and tricarboxylic acids. It represents the final common stage of oxidative breakdown of carbohydrates, fats, and proteins (amino acids) into CO_2 and H_2O. In the 1930s, Sir Hans Krebs demonstrated that dicarboxylic acids could accelerate the conversion of succinate, fumarate, malate, and

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oxaloacetate, showing a catalytic effect. Later, the most important reaction of the Krebs cycle was identified as the formation of citric acid from oxaloacetate and pyruvate.

The Krebs cycle is a key stage of aerobic respiration, widely occurring in the cells of animals, plants, and microorganisms. The cycle reactions (10–12 in total) take place in mitochondria. The cycle begins with the formation of citric acid and ends with the regeneration of oxaloacetate. During this process, 2 molecules of CO_2 are released, and a series of coenzymes of dehydrogenase enzymes (see Coenzymes) are reduced (4 molecules of NADH and 1 molecule of $FADH_2$).

In the reactions of the Krebs cycle, dicarboxylic acids such as α-ketoglutarate, succinate, fumarate, malate, oxaloacetate, and tricarboxylic acids such as citrate, cis-aconitate, isocitrate, and oxalosuccinate participate. The substrates involved in the Krebs cycle also include acetic acid, which is formed during the active breakdown of fatty acids and the decarboxylation of pyruvate derived from carbohydrates. When pyruvate is completely oxidized, 15 molecules of ATP are synthesized; oxidation of one glucose molecule produces 38 molecules of ATP.

Intermediates of the Krebs cycle can leave the cycle to participate in various metabolic reactions. For example, oxaloacetate is involved in gluconeogenesis, succinate in porphyrin synthesis, and acetate in fatty acid synthesis. The CO_2 released from the Krebs cycle serves as a primary source for carboxylation reactions. In oil-producing plants and some microorganisms, the Krebs cycle is partially modified, resulting in the glyoxylate cycle.

Main Section

The Krebs cycle (citric acid cycle) is the central stage of cellular respiration and takes place in the mitochondrial matrix. This cycle ensures the complete oxidation of acetyl-CoA, which is produced from the breakdown of various organic substances such as carbohydrates, fats, and proteins. As a result of this process, energy carriers including NADH, $FADH_2$, and GTP/ATP are generated.

The Essence of the Krebs Cycle

The Krebs cycle is a sequence of eight stages of complex oxidation–reduction reactions. Its primary function is to extract high-energy electrons from organic molecules and transfer them to the electron transport chain.

Main Stages of the Cycle

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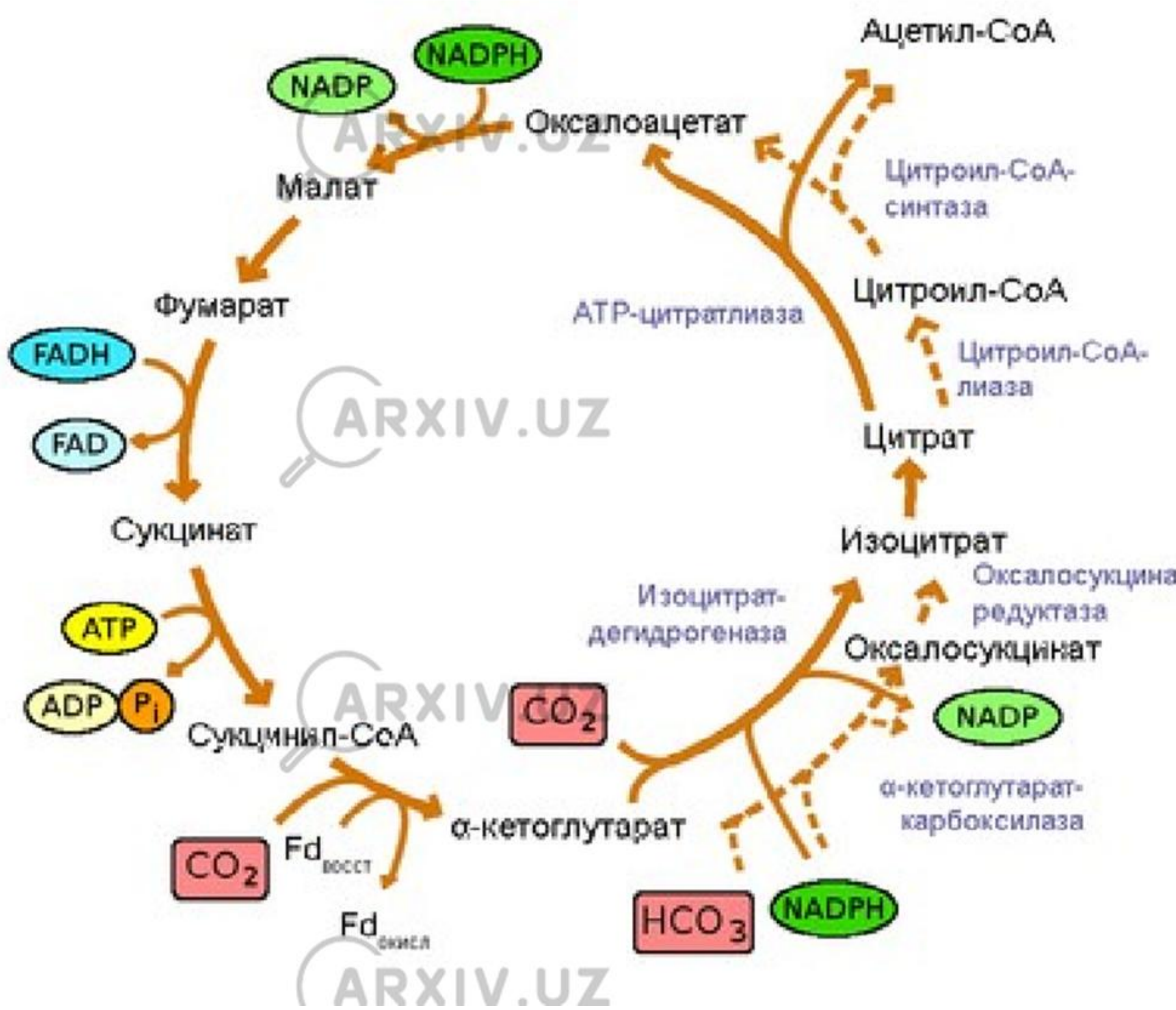

1. Acetyl-CoA + Oxaloacetate → Citrate

The Krebs cycle begins with the condensation of acetyl-CoA (a 2-carbon molecule) with oxaloacetate (a 4-carbon molecule) to form citrate (a 6-carbon molecule). This reaction is catalyzed by the enzyme citrate synthase and requires energy. This step is critical as it marks the initiation of the cycle.

2. Citrate → Isocitrate

Citrate undergoes structural rearrangement to form isocitrate. First, citrate is converted to cis-aconitate, which then undergoes hydration to form isocitrate. This reaction is catalyzed by the enzyme aconitase. This step prepares the molecule for subsequent oxidation.

3. Isocitrate → α-Ketoglutarate + CO_2

Isocitrate is oxidized, releasing one molecule of carbon dioxide (CO_2) and generating NADH, which will be used for ATP production in the electron transport chain. The enzyme responsible is isocitrate dehydrogenase. As a result, a 5-carbon molecule, α-ketoglutarate, is formed.

4. α-Ketoglutarate → Succinyl-CoA + CO_2

α-Ketoglutarate undergoes oxidative decarboxylation, releasing another molecule of CO_2 and producing NADH. This reaction is catalyzed by the α-ketoglutarate dehydrogenase complex. The product is a 4-carbon molecule, succinyl-CoA.

5. Succinyl-CoA → Succinate

Succinyl-CoA is converted to succinate through substrate-level phosphorylation, producing ATP or GTP. The enzyme catalyzing this reaction is succinyl-CoA synthetase. At this stage, the cycle generates the 4-carbon succinate molecule.

6. Succinate → Fumarate

Succinate is oxidized to fumarate, producing $FADH_2$ in the process. This reaction is catalyzed by succinate dehydrogenase. Fumarate is a 4-carbon molecule formed as a result.

7. Fumarate → Malate

Fumarate undergoes hydration to form malate. This reaction is catalyzed by fumarase. At this stage, the molecule is prepared for the generation of NADH in the subsequent step.

8. Malate → Oxaloacetate

Malate is oxidized to regenerate oxaloacetate, producing another molecule of NADH. The enzyme catalyzing this reaction is malate dehydrogenase. Oxaloacetate is now ready to combine with a new molecule of acetyl-CoA, completing the cycle and preparing the system for the next round.

Biological Significance of the Krebs Cycle

The Krebs cycle plays a central role in cellular metabolism and is essential for maintaining energy homeostasis in living organisms. One of its primary functions is **energy production**. During the cycle, NADH and $FADH_2$ are generated as high-energy electron carriers. These molecules transfer electrons to the electron transport chain, driving oxidative phosphorylation and resulting in the synthesis of a substantial amount of ATP. This process ensures that cells have a continuous supply of energy to support vital physiological activities, including muscle contraction, active transport, and biosynthetic reactions.

In addition to its role in energy generation, the Krebs cycle serves as a **metabolic hub**. Intermediates of the cycle act as precursors for the biosynthesis of numerous biomolecules, including amino acids, fatty acids, and porphyrins. For example, oxaloacetate can be used for gluconeogenesis, while α-ketoglutarate provides a source for certain amino acids. Succinate and other intermediates contribute to the synthesis of heme and other essential compounds. This central role of the Krebs cycle allows the cell to efficiently coordinate energy production with the generation of building blocks needed for growth, repair, and specialized functions.

Moreover, the Krebs cycle is **amphibolic**, meaning it participates in both catabolic and anabolic processes. On the one hand, it facilitates the complete oxidation of carbohydrates, fats, and proteins to produce energy. On the other hand, it provides essential intermediates for biosynthetic pathways. This dual function makes the cycle a crucial connector between catabolism and anabolism, integrating different metabolic pathways and maintaining the overall balance of cellular metabolism.

Overall, the biological significance of the Krebs cycle extends beyond ATP production. It acts as a central node in metabolism, linking energy generation with biosynthesis, and enabling cells to respond dynamically to varying nutrient availability and energy demands. Understanding the Krebs cycle is therefore fundamental for studying cellular metabolism, physiology, and the biochemical basis of health and disease.

Conclusion

The Krebs cycle serves as a fundamental mechanism for regulating cellular energy balance and metabolic processes. The stepwise reactions that occur within the cycle not only generate energy carriers but also produce intermediate metabolites essential for various biosynthetic pathways. For this reason, the Krebs cycle is considered a central and universal process in living cell metabolism. As a critical stage of cellular respiration, the Krebs cycle plays a major role in supplying the organism with energy. During the cycle, acetyl-CoA undergoes a series of biochemical reactions, leading to the release of carbon dioxide and the formation of energy-rich molecules such as NADH and $FADH_2$. These molecules subsequently participate in ATP synthesis during oxidative phosphorylation, providing the energy required for numerous cellular functions. The significance of the Krebs cycle extends beyond energy production. It occupies a central position in cellular metabolism, supplying intermediate compounds necessary for the synthesis of amino acids, fatty acids, nucleotides, and other biologically important molecules. Therefore, the Krebs cycle represents one of the most essential biochemical processes that sustain the life and proper functioning of living organisms.

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