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The Citric Acid Cycle: Historical Discovery, Biochemical Mechanisms, and Its Impact on Life Sciences

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Abstract: ***With the rapid development of metabolomics and systems biology, scientists have made significant strides in exploring the regulatory mechanisms of the citric acid cycle, its associations with various diseases, and its applications in bioengineering. This paper reviews the historical discovery of the citric acid cycle, analyzes its biochemical mechanisms, and discusses its pivotal role in modern life sciences. By examining breakthroughs in early metabolic research, particularly advancements in glycolysis, citric acid metabolism, and enzymology, this paper reveals how the citric acid cycle was discovered based on the foundational work of previous studies. It also elaborates on how this scientific breakthrough has propelled theoretical innovations in the fields of metabolism and cell biology. Through a comprehensive analysis of this milestone discovery, the paper aims to highlight the fundamental position of the citric acid cycle in life sciences and its lasting impact.***

Keywords: Citric acid cycle, Metabolic pathways, Biochemistry**.**

1. Introduction

The citric acid cycle (CAC), also known as the tricarboxylic acid cycle or Krebs cycle, is one of the most important metabolic pathways in the cells of aerobic organisms (Gupta & Gupta, 2021). This cycle serves not only as the final common pathway for the degradation of carbohydrates, lipids, and proteins, but also as a crucial hub that links the metabolism of the three major nutrients, playing a vital role in maintaining cellular energy balance. Through the CAC, organisms efficiently oxidize pyruvate and, via a series of enzyme-catalyzed reactions, generate adenosine triphosphate (ATP), providing energy for cellular processes (Arnold & Finley, 2023).

The discovery of the CAC represented a revolutionary breakthrough in 20th-century biochemistry. In 1937, British biochemist Hans Adolf Krebs systematically elucidated the fundamental mechanisms of cellular energy metabolism (Krebs & Johnson, 1980). This landmark discovery not only established the theoretical foundation for modern metabolic biology but also had a profound influence on the advancement of cell biology, medicine, nutrition, and biotechnology (Roosterman & Cottrell, 2021).

With the continuous advancement of research methodologies, scientists have delved deeper into the regulatory mechanisms of the CAC, its associations with diseases, and its applications in bioengineering. In recent years, the development of metabolomics and systems biology has further enhanced our understanding of the cycle's functions and its intricate regulatory network (Arnold & Finley, 2023). This paper aims to systematically review the discovery of the CAC, explore its biochemical mechanisms, and analyze its significant role in contemporary life sciences research, with the goal of fully showcasing the far-reaching impact of this scientific breakthrough across various biological fields.

2. The Background of Biochemical Research in the Early 20th Century

In the early 20th century, biochemistry gradually evolved from an interdisciplinary research field into an independent discipline, achieving a series of groundbreaking advances in metabolic research. Utilizing advanced analytical techniques, scientists delved into the chemical reactions within living organisms, progressively unveiling how energy conversion and substance synthesis are accomplished through a series of enzyme-catalyzed reactions. These studies not only laid the theoretical foundation for the discovery of the CAC but also provided critical support for the subsequent development of fields such as biochemistry and cell biology.

2.1 Key Breakthroughs in Early Metabolic Research

From the late 19th to early 20th century, the scientific community began to recognize the inseparable relationship between the life processes of organisms and chemical reactions. In 1907, British biochemists Frederick Gowland Hopkins and Walter Morley Fletcher published their pioneering work in the Journal of Physiology revealing the role of lactic acid in muscle contraction (Poole et al., 2021). This discovery marked a shift toward molecular-level exploration in biochemical metabolism and provided a new perspective and theoretical framework for subsequent energy metabolism research.

At the same time, French physiologist Claude Bernard proposed the theory of "milieu intérieur" (internal environment stability), emphasizing the importance of metabolic balance in sustaining life activities (Rheinberger, 2023). In 1897, German chemist Eduard Buchner discovered that yeast cell extracts could catalyze the breakdown of sugars in the absence of intact cells, establishing the central role of enzymes as catalysts in metabolic reactions (Kohler, 1972).

For this groundbreaking work, Buchner was awarded the Nobel Prize in Chemistry in 1907. His discovery provided a solid theoretical foundation for the study of enzyme-catalyzed reactions in metabolic pathways and further propelled the independent development of biochemistry.

2.2 The Discovery of Metabolic Intermediates and the Development of Analytical Techniques

In the early 20th century, scientists began systematically studying metabolic products in animal tissues and cells using chemical analysis methods and physiological experimental techniques (Alvarez-Mamani et al., 2024). Between 1906 and 1920, researchers successfully isolated approximately 60 metabolic intermediates, including succinate, fumarate, and malate, which were later confirmed as key components of the CAC (Notley et al., 2023).

At the same time, the continuous development of chromatographic analysis, electrophoresis, and spectroscopic techniques enabled scientists to more precisely determine the chemical composition of metabolic products and their transformation processes in living organisms. For example, the famous enzyme kinetics equation proposed by Leonor Michaelis and Maud Menten in 1913 laid the theoretical foundation for understanding the rates of metabolic reactions and the mechanisms of enzyme action (Cornish-Bowden, 2015). These technological innovations greatly facilitated the exploration of metabolic pathways and provided more effective tools for future metabolic research.

2.3 Research on the Glycolytic Pathway

In the early 20th century, scientists progressively elucidated the core processes of carbohydrate metabolism. In 1935, British physiologist Archibald Vivian Hill, German biochemists Otto Meyerhof and Otto Warburg, among others, systematically described the glycolytic pathway, through which glucose is broken down into lactate or ethanol via a series of enzyme-catalyzed reactions (Grüning & Ralser, 2021). By identifying multiple intermediate metabolites in the glycolytic pathway, they identified key enzymes (such as hexokinase, phosphofructokinase, and pyruvate kinase) and their cofactors (such as NAD+ and ATP). This research not only advanced the field of energy metabolism but also provided important theoretical underpinnings for the discovery of the CAC.

The breakthroughs in glycolysis research laid the foundation for studying metabolic pathways, revealing the transformation of metabolites within cells and the enzyme reactions required, which in turn provided experimental support and theoretical frameworks for the further investigation of other key metabolic pathways, such as the CAC and oxidative phosphorylation.

2.4 Advances in Citric Acid Metabolism Research

In the 1930s, scientists began to widely explore the role of citric acid and its derivatives in biological metabolism. In 1937, Sheffield discovered that citrates could catalyze the oxidation of succinate (Stern & Melnick, 1939). Simultaneously, Carl Martius and Franz Knoop studied citric acid metabolism, revealing its widespread occurrence in various tissues, such as the liver and muscle (Gupta & Gupta, 2021). German scientist Albert Szent-Györgyi, in his research on succinate dehydrogenase, further clarified the pivotal role of citric acid in oxidative metabolism (Wang & Lou, 2024).

2.5 Insights from the Research Background for the Discovery of the CAC

With the rise of enzymology, the identification of metabolic intermediates, and progress in fields such as glycolysis and citric acid metabolism, researchers gradually recognized that the metabolic processes within living organisms are not isolated chemical reactions but part of a systematized and interconnected network (Kierans & Taylor, 2024). This shift in perspective prompted scientists to reconsider metabolic processes at the molecular level, providing new approaches and methodologies that contributed to the discovery of the CAC.

In this context, Krebs was able to draw upon the profound analysis of metabolites by earlier researchers, particularly the breakthroughs in enzyme-catalyzed reactions and metabolic pathways, to conduct systematic experimental studies. Through the use of isotopic tracer techniques and in vitro enzyme catalysis experiments, he successfully uncovered the full mechanism of the CAC. The key to this discovery lay in the cumulative exploration of metabolic pathways by previous researchers, particularly the advancements in glycolysis, citric acid metabolism, and enzymology, which provided Krebs with essential experimental support and a theoretical framework.

Thus, early research provided crucial insights that led to the discovery of the CAC. These studies not only clarified the key enzymes and intermediates in metabolic processes but also revealed the tight interconnections between metabolic reactions, ultimately facilitating the proposition and understanding of the CAC. The discovery of the CAC was an innovative synthesis based on the accumulated metabolic research, reflecting a shift from localized breakthroughs to a holistic understanding, and offering a more systematic and comprehensive perspective for subsequent biochemical studies.

3. Discovery of the CAC

3.1 Academic Background of Hans Adolf Krebs

Hans Adolf Krebs, born in 1900 in Hildesheim, Germany, into a Jewish family, pursued medical education at the University of Göttingen and the University of Freiburg, earning his medical degree from the University of Hamburg in 1925. He furthered his studies in chemistry at the University of Berlin and, from 1926 to 1930, worked in the laboratory of the renowned biochemist Otto Warburg, focusing on cellular respiration and biological oxidation. This experience not only honed his experimental skills but also laid a solid theoretical foundation for his subsequent metabolic research. In 1933, due to Nazi anti-Semitic policies, Krebs was forced to leave Germany and moved to the United Kingdom. After a brief period at the University of Cambridge, he was appointed in 1935 as a faculty member in the Department of Biochemistry

at the University of Sheffield, where he began conducting independent research. During this time, his focus gradually shifted toward understanding the core mechanisms of energy metabolism within biological organisms.

3.2 Research Process and Key Discoveries

3.2.1 Early Research

In 1933, while reviewing literature on the metabolism of nutrients, Krebs systematically organized known metabolic products and their interrelationships. He noticed that, although the roles of certain metabolic intermediates were understood, the overall mechanism remained unclear. In particular, the relationships between cis-aconitate and oxaloacetate seemed to involve an unidentified critical link. Krebs hypothesized that these metabolites might be interconverted through a cyclical process that ultimately contributed to the release of energy.

3.2.2 Key Breakthrough

In 1937, after four years of systematic experimentation, Krebs made a significant breakthrough during studies involving pigeon breast muscle tissue. He discovered that the addition of citrate to the tissue samples significantly increased the rate of oxygen consumption, while also extending the tissue's survival time to three times the normal duration. Moreover, through radioactive isotope tracing experiments, Krebs demonstrated that citrate not only accumulated within cells but also underwent further metabolism, producing several important metabolic intermediates. This observation suggested that citrate's involvement was crucial to energy release. Further investigations revealed that citrate could be converted into other tricarboxylic compounds, such as α-ketoglutarate, succinate, and malate, through a series of enzymatic reactions. Ultimately, oxaloacetate was regenerated, allowing the cycle to continue. Notably, this process was coupled with ATP (adenosine triphosphate) synthesis, linking it directly to cellular energy metabolism.

3.2.3 Theoretical Framework

After refining his experimental data, Krebs proposed the complete theory of the tricarboxylic acid (TCA) cycle, also known as the CAC or Krebs cycle. He identified acetyl-CoA as the initiating substrate of the cycle, which is derived not only from the oxidation of glucose but also from the breakdown of fats and proteins. This theory illuminated how the metabolic pathways of carbohydrates, lipids, and proteins are interconnected, ultimately providing energy to the organism. Krebs's discovery revealed that the CAC is the central process of cellular respiration and a crucial hub for the interconversion of large biomolecules.

3.3 Impact of the Research

Initially, Krebs submitted his findings to Nature, but they were rejected because the reviewers did not recognize their significance. Subsequently, in 1937, he published a paper titled "The Role of Citric Acid in Intermediate Metabolism" in Enzymologia. The research quickly garnered attention in the academic community and was regarded as a landmark achievement in biochemistry. Krebs's work revolutionized the understanding of biological energy metabolism and laid the theoretical groundwork for modern biochemistry, medicine, and bioengineering. In 1953, Krebs, along with Fritz Lipmann, was awarded the Nobel Prize in Physiology or Medicine for their groundbreaking research on metabolic processes, particularly the discovery of the CAC. This accomplishment not only enhanced humanity's understanding of cellular energy metabolism but also provided a crucial theoretical foundation for the study of metabolic diseases, such as diabetes and cancer.

4. The Scientific Significance of the Discovery of the CAC

4.1 Impact on Metabolic Biology

The discovery of the CAC laid the foundation for modern metabolic biology and had a profound impact on the study of energy metabolism in living organisms. The CAC revealed a shared core metabolic pathway for the degradation of carbohydrates, lipids, and proteins, providing a unified theoretical framework for understanding biochemical processes within cells (Castro-Guarda & Evans, 2025). Through this cycle, organisms can convert various nutrients—such as glucose, fatty acids, and amino acids—into usable energy forms for cellular functions. This discovery highlighted the integrative nature of metabolism, suggesting that despite the structural and metabolic differences of various nutrients, they ultimately converge in the CAC, contributing to the cellular energy production necessary to meet the organism's energy demands across various physiological states.

Furthermore, the CAC systematically elucidated how cells release and store energy through a series of orderly chemical reactions, uncovering key steps in ATP synthesis, particularly the conversion of chemical energy into forms that cells can utilize through oxidative phosphorylation (McIlwain, 2024). Oxidative phosphorylation is not only the core mechanism for cellular energy generation but also involves important biological molecules and reaction pathways, such as the electron transport chain and ATP synthase. The analysis of this mechanism has advanced our fundamental understanding of energy conversion principles and provided crucial experimental methods and theoretical foundations for further research, especially in areas like metabolic regulation, cellular energy homeostasis, and the study of various metabolic diseases. Thus, the discovery of the CAC represents not only a significant milestone in metabolic research but also a foundational framework for biology, medicine, and biochemistry, significantly advancing our understanding of energy metabolism and providing solid theoretical support for subsequent academic exploration and clinical research.

4.2 Advancement in Related Disciplines

The discovery of the CAC holds substantial importance not only in metabolic biology but also in several other scientific disciplines, including biochemistry, cell biology, and medical research.

In biochemistry, the discovery of the CAC spurred the

development of methodologies for studying metabolic pathways, making tools like isotope tracing and metabolic flux analysis critical in cellular metabolism research (Grankvist et al., 2024). It also promoted advances in enzymology, enabling the isolation, purification, and functional analysis of key metabolic enzymes. Furthermore, research on the CAC laid the groundwork for the study of metabolic regulation, enhancing our understanding of metabolic homeostasis and feedback mechanisms.

In the field of cell biology, the CAC deepened our understanding of cellular energy metabolism, particularly the central role of mitochondria in bioenergetics (S. Liu et al., 2024). This research also facilitated the exploration of mitochondrial dysfunction and its relationship with various diseases. Additionally, the CAC's discovery accelerated the study of cellular metabolic networks, providing a theoretical framework for analyzing cellular signal transduction and metabolic reprogramming.

In medical research, the CAC has provided a critical theoretical basis for studying metabolic diseases. The metabolic pathways and energy conversion mechanisms revealed by the cycle have guided the pathophysiological research on conditions such as diabetes, cancer, and mitochondrial diseases (Liu et al., 2025). Moreover, the discovery has facilitated drug development and the formulation of therapeutic strategies, enabling innovative drug research targeting metabolic pathway mechanisms. It has also promoted the development of nutrition science by providing scientific evidence for balanced diets and metabolic equilibrium.

4.3 Continued Influence on Modern Life Sciences

As scientific and technological advancements continue, the discovery of the CAC not only catalyzed a paradigm shift in the study of metabolic pathways but also exerted a profound influence on the development of cutting-edge disciplines, including modern metabolomics and proteomics. Notably, innovations in metabolic network analysis methods, such as mass spectrometry (MS) and nuclear magnetic resonance (NMR), have enhanced the precision and efficiency of identifying and studying the dynamic changes of metabolic products (Song et al., 2025). These technological advancements allow researchers to analyze the complexity of metabolic processes across higher spatial and temporal scales, uncovering the interactions and regulatory mechanisms of intricate intracellular metabolic networks.

The rise of metabolomics exemplifies the scientific community's ability to explore the dynamic changes of metabolites and their physiological functions through systems biology approaches (Baharum & Azizan, 2018). Metabolomics analysis not only focuses on the level fluctuations of specific metabolites but also involves examining the network reorganization of metabolites under different physiological and disease conditions and their impact on cellular function. Systems biology has thrived in this context, combining mathematical modeling with experimental data to further analyze the complexity of biological systems. This approach has helped scientists better understand the synergistic interactions between metabolic pathways and their critical role in maintaining cellular homeostasis. The core philosophy of systems biology emphasizes the importance of analyzing biological systems from a holistic perspective, advancing bioinformatics and providing robust theoretical support for precision medicine and personalized treatments.

Additionally, synthetic biology, an emerging innovation in life sciences, is based on the theoretical framework of the CAC (Karim et al., 2024). It aims to engineer metabolic pathways for biomanufacturing and the application of synthetic biotechnology. For instance, modifying microbial metabolic pathways to optimize energy generation or produce industrial compounds has advanced technology in fields such as bioenergy, environmental protection, and pharmaceutical production. These applications not only enrich the theoretical system of metabolic engineering but also provide new technological routes to address global challenges such as the energy crisis and environmental pollution.

In summary, the theory of the CAC not only established a solid foundation for modern metabolic biology but also plays a central role in the emerging fields of metabolomics, systems biology, and synthetic biology. It continues to drive the development of life sciences, fostering interdisciplinary integration and innovation while elucidating the central role of metabolic mechanisms in maintaining life processes. As technology continues to advance, the study of the CAC will continue to provide essential theoretical frameworks and methodological support for revealing the complexities of biological phenomena within living organisms.

5. Conclusion

The discovery of the CAC, regarded as one of the most significant breakthroughs in life sciences during the 20th century, has had a profound and lasting impact. The elucidation of this metabolic pathway not only provided a clear understanding of the fundamental principles of energy metabolism in living organisms but also established a robust theoretical foundation for various research fields within modern life sciences. By integrating the metabolism of carbohydrates, lipids, and proteins, the CAC established the core framework for the conversion of substances and the release of energy, offering crucial insights into the mechanisms of metabolic regulation and energy transformation within cells. This has driven further advancements in biology, chemistry, and medicine.

Although the foundational theories of the CAC have been extensively explained, current research continues to delve deeper, particularly in the areas of fine-tuned regulatory mechanisms, its role in disease development, and its potential applications in biotechnology. In recent years, scholars have increasingly focused on the precise regulation of enzyme activities within the CAC, seeking to uncover the molecular foundations that maintain metabolic homeostasis. Furthermore, the association between metabolic disturbances in the CAC and the development of various diseases, such as cancer, neurodegenerative diseases, and metabolic syndromes, has become a key area of biomedical research. Investigators are exploring the potential of this cycle in disease prevention and treatment, with the goal of developing novel diagnostic

and therapeutic strategies through the regulation of key enzymes within the cycle.

At the same time, the broad applications of the CAC in biosynthesis and energy metabolism have generated significant interest, particularly in the fields of industrial biotechnology and medical metabolic engineering. The potential applications of the CAC are viewed as having substantial promise. With the rise of emerging disciplines such as synthetic biology and metabolic engineering, the reconstruction and optimization of metabolic pathways based on the CAC have become essential tools for advancing green energy, environmental protection, and biopharmaceutical industries.

Looking forward, as interdisciplinary fields such as metabolomics, systems biology, and synthetic biology continue to evolve and new analytical technologies advance, research on the CAC will further deepen, pushing the frontiers of life sciences. We have strong reasons to believe that a deeper exploration of this cycle will not only reveal more complex metabolic networks but also provide new theoretical foundations and technical approaches for diagnosing and treating metabolic diseases. This research is set to expand the field of life sciences and bring about revolutionary breakthroughs in health, environmental sustainability, and the biological industry.

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