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Tribute to Bernhard Kadenbach – Cytochrome *c* oxidase: from subunits to regulatory functions

Sebastian Vogt[1], Madeline Günther[1], Maik Hüttemann[2]

1 Department of Cardiac and Thoracic Vascular Surgery, Philipps-University Marburg, Universitätsklinikum Gießen and Marburg GmbH, 35043 Marburg, Germany
2 Center for Molecular Medicine and Genetics, Wayne State University School of Medicine Detroit, MI, U.S.A.
* Corresponding author: vogts@med.uni-marburg.de

Summary

Bernhard Kadenbach was a German biochemist whose research advanced our understanding of mitochondrial cytochrome *c* oxidase (Complex IV, CIV) and its regulation. In the 1980s, he discovered that mammalian CIV consists of 13 tightly bound subunits, a finding later confirmed through structural analysis. Besides the structural studies of CIV, his research focused on the role of tissue-specific isoforms of CIV subunits, its allosteric regulation by the ATP/ADP ratio, and phosphorylation mechanisms, proposing a "second mechanism of respiratory control" that modulates energy transformation and minimizes reactive oxygen species (ROS). Kadenbach's insights into CIV regulation, tissue-specific isoforms, and metabolic control remain influential for ongoing mitochondrial research and potential therapeutic applications.

1. Early life and academic journey

Bernhard Kadenbach was born on August 21, 1933, in Luckenwalde and passed away on April 14, 2021, in Marburg. After graduating from high school, he studied chemistry at the Humboldt University in Berlin. He completed his diploma thesis at the German Academy of Sciences in Berlin-Buch.

In 1960, he spent a research internship at the Wenner-Gren Institute in Stockholm. He received his doctorate from the Philipps University Marburg in 1964. From 1968, he worked as a research associate at the University of Munich. In 1970 he completed his habilitation at the University of Constance. From 1971-1973 he was a senior scientist and lecturer at the Laboratory of Biochemistry at the Swiss Federal Institute of Technology in Zurich. In 1973, he became Professor of Biochemistry at the Department of Chemistry at the University of Marburg. From 2003 to 2010, he conducted research in the Laboratory of Cardiac Surgery at the University's Biomedical Research Center.

2. Pioneering work on mitochondrial cytochrome *c* oxidase and the debate over the 14th subunit NDUFA4

His scientific work was founded in the late 1960s through his investigations into the cytoplasmic biosynthesis of mitochondrial proteins, initially using cytochrome *c* (cyt *c*) as a model system (Kadenbach 1960). By studying cyt *c*, Kadenbach was able to uncover principles about the synthesis and assembly of this protein, knowledge that could be applied to other mitochondrial proteins like cytochrome *c* oxidase (Complex IV, CIV). In this regard, he showed that some subunits of CIV are synthesized in the cytosol, while others are produced within the mitochondria. In 1983, Kadenbach and his colleagues demonstrated that CIV protein complexes, purified from the mitochondria of several mammals, are composed of 13 distinct subunits (Kadenbach et al 1983). This discovery, which revealed a surprisingly large number of subunits, was not widely acknowledged by mitochondriologists for a considerable time and became a subject of intense debate. Thirteen years later, definitive proof was provided by Yoshikawa and colleagues, who elucidated the crystal structure of the enzyme, revealing the precise arrangement of the 13 proteins in relation to one another (Yoshikawa 1997; Yoshikawa et al 1998; Yoshikawa et al 2012). Then, Kadenbach raised concerns about NDUFA4, identified by Balsa et al 2012, as the 14th subunit and described this protein complex as a permanent component of the holoenzyme. He proposed that the association of this subunit might be influenced by transitions between dimerization and monomerization, or by variations in supercomplex formation within the inner mitochondrial membrane (Kadenbach 2017; Ramzan et al 2019). The likely reason this subunit was overlooked in earlier studies, was its weak binding affinity to the CIV core subunits and was therefore lost during enzyme purification. Recent studies have demonstrated that NDUFA4 is the 14th subunit of CIV and represents a hinge region in the dimer that can be modified (Zong et al 2018), for instance, during inflammation (Lee et al 2021). Therefore, it can be assumed that this small subunit has an important function for the entire holoenzyme (Pitceathly et al 2013).

3. Isoform diversity and tissue-specific functions

Although CIV complexes share the same enzymatic function in bacteria and mammals, they differ in their structural complexity. Bacterial forms of CIV consist of only 2-4 subunits, whereas mammalian CIV contains 14 subunits, with 11 of them encoded by nuclear DNA. In mammals, these additional subunits are now recognized as important factors for the precise regulation of mitochondrial function and the adaptation to specific cellular and tissue demands. For the first time, Kadenbach and his research group identified tissue-specific isoforms of the CIV subunits VIa, VIIa, and VIII and demonstrated differences in the kinetic activity of the enzyme isolated from different organs (Kadenbach

et al 2000; Kadenbach, Hüttemann 2015). Immunohistochemical studies further revealed variable expression patterns of CIV isoenzymes in different human muscle fiber types, providing additional insights into tissue-specific regulation (Johnson et al 1988; Müller-Höcker et al 1986; Oldfors et al 1992; Romero et al 1990). One particularly important example of isoform specialization is subunit IV, which has a lung-specific isoform that plays a key role in hypoxia sensing, where it mediates the adaptive response of hypoxic pulmonary vasoconstriction, a mechanism required for optimizing oxygen uptake under low oxygen conditions (Aras et al 2013; Hüttemann et al 2012b; Sommer et al 2017).

Kadenbach's lab also made outstanding contributions to isolating and sequencing the cDNAs of several CIV subunits, including the heart- and the liver-specific variants of subunit VIa, as well as determining the chromosomal gene structures of subunits VIa and VIc (Schneyder et al 1991; Arnold, Kadenbach 1997). Moreover, their work demonstrated developmental-stage-specific expression patterns, showing distinct subunit compositions in fetal versus adult human tissues. These findings revealed an additional layer of regulation, highlighting how CIV adapts not only to tissue-specific, but also developmental-stage-specific metabolic requirements.

4. ATP binding and allosteric control mechanisms

A special aspect of his work focused on the kinetics and regulation of CIV activity and its medical implications (Kadenbach et al 2004; Kadenbach et al 2009). By conducting binding studies, Kadenbach and colleagues identified 10 ADP/ATP binding sites on isolated CIV from bovine heart. This finding was supported by the CIV crystal structure, which revealed the incorporation of 10 cholate molecules due to their spatial similarity to ADP. Using liposomes, the stoichiometric analyses of proton transport in isolated CIV confirmed that CIV activity is functionally regulated by the ATP/ADP ratio. (Kadenbach et al 1998; Arnold, Kadenbach 1997; Arnold, Kadenbach 1999).

Following the importance of this finding, Kadenbach postulated the "second mechanism for respiratory control", based on the allosteric binding of ATP/ADP specifically to subunit IV of CIV. Between 2000 and 2011, Kadenbach extended this research to propose a hypothesis linking CIV regulation to aging and the onset of degenerative diseases in humans and animals. His work was in line with Mitchell's theory, which describes the proton motive force (*pmf*) across the inner mitochondrial membrane as the energy-rich intermediate of oxidative phosphorylation. *pmf* thereby consists of both an electrical ($\Delta\Psi_{mt}$) and a chemical component (ΔpH), generated by Complexes I, III, and IV (CI, CIII, CIV) of the electron transfer system, driving ATP synthase for ATP production (Ramzan et al 2021).

The free energy generated by electron transfer in proton pumps is sufficient to establish a *pmf* of approximately 240 mV. However, the proton permeability of biological membranes increases sharply above 130 mV, resulting in energy loss at higher membrane potentials ($\Delta\Psi_{mt}$ > 140 mV). Furthermore, at $\Delta\Psi_{mt}$ > 140 mV, the production of the superoxide radical anion ($O_2^{\cdot-}$) in CI and CIII increases, correlating with the rising $\Delta\Psi_{mt}$. The $O_2^{\cdot-}$ anion and its neutral conversion product H_2O_2 are responsible for the development of oxidative stress, a key contributor to aging and the progression of degenerative diseases. To address this, Kadenbach proposed a novel mechanism independent of conventional respiratory control, which prevents excessive activity of CIV in the electron transfer system at high ATP/ADP ratios. This mechanism maintains $\Delta\Psi_{mt}$

at an optimal intermediate level, thereby reducing ROS production and preserving the efficiency of oxidative phosphorylation. According to his hypothesis, this regulation is mediated by specific phosphorylations of CIV subunits and a cAMP-driven dimerization of the enzyme, which results in allosteric inhibition of its activity. Together, these processes optimize mitochondrial function under changing metabolic demands (Kadenbach et al 2010; Kadenbach et al 2013; Kadenbach 2020; Kadenbach 2021).

In cooperation with his final PhD student Rabia Ramzan, Kadenbach explored the challenges of measuring allosteric ATP inhibition of CIV in isolated mitochondria. Their work demonstrated that full ATP inhibition of CIV can only be achieved using an ATP-regenerating system composed of phosphoenolpyruvate and pyruvate kinase, as confirmed through kinetic measurements (Ramzan et al 2010; Ramzan et al 2017; Ramzan et al 2022).

To explain their findings, they postulated a mechanism in which the $\Delta\Psi_{mt}$ in living cells and tissues is maintained at intermediate levels (80-130 mV) under conditions of a high ATP/ADP matrix ratio. This contrasts with the higher $\Delta\Psi_{mt}$ values (180-220 mV) typically measured in isolated mitochondria. In collaboration with Katrin Staniek (Vienna, Austria), they observed a reversible decrease in $\Delta\Psi_{mt}$ from 233 to 123 mV, following the addition of phosphoenolpyruvate and pyruvate kinase. This was assessed using a tetraphenylphosphonium (TPP^+) electrode in isolated rat liver mitochondria, with glutamate and malate as substrates (Ramzan et al 2010).

The observed decrease in $\Delta\Psi_{mt}$ was attributed to the reversal of the gluconeogenic enzymes, paticularly pyruvate carboxylase and phosphoenolpyruvate carboxykinase, which facilitated the production of ATP and GTP leading to an increase in the ATP/ADP ratio within the matrix. Notably, no decrease in $\Delta\Psi_{mt}$ was observed in rat heart mitochondria lacking these glyconeogenic enzymes. These findings indeed led to the conclusion that high matrix ATP/ADP ratios are maintained at intermediate $\Delta\Psi_{mt}$ levels through the allosteric ATP inhibition of CIV, thus decreasing the formation of ROS. Therefore, they proposed that in living eukaryotic organisms, respiration is primarily regulated through $\Delta\Psi_{mt}$ -independent "allosteric ATP inhibition of CIV". Under conditions of cellular stress, however, this mechanism may be deactivated, allowing respiration to shift to traditional respiratory control as described by Mitchell's chemiosmotic theory, where regulation is dependent on $\Delta\Psi_{mt}$.

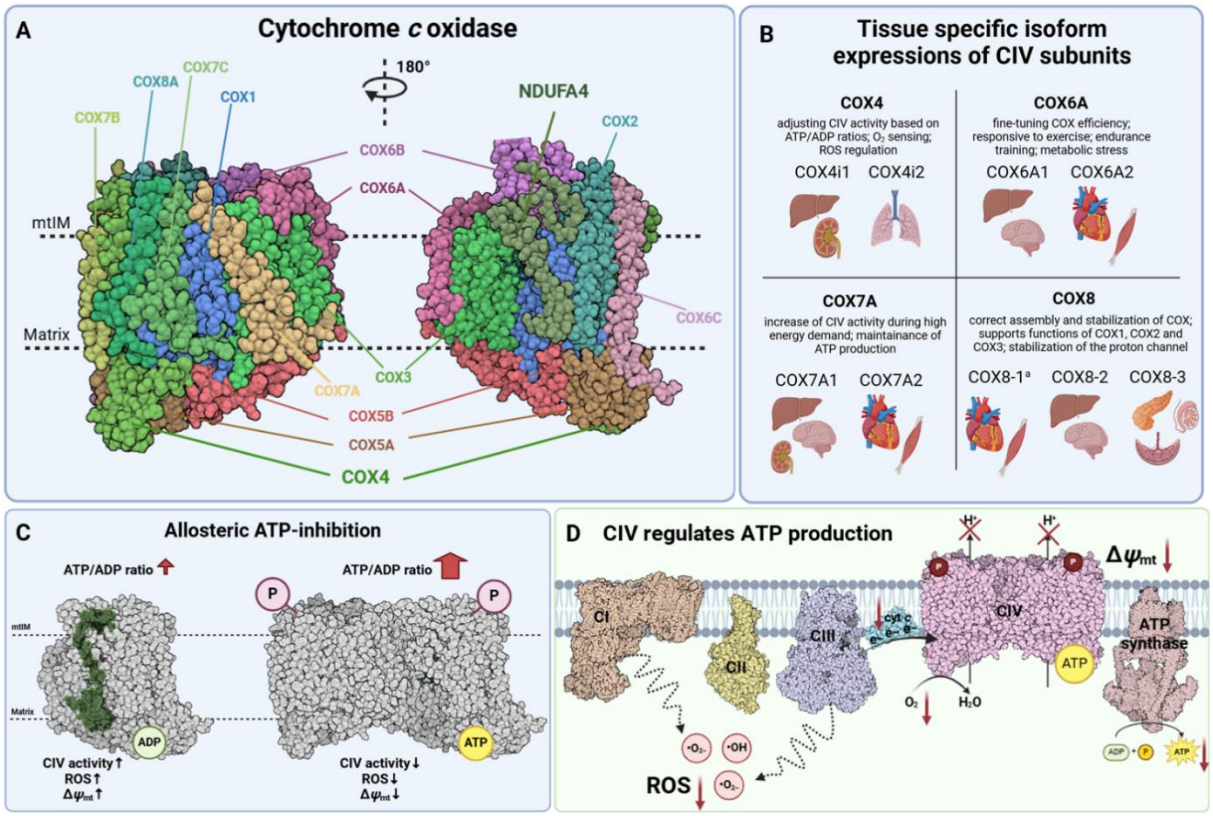

Figure 1: Cytochrome *c* oxidase (CIV) is the regulatory center of OXPHOS. (A) Molecular structure of CIV. CIV is embedded in the inner mitochondrial membrane (mtIM) and consists of 14 subunits. Key subunits such as COX1, COX2, COX3, COX4 and the regulatory subunits COX6A, COX6B, COX7A, COX7B, COX7C and COX8 are highlighted. **(B)** Tissue-specific isoform expression of CIV subunits. Different isoforms of CIV subunits are expressed in a tissue-dependent manner, optimizing mitochondrial function for specific metabolic demands. COX4 isoforms regulate CIV activity based on ATP/ADP ratios, O_2 availability, and ROS production. COX6A isoforms optimize enzyme efficiency in response to metabolic stress and exercise. COX7A isoforms enhance actvity during high-energy demand. COX8 isoforms stabilize the enzyme complex and proton channel. **(C)** Allosteric ATP inhibition of CIV. CIV activity is modulated by the ATP/ADP ratio. When ATP levels are high, cAMP-dependent protein kinase A (PKA) phosphorylates CIV, shifting NDUFA (green) from CIV to CI, promoting CIV dimerization. This dynamic regulation reduces enzyme activity, lowering mitochondrial membrane potential ($\Delta\psi_{mt}$) and ROS production. In contrast, when ADP levels are high, CIV and CI are dephosphorylated, mediating the detachment of NDUFA from CI and its binding to CIV. This promotes the monomerization of CIV, supporting ATP synthesis and maintaining mitochondrial function. **(D)** CIV regulation of ATP production and ROS balance. CIV controls OXPHOS by maintaining electron flow through the ETS. When ATP levels are sufficient, phosphorylation of CIV downregulates its activity, preventing excessive proton pumping and ROS formation. This regulatory mechanism maintains mitochondrial health and prevents oxidative-stress related diseases.
Figure was created using BioRender and protein structures were obtained from the Protein Data Bank (PDB).

5. Innovations in understanding CIV regulation and disease

Degenerative diseases are attributed, among other factors, to enhanced mitochondrial ROS production, especially under stress or excessive workload, where ROS generation rises alongside an increase in the $\Delta\Psi_{mt}$. During these conditions, the allosteric protective mechanism is switched off in order to maximize the ATP synthesis rate, even though at the cost of reduced efficiency. Thus Kadenbach hypothesized that an overload of neuronal signals leads to dephosphorylation of the enzyme which abolishes the control of enzymatic activity by the ATP/ADP ratio. This is followed by an increase in $\Delta\Psi_{mt}$ and mitochondrial ROS production. Consequently, "oxidative stress" seems to represent a condition in which the control of CIV activity by allosteric ATP inhibition is compromised. Elevated ROS levels can subsequently damage mitochondria and disrupt the enzymatic regulation. This again, results in a breakdown of the ATP/ADP allosteric control, promoting excessive electron flow through the electron transfer system, further increasing ROS production and worsening oxidative stress.

Bernhard Kadenbach's research consistently focused on the influence of ATP binding on electron transfer within the electron transfer system, with a particular focus on its regulatory mechanisms. Phosphorylation of the enzyme has an important impact in this process. While numerous phosphorylation sites have been identified in mammalian CIV, only few of these have been functionally characterized to date. Notable examples include in rabbit heart: I-Ser115, I-Ser116, IV-Thr52 and Vb-Ser40; in bovine liver: I-Tyr304; in bovine heart: II-Ser126; IV-Tyr11; IV-Ser34, Va-Ser4 and Va-Thr35; VIa-H-Thr11 and in HeLa cells: IV-Ser67, IV-Ser136, and Va-Thr38. The abundance of known phosphorylation sites in mammalian CIV indicates the presence of multiple regulatory pathways influencing the enzyme. These have not been directly linked to specific physiological functions so far, leaving much to uncover about their exact roles in the enzymes regulation (Helling et al 2008; Helling et al 2012a; Helling et al 2012b; Hüttemann et al 2012a).

However, not only these phosphorylations of CIV play a role in the "Kadenbach Theory", referring to ATP that acts as an allosteric inhibitor of CIV, helping to regulate OXPHOS efficiency and mitochondrial ROS production under physiological conditions. Moreover, cyt *c* is now regarded as an additional factor in regulating ATP inhibition of CIV via tissue-specific post-translational modifications (Kalpage et al 2019). Phosphorylation and acetylation of cyt *c* can modulate its electron transfer capacity and with this the efficiency of ATP-inhibition. Recent findings show that the impact of cyt *c* phosphorylation varies across tissues, with tissue-specific kinases targeting different residues, leading to either an increase or decrease in its activity and finally influencing mitochondrial respiration rates. So far, five phosphorylation sites of cyt *c* have been characterized by the research group of Hüttemann and colleagues: Tyr97, Tyr48, Thr28, Ser47 and Thr58. All five phosphorylation sites partially inhibit respiration, leading to optimal intermediate mitochondrial membrane potentials and low ROS production under physiological conditions. Four of the phosphorylations lead to an inhibition of the apoptotic functions of cyt *c*, suggesting a cytoprotective role of phosphorylated cyt *c*. Interestingly, these phosphorylations are lost under stress conditions such as ischemia. This promotes maximal ETS flux during reperfusion, hyperpolarization of mitochondrial membrane potential, excessive ROS formation and apoptosis (Kalpage et al 2020).

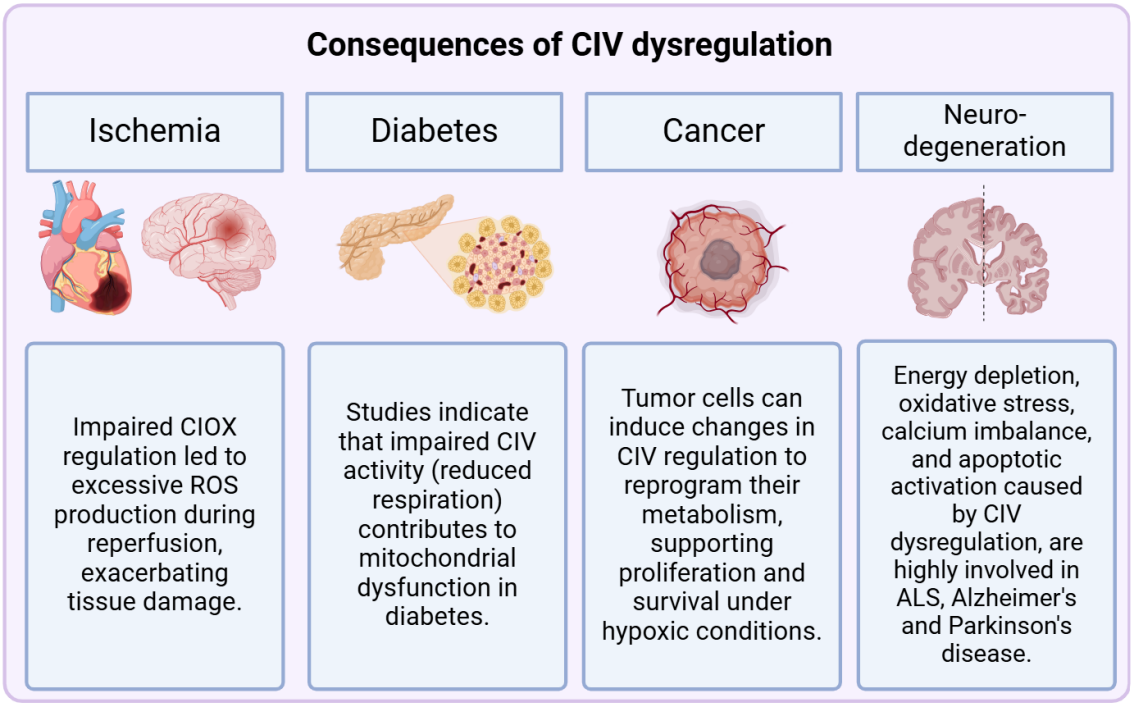

Figure 2: Cytochrome *c* oxidase (CIV) dysregulation and its implications in disease. CIV is the rate-limiting step of the mitochondrial electron transfer system, essential for the reduction of oxygen to water and the generation of ATP. Tight regulation of CIV maintains energy homeostasis and controls ROS production. CIV dysregulation can cause mitochondrial impairment that is associated with ischemia, diabetes, cancer and neurodegeneration. Targeting CIV activity may be a promising approach to restore mitochondrial function counteracting disease progression.

6. Legacy and continuing influence on mitochondrial research

This brings the Kadenbach Theory back into a new round of discussion. It remains unclear whether the electron transfer from cyt *c* to CIV, regulated by post-translational modifications of both cyt *c* and CIV, is the rate-limiting step of the ETS or whether the structure-dependent enzyme activity of CIV serves as the primary regulatory switch, as previously hypothesized. This regulation may be impaired in conditions such as ischemia-reperfusion injury and neurodegenerative disorders due to elevated ROS production. Additionally, during cancer progression, post-translational modifications of cyt *c* can serve as a mechanism to bypass apoptosis.

Even after his retirement, Kadenbach remained actively engaged in research at the Cardiac Surgery Laboratory of the University Hospital in Marburg, collaborating with Sebastian Vogt to demonstrate the clinical relevance of his work. Among their findings, they discovered that the switch between “active” and “relaxed” tissue respiration is a pivotal mechanism in the induction of heat shock proteins (Vogt et al 2011; Vogt et al 2019). This effect is also observed in the “preconditioning” of biological tissues and in myocardial insufficiency (Kadenbach et al 2011; Kadenbach et al 2013; Vogt et al 2018; Vogt et al 2021; Vogt et al 2024). CIV is now recognized as an enzyme with tissue-specific and function-specific subunit isoforms, posttranslational modifications, and allosteric control. Current research highlights the importance of the 4I2 isoform, particularly in the context of hypoxia, driving a variety of research projects worldwide.

In conclusion, CIV is an enzyme with a multitude of facets that currently range from quantum-physical relevance to therapy optimization in cancer patients and heart disease. The foresight of the outstanding role of CIV remains the merit of Bernhard Kadenbach.

Abbreviations

CI	Complex I	cyt *c*	cytochrome *c*
CII	Complex II, sucinate dehydrogenase	ETS	electron transfer system
		pmF	protonmotive force
CIII	Complex III	ROS	reactive oxygen species
CIV	Complex IV, cytochrome *c* oxidase	$\Delta\Psi_{mt}$	mitochondrial membrane potential [mV]

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