Mitochondrial Electron Transport Chain and Its Role in Oxidative Phosphorylation and Mitochondrial Dysfunction: A Survey

Abstract

The mitochondrial electron transport chain (ETC) is a critical component of cellular respiration, facilitating oxidative phosphorylation and ATP synthesis. Comprising complexes I-IV and supercomplexes (SCs), the ETC plays a vital role in maintaining cellular energy homeostasis by transferring electrons and establishing a proton gradient across the inner mitochondrial membrane. Complex I turnover is particularly crucial, as it initiates electron transport and supports mitochondrial membrane potential. However, disruptions in complex I function can lead to bioenergetic deficits and contribute to mitochondrial dysfunction, which is implicated in the pathogenesis of various diseases, including neurodegenerative disorders, metabolic syndromes, and cancer. Reverse electron transport (RET), a process where electrons flow backward through complex I, can occur under certain conditions, leading to the production of reactive oxygen species (ROS). While ROS are essential for cellular signaling at physiological levels, excessive ROS production can result in oxidative stress, damaging cellular structures and contributing to disease progression. Supercomplexes (SCs), assemblies of multiple ETC complexes, play a crucial role in optimizing electron transport efficiency, reducing energy loss, and minimizing ROS production, thereby maintaining mitochondrial function and cellular energy metabolism. Understanding the mechanisms regulating complex I turnover, RET, and supercomplex assembly is essential for elucidating the pathophysiology of mitochondrial dysfunction and its role in various diseases. This survey highlights the significance of the ETC and its components in cellular energy metabolism, mitochondrial dynamics, and disease pathogenesis, emphasizing the need for targeted therapeutic strategies to address mitochondrial dysfunction and its associated pathologies.

1 Introduction

1.1 Significance of the Mitochondrial Electron Transport Chain

The mitochondrial electron transport chain (ETC) is essential for cellular energy production, facilitating oxidative phosphorylation through the transfer of electrons across complexes I-IV, which drives ATP synthesis. This process converts energy from NADH:ubiquinone oxidoreduction into a proton gradient across the inner mitochondrial membrane, crucial for ATP production and metabolic balance [1, 2]. The efficiency of the ETC is vital for cellular homeostasis, enabling adaptation to varying energy demands.

Beyond energy production, the ETC plays a significant role in mitochondrial dynamics and metabolism. The murburn concept suggests that ATP synthesis may involve radical-mediated processes, offering a novel perspective on mitochondrial oxidative phosphorylation [3]. This highlights the ETC's involvement in reactive oxygen species (ROS) production, which is crucial for cellular signaling but can induce oxidative stress if unregulated.

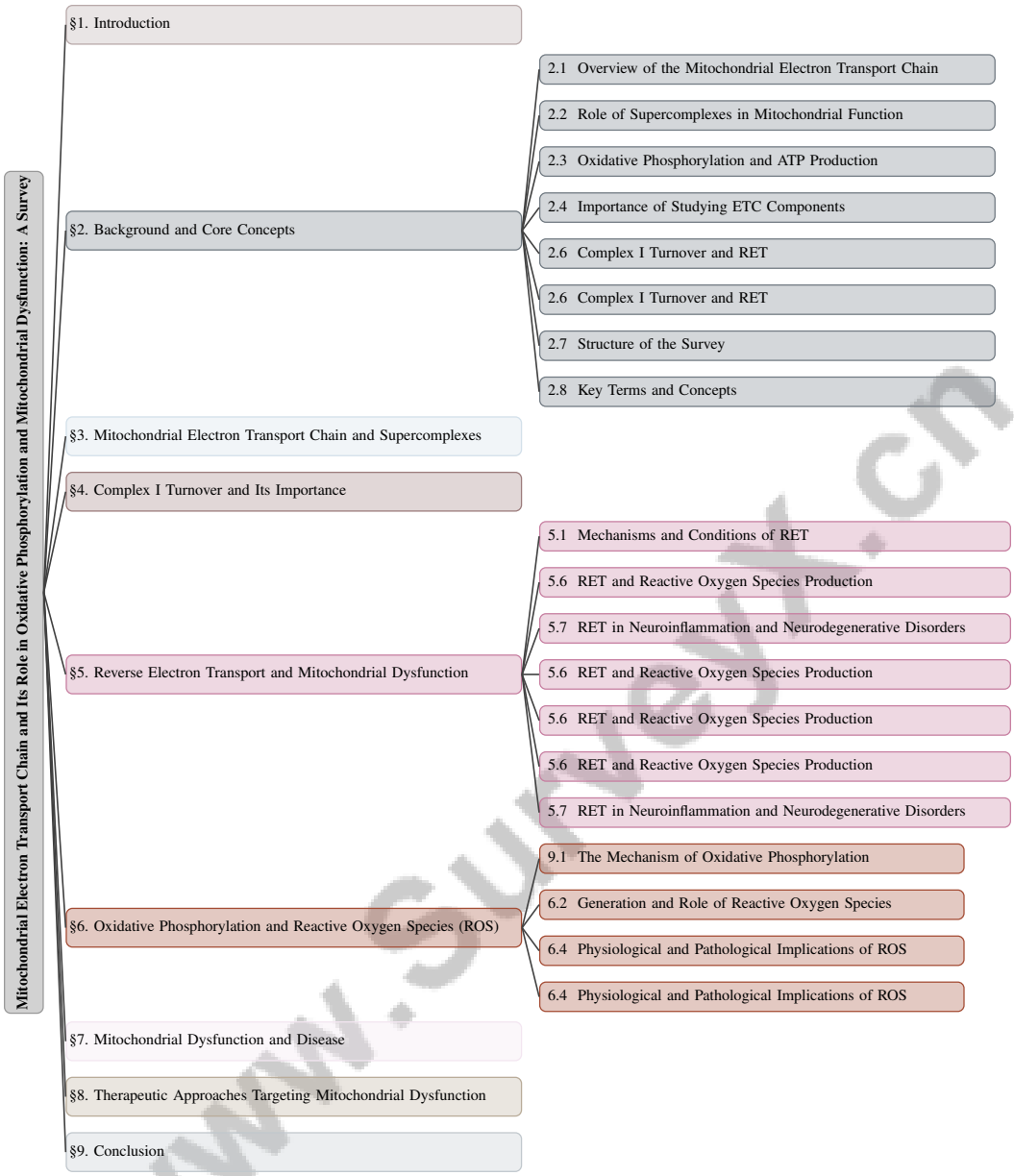


Figure 1: chapter structure

The ETC's importance extends to disease pathophysiology. In glioblastoma (GBM), oxidative metabolism driven by the ETC is critical for tumor recurrence and aggressiveness, necessitating a deeper understanding of the ETC's role in treatment challenges [4]. Mitochondrial dysfunction and impaired ETC activity are also linked to heart failure, underscoring the need to elucidate mechanisms connecting mitochondrial failure to cardiac impairment [5]. Furthermore, the ETC's role in metabolic reprogramming is evident in diseases like Parkinson's disease (PD), where understanding mitochondrial components is essential [6]. The decline of coenzyme Q10, a key ETC component, with age and pathology emphasizes the necessity of maintaining ETC function to prevent mitochondrial dysfunction [7].

Understanding the ETC is critical for addressing mitochondrial dysfunction across various diseases, including kidney stone disease, where oxidative stress and mitochondrial dysfunction contribute to calcium oxalate crystal formation [8]. The ETC is thus central to cellular physiology, linking energy production with homeostasis and adaptation to physiological challenges.

AI-generated, for reference only.

1.2 Importance of Studying ETC Components

Investigating individual components of the mitochondrial electron transport chain (ETC), including complexes I-IV and supercomplexes (SCs), is vital for elucidating their distinct roles in cellular metabolism and mitochondrial function. Each complex uniquely contributes to oxidative phosphorylation, where electron transfer is coupled with proton translocation across the inner mitochondrial membrane to establish a proton-electrochemical gradient necessary for ATP synthesis [9, 10]. A comprehensive analysis of these complexes is essential for understanding their specific contributions to energy conversion and metabolic regulation.

Supercomplexes, which consist of multiple ETC complexes, enhance electron transport efficiency and maintain mitochondrial dynamics. Insights into the structural properties and biogenesis of SCs, as well as the effects of mitochondrial DNA mutations on their assembly, are crucial for deciphering the mechanisms underlying mitochondrial dysfunction [11]. Methodological advancements, such as blue native electrophoresis, have improved the separation of mitochondrial proteins and quantification of coenzyme Q10 within supercomplexes, enhancing our understanding of mitochondrial integrity and function [7].

The relevance of ETC components extends to disease contexts, such as kidney stone disease, where mitochondrial functions are implicated in calcium oxalate nephrolithiasis [8]. Moreover, the interplay between ETC activity and cellular signaling pathways across various pathophysiological conditions underscores the importance of these components in disease mechanisms. Systematic study of ETC components can reveal intricate relationships between mitochondrial function, cellular metabolism, and disease progression, thereby identifying potential therapeutic targets for mitochondrial dysfunction.

1.3 Complex I Turnover and RET

Complex I, or NADH:ubiquinone oxidoreductase, is pivotal in the mitochondrial electron transport chain (ETC), initiating electron transfer from NADH to ubiquinone while coupling with proton translocation across the inner mitochondrial membrane to generate the proton motive force necessary for ATP synthesis [12]. The turnover of complex I is crucial for maintaining mitochondrial membrane potential and ensuring efficient energy production, particularly under conditions where the ETC is disrupted [13]. Dysfunction in complex I can lead to significant bioenergetic deficits, contributing to mitochondrial dysfunction and the pathogenesis of various diseases [14].

Reverse electron transport (RET) occurs when electrons flow backward through complex I, typically driven by a high proton motive force and elevated succinate levels. RET is implicated in ROS production, which can have dual roles in cellular signaling and oxidative stress [15]. Specifically, RET has been identified as a critical factor in the inflammatory response of macrophages activated by lipopolysaccharides (LPS) and succinate, contributing to ROS generation and subsequent inflammatory signaling [16]. This process is significant in neuroinflammation and neurodegenerative diseases, where mitochondrial dysfunction and sustained inflammatory responses play key roles in disease progression.

Understanding the mechanisms regulating complex I turnover and conditions promoting RET is essential for elucidating their roles in mitochondrial function and dysfunction. The interplay between complex I activity, RET, and ROS production underpins numerous pathological conditions, including cancer, where altered mitochondrial function and metabolic shifts are observed. Furthermore, the metabolic shift from glycolysis to oxidative phosphorylation (OXPHOS) in glioblastoma (GBM) cells highlights the importance of complex I and mitochondrial function in therapeutic resistance [4]. Thus, a comprehensive understanding of complex I turnover and RET is critical for developing strategies to mitigate mitochondrial dysfunction and its associated pathologies.

1.4 Structure of the Survey

This survey systematically explores the mitochondrial electron transport chain (ETC) and its implications in oxidative phosphorylation and mitochondrial dysfunction. The paper begins with an **Introduction**, emphasizing the significance of the ETC in cellular energy production and its broader impact on cellular homeostasis and disease pathophysiology. It also highlights the necessity of

studying ETC components, including complexes I-IV and supercomplexes (SCs), and introduces complex I turnover and reverse electron transport (RET).

Following the introduction, **Section 2: Background and Core Concepts** provides a comprehensive overview of the ETC, detailing the structure and function of complexes I-IV and supercomplexes, while explaining oxidative phosphorylation and defining key terms related to the ETC.

delves into the structural and functional interrelationships among the ETC's key components: complexes I-IV and ATP synthase (complex V). This section discusses the organization of these complexes into supercomplexes, such as the respirasome (comprising CI, CIII2, and CIV), which enhances electron transfer efficiency and ATP production during oxidative phosphorylation. Recent advancements in cryo-electron microscopy that elucidate supercomplex architecture and their roles in maintaining mitochondrial integrity, regulating electron flow, and minimizing ROS production are also highlighted [11, 17, 18, 19].

provides an in-depth analysis of complex I's pivotal role within the ETC of mitochondria, focusing on its turnover rate and regulatory mechanisms. The section discusses how complex I, as part of larger supercomplexes, facilitates electron transfer from NADH to ubiquinone, influencing cellular energy metabolism and the maintenance of the NAD+ pool. It also explores recent structural studies revealing the turnover-ready state of complex I, emphasizing its significance in understanding mitochondrial dynamics and implications for conditions such as Parkinson's disease [11, 12, 20].

examines conditions that facilitate reverse electron transport (RET) in mitochondria, particularly during ischemia/reperfusion injury, and its potential consequences, such as increased ROS production and subsequent mitochondrial dysfunction. The section discusses metabolic pathways contributing to RET and how targeting these pathways could offer therapeutic strategies to mitigate cardiac damage during events like myocardial infarction [21, 22].

analyzes oxidative phosphorylation's role in energy production and the generation of ROS, detailing their complex dual role in cellular signaling and oxidative stress. It emphasizes the need for precise identification and measurement of specific ROS, such as hydrogen peroxide (HO) and superoxide, to better understand their signaling pathways and interactions within complex biological systems, paving the way for improved therapeutic strategies in redox medicine [23, 24, 25, 26].

investigates mitochondrial dysfunction and its association with diseases such as neurodegenerative disorders, metabolic syndromes, and cancer. This review highlights mechanisms of mitochondrial dysfunction, detailing their contributions to the pathogenesis of diseases like Parkinson's and Alzheimer's, as well as metabolic and cardiovascular diseases, by examining mitochondrial dynamics, oxidative stress, and protein interactions in cellular health and disease progression [27, 5, 28, 29, 30].

provides an overview of established and innovative therapeutic strategies aimed at addressing mitochondrial dysfunction. This includes the use of antioxidants to mitigate oxidative stress, mitochondrial transplantation to replenish damaged organelles, and targeted interventions manipulating mitochondrial dynamics and supercomplex formation. These approaches are critical given the role of mitochondrial dysfunction in various diseases, highlighting the potential for these therapies to improve patient outcomes across a range of conditions [31, 32, 5, 29].

The paper concludes with , which summarizes the survey's key findings, underscoring the significance of ETC supercomplexes in oxidative phosphorylation and their implications for mitochondrial dysfunction. The conclusion highlights potential therapeutic avenues arising from understanding these mechanisms and identifies specific areas for future research, particularly in enhancing ATP synthesis efficiency and mitigating ROS production during pathological conditions like cardiac ischemia-reperfusion [11, 33, 17].The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Overview of the Mitochondrial Electron Transport Chain

The mitochondrial electron transport chain (ETC) is a critical component of cellular respiration, responsible for generating adenosine triphosphate (ATP) through oxidative phosphorylation. This process is central to cellular energy metabolism and occurs within the inner mitochondrial membrane, where the ETC is composed of four primary protein complexes (I-IV) and associated mobile electron

carriers [4]. These complexes work in concert to transfer electrons from nutrient oxidation to molecular oxygen, culminating in the production of water and ATP [7].

Complex I, or NADH:ubiquinone oxidoreductase, acts as the initial entry point for electrons into the ETC. It facilitates the oxidation of NADH and transfers electrons to ubiquinone, thereby initiating the electron transport process and contributing to the establishment of a proton gradient across the inner mitochondrial membrane. This proton gradient is vital for ATP synthesis, as it powers ATP synthase (complex V) to convert adenosine diphosphate (ADP) into ATP [4].

Complex II, known as succinate dehydrogenase, also participates in the electron transfer process by channeling electrons from succinate to ubiquinone, further supporting the proton gradient necessary for ATP production. Complex III, the cytochrome bc1 complex, plays a crucial role in transferring electrons from ubiquinol to cytochrome c, while simultaneously facilitating proton translocation across the inner mitochondrial membrane. This step is essential for maintaining the proton motive force required for ATP synthesis [4].

The electron transport chain concludes at complex IV, or cytochrome c oxidase, where electrons are transferred to molecular oxygen, the terminal electron acceptor, resulting in the formation of water. This step is vital for the completion of the electron transport cycle and the continuation of ATP production [7].

The efficiency of the ETC is enhanced by the formation of supercomplexes (SCs), which optimize electron transport and minimize energy loss, thereby reducing the production of reactive oxygen species (ROS) . Coenzyme Q10, a crucial component of the ETC, plays a significant role in mitochondrial function, and its levels can be affected by various physiological conditions [34]. This highlights the importance of maintaining optimal levels of coenzyme Q10 for efficient mitochondrial function and cellular energy production.

A comprehensive understanding of the complex architecture and operational dynamics of the electron transport chain (ETC), including the pivotal role of supercomplexes, is crucial for clarifying the mechanisms underlying oxidative phosphorylation. This knowledge is particularly important for investigating the pathophysiology of mitochondrial dysfunction-related diseases, such as neurodegenerative disorders and metabolic syndromes. Recent advancements in structural biology, including cryo-electron microscopy, have elucidated the organization of ETC complexes into supercomplexes, which enhance electron transfer efficiency and may mitigate reactive oxygen species production, thereby contributing to mitochondrial integrity and function. [11, 17]

2.2 Role of Supercomplexes in Mitochondrial Function

Supercomplexes (SCs) in the mitochondrial electron transport chain (ETC) represent higher-order assemblies of individual complexes, such as the association between cytochrome c oxidase (complex IV) and cytochrome bc1 (complex III), which are crucial for optimizing mitochondrial function [35]. These supramolecular structures facilitate enhanced electron transfer efficiency, thereby reducing the likelihood of electron leakage and subsequent reactive oxygen species (ROS) production, which is essential for maintaining mitochondrial integrity and function [17].

The organization of supercomplexes plays a pivotal role in the stability and catalytic efficiency of the mitochondrial respiratory chain, particularly in mammals. By stabilizing individual complexes, supercomplexes ensure efficient electron transport and minimize the dissipation of the proton motive force, which is crucial for ATP synthesis [36]. This stability is vital not only for normal physiological conditions but also under stress conditions, such as cardiac ischemia-reperfusion (IR), where the degradation of supercomplexes can lead to impaired mitochondrial function [33].

Furthermore, research has elucidated that supercomplexes may enhance the stability of individual ETC components, potentially improving the overall electron transport efficiency and reducing the production of ROS [11]. This is particularly important in pathological conditions where mitochondrial dysfunction is prevalent, as the maintenance of supercomplex integrity could mitigate oxidative damage and preserve cellular energy metabolism.

2.3 Oxidative Phosphorylation and ATP Production

Oxidative phosphorylation (OXPHOS) is a fundamental metabolic process within the mitochondria, crucial for the production of adenosine triphosphate (ATP), the primary energy currency of the cell. The process of ATP synthesis during cellular respiration is primarily driven by the oxidative phosphorylation electron transport chain (OXPHOS-ETC), which is composed of five large protein complexes (Complexes I, II, III, IV, and V) located in the inner mitochondrial membrane. This chain facilitates the transfer of electrons harvested from the metabolism of sugars, proteins, and fats to molecular oxygen, generating an electrochemical proton gradient across the membrane, which is essential for ATP production. Recent studies have revealed that these complexes are organized into supercomplexes, such as the respirasome, enhancing our understanding of their assembly and functional dynamics in energy conversion. [11, 9]. The ETC functions by transferring electrons through a series of protein complexes, ultimately resulting in the production of ATP via the phosphorylation of adenosine diphosphate (ADP) by ATP synthase .

The generation of ATP through oxidative phosphorylation is crucial for maintaining cellular energy homeostasis, supporting various biological processes such as muscle contraction, cellular signaling, and biosynthesis [1]. The electron transport chain (ETC) is composed of four multi-subunit complexes (I-IV) embedded in the inner mitochondrial membrane. These complexes work in concert to transfer electrons from reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) to molecular oxygen, resulting in the formation of water and the generation of a proton gradient across the inner mitochondrial membrane [12].

The importance of the ETC extends beyond its role in energy production. It is intricately linked to the regulation of mitochondrial dynamics and cellular homeostasis. The electron transfer process contributes to the formation of a proton gradient, which drives ATP synthesis through ATP synthase [1]. This process is not only essential for energy production but also plays a vital role in various cellular functions, including cell proliferation and survival, as evidenced by studies showing that increased oxidative phosphorylation levels promote cell proliferation and tumorigenesis in colorectal cancer (CRC) [37].

Furthermore, the mitochondrial electron transport chain (ETC) is a significant source of reactive oxygen species (ROS), which at physiological levels, function as signaling molecules. However, excessive ROS production can lead to oxidative stress, contributing to cellular damage and disease progression . The balance between ATP production and ROS generation is tightly regulated by the ETC components, including complex I, which plays a pivotal role in both electron transfer and the generation of reactive oxygen species [1].

In the context of disease, dysregulation of the ETC and mitochondrial dysfunction have been implicated in various pathological conditions. For instance, in colorectal cancer (CRC), elevated levels of oxidative phosphorylation, driven by enhanced complex I activity, have been associated with increased cell proliferation and tumorigenesis [37]. Similarly, in neurodegenerative disorders such as Parkinson's disease, impaired mitochondrial function has been identified as a contributing factor to disease progression, necessitating further research into mitochondrial components and their roles [6].

2.4 Importance of Studying ETC Components

The study of individual components within the mitochondrial electron transport chain (ETC), including complexes I-IV and supercomplexes (SCs), is essential for a comprehensive understanding of mitochondrial function and its implications for cellular metabolism [34]. Each complex plays a unique role in the electron transport process, contributing to the efficient production of ATP and the maintenance of cellular homeostasis.

Complex I, also known as NADH:ubiquinone oxidoreductase, is particularly significant due to its role as the entry point for electrons into the ETC. The enzyme facilitates the transfer of electrons from NADH to ubiquinone, a critical step in the electron transport chain that generates a proton gradient across the inner mitochondrial membrane. This gradient is subsequently harnessed by ATP synthase to synthesize adenosine triphosphate (ATP), the primary energy currency of the cell, thereby supporting essential cellular functions such as growth, repair, and survival. [38, 9, 19]

Supercomplexes (SCs), composed of various combinations of ETC complexes, have been identified as crucial for the optimized function of the ETC. These structures enhance the efficiency of electron

transfer and minimize the production of reactive oxygen species (ROS), which are potentially harmful byproducts of mitochondrial respiration . Understanding the assembly and regulation of these SCs is vital for elucidating their role in mitochondrial function and their impact on cellular energy metabolism [34].

2.5 Complex I Turnover and RET

Complex I, also known as NADH:ubiquinone oxidoreductase, plays an essential role in the mitochondrial electron transport chain (ETC) by catalyzing the transfer of electrons from NADH to ubiquinone, a process that is vital for the generation of ATP through oxidative phosphorylation . The turnover rate of mitochondrial complex I is crucial for sustaining efficient electron transport and cellular energy production, as it directly influences the generation of ATP and the regulation of mitochondrial membrane potential. Additionally, a balanced turnover of complex I helps mitigate the production of reactive oxygen species (ROS), which, if accumulated, can contribute to oxidative damage and lead to mitochondrial dysfunction, thereby impacting overall cellular health and function. This relationship is particularly significant in contexts such as ischemia/reperfusion injury, where excessive ROS production can exacerbate tissue damage. [13, 22, 39, 12, 21]

Reverse electron transport (RET) is a phenomenon where electrons flow in the opposite direction through complex I, typically under conditions of high proton motive force and a reduced electron transport chain [34]. Although RET can play a role in cellular signaling, excessive RET is associated with increased production of reactive oxygen species (ROS), which can lead to oxidative stress and mitochondrial damage [1]. This has significant implications for understanding the pathogenesis of various diseases, including neurodegenerative disorders, where mitochondrial dysfunction is a key contributing factor [6].

Given the complexity and centrality of the ETC in cellular metabolism, studying its individual components, including complexes I-IV and supercomplexes, is crucial for a comprehensive understanding of cellular bioenergetics . Supercomplexes, in particular, are thought to enhance the efficiency of electron transport and reduce reactive oxygen species (ROS) production, thereby maintaining cellular homeostasis [12]. Understanding the role of complex I turnover and reverse electron transport (RET) is also essential, as these processes are critical in the regulation of mitochondrial function and can contribute to mitochondrial dysfunction under certain conditions .

2.6 Complex I Turnover and RET

Complex I, also known as NADH:ubiquinone oxidoreductase, plays a pivotal role in the mitochondrial electron transport chain (ETC) by catalyzing the transfer of electrons from NADH to ubiquinone, a process that is vital for the initiation of the electron transport chain and subsequent ATP synthesis . The turnover of complex I, referring to its rate of electron transfer and regeneration, is a critical determinant of mitochondrial efficiency and cellular energy homeostasis [1].

Reverse electron transport (RET) is a phenomenon that occurs when electrons flow in the opposite direction through complex I, typically under conditions of high proton motive force and reduced ubiquinone pool [37]. Although RET is a natural process that can contribute to cellular signaling, excessive RET is implicated in increased reactive oxygen species (ROS) production, which can lead to oxidative stress and mitochondrial dysfunction [40].

The regulation of complex I turnover is a key factor in maintaining mitochondrial function, as dysregulation can lead to various pathophysiological conditions, including neurodegenerative disorders and cancer . For instance, complex I dysfunction has been linked to the pathogenesis of neurodegenerative diseases, such as Parkinson's disease (PD), where mitochondrial dysfunction is a characteristic feature [6]. Furthermore, complex I has been implicated in cancer, with studies suggesting that its dysfunction may contribute to cancer progression and tumorigenesis [37].

In addition to its role in electron transfer, complex I is a key player in the process of reverse electron transport (RET), which can occur under certain conditions, such as high proton motive force and elevated NADH/NAD+ ratios . While RET is a physiological process that can contribute to ATP synthesis and redox signaling, it also has the potential to generate excessive reactive oxygen species (ROS), leading to oxidative stress and mitochondrial dysfunction [34]. This dual role of RET is

particularly significant in the context of neurodegenerative diseases, where dysregulated mitochondrial function has been implicated in disease progression [6].

2.7 Structure of the Survey

This survey is systematically organized into several sections to provide a comprehensive understanding of the mitochondrial electron transport chain (ETC) and its implications for oxidative phosphorylation and mitochondrial dysfunction. The introductory section outlines the significance of the ETC and the necessity of studying its components, including complexes I-IV and supercomplexes (SCs), as well as the importance of understanding complex I turnover and reverse electron transport (RET) mechanisms in mitochondrial function and dysfunction.

In the subsequent section, "Background and Core Concepts," we will delve into the structural and functional aspects of the ETC, elucidating the process of oxidative phosphorylation and defining key terms associated with the ETC. The following section, "Mitochondrial Electron Transport Chain and Supercomplexes," will explore the role of supercomplexes in enhancing electron transport efficiency and their impact on reactive oxygen species (ROS) production.

The discussion will then shift to "Complex I Turnover and Its Importance," where we will examine the regulation of complex I turnover and its implications for mitochondrial function and dysfunction, particularly in the context of diseases. The study titled "Reverse Electron Transport and Mitochondrial Dysfunction" will explore the intricate mechanisms and specific conditions that precipitate reverse electron transport (RET) in mitochondria, particularly focusing on its role in the production of excessive reactive oxygen species (ROS) and the subsequent mitochondrial dysfunction. This investigation will also consider the implications of RET in pathological states, such as ischemia/reperfusion injury and obesity-related metabolic disturbances, highlighting potential therapeutic strategies aimed at mitigating its detrimental effects on cellular metabolism and health. [38, 21, 22]

Furthermore, "Oxidative Phosphorylation and Reactive Oxygen Species (ROS)" will analyze the dual role of ROS in cellular signaling and oxidative stress, and their physiological and pathological implications. The survey will delve into the topic of "Mitochondrial Dysfunction and Disease," examining the critical role of mitochondrial dysfunction in the development and progression of various conditions, including neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases, metabolic syndromes like type 2 diabetes, and various forms of cancer. This exploration will highlight the underlying mechanisms by which mitochondrial impairment contributes to these diseases, including its impact on cellular processes such as energy production, oxidative stress, and inflammation, as well as potential therapeutic interventions aimed at restoring mitochondrial function. [41, 42, 29, 30, 14]

The paper will provide a comprehensive review of "Therapeutic Approaches Targeting Mitochondrial Dysfunction," detailing both current and emerging strategies aimed at addressing mitochondrial dysfunction and its related pathologies. This includes an in-depth discussion of therapeutic interventions such as the use of antioxidants to combat oxidative stress, mitochondrial transplantation to replace damaged organelles, and innovative approaches to manipulate mitochondrial dynamics and supercomplex formation. These strategies are crucial for mitigating the effects of mitochondrial dysfunction, which plays a significant role in various diseases, including neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes. [31, 27, 5, 32, 29]

2.8 Key Terms and Concepts

The mitochondrial electron transport chain (ETC) is an intricate system of protein complexes and associated molecules located within the inner mitochondrial membrane. It is essential for cellular respiration, facilitating the transfer of electrons from reduced cofactors, such as NADH and FADH2, to molecular oxygen, which culminates in the synthesis of adenosine triphosphate (ATP) through oxidative phosphorylation . This process is critical for maintaining cellular energy homeostasis, as it generates a proton gradient across the inner mitochondrial membrane, which is harnessed by ATP synthase to produce ATP [1].

The Krebs cycle, also known as the citric acid cycle, is a central metabolic pathway that contributes to the production of reduced cofactors NADH and FADH2, which are essential substrates for the

ETC [2]. The efficient operation of the ETC is crucial for converting the chemical energy stored in these cofactors into ATP, the primary energy currency of the cell.

Supercomplexes (SCs) are higher-order assemblies of individual ETC complexes, such as the association between complexes I, III, and IV. These structures enhance electron transport efficiency by facilitating substrate channeling and reducing the production of reactive oxygen species (ROS), which are byproducts of mitochondrial respiration . The formation and stability of SCs are critical for optimizing the catalytic efficiency of the ETC and maintaining mitochondrial function [11].

Complex I turnover refers to the dynamic process by which complex I, or NADH:ubiquinone oxidoreductase, facilitates the transfer of electrons from NADH to ubiquinone, contributing to the establishment of the proton motive force necessary for ATP synthesis [12]. The regulation of complex I turnover is pivotal in maintaining mitochondrial membrane potential and ensuring effective energy production, as disruptions in complex I function can lead to mitochondrial dysfunction and various diseases .

Reverse electron transport (RET) occurs when electrons flow in the reverse direction through complex I, typically driven by a high proton motive force and elevated concentrations of succinate or reduced ubiquinone [34]. RET is implicated in the production of reactive oxygen species (ROS), which play dual roles in cellular signaling and oxidative stress [40]. This process is significant in the context of neuroinflammation and neurodegenerative diseases, where mitochondrial dysfunction and sustained inflammatory responses are key contributors to disease progression .

Mitochondrial dysfunction refers to the impaired function of the ETC, leading to insufficient ATP production and an imbalance in cellular energy homeostasis. Mitochondrial dysfunction is a critical factor in a range of diseases, prominently including neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases, as well as metabolic syndromes like type 2 diabetes and various forms of cancer. This dysfunction disrupts essential cellular processes, leading to increased inflammation and oxidative stress, which are implicated in the progression of these age-related diseases. Understanding the mechanisms by which mitochondrial dysfunction contributes to these conditions is vital for developing effective therapies and interventions. [27, 30, 6, 28]. Disruptions in mitochondrial biogenesis, dynamics, and the balance between mitochondrial fission and fusion are key mechanisms underlying mitochondrial dysfunction .

Reactive oxygen species (ROS) are byproducts of mitochondrial respiration that play dual roles in cellular processes. At physiological levels, ROS function as signaling molecules, but excessive production can lead to oxidative stress, causing damage to cellular structures and contributing to disease development . The balance between ROS generation and elimination is crucial for maintaining cellular homeostasis and preventing mitochondrial dysfunction [43]. Understanding the roles of ROS in both physiological signaling and pathological oxidative stress is vital for elucidating their impact on cellular function and disease pathogenesis.

In understanding the complexities of mitochondrial function, it is crucial to examine the organization of the electron transport chain (ETC) and its supercomplexes. This hierarchical structure plays a significant role in the efficiency of electron transport, as well as in the broader implications for mitochondrial dysfunction and disease. Figure 2 illustrates this structure, highlighting not only the organization and function of the various ETC components but also the impact of supercomplex assembly on overall mitochondrial health. By visualizing these relationships, we can better appreciate the intricate dynamics at play within the mitochondria and their relevance to cellular energy metabolism and pathology.

3 Mitochondrial Electron Transport Chain and Supercomplexes

3.1 Structure and Function of the Electron Transport Chain

The mitochondrial electron transport chain (ETC) is central to cellular respiration, enabling ATP production via oxidative phosphorylation (OXPHOS). It consists of five protein complexes (I-V) within the inner mitochondrial membrane, facilitating electron transfer from NADH and FADH2 to oxygen, forming a proton gradient crucial for ATP synthesis. The formation of supercomplexes enhances electron transfer efficiency and reduces reactive oxygen species (ROS) production, vital for cellular energy metabolism and mitochondrial function [11, 9, 19, 17, 18]. Understanding ETC

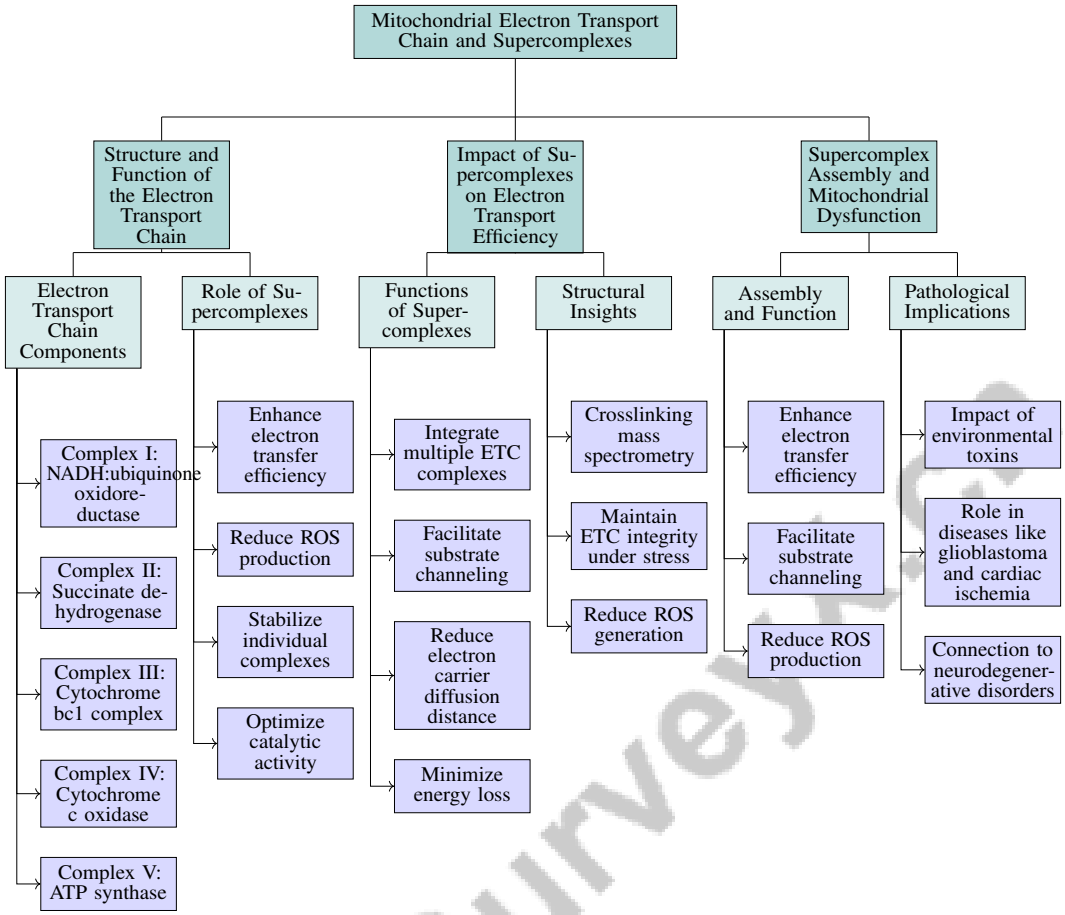


Figure 2: This figure illustrates the hierarchical structure of the mitochondrial electron transport chain and supercomplexes, highlighting the organization and function of ETC components, the impact of supercomplexes on electron transport efficiency, and the implications of supercomplex assembly for mitochondrial dysfunction and disease.

regulation and OXPHOS is crucial, as dysfunctions are linked to metabolic disorders, including cancer.

Complex I, or NADH:ubiquinone oxidoreductase, is the largest ETC component, initiating electron transfer from NADH to ubiquinone, coupled with proton translocation to generate the proton motive force for ATP synthesis. PHB2 is crucial for Complex I stability and function, essential for mitochondrial efficiency [44]. Complex II, or succinate dehydrogenase, provides an alternative electron entry, catalyzing succinate to fumarate conversion and transferring electrons to ubiquinone without contributing directly to the proton gradient [7, 37]. Complex III, the cytochrome bc1 complex, transfers electrons from ubiquinol to cytochrome c, facilitating proton translocation and contributing to the proton gradient for ATP synthase (Complex V) [4]. Complex IV, or cytochrome c oxidase, transfers electrons to oxygen, forming water and maintaining the proton motive force for ATP synthesis [7].

Supercomplexes (SCs) significantly enhance ETC efficiency by optimizing electron transfer, minimizing energy loss, and reducing ROS production. Cryo-electron microscopy has revealed their structural configurations, highlighting their role in stabilizing individual complexes and optimizing catalytic activity [11, 36, 17]. Understanding ETC dynamics, including the roles of complexes I-IV and supercomplexes, is essential for elucidating oxidative phosphorylation mechanisms and the pathophysiology of mitochondrial dysfunction-related diseases, such as neurodegenerative disorders and metabolic syndromes.

3.2 Impact of Supercomplexes on Electron Transport Efficiency

Supercomplexes (SCs) within the mitochondrial ETC integrate multiple complexes, such as I, III, and IV, to enhance electron transport efficiency and reduce ROS generation, optimizing mitochondrial function and cellular energy metabolism via OXPHOS. Noncoding RNAs regulate the ETC, modulating enzymatic complex activity and facilitating supercomplex formation, enhancing energy conversion and minimizing oxidative stress [11, 9, 18]. SCs facilitate substrate channeling between ETC complexes, reducing electron carrier diffusion distance and minimizing energy loss through heat dissipation, thus enhancing electron transfer efficiency and coupling to ATP synthesis [11].

Crosslinking mass spectrometry has provided insights into supercomplex native structure and function, overcoming traditional technique limitations [17]. Although SCs may not significantly enhance individual complex catalytic activity, they stabilize the ETC [36]. This structural stability is crucial for maintaining ETC integrity, especially under metabolic stress conditions that increase ROS production risk [36]. By ensuring close ETC complex proximity, SCs facilitate efficient electron transfer, reduce ROS generation, and maintain the proton motive force necessary for ATP synthesis [11].

Understanding SCs' impact on electron transport efficiency and ROS production is critical for elucidating mitochondrial function and dysfunction mechanisms. Insights into SC structural organization and assembly can enhance therapeutic strategies aimed at preserving mitochondrial integrity and function, particularly in conditions with elevated oxidative stress and mitochondrial damage, such as neurodegenerative disorders like Alzheimer's and Parkinson's disease. SCs' role in improving electron transport efficiency and reducing ROS production may inform interventions targeting mitochondrial dysfunction and enhancing cellular energetics during disease progression [11, 36, 33, 14].

3.3 Supercomplex Assembly and Mitochondrial Dysfunction

Supercomplexes (SCs) assembly within the mitochondrial ETC is crucial for mitochondrial function and cellular energetics. SCs form by associating ETC complexes, such as I, III, and IV, into functional units, enhancing electron transfer efficiency, facilitating substrate channeling, and reducing ROS production [35]. SCs' structural organization optimizes electron transport and minimizes energy loss, maintaining the proton motive force needed for ATP synthesis [36]. Their stability and functional integrity are essential for preventing excessive ROS production, which can lead to oxidative stress and mitochondrial dysfunction [35].

Supercomplex integrity can be compromised under pathological conditions, such as environmental toxin exposure. Complex III is susceptible to cadmium inhibition, increasing ROS production and impairing mitochondrial function [37]. This highlights the importance of understanding factors influencing SC assembly and stability, as disruptions contribute to mitochondrial dysfunction and cell death [33]. In disease contexts, SCs' role in mitochondrial dysfunction is increasingly recognized. In glioblastoma (GBM) cells, SC assembly is linked to enhanced radioresistance, suggesting a connection between mitochondrial function and tumor progression [45]. Additionally, SC disruption during cardiac ischemia-reperfusion compromises cellular energetics, emphasizing the need to understand SC assembly and stability mechanisms.

Investigating SC assembly and its implications for mitochondrial dysfunction is essential for elucidating the relationships between mitochondrial organization, ETC efficiency, and disease mechanisms. Recent studies indicate that SC assembly enhances electron transfer efficiency and minimizes ROS production, particularly relevant in age-related neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Understanding SC biogenesis, structural properties, and regulatory factors influencing formation will provide critical insights into mitochondrial pathophysiology and potential therapeutic targets for these conditions [11, 36, 14, 17]. By elucidating SC formation and stability mechanisms, researchers can identify therapeutic targets for mitigating mitochondrial dysfunction and its associated pathologies.

4 Complex I Turnover and Its Importance

Table 3 provides a comprehensive comparison of the functional roles, disease associations, and regulatory mechanisms of Complex I, emphasizing its significance in mitochondrial health and disease. The turnover of Complex I is not only crucial for its role in the mitochondrial electron

Category	Feature	Method
Complex I Turnover and Regulation	Metal Ion Regulation	TM[46]

Table 1: This table summarizes the methods employed in the study of Complex I turnover and regulation, specifically focusing on the role of metal ion regulation. The method referenced, TM, is cited from Ramchandani et al. (2021), highlighting its relevance in understanding the interplay between Complex I activity and mitochondrial health.

Category	Feature	Method
Complex I Turnover and Regulation	Metal Ion Regulation	TM[46]

Table 2: This table summarizes the methods employed in the study of Complex I turnover and regulation, specifically focusing on the role of metal ion regulation. The method referenced, TM, is cited from Ramchandani et al. (2021), highlighting its relevance in understanding the interplay between Complex I activity and mitochondrial health.

transport chain but also plays a significant part in various regulatory mechanisms that modulate mitochondrial function, including the assembly of supercomplexes, the maintenance of the proton motive force, and the interplay with other mitochondrial complexes, which are essential for effective energy production and cellular health. [11, 12, 6, 20]. Understanding these regulatory processes is essential, as they not only dictate the efficiency of electron transfer but also modulate the production of reactive oxygen species (ROS) and the overall bioenergetic landscape of the cell. Table 2 presents a concise overview of the methodological approach used to investigate the regulatory mechanisms of Complex I turnover, emphasizing the significance of metal ion regulation in mitochondrial function. This leads us to explore the specific aspects of Complex I turnover and its regulation, which are critical in maintaining mitochondrial health and preventing dysfunction.

4.1 Complex I Turnover and Regulation

4.2 Complex I Turnover and Regulation

Complex I, or NADH:ubiquinone oxidoreductase, is the largest and first enzyme complex in the mitochondrial electron transport chain (ETC), playing a vital role in cellular respiration by catalyzing the transfer of electrons from NADH to ubiquinone . This process is coupled with the translocation of protons across the inner mitochondrial membrane, contributing to the establishment of the proton motive force necessary for ATP synthesis through oxidative phosphorylation [1]. The efficient turnover of complex I is essential for maintaining mitochondrial membrane potential and ensuring effective energy production, particularly under conditions where the ETC is perturbed .

The regulation of complex I turnover is intricately linked to the cellular redox state, particularly the NADPH/NADP+ ratio, which plays a crucial role in maintaining the balance between electron transport and reactive oxygen species (ROS) production . A high proton motive force, often seen in conditions of increased metabolic demand or pathological states, can drive reverse electron transport (RET) through complex I, leading to the generation of ROS . RET, while part of normal cellular signaling, can contribute to oxidative stress and mitochondrial dysfunction when dysregulated [40].

The interplay between complex I turnover, RET, and ROS production is a critical factor in the pathophysiology of various diseases. For instance, in neurodegenerative disorders such as Parkinson's disease (PD), complex I dysfunction is a hallmark feature, where impaired mitochondrial function and increased ROS production contribute to neuronal damage and disease progression [6]. Similarly, in cancer, altered mitochondrial function and metabolic reprogramming have been implicated in tumorigenesis, with complex I playing a significant role in these processes .

Investigating the mechanisms that regulate complex I turnover and the conditions that promote reverse electron transport (RET) is essential for understanding their roles in mitochondrial function and dysfunction. The interplay between complex I activity, RET, and ROS production is a critical factor underlying many pathological conditions, including neurodegenerative disorders and cancer [46]. By elucidating these mechanisms, researchers can identify potential therapeutic targets for mitigating mitochondrial dysfunction and its associated pathologies.

4.3 Implications of Complex I Dysfunction

Complex I, or NADH:ubiquinone oxidoreductase, is an essential component of the mitochondrial electron transport chain (ETC), where it plays a pivotal role in initiating electron transfer from NADH to ubiquinone. This process is crucial for establishing the proton gradient across the inner mitochondrial membrane, which drives ATP synthesis through oxidative phosphorylation . The efficient turnover of complex I is vital for maintaining mitochondrial membrane potential and ensuring optimal energy production. Disruption in complex I function can lead to significant bioenergetic deficits, contributing to mitochondrial dysfunction and the pathogenesis of various diseases [14].

Complex I dysfunction has been extensively implicated in the pathogenesis of neurodegenerative disorders, particularly Parkinson's disease (PD). In PD, complex I deficiency is a hallmark feature, where impaired mitochondrial function and increased production of reactive oxygen species (ROS) exacerbate oxidative stress, leading to the progressive degeneration of dopaminergic neurons in the substantia nigra [6]. This neuronal loss is a key characteristic of Parkinson's disease and contributes to the motor and non-motor symptoms associated with the disorder [6].

Furthermore, complex I dysfunction has been implicated in other neurodegenerative disorders, such as Alzheimer's disease (AD), where mitochondrial dysfunction and oxidative stress are believed to play a role in disease progression [6]. In these conditions, impaired complex I activity can exacerbate oxidative stress, leading to neuronal damage and cell death, which are hallmarks of neurodegenerative diseases [40].

In addition to neurodegenerative disorders, complex I dysfunction has been associated with other pathological conditions, such as cardiovascular diseases and cancer. In heart failure, impaired complex I activity contributes to mitochondrial dysfunction and energy deficits, which are critical factors in the progression of cardiac impairment [5]. Similarly, in cancer, complex I dysfunction is implicated in metabolic reprogramming and tumorigenesis, where altered mitochondrial function supports the metabolic demands of rapidly proliferating cancer cells [37].

Reverse electron transport (RET), a process where electrons flow backward through complex I, is another significant aspect of complex I dysfunction. RET is typically driven by a high proton motive force and elevated concentrations of succinate, contributing to the production of ROS [34]. While RET can serve as a mechanism for cellular signaling, its dysregulation is associated with increased oxidative stress and mitochondrial damage, which are key contributors to various diseases, including neurodegenerative disorders [40].

A comprehensive understanding of the consequences of complex I dysfunction and the mechanisms driving reverse electron transport (RET) is essential for unraveling the pathophysiology of mitochondrial dysfunction-related diseases, particularly as RET is linked to the production of reactive oxygen species during ischemia/reperfusion injury, which can exacerbate tissue damage in conditions such as myocardial infarction. [21, 22]. Such insights can inform the development of targeted therapeutic strategies to mitigate the adverse effects of complex I dysfunction and its role in disease progression .

4.4 Complex I and Supercomplex Assembly

Complex I, or NADH:ubiquinone oxidoreductase, serves as the primary entry point for electrons into the mitochondrial electron transport chain (ETC) and is pivotal for the initiation and maintenance of the proton motive force required for ATP synthesis . Its turnover, which refers to the rate at which it facilitates electron transfer, is crucial for the overall efficiency of mitochondrial energy production and cellular homeostasis [1]. Disruptions in the assembly or function of complex I are closely associated with increased production of reactive oxygen species (ROS), contributing to oxidative stress and mitochondrial dysfunction [40].

In the context of supercomplexes (SCs), complex I often associates with other ETC components, such as complex III (cytochrome bc1) and complex IV (cytochrome c oxidase), to form higher-order assemblies. These supercomplexes are thought to optimize electron transport by facilitating substrate channeling and reducing the diffusion distance for electron carriers, which minimizes energy loss and ROS production . The structural stability provided by these supercomplexes is particularly crucial in maintaining the integrity and efficiency of the mitochondrial respiratory chain, especially under conditions of stress or impaired complex assembly [36].

In brain cells, the assembly and stability of supercomplexes are vital for sustaining high energy demands and maintaining neuronal function. The brain, being one of the most energy-demanding organs, relies heavily on efficient mitochondrial function to support synaptic activity and neuronal signaling [36]. Disruptions in supercomplex assembly can lead to compromised electron transport efficiency, increased ROS production, and mitochondrial dysfunction, all of which are implicated in the pathogenesis of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases .

Methodological advancements, such as crosslinking mass spectrometry, have been instrumental in providing deeper insights into the native structures and dynamics of supercomplexes, helping to bridge significant gaps in our understanding of their precise roles in mitochondrial function and disease pathology . These insights are particularly relevant in the context of brain cells, where the maintenance of supercomplex integrity is vital for preventing oxidative damage and preserving neuronal health [36].

Furthermore, the relationship between complex I activity and supercomplex assembly is of particular interest, as complex I is not only a critical component of the ETC but also plays a significant role in the formation and stability of supercomplexes. The cooperative assembly model suggests that supercomplexes are formed through the binding of precursors from individual complexes, which may not necessarily enhance respiration rates but provide structural stability to the ETC . This structural stability is crucial for maintaining mitochondrial function, particularly in high-energy-demanding tissues such as the brain, where mitochondrial dysfunction is a hallmark of various neurodegenerative diseases [6].

Overall, understanding the relationship between complex I activity and supercomplex assembly is essential for elucidating the mechanisms underlying mitochondrial function and dysfunction. Understanding the mechanisms of mitochondrial dysfunction is crucial for developing therapeutic strategies that aim to preserve mitochondrial integrity and function, especially in neurodegenerative diseases like Parkinson's disease and age-related conditions, where mitochondrial impairment is a significant contributor to disease progression and cellular decline. Recent research has identified novel therapeutic targets within mitochondrial biology, highlighting their essential role in the pathophysiology of these diseases and offering new avenues for drug development aimed at restoring mitochondrial health. [29, 30, 32]

Feature	Complex I Turnover and Regulation	Implications of Complex I Dysfunction	Complex I and Supercomplex Assembly
Function	Electron Transfer	Proton Gradient Maintenance	Supercomplex Formation
Role in Disease	Neurodegenerative Disorders	Parkinson's Disease	Mitochondrial Dysfunction
Regulatory Mechanism	Nadph/nadp+ Ratio	Ret Dysregulation	Structural Stability

Table 3: Overview of the functional roles, disease implications, and regulatory mechanisms associated with Complex I in the mitochondrial electron transport chain. The table highlights the critical aspects of electron transfer, proton gradient maintenance, and supercomplex assembly, along with their relevance to neurodegenerative disorders and mitochondrial dysfunction.

5 Reverse Electron Transport and Mitochondrial Dysfunction

To fully appreciate the implications of reverse electron transport (RET) within the context of mitochondrial dysfunction, it is crucial to explore the underlying mechanisms and conditions that facilitate this process. RET is not merely a byproduct of mitochondrial activity; rather, it plays a significant role in the generation of reactive oxygen species (ROS) and the subsequent oxidative stress that can lead to cellular damage and disease. This section will delve into the specific mechanisms and conditions that promote RET, highlighting its relevance in various pathological states, including neurodegenerative disorders and metabolic syndromes.

5.1 Mechanisms and Conditions of RET

Reverse electron transport (RET) is a specialized process within the mitochondrial electron transport chain (ETC) wherein electrons are transferred in the opposite direction through complex I, moving from ubiquinol to NAD+. This process is facilitated by a high proton motive force and is significant in various physiological contexts, such as the generation of reactive oxygen species (ROS) during ischaemia/reperfusion injury in myocardial infarction, as well as in the activation of myeloid cells in chronic neurological diseases. Understanding RET's role in these pathological states opens avenues

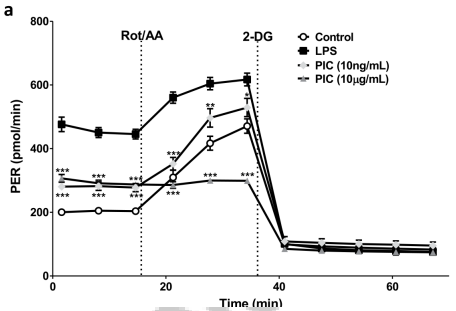
for potential therapeutic interventions aimed at mitigating oxidative damage and improving cellular health. [19, 22, 47, 9]. This phenomenon is typically facilitated by elevated levels of succinate and a reduced electron transport chain, conditions often present during heightened metabolic activity or stress .

The occurrence of RET is closely associated with the metabolic state of the cell, particularly during ischemic events or in pathological conditions such as obesity, where succinate accumulation is prevalent . Under these circumstances, the high proton motive force across the inner mitochondrial membrane drives the reverse flow of electrons, leading to the production of mitochondrial reactive oxygen species (mtROS) . While mtROS function as critical signaling molecules at physiological levels, their excessive production can result in oxidative stress and contribute to mitochondrial dysfunction, a key factor in the pathogenesis of various diseases [40].

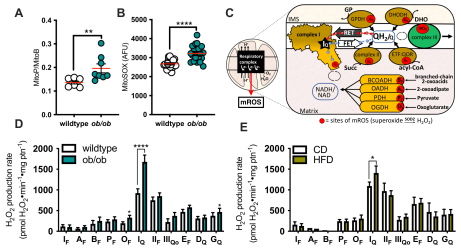
RET has been implicated in the activation and inflammatory state of myeloid cells, where it plays a crucial role in sustaining pro-inflammatory responses through mtROS production [48]. In macrophages, RET can be triggered by factors such as lipopolysaccharides (LPS) and succinate, leading to increased ROS production and inflammatory signaling . This process is particularly significant in the context of neuroinflammation and neurodegenerative disorders, where prolonged inflammatory responses and mitochondrial dysfunction are critical contributors to disease progression .

The role of RET in disease is further underscored in cancer, where metabolic reprogramming allows cancer cells to exploit RET for survival and proliferation. Myc deregulation, for instance, can result in altered metabolic conditions that may facilitate RET in cancer cells [49]. This metabolic flexibility enables cancer cells to adapt to varying environmental conditions, promoting their survival and proliferation [32].

Despite its physiological roles, the dysregulation of RET and the associated excessive ROS production can exacerbate oxidative stress and mitochondrial damage, contributing to various pathologies, including ischemia-reperfusion (I/R) injury [22]. The interplay between RET, complex I activity, and ROS production is critical in understanding the pathogenesis of diseases characterized by mitochondrial dysfunction, such as neurodegenerative disorders and metabolic syndromes .



(a) Effect of Rot/AA and 2-DG on PER (pmol/min) in Control, LPS, PIC (10ng/mL), and PIC (10g/mL) groups over time[50]



(b) Mitochondrial Dysfunction in Ob/Ob Mice: Implications for Mitochondrial Dysfunction in Ob/Ob Mice: Implications for Health and Disease[38]

Figure 3: Examples of Mechanisms and Conditions of RET

As shown in Figure 3, In exploring the intricate dynamics of reverse electron transport (RET) and mitochondrial dysfunction, it is crucial to understand the mechanisms and conditions under which RET occurs, as well as its broader implications for health and disease. The provided examples offer a comprehensive look into these phenomena. The first figure illustrates the impact of Rotenone/Antimycin A (Rot/AA) and 2-deoxy-D-glucose (2-DG) on proton efflux rate (PER) across various experimental groups, including control, LPS, and two concentrations of PIC. By plotting these effects over a 60-minute timeframe, the graph provides insight into how these agents influence mitochondrial activity under different conditions. Meanwhile, the second figure delves into the realm of mitochondrial dysfunction within the context of obesity, particularly in Ob/Ob mice. This scientific diagram highlights how obesity can alter mitochondrial function, offering a visual depiction of the consequential health implications. Together, these examples underscore the complex interplay between RET and mitochondrial health, emphasizing the importance of understanding these processes in the context of disease and therapeutic interventions. [**?**]ahmed2019differential,goncalves2023ubiquinone)

AI-generated, for reference only.

5.2 RET and Reactive Oxygen Species Production

Reverse electron transport (RET) is a critical phenomenon within the mitochondrial electron transport chain (ETC) that occurs when electrons flow backward from reduced ubiquinol to complex I, driven by a high proton motive force and elevated concentrations of succinate [34]. This process, while a natural aspect of mitochondrial function, can lead to the generation of reactive oxygen species (ROS), which play dual roles in cellular physiology .

Under normal physiological conditions, ROS function as signaling molecules that regulate various cellular processes, including cell proliferation, differentiation, and apoptosis [40]. However, excessive ROS production, often resulting from dysregulated reverse electron transport (RET) through complex I, can lead to oxidative stress, mitochondrial dysfunction, and cellular damage . This imbalance between ROS generation and elimination is a key factor in the pathogenesis of numerous diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer .

The role of RET in ROS production is particularly significant in the context of neurodegenerative diseases, where increased ROS levels contribute to neuronal damage and disease progression. For instance, in Parkinson's disease (PD), complex I dysfunction and elevated ROS production are associated with the degeneration of dopaminergic neurons in the substantia nigra, a hallmark feature of the disease [6]. Similarly, in Alzheimer's disease (AD), mitochondrial dysfunction and oxidative stress are believed to contribute to the pathological processes underlying the disease [6].

A comprehensive understanding of how reverse electron transport (RET) contributes to the production of reactive oxygen species (ROS) in mitochondria is essential for clarifying the underlying mechanisms of mitochondrial dysfunction and its implications for disease progression, particularly in the context of cardiac pathologies such as ischemia/reperfusion injury, where ROS play a dual role in both signaling and pathological damage. [22, 43, 26]. Insights into these processes can inform the development of therapeutic strategies aimed at mitigating the adverse effects of excessive ROS production and oxidative stress, which are implicated in a wide range of diseases, including neurodegenerative disorders and cancer .

5.3 RET in Neuroinflammation and Neurodegenerative Disorders

Reverse electron transport (RET) within the mitochondrial electron transport chain (ETC) has been increasingly recognized for its role in the pathogenesis of neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD). RET occurs when electrons flow in the reverse direction through complex I, typically under conditions of high proton motive force and elevated concentrations of succinate . The process of generating reactive oxygen species (ROS) is crucial in cellular signaling, as these oxidant molecules play diverse roles in physiological functions. However, when produced in excess, ROS can disrupt cellular homeostasis, leading to oxidative stress, which is implicated in neuronal damage and the progression of neurodegenerative diseases. Specifically, key ROS such as hydrogen peroxide (HO) and superoxide anions (O·) are involved in redox signaling pathways that regulate stress responses and metabolic adaptation. Understanding the balance between ROS as signaling agents and their pathological effects is essential for developing targeted therapeutic strategies in redox medicine to mitigate oxidative damage in the nervous system. [23, 25, 26]

In the context of neurodegenerative disorders, RET has been implicated in the pathogenesis of diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD), where mitochondrial dysfunction and oxidative stress are key contributors to disease progression [6]. In PD, for instance, complex I dysfunction and increased ROS production have been identified as critical factors in the degeneration of dopaminergic neurons, which is a hallmark feature of the disease [6].

Moreover, RET has been associated with the metabolic reprogramming observed in various cancers, including colorectal cancer (CRC), where altered mitochondrial function supports the energy demands of rapidly proliferating tumor cells [37]. The increased production of ROS through RET can exacerbate oxidative stress and contribute to tumorigenesis, highlighting the importance of understanding the conditions that promote RET and its role in cancer progression [37].

In addition to its role in cancer, RET has been implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). In these conditions, mitochondrial dysfunction and the associated increase in ROS production contribute to neuronal damage

and disease progression [6]. The relationship between RET, ROS production, and neuroinflammation is particularly significant in understanding the mechanisms underlying these disorders and developing potential therapeutic strategies .

Overall, the study of reverse electron transport (RET) and its implications for mitochondrial function and dysfunction is crucial for understanding the complex interplay between electron transport, ROS production, and disease pathogenesis. By clarifying the mechanisms through which reverse electron transport (RET) influences mitochondrial function, researchers can pinpoint specific therapeutic targets that may help alleviate mitochondrial dysfunction and its related diseases, such as neurodegenerative disorders, metabolic syndromes, and cardiovascular diseases. This understanding is crucial, as mitochondrial dynamics—including fission, fusion, and mitophagy—are integral to maintaining cellular health and preventing the onset of various pathologies. [29, 27, 22, 31]

5.4 RET and Reactive Oxygen Species Production

Reverse electron transport (RET) is a critical process within the mitochondrial electron transport chain (ETC) that can lead to the production of reactive oxygen species (ROS), which are byproducts of mitochondrial respiration [34]. RET occurs when electrons flow in the reverse direction through complex I, typically under conditions of high proton motive force and an elevated reduction state of the electron transport chain [37].

The generation of ROS through RET plays a dual role in cellular physiology. At physiological levels, ROS function as signaling molecules, modulating various cellular processes, including cell proliferation, differentiation, and apoptosis [40]. However, excessive ROS production can lead to oxidative stress, which is implicated in the pathogenesis of numerous diseases, including neurodegenerative disorders and metabolic syndromes .

In the context of neurodegenerative diseases, such as Parkinson's disease (PD), excessive ROS production resulting from dysregulated RET and impaired mitochondrial function contributes to the progressive degeneration of dopaminergic neurons in the substantia nigra [6]. This oxidative damage is a key factor in the pathophysiology of PD, highlighting the need for further research into the mechanisms underlying RET and its impact on mitochondrial function [40].

A comprehensive understanding of the conditions and mechanisms that trigger reverse electron transport (RET) in mitochondria is crucial for clarifying its role in mitochondrial dysfunction, particularly in the context of diseases such as myocardial infarction and neuroinflammatory disorders. RET at mitochondrial complex I has been identified as a significant source of superoxide production during ischemia/reperfusion injury, which contributes to cellular damage. Additionally, in chronic neurological diseases like multiple sclerosis, RET in myeloid cells has been linked to sustained neuroinflammation and neurotoxic damage. Therefore, elucidating the pathways that facilitate RET not only enhances our knowledge of mitochondrial pathophysiology but also opens avenues for targeted therapeutic strategies aimed at mitigating its deleterious effects in various disease states. [47, 6, 22]. By investigating the factors that influence RET and its impact on reactive oxygen species (ROS) production, researchers can develop targeted therapeutic strategies to mitigate oxidative stress and its associated pathologies .

5.5 RET and Reactive Oxygen Species Production

Reverse electron transport (RET) is a physiological process within the mitochondrial electron transport chain (ETC) that can lead to the production of reactive oxygen species (ROS), which play dual roles in cellular signaling and oxidative stress [34]. RET occurs when electrons flow in the reverse direction through complex I, driven by a high proton motive force and an elevated concentration of succinate . This process can result in the generation of superoxide, a reactive oxygen species that can lead to oxidative damage and contribute to mitochondrial dysfunction and cellular injury .

The production of reactive oxygen species (ROS) through the process of redox signaling has profound implications for both physiological functions, such as cellular adaptation to stress and metabolic regulation, and pathological conditions, including neurodegenerative diseases and hypertension, where an imbalance in ROS levels can contribute to disease progression and complications. [23, 25, 26]. At normal levels, ROS function as signaling molecules, playing a role in cellular processes such as apoptosis, proliferation, and immune responses . However, excessive ROS production can lead

to oxidative stress, which is implicated in a wide range of diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer .

In neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), the dysregulation of reverse electron transport (RET) leads to excessive production of reactive oxygen species (ROS), which has been recognized as a significant contributor to neuronal damage and the progression of these diseases. Recent research highlights that mitochondrial dysfunction, particularly involving the electron transport chain (ETC), is central to the pathophysiology of PD, with numerous genes implicated in mitochondrial regulation and their roles in exacerbating oxidative stress and neurodegeneration. Understanding these mechanisms not only sheds light on the disease progression but also opens avenues for potential therapeutic interventions targeting mitochondrial health and ROS management. [29, 6]. In particular, RET has been implicated in the inflammatory response of macrophages activated by lipopolysaccharides (LPS) and succinate, where it contributes to oxidative stress and neuronal damage .

The dual role of reactive oxygen species (ROS) in cellular signaling and oxidative stress underscores the importance of understanding the mechanisms and conditions that lead to RET and its impact on mitochondrial function and dysfunction [40]. By elucidating the processes that drive RET and its contribution to ROS production, researchers can gain valuable insights into the pathophysiology of diseases associated with mitochondrial dysfunction and develop targeted therapeutic strategies to mitigate their impact .

5.6 RET and Reactive Oxygen Species Production

Reverse electron transport (RET) within the mitochondrial electron transport chain (ETC) is a critical process where electrons flow backward from complex II to complex I, facilitated by a high proton motive force and elevated concentrations of succinate . The reverse flow of electrons through the mitochondrial electron transport chain can result in an excessive production of reactive oxygen species (ROS). While ROS play crucial roles as signaling molecules at physiological levels, their overproduction can lead to oxidative stress, which damages cellular components and disrupts normal cellular functions. This imbalance in ROS levels is particularly relevant in various pathological contexts, including cancer and hypertension, where altered ROS homoeostasis contributes to disease progression and cellular dysfunction. [25, 45, 51, 26, 21]

The production of ROS through RET is particularly significant in the context of mitochondrial dysfunction and disease pathogenesis. Excessive ROS production can lead to oxidative damage of lipids, proteins, and DNA, contributing to cellular dysfunction and death . Oxidative stress, characterized by an imbalance in the production and elimination of reactive oxygen species (ROS), plays a crucial role in the development and progression of a range of diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, cardiovascular conditions linked to hypertension, and various forms of cancer. This imbalance can lead to mitochondrial dysfunction and inflammation, further exacerbating the pathological processes associated with these diseases. Understanding the mechanisms by which oxidative stress influences these conditions is essential for developing targeted therapeutic strategies aimed at restoring redox balance and improving patient outcomes. [30, 25, 26]

In neurodegenerative disorders such as Parkinson's disease (PD), increased ROS production due to RET has been implicated in the degeneration of dopaminergic neurons in the substantia nigra, a hallmark feature of the disease [6]. Similarly, in Alzheimer's disease (AD), mitochondrial dysfunction and oxidative stress are believed to play crucial roles in disease progression, with RET contributing to the increased production of ROS [6].

Moreover, the interplay between RET, ROS production, and mitochondrial dysfunction is also relevant in the context of cancer. In glioblastoma (GBM), enhanced mitochondrial function through COX4-1 expression has been shown to reduce ROS production, linking RET to mitochondrial dysfunction and tumor progression [4]. This highlights the importance of understanding the conditions that promote RET and its impact on ROS generation and cellular metabolism [22].

The dual role of reactive oxygen species (ROS) as both essential signaling molecules and contributors to oxidative stress highlights the critical need for maintaining a precise balance in mitochondrial function. This balance is vital for cellular homeostasis, as physiological levels of ROS, particularly hydrogen peroxide (H2O2) and superoxide anion radicals, play key roles in redox signaling pathways that regulate metabolic processes and stress responses. Disruption of this balance can lead to

pathological conditions, underscoring the importance of targeted strategies in redox medicine to manage ROS levels and their effects on cellular health. [45, 23, 25, 26]. While physiological levels of ROS are necessary for normal cellular processes, excessive ROS production can lead to oxidative damage and contribute to the pathogenesis of various diseases . Elucidating the mechanisms underlying RET and its contribution to ROS production is essential for understanding the complex interplay between mitochondrial function, oxidative stress, and disease progression .

5.7 RET in Neuroinflammation and Neurodegenerative Disorders

Reverse electron transport (RET) within the mitochondrial electron transport chain (ETC) has emerged as a significant contributor to neuroinflammation and neurodegenerative disorders. RET occurs when electrons flow backward through complex I, typically driven by a high proton motive force and elevated succinate levels, leading to the production of reactive oxygen species (ROS) [52]. The excessive ROS generated during RET can exacerbate oxidative stress, a key factor in the pathogenesis of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD).

In Parkinson's disease, mitochondrial dysfunction is a hallmark feature, where impaired electron transport and increased ROS production contribute to the degeneration of dopaminergic neurons [52]. This neuronal damage is further compounded by neuroinflammatory processes, which are driven by ROS and other inflammatory mediators. The interaction between RET-induced ROS production and neuroinflammation plays a crucial role in the progression of PD, highlighting the importance of targeting mitochondrial dysfunction as a therapeutic strategy [52].

The role of supercomplexes in modulating mitochondrial function and their implications for neurodegenerative disorders have also been explored. Supercomplexes are higher-order assemblies of ETC complexes that enhance electron transport efficiency and minimize ROS production [36]. A better understanding of supercomplex formation and stability could provide insights into mitigating mitochondrial dysfunction and its associated pathologies in neurodegenerative diseases [36].

Additionally, the complex interactions between -synuclein, a protein implicated in PD, mitochondrial dysfunction, and neuroinflammatory processes have been identified as critical factors in neurodegenerative disorders [28]. The aggregation of -synuclein can disrupt mitochondrial function, leading to increased ROS production and further exacerbating neuroinflammation. This interplay between -synuclein and mitochondrial dysfunction underscores the multifaceted nature of neurodegenerative diseases and the need for comprehensive therapeutic approaches [28].

Revised Sentence: "Overall, reverse electron transport (RET) in myeloid cells significantly contributes to neuroinflammation and the progression of neurodegenerative disorders by exacerbating oxidative stress and mitochondrial dysfunction, which are linked to the chronic activation of these immune cells and the subsequent production of neurotoxic factors." [47, 30]. Understanding the mechanisms underlying RET and its impact on mitochondrial health is essential for developing targeted interventions to alleviate the burden of neurodegenerative diseases.

6 Oxidative Phosphorylation and Reactive Oxygen Species (ROS)

To fully appreciate the intricate relationship between oxidative phosphorylation and the generation of reactive oxygen species (ROS), it is essential to first explore the underlying mechanisms of oxidative phosphorylation itself. This process not only functions as the primary mechanism for ATP production in eukaryotic cells through the establishment of a proton gradient via the electron transport chain, but it also significantly contributes to the generation of reactive oxygen species (ROS) as byproducts of electron transport, which can have diverse biological roles ranging from cellular signaling to potential pathological damage. [9, 26]. Understanding the mechanism of oxidative phosphorylation will provide valuable insights into how energy transduction is coupled with the dynamics of ROS generation and their subsequent impact on cellular physiology. Thus, we now turn our attention to the detailed mechanisms involved in oxidative phosphorylation.

6.1 The Mechanism of Oxidative Phosphorylation

Oxidative phosphorylation is a fundamental metabolic process in mitochondria, responsible for the majority of ATP production in eukaryotic cells. This process occurs in the inner mitochondrial

membrane and involves the electron transport chain (ETC) and ATP synthase, which work together to convert the energy derived from electron transfer into a proton gradient that drives ATP synthesis [48]. The ETC comprises complexes I-IV, which facilitate electron transfer from reduced cofactors, such as NADH and FADH2, to molecular oxygen, resulting in the formation of water and the generation of a proton gradient across the inner mitochondrial membrane [3].

The proton gradient, also known as the proton motive force, is a critical component of oxidative phosphorylation, as it provides the energy required for ATP synthase to phosphorylate adenosine diphosphate (ADP) into adenosine triphosphate (ATP). This chemiosmotic mechanism, as described by the bond graph approach, effectively models the energy transduction processes involved in ATP synthesis, highlighting the importance of maintaining the proton gradient for efficient energy conversion [48].

Recent studies have demonstrated that calcium oscillations can further optimize mitochondrial ATP production, achieving a maximum efficiency of about 30

The murburn concept offers an alternative perspective on oxidative phosphorylation, suggesting that dissipative reactive oxygen species (DROS) can stabilize and modulate the reaction environment, facilitating ATP synthesis without relying solely on a strict proton gradient [3]. This concept challenges traditional views of mitochondrial energy transduction and underscores the complexity of oxidative phosphorylation as a dynamic and adaptable process.

Oxidative phosphorylation is a fundamental process in cellular energy metabolism, as it generates adenosine triphosphate (ATP), which is essential for a wide array of cellular functions, including those that support cell proliferation and metabolic reprogramming in cancer cells. Given the critical role of mitochondria as hubs of metabolic activity, understanding and potentially manipulating the pathways involved in oxidative phosphorylation could provide new therapeutic strategies to target cancer cell growth and improve the efficacy of chemotherapeutic agents. [53, 54]. Understanding the mechanisms underlying this process, including the roles of calcium dynamics, thermodynamic efficiency, and alternative concepts like murburn, is essential for elucidating the intricacies of mitochondrial function and its implications for cellular physiology and disease.

6.2 Generation and Role of Reactive Oxygen Species

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, which are primarily generated as byproducts of the electron transport processes within the mitochondrial electron transport chain (ETC), particularly at complexes I and III . During oxidative phosphorylation, the leakage of electrons from these complexes can lead to the partial reduction of oxygen, resulting in the formation of ROS [23]. While traditionally viewed as harmful due to their potential to cause oxidative damage to lipids, proteins, and nucleic acids, ROS at physiological levels serve as crucial signaling molecules, regulating various cellular processes such as proliferation, differentiation, and apoptosis [40].

The dual role of reactive oxygen species (ROS) in cellular physiology is well-established; at low physiological concentrations, ROS act as critical signaling molecules that facilitate cellular communication, metabolic regulation, and adaptation to environmental stressors, while excessive ROS production can induce oxidative stress, resulting in damage to vital cellular components such as lipids, proteins, and DNA. Specifically, hydrogen peroxide (HO) and superoxide anion radicals (O·) are key players in redox signaling, generated under the influence of growth factors and cytokines through various enzymes, including NADPH oxidases and components of the mitochondrial electron transport chain. Understanding the precise roles and mechanisms of these oxidants is essential for translating research findings into therapeutic strategies aimed at mitigating oxidative damage and enhancing cellular resilience. [23, 24, 25, 26]. This oxidative stress is a key factor in the pathogenesis of various diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer .

In the context of neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), increased ROS production due to mitochondrial dysfunction is a critical factor in disease progression. For instance, in PD, complex I dysfunction and elevated ROS levels contribute to the degeneration of dopaminergic neurons in the substantia nigra, a hallmark feature of the disease [6]. Similarly, in AD, mitochondrial dysfunction and oxidative stress are believed to play a significant role in the pathological processes underlying the disease [6].

The generation of reactive oxygen species (ROS) by metallic nanoparticles (NPs) has been identified as a significant contributor to the pathogenesis of various diseases, including essential hypertension, as ROS play critical roles in cellular signaling and can lead to oxidative stress, which is implicated in the development and progression of this condition. Factors such as the size, shape, and chemical composition of the nanoparticles influence the amount of ROS produced, further complicating their biological effects and potential therapeutic applications. [25, 16, 23, 24, 26]. The role of ROS in essential hypertension is particularly noteworthy, as they serve as both signaling molecules and contributors to pathological processes, influencing vascular tone and contributing to endothelial dysfunction .

The DCFH-DA method has been utilized to detect ROS in vivo, providing valuable insights into the quantification of oxidative stress in various biological systems [55]. This method involves the conversion of non-fluorescent dichlorodihydrofluorescein diacetate (DCFH-DA) to a fluorescent form in the presence of ROS, allowing for the quantification of oxidative stress levels in different cellular contexts .

The dual role of reactive oxygen species (ROS) in cellular signaling and oxidative stress highlights the critical need for maintaining a precise balance in mitochondrial function, as both excessive and insufficient ROS levels can disrupt cellular homeostasis and contribute to various pathologies, including cardiovascular diseases and neurodegenerative disorders. This balance is particularly important given that specific ROS, such as hydrogen peroxide (H2O2), act as essential signaling molecules that facilitate cellular adaptation to stress, while their overproduction can lead to oxidative damage and disease progression. Understanding the intricate mechanisms of ROS signaling, especially within mitochondrial contexts, is vital for developing targeted therapeutic strategies in redox medicine. [25, 45, 23, 26, 43]. While physiological levels of ROS are essential for cellular signaling and homeostasis, excessive ROS production can lead to oxidative damage, contributing to the pathogenesis of various diseases, including neurodegenerative disorders and metabolic syndromes . Understanding the mechanisms underlying ROS generation during oxidative phosphorylation and their impact on cellular processes is crucial for elucidating the pathophysiology of diseases associated with mitochondrial dysfunction and for developing targeted therapeutic strategies to mitigate their effects .

6.3 Physiological and Pathological Implications of ROS

Reactive oxygen species (ROS) are byproducts of mitochondrial respiration, playing dual roles in cellular physiology as both signaling molecules and mediators of oxidative stress. At physiological levels, ROS function as essential signaling molecules that regulate various cellular processes, including cell proliferation, differentiation, and apoptosis . They are involved in the regulation of cellular signaling pathways, such as those mediated by calcium and redox-sensitive transcription factors, which play critical roles in maintaining cellular homeostasis [40].

However, excessive production of reactive oxygen species (ROS) can lead to oxidative stress, resulting in damage to cellular components, including lipids, proteins, and DNA. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, plays a pivotal role in the development of various diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's disease, cardiovascular diseases, and cancer. This phenomenon is closely linked to mitochondrial dysfunction, which not only contributes to the pathogenesis of these conditions but also affects cellular processes like energy production and inflammation. Understanding the intricate mechanisms of oxidative stress and its impact on health is crucial for developing targeted therapies aimed at mitigating its harmful effects. [25, 23, 26, 30, 43]. In particular, mitochondrial dysfunction and increased ROS production have been implicated in the pathogenesis of neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), where oxidative stress contributes to neuronal damage and disease progression .

The interplay between reactive oxygen species (ROS) production and mitochondrial function is further highlighted in the context of cancer, where altered mitochondrial function and increased ROS levels have been associated with tumorigenesis and cancer progression [37]. In colorectal cancer (CRC), for instance, enhanced oxidative phosphorylation and increased complex I activity have been linked to increased cell proliferation and tumor growth [37].

Moreover, the role of ROS in essential hypertension has been explored, where they serve as both signaling molecules and contributors to pathological processes, influencing vascular tone and con-

tributing to endothelial dysfunction . The production of ROS by metallic nanoparticles (NPs) has also been identified as a significant factor in NP-induced cytotoxicity, differentiation, and therapeutic applications [24].

A comprehensive understanding of the diverse roles of reactive oxygen species (ROS) in both physiological and pathological contexts is essential for clarifying their intricate involvement in cellular functions and the mechanisms underlying disease development. This includes recognizing the distinct properties and biological functions of various ROS, such as hydrogen peroxide (HO) and superoxide, which serve as critical signaling molecules that mediate cellular responses to environmental stressors and contribute to the pathogenesis of conditions like hypertension, neurodegenerative diseases, and cancer. Advances in precise measurement and targeted manipulation of specific ROS pathways are crucial for translating this knowledge into effective therapeutic strategies in redox medicine. [23, 24, 25, 26]. By investigating the mechanisms underlying ROS generation and their impact on cellular processes, researchers can develop targeted therapeutic strategies aimed at mitigating oxidative stress and its associated pathologies .

6.4 Physiological and Pathological Implications of ROS

Reactive oxygen species (ROS) are crucial byproducts of the mitochondrial electron transport chain (ETC) that play dual roles in cellular physiology, acting both as signaling molecules and agents of oxidative stress . Under physiological conditions, ROS serve as essential signaling molecules, regulating critical cellular processes such as cell proliferation, differentiation, and apoptosis [40]. These reactive molecules are involved in various redox-sensitive signaling pathways, influencing cellular responses to external stimuli and maintaining homeostasis [26].

The production of reactive oxygen species (ROS) is closely associated with oxidative phosphorylation, primarily occurring within the mitochondrial electron transport chain (ETC), which comprises multiple complexes (I-IV) and electron carriers such as ubiquinone and cytochrome c. During this process, electrons derived from metabolic substrates like NADH and succinate are transferred through the ETC, facilitating ATP synthesis while simultaneously generating a proton gradient. However, some electrons can escape this pathway and react with molecular oxygen, leading to ROS formation at specific sites within the ETC, particularly in complexes I, II, and III. This ROS production plays a dual role in cellular signaling, influencing processes such as cell proliferation and survival, but excessive ROS levels can result in significant cellular damage and contribute to various diseases. Additionally, oncogenic pathways can further enhance ROS generation by altering electron flow and the structural organization of the ETC, creating a feedback loop that maintains elevated ROS levels characteristic of cancer cells. [53, 9, 19, 51, 26]. During oxidative phosphorylation, the leakage of electrons from complexes I and III can lead to the partial reduction of oxygen, resulting in the formation of ROS . While physiological levels of ROS play a role in normal cellular signaling, excessive ROS production can lead to oxidative stress, causing damage to cellular structures, including lipids, proteins, and DNA .

Oxidative stress, resulting from an imbalance between ROS production and the cellular antioxidant defense system, is a key factor in the pathogenesis of numerous diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer . In neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), mitochondrial dysfunction and increased ROS production contribute to neuronal damage and disease progression . The excessive ROS levels in these conditions exacerbate oxidative stress, leading to the degeneration of neurons and the progression of neurodegenerative diseases [6].

In cancer, the role of ROS is particularly significant, as they can promote tumorigenesis through the induction of genetic mutations and the activation of signaling pathways that drive cancer cell proliferation and survival [56]. This dual role of ROS as both signaling molecules and mediators of oxidative damage underscores the complexity of their involvement in disease pathogenesis.

The interplay between ROS production and mitochondrial function is further highlighted in the context of cardiovascular diseases, where increased ROS levels contribute to oxidative stress, endothelial dysfunction, and vascular damage . The generation of ROS by metallic nanoparticles (NPs) has also been identified as a significant factor in NP-induced cytotoxicity, differentiation, and therapeutic applications [24].

Recent advancements in redox research have emphasized the need for precise definitions and analytical tools to better understand the roles of specific oxidants in cellular processes and their potential therapeutic benefits [26]. The encapsulation of cerium oxide nanoparticles within electrospun poly--caprolactone (PCL) fibers has been shown to mitigate cytotoxic effects while enhancing cell viability and antioxidant activity, offering potential therapeutic benefits in contexts where oxidative stress is a contributing factor .

7 Mitochondrial Dysfunction and Disease

7.1 Neurodegenerative Disorders and Mitochondrial Dysfunction

Mitochondrial dysfunction is pivotal in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), where it contributes to neuronal degeneration through impaired energy production, oxidative stress, and disrupted mitochondrial dynamics and quality control. In AD, mitochondrial dysfunction is linked to pathological tau protein and amyloid plaque accumulation, while in PD, it affects both sporadic and familial forms by regulating mitochondrial biology, presenting new therapeutic targets [57, 30, 29]. Complex I dysfunction and increased reactive oxygen species (ROS) production are particularly crucial in PD, exacerbating oxidative stress and neuronal damage [40].

The interaction between -synuclein and mitochondrial dynamics in PD exacerbates dopaminergic neuron degeneration, a disease hallmark. Similarly, in AD, mitochondrial dysfunction and oxidative stress drive disease progression by damaging lipids, proteins, and DNA [57]. The interplay between mitochondrial dysfunction, oxidative stress, and neuroinflammation is a critical research area, emphasizing the need for targeted interventions to preserve mitochondrial function and mitigate oxidative damage. A central challenge in PD is determining whether mitochondrial dysfunction initiates or propagates neuronal degeneration [58].

Beyond PD and AD, mitochondrial dysfunction impacts other neurodegenerative disorders, including depression, where alterations in neurogenesis and inflammation are implicated. Understanding mitochondrial dysfunction in these conditions provides insights into disease progression and underscores the need for targeted strategies to preserve mitochondrial health and reduce oxidative damage [58].

7.2 Metabolic Syndromes and Mitochondrial Dysfunction

Mitochondrial dysfunction is increasingly recognized as a critical factor in metabolic syndromes, including insulin resistance, obesity, dyslipidemia, hypertension, and type 2 diabetes mellitus. This dysfunction disrupts essential cellular processes like energy production and oxidative stress management, leading to metabolic disturbances. Recent studies highlight mechanisms linking mitochondrial impairment to insulin resistance, particularly through ceramide accumulation and coenzyme Q deficiency, underscoring the importance of mitochondrial health in maintaining metabolic homeostasis [59, 60, 30, 57]. These syndromes are characterized by metabolic derangements associated with mitochondrial function alterations, including morphological changes, oxidative stress, and abnormalities in mitophagy and mitochondrial transfer.

The role of mitochondrial dysfunction in metabolic syndromes involves changes in mitochondrial biogenesis, dynamics, and interactions with other organelles, such as the endoplasmic reticulum (ER), which are crucial for maintaining mitochondrial proteostasis and cellular homeostasis [39]. In AD, disruptions in mitochondrial dynamics, including fission and fusion processes, have been implicated in disease pathogenesis [39].

Pharmacological agents like acetaminophen can induce mitochondrial dysfunction through the formation of reactive metabolites that deplete glutathione and induce oxidative stress [61]. In contrast, the mitochondrial toxicity of drugs like diclofenac and isoniazid is less understood and warrants further investigation [61].

The interplay between mitochondrial dysfunction and metabolic syndromes is further complicated by oxidative stress, a key factor in these conditions' pathogenesis. Excessive ROS production within the mitochondrial ETC can lead to oxidative damage, contributing to insulin resistance and other metabolic abnormalities [60]. The dual role of ROS as signaling molecules and oxidative stress

mediators presents challenges for therapeutic interventions, necessitating a balance to avoid disrupting their physiological functions.

7.3 Mitochondrial Dysfunction in Cancer

Mitochondrial dysfunction is increasingly recognized as a critical factor in cancer development and progression. Mitochondria play a central role in cellular energy metabolism, and their dysfunction can lead to significant metabolic reprogramming, a cancer cell hallmark [60]. The altered bioenergetic state in cancer cells supports rapid proliferation and survival, contributing to tumorigenesis and cancer progression.

A key aspect of mitochondrial dysfunction in cancer is its impact on metabolic flexibility, allowing cancer cells to adapt to varying environmental conditions like hypoxia and nutrient deprivation by shifting between glycolysis and oxidative phosphorylation (OXPHOS) to meet energy demands [60]. This ability is crucial for cancer cell survival and proliferation, particularly in the tumor microenvironment, where nutrient and oxygen availability can be limited.

Mitochondrial dysfunction is also linked to ROS production, which can exert both pro-tumorigenic and anti-tumorigenic effects [60]. At low to moderate levels, ROS can promote cell proliferation and survival by activating signaling pathways that support cancer growth and metastasis. However, excessive ROS production can lead to oxidative stress, damaging cellular components and contributing to cancer progression [60].

Moreover, the role of mitochondrial dysfunction in cancer is further complicated by environmental influences that modulate mitochondrial function and contribute to disease pathogenesis, including conditions such as autism spectrum disorder (ASD) [62]. Although the specific pathways through which mitochondrial dysfunction affects cancer progression remain to be fully elucidated, ongoing research underscores the importance of understanding these mechanisms for developing targeted therapeutic strategies [60].

8 Therapeutic Approaches Targeting Mitochondrial Dysfunction

Exploring therapeutic strategies to counter mitochondrial dysfunction is crucial for improving mitochondrial integrity and function across various diseases, including neurodegenerative disorders, metabolic syndromes, and cancer. This section delves into targeted interventions that directly address mitochondrial dysfunction, a significant factor in these pathologies. Understanding these therapies' mechanisms is essential for advancing treatment of mitochondrial-related diseases.

8.1 Therapeutic Strategies Targeting Mitochondrial Dysfunction

Targeted strategies are vital for addressing mitochondrial dysfunction in diseases like neurodegenerative disorders, metabolic syndromes, and cancer, where impaired electron transport chain (ETC) activity and increased reactive oxygen species (ROS) production play a critical role [5]. Enhancing mitochondrial function by optimizing coenzyme Q10 dynamics can improve ETC efficiency and reduce ROS production, particularly relevant in Parkinson's disease (PD) and Alzheimer's disease (AD) [7, 5]. Inhibition of monoamine oxidase (MAO), which contributes to ROS production, has also been proposed [5].

In cancer, targeting mitochondrial metabolism and complex I dysfunction can improve treatment outcomes and overcome resistance [5]. Selective ROS inhibitors and optimized antioxidant therapies are suggested for oxidative stress-related pathologies like hypertension and metabolic syndromes [5]. Understanding mitochondrial dysfunction mechanisms is crucial for developing therapies addressing these diseases' root causes.

8.2 Antioxidant Therapies

Antioxidant therapies offer potential for reducing oxidative stress and enhancing mitochondrial function across diseases such as neurodegenerative disorders, cardiovascular diseases, and cancer [31, 32, 29, 30, 43]. While ROS are vital for cellular signaling, excess production leads to oxidative

damage and disease progression. Antioxidants aim to balance ROS production and elimination, preserving mitochondrial function.

N-acetylcysteine (NAC) shows promise in mitigating oxidative stress and improving cellular health, particularly in cartilage injury [63]. Future research should explore NAC and other antioxidants in various pathological conditions [63]. Nanoceria, a redox-active form of cerium oxide, is under investigation for its antioxidant properties, though inconsistent findings challenge its biological understanding [16, 64, 24, 26, 65]. Further research is needed to optimize its therapeutic potential.

Antioxidant therapies hold promise for restoring mitochondrial function and reducing oxidative damage in neurodegenerative disorders like PD and AD, where mitochondrial dysfunction and oxidative stress drive disease progression [29, 28]. Understanding oxidative stress and mitochondrial health interplay is crucial for developing effective interventions.

8.3 Mitochondrial Transplantation

Mitochondrial transplantation is a promising strategy to tackle mitochondrial dysfunction in conditions like neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes [66]. This approach involves transferring healthy mitochondria into dysfunctional cells to restore function and improve energy metabolism.

Mitochondrial transplantation replenishes functional mitochondria, enhancing energy production and reducing ROS [66]. It may mitigate oxidative stress and related pathologies, key contributors to various diseases. In neurodegenerative disorders such as PD and AD, it offers potential by restoring mitochondrial function and reducing oxidative stress [39].

Success depends on donor mitochondria selection, protocol optimization, and patient identification [66]. Preclinical studies demonstrate its feasibility and efficacy in various models, highlighting its potential as a novel therapeutic approach [66]. Continued research aims to elucidate transplantation mechanisms and expand its applicability to a broader range of conditions [66].

8.4 Targeting Mitochondrial Dynamics

Mitochondrial dynamics, including fission, fusion, and mitophagy, are vital for maintaining mitochondrial function and cellular homeostasis. These processes allow mitochondria to adapt to energy demands and environmental changes, ensuring efficient energy production and removal of damaged mitochondria [67]. Dysregulation of these dynamics is implicated in various conditions, such as neurodegenerative disorders, cardiovascular diseases, and cancer [42].

Targeting mitochondrial dynamics offers a therapeutic approach for addressing dysfunction and associated pathologies. Research should focus on small molecules mimicking ATP binding to NOX4, a regulator of mitochondrial dynamics, potentially reducing drug resistance in cancer [67]. This approach could enhance function and mitigate oxidative stress, preserving energy metabolism and preventing damage.

In PD, mitochondrial dysfunction and oxidative stress significantly contribute to disease progression. Recent studies highlight the importance of understanding molecular mechanisms leading to dysfunction, particularly complex I turnover and reverse electron transport (RET) in ROS production [29, 21, 6]. This research identifies potential therapeutic targets for mitigating dysfunctions in PD.

Modulating mitochondrial dynamics, including fission and fusion, is promising for addressing dysfunction in diseases like neurodegenerative disorders and cancer [36]. Changes in dynamics are implicated in PD pathogenesis, where impaired function and increased ROS contribute to damage and progression. Future research should explore the role of mitochondrial dynamics in energy metabolism and inform targeted therapies for various diseases [6].

Understanding mitochondrial dynamics and cellular signaling interplay is crucial, with studies emphasizing the importance of molecular mechanisms in disease pathogenesis [65]. Targeting these dynamics can lead to novel therapeutic strategies for mitochondrial-related disorders [65].

9 Conclusion

9.1 The Mechanism of Oxidative Phosphorylation

Oxidative phosphorylation is a fundamental mitochondrial process, where ATP is synthesized from ADP and inorganic phosphate, driven by the electron transport chain (ETC). This chain comprises four primary complexes (I-IV) situated within the inner mitochondrial membrane, facilitating electron transfer from reduced cofactors like NADH and FADH2 to oxygen, thereby creating a proton gradient. This gradient is crucial for ATP synthase (complex V) activity, which converts ADP into ATP, providing energy for critical cellular functions such as muscle contraction and biosynthesis.

The organization of ETC components into supercomplexes (SCs) significantly enhances oxidative phosphorylation efficiency by optimizing electron flow and reducing reactive oxygen species (ROS) production, thus maintaining mitochondrial integrity and energy homeostasis. The formation and stability of these SCs are vital for maximizing the ETC's catalytic efficiency and minimizing energy dissipation as heat.

Additionally, the murburn concept offers a novel perspective, suggesting that dissipative reactive oxygen species (DROS) play a beneficial role in coupling electron transport with ATP synthesis, challenging traditional views that focus solely on the proton gradient. This highlights the complexity of mitochondrial energy transduction and the need for a deeper understanding of oxidative phosphorylation.

Comprehending these intricate processes is pivotal for insights into mitochondrial function and its impact on cellular physiology and disease. Future research should focus on unraveling the detailed mechanisms of oxidative phosphorylation and developing innovative therapeutic strategies to address mitochondrial dysfunction, which holds promise for treating neurodegenerative diseases, metabolic disorders, and cancer. Expanding our understanding of the relationship between oxidative phosphorylation, ROS production, and mitochondrial dysfunction will aid in identifying therapeutic targets and devising strategies to mitigate the effects of mitochondrial impairments in various pathological conditions.

References

[1] Kelath Murali Manoj. Murburn concept: A facile explanation for oxygen-centered cellular respiration, 2017.

[2] V. I. Grytsay and I. V. Musatenko. Self-organization and fractality in a metabolic process of the krebs cycle, 2017.

[3] Kelath Murali Manoj and Abhinav Parashar. Unveiling adp-binding sites and channels in respiratory complexes: Validation of murburn concept as a holistic explanation for oxidative phosphorylation, 2018.

[4] Claudia R Oliva, Md Yousuf Ali, Susanne Flor, and Corinne E Griguer. Cox4-1 promotes mitochondrial supercomplex assembly and limits reactive oxide species production in radioresistant gbm. *Cell Stress*, 6(4):45, 2022.

[5] Bo Zhou, Rong Tian, et al. Mitochondrial dysfunction in pathophysiology of heart failure. *The Journal of clinical investigation*, 128(9):3716–3726, 2018.

[6] Jeng-Lin Li, Tai-Yi Lin, Po-Lin Chen, Ting-Ni Guo, Shu-Yi Huang, Chun-Hong Chen, Chin-Hsien Lin, and Chih-Chiang Chan. Mitochondrial function and parkinson's disease: from the perspective of the electron transport chain. *Frontiers in molecular neuroscience*, 14:797833, 2021.

[7] Kyousuke Sugawara, Seiji Sato, Yuto Tanaka, Akari Nakamura, Akio Fujisawa, Yorihiro Yamamoto, and Misato Kashiba. Method for detecting coq10 incorporation in the mitochondrial respiratory chain supercomplex. *Journal of Clinical Biochemistry and Nutrition*, 72(3):207, 2023.

[8] Sakdithep Chaiyarit and Visith Thongboonkerd. Mitochondrial dysfunction and kidney stone disease. *Frontiers in Physiology*, 11:566506, 2020.

[9] Rona R Ramsay. Electron carriers and energy conservation in mitochondrial respiration. *ChemTexts*, 5(2):9, 2019.

[10] L. A. Arias-Hernández, R. T. Paez-Hernández, and F. Angulo-Brown. A first–order irreversible thermodynamic approach to a simple energy converter, 2007.

[11] James A Letts and Leonid A Sazanov. Clarifying the supercomplex: the higher-order organization of the mitochondrial electron transport chain. *Nature structural & molecular biology*, 24(10):800–808, 2017.

[12] Bozhidar S Ivanov, Hannah R Bridges, Owen D Jarman, and Judy Hirst. Structure of the turnover-ready state of an ancestral respiratory complex i. *Nature Communications*, 15(1):9340, 2024.

[13] Karthik Vasan, Matt Clutter, Sara Fernandez Dunne, Mariam D George, Chi-Hao Luan, Navdeep S Chandel, and Inmaculada Martínez-Reyes. Genes involved in maintaining mitochondrial membrane potential upon electron transport chain disruption. *Frontiers in Cell and Developmental Biology*, 10:781558, 2022.

[14] Gisela V Novack, Pablo Galeano, Eduardo M Castaño, and Laura Morelli. Mitochondrial supercomplexes: Physiological organization and dysregulation in age-related neurodegenerative disorders. *Frontiers in endocrinology*, 11:600, 2020.

[15] Rianne Kloosterman. *The Effect of SK Channel Activation on Reverse Electron Transport in Inflammation*. PhD thesis, 2019.

[16] Sarah Triboulet, Catherine Aude-Garcia, Marie Carrière, Hélène Diemer, Fabienne Proamer, Aurélie Habert, Mireille Chevallet, Véronique Collin-Faure, Jean-Marc Strub, Daniel Hanau, Alain Van Dorsselaer, Nathalie Herlin-Boime, and Thierry Rabilloud. Molecular responses of mouse macrophages to copper and copper oxide nanoparticles inferred from proteomic analyses, 2013.

[17] Sehwan Jang and Sabzali Javadov. Current challenges in elucidating respiratory supercomplexes in mitochondria: methodological obstacles. *Frontiers in physiology*, 9:238, 2018.

[18] Ami Kobayashi, Toshihiko Takeiwa, Kazuhiro Ikeda, and Satoshi Inoue. Roles of noncoding rnas in regulation of mitochondrial electron transport chain and oxidative phosphorylation. *International Journal of Molecular Sciences*, 24(11):9414, 2023.

[19] Ru-Zhou Zhao, Shuai Jiang, Lin Zhang, and Zhi-Bin Yu. Mitochondrial electron transport chain, ros generation and uncoupling. *International journal of molecular medicine*, 44(1):3–15, 2019.

[20] Irene Lopez-Fabuel, Monica Resch-Beusher, Monica Carabias-Carrasco, Angeles Almeida, and Juan P Bolaños. Mitochondrial complex i activity is conditioned by supercomplex i–iii 2–iv assembly in brain cells: Relevance for parkinson's disease. *Neurochemical research*, 42:1676–1682, 2017.

[21] Alexander S Milliken, Chaitanya A Kulkarni, and Paul S Brookes. Complex effects of ph on ros from mitochondrial complex ii driven complex i reverse electron transport challenge its role in tissue reperfusion injury. *bioRxiv*, pages 2020–08, 2020.

[22] Hiran A Prag, Michael P Murphy, and Thomas Krieg. Preventing mitochondrial reverse electron transport as a strategy for cardioprotection. *Basic Research in Cardiology*, 118(1):34, 2023.

[23] Helmut Sies and Dean P Jones. Reactive oxygen species (ros) as pleiotropic physiological signalling agents. *Nature reviews Molecular cell biology*, 21(7):363–383, 2020.

[24] Ahmed Abdal Dayem, Mohammed Kawser Hossain, Soo Bin Lee, Kyeongseok Kim, Subbroto Kumar Saha, Gwang-Mo Yang, Hye Yeon Choi, and Ssang-Goo Cho. The role of reactive oxygen species (ros) in the biological activities of metallic nanoparticles. *International journal of molecular sciences*, 18(1):120, 2017.

[25] Gabriele Togliatto, Giusy Lombardo, and Maria Felice Brizzi. The future challenge of reactive oxygen species (ros) in hypertension: from bench to bed side. *International journal of molecular sciences*, 18(9):1988, 2017.

[26] Helmut Sies, Vsevolod V Belousov, Navdeep S Chandel, Michael J Davies, Dean P Jones, Giovanni E Mann, Michael P Murphy, Masayuki Yamamoto, and Christine Winterbourn. Defining roles of specific reactive oxygen species (ros) in cell biology and physiology. *Nature reviews Molecular cell biology*, 23(7):499–515, 2022.

[27] Wen Chen, Huakan Zhao, and Yongsheng Li. Mitochondrial dynamics in health and disease: mechanisms and potential targets. *Signal transduction and targeted therapy*, 8(1):333, 2023.

[28] Emily M Rocha, Briana De Miranda, and Laurie H Sanders. Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in parkinson's disease. *Neurobiology of disease*, 109:249–257, 2018.

[29] Jin-Sung Park, Ryan L Davis, and Carolyn M Sue. Mitochondrial dysfunction in parkinson's disease: new mechanistic insights and therapeutic perspectives. *Current neurology and neuroscience reports*, 18:1–11, 2018.

[30] Sydney Bartman, Giuseppe Coppotelli, and Jaime M Ross. Mitochondrial dysfunction: a key player in brain aging and diseases. *Current Issues in Molecular Biology*, 46(3):1987–2026, 2024.

[31] Yao Zong, Hao Li, Peng Liao, Long Chen, Yao Pan, Yongqiang Zheng, Changqing Zhang, Delin Liu, Minghao Zheng, and Junjie Gao. Mitochondrial dysfunction: mechanisms and advances in therapy. *Signal transduction and targeted therapy*, 9(1):124, 2024.

[32] Giovanna Gallo, Speranza Rubattu, and Massimo Volpe. Mitochondrial dysfunction in heart failure: from pathophysiological mechanisms to therapeutic opportunities. *International journal of molecular sciences*, 25(5):2667, 2024.

[33] Sehwan Jang, Taber S Lewis, Corey Powers, Zaza Khuchua, Christopher P Baines, Peter Wipf, and Sabzali Javadov. Elucidating mitochondrial electron transport chain supercomplexes in the heart during ischemia–reperfusion. *Antioxidants & redox signaling*, 27(1):57–69, 2017.

[34] Charlotte Récapet, Mathilde Arrivé, Blandine Doligez, and Pierre Bize. Antioxidant capacity is repeatable across years but does not consistently correlate with a marker of peroxidation in a free-living passerine bird, 2019.

[35] Andrew M Hartley, Natalya Lukoyanova, Yunyi Zhang, Alfredo Cabrera-Orefice, Susanne Arnold, Brigitte Meunier, Nikos Pinotsis, and Amandine Maréchal. Structure of yeast cytochrome c oxidase in a supercomplex with cytochrome bc 1. *Nature structural & molecular biology*, 26(1):78–83, 2019.

[36] Michele Brischigliaro, Alfredo Cabrera-Orefice, Susanne Arnold, Carlo Viscomi, Massimo Zeviani, and Erika Fernández-Vizarra. Structural rather than catalytic role for mitochondrial respiratory chain supercomplexes. *elife*, 12:RP88084, 2023.

[37] Jacopo Junio Valerio Branca, Alessandra Pacini, Massimo Gulisano, Niccolò Taddei, Claudia Fiorillo, and Matteo Becatti. Cadmium-induced cytotoxicity: effects on mitochondrial electron transport chain. *Frontiers in cell and developmental biology*, 8:604377, 2020.

[38] Renata LS Goncalves, Zeqiu Branden Wang, Karen E Inouye, Grace Yankun Lee, Xiaorong Fu, Jani Saksi, Clement Rosique, Gunes Parlakgul, Ana Paula Arruda, Sheng Tony Hui, et al. Ubiquinone deficiency drives reverse electron transport to disrupt hepatic metabolic homeostasis in obesity. *bioRxiv*, pages 2023–02, 2023.

[39] Hua Wang, Sheng-Yuan Yu, Sofus Nielsen, Xing Wang, and Wei-Wei Zhao. Mitochondrial complex i: the key to sustained microglia activation and neuroinflammation maintenance. *Military Medical Research*, 11(1):47, 2024.

[40] Rüdiger Hardeland. Melatonin and the electron transport chain. *Cellular and Molecular Life Sciences*, 74:3883–3896, 2017.

[41] Niamh MC Connolly, Pierre Theurey, Vera Adam-Vizi, Nicolas G Bazan, Paolo Bernardi, Juan P Bolaños, Carsten Culmsee, Valina L Dawson, Mohanish Deshmukh, Michael R Duchen, et al. Guidelines on experimental methods to assess mitochondrial dysfunction in cellular models of neurodegenerative diseases. *Cell Death & Differentiation*, 25(3):542–572, 2018.

[42] SB Larsen, Z Hanss, and R Krüger. The genetic architecture of mitochondrial dysfunction in parkinson's disease. *Cell and tissue research*, 373:21–37, 2018.

[43] Jessica N Peoples, Anita Saraf, Nasab Ghazal, Tyler T Pham, and Jennifer Q Kwong. Mitochondrial dysfunction and oxidative stress in heart disease. *Experimental & molecular medicine*, 51(12):1–13, 2019.

[44] Lin Ren, Li Meng, Jing Gao, Mingdian Lu, Chengyu Guo, Yunyun Li, Ziye Rong, and Yan Ye. Phb2 promotes colorectal cancer cell proliferation and tumorigenesis through ndufs1-mediated oxidative phosphorylation. *Cell Death & Disease*, 14(1):44, 2023.

[45] Charlotte Graham, Rhoda Stefanatos, Angeline EH Yek, Ruth V Spriggs, Samantha HY Loh, Alejandro Huerta Uribe, Tong Zhang, L Miguel Martins, Oliver DK Maddocks, Filippo Scialo, et al. Mitochondrial ros signalling requires uninterrupted electron flow and is lost during ageing in flies. *Geroscience*, 44(4):1961–1974, 2022.

[46] Divya Ramchandani, Mirela Berisa, Diamile A Tavarez, Zhuoning Li, Matthew Miele, Yang Bai, Sharrell B Lee, Yi Ban, Noah Dephoure, Ronald C Hendrickson, et al. Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis. *Nature communications*, 12(1):7311, 2021.

[47] L Peruzzotti-Jametti, CM Willis, R Hamel, G Krzak, JA Reisz, HA Prag, V Wu, Y Xiang, AMR van den Bosch, AM Nicaise, et al. Mitochondrial reverse electron transport in myeloid cells perpetuates neuroinflammation. *bioRxiv*, pages 2024–01, 2024.

[48] Peter Gawthrop. Bond graph modelling of chemiosmotic biomolecular energy transduction, 2017.

[49] Eric S Goetzman and Edward V Prochownik. The role for myc in coordinating glycolysis, oxidative phosphorylation, glutaminolysis, and fatty acid metabolism in normal and neoplastic tissues. *Frontiers in endocrinology*, 9:129, 2018.

[50] Duale Ahmed, David Roy, Allison Jaworski, Alexander Edwards, Alfonso Abizaid, Ashok Kumar, Ashkan Golshani, and Edana Cassol. Differential remodeling of the electron transport chain is required to support tlr3 and tlr4 signaling and cytokine production in macrophages. *Scientific Reports*, 9(1):18801, 2019.

[51] Vittoria Raimondi, Francesco Ciccarese, and Vincenzo Ciminale. Oncogenic pathways and the electron transport chain: a dangeros liaison. *British journal of cancer*, 122(2):168–181, 2020.

[52] Carmen de la Fuente, Derek G Burke, Simon Eaton, and Simon JR Heales. Inhibition of neuronal mitochondrial complex i or lysosomal glucocerebrosidase is associated with increased dopamine and serotonin turnover. *Neurochemistry International*, 109:94–100, 2017.

[53] Kelath Murali Manoj. Mitochondrial oxidative phosphorylation: Debunking the concepts of electron transport chain, proton pumps, chemiosmosis and rotary atp synthesis, 2017.

[54] Kaylee B Punter, Charles Chu, and Edmond YW Chan. Mitochondrial dynamics and oxidative phosphorylation as critical targets in cancer. *Endocrine-related cancer*, 30(1), 2023.

[55] Jainendra Pathak, Ananya Chatterjee, Shailendra P Singh, Rajeshwar P Sinha, et al. Detection of reactive oxygen species (ros) in cyanobacteria using the oxidant-sensing probe 2', 7'-dichlorodihydrofluorescein diacetate (dcfh-da). *Bio-protocol*, 7(17):e2545–e2545, 2017.

[56] Paolo Ettore Porporato, Nicoletta Filigheddu, José Manuel Bravo-San Pedro, Guido Kroemer, and Lorenzo Galluzzi. Mitochondrial metabolism and cancer. *Cell research*, 28(3):265–280, 2018.

[57] Wenzhang Wang, Fanpeng Zhao, Xiaopin Ma, George Perry, and Xiongwei Zhu. Mitochondria dysfunction in the pathogenesis of alzheimer's disease: recent advances. *Molecular neurodegeneration*, 15:1–22, 2020.

[58] Ana Belen Malpartida, Matthew Williamson, Derek P Narendra, Richard Wade-Martins, and Brent J Ryan. Mitochondrial dysfunction and mitophagy in parkinson's disease: from mechanism to therapy. *Trends in biochemical sciences*, 46(4):329–343, 2021.

[59] Alexis Diaz-Vegas, Søren Madsen, Kristen C Cooke, Luke Carroll, Jasmine XY Khor, Nigel Turner, Xin Y Lim, Miro A Astore, Jonathan C Morris, Anthony S Don, et al. Mitochondrial electron transport chain, ceramide, and coenzyme q are linked in a pathway that drives insulin resistance in skeletal muscle. *Elife*, 12:RP87340, 2023.

[60] Xinyu Li, Wei Zhang, Qingtai Cao, Zeyu Wang, Mingyi Zhao, Linyong Xu, and Quan Zhuang. Mitochondrial dysfunction in fibrotic diseases. *Cell death discovery*, 6(1):80, 2020.

[61] Anup Ramachandran, Ruben GJ Visschers, Luqi Duan, Jephte Y Akakpo, and Hartmut Jaeschke. Mitochondrial dysfunction as a mechanism of drug-induced hepatotoxicity: current understanding and future perspectives. *Journal of clinical and translational research*, 4(1):75, 2018.

[62] Shannon Rose, Dmitriy M Niyazov, Daniel A Rossignol, Michael Goldenthal, Stephen G Kahler, and Richard E Frye. Clinical and molecular characteristics of mitochondrial dysfunction in autism spectrum disorder. *Molecular diagnosis & therapy*, 22(5):571–593, 2018.

[63] Georgi I. Kapitanov, Bruce P. Ayati, and James A. Martin. Modeling the effect of blunt impact on mitochondrial dysfunction in cartilage, 2016.

[64] Megan S. Lord, Jean Francois Berret, Sanjay Singh, Ajayan Vinu, and Ajay S. Karakoti. Redox active cerium oxide nanoparticles: Current status and burning issues, 2021.

[65] Ummay Mowshome Jahan, Brianna Blevins, Sergiy Minko, and Vladimir Reukov. Advancing biomedical applications: Antioxidant and biocompatible cerium oxide nanoparticle-integrated poly-$\epsilon - caprolactone fibers$, 2024.

[66] Hui Yang, Qingqing Li, Xingxing Chen, Mingzhe Weng, Yakai Huang, Qiwen Chen, Xiaocen Liu, Haoyu Huang, Yanhuizhi Feng, Hanyu Zhou, et al. Targeting sox13 inhibits assembly of respiratory chain supercomplexes to overcome ferroptosis resistance in gastric cancer. *Nature Communications*, 15(1):4296, 2024.

[67] Karthigayan Shanmugasundaram, Bijaya K Nayak, William E Friedrichs, Dharam Kaushik, Ronald Rodriguez, and Karen Block. Nox4 functions as a mitochondrial energetic sensor coupling cancer metabolic reprogramming to drug resistance. *Nature communications*, 8(1):997, 2017.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.