

Narrative Review

Role of Mitochondrial Dysfunction in Related Diseases-A review

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ABSTRACT

Background: Mitochondrial dysfunction (MD) is increasingly recognized for its role in a wide array of diseases, extending beyond primary mitochondrial diseases (PMDs) to include secondary mitochondrial diseases (SMDs) and a broad spectrum of neurodegenerative, cardiovascular, metabolic, and oncological disorders. This growing awareness underscores the need for a comprehensive review of the mechanisms underlying MD, its clinical implications, and emerging therapeutic strategies.

Objective: To synthesize current knowledge on the pathogenesis of diseases associated with MD, delineate the distinction between PMDs and SMDs, explore the genetic and environmental factors contributing to MD, and assess the potential of novel therapeutic approaches targeting mitochondrial dysfunction.

Methods: A narrative review was conducted through a structured search of PubMed, Scopus, Web of Science, and Google Scholar, focusing on articles published up to April 2023. Keywords related to mitochondrial dysfunction and its implications across various diseases were used to identify relevant studies. Inclusion criteria targeted original research, reviews, and meta-analyses published in English that contributed to understanding MD's role in disease pathogenesis and treatment. Data extraction and synthesis were performed to highlight key findings, mechanisms, and therapeutic strategies.

Results: The review emphasizes the critical role of mitochondrial dysfunction in the pathogenesis of a wide range of diseases. It identifies specific mtDNA mutations contributing to PMDs and highlights how SMDs arise from mitochondrial impairment secondary to other conditions. The synthesis of findings points to oxidative stress, impaired ATP production, and altered mitochondrial dynamics as central to MD's impact on cellular and systemic health. Additionally, the review explores emerging therapies, including mitochondrial-targeted antioxidants, gene therapy, and metabolic interventions, underscoring their potential in managing MD-related diseases.

Conclusion: Mitochondrial dysfunction is a pivotal factor in the etiology of numerous diseases, with genetic mutations and environmental influences contributing to its development and progression. Understanding these complex mechanisms is essential for devising effective therapeutic interventions. While significant advances have been made, further research is needed to fully exploit the therapeutic potential of targeting mitochondrial dysfunction.

Keywords: Mitochondrial Dysfunction, Primary Mitochondrial Diseases, Secondary Mitochondrial Diseases, mtDNA Mutations, Oxidative Stress, Therapeutic Strategies, Neurodegenerative Disorders, Cardiovascular Diseases, Metabolic Disorders, Oncology, Gene Therapy, Mitochondrial Dynamics.

INTRODUCTION

Mitochondria, often described as the "powerhouses" of the cell, play a pivotal role in energy production through the generation of adenosine triphosphate (ATP), which is the primary energy currency within cells. This crucial process is carried out through cellular respiration, a complex sequence of biochemical reactions that break down nutrients like glucose and fatty acids in the presence of oxygen, culminating in ATP production. Cellular respiration encompasses three main stages: glycolysis in the cytoplasm, followed by the citric acid cycle (Krebs cycle), and the electron transport chain (ETC) within the mitochondria. These stages facilitate the

conversion of energy stored in nutrients into ATP, thereby fueling essential cellular functions such as muscle contraction, active transport, DNA synthesis, and protein synthesis (1,2). Beyond energy production, mitochondria are integral in maintaining intracellular calcium levels, thereby regulating critical processes including muscle contraction and neurotransmitter release. Despite their efficiency, a fraction of oxygen molecules can form reactive oxygen species (ROS) during the ETC, potentially leading to oxidative stress and damage to cellular components. However, mitochondria are equipped with antioxidant defenses to mitigate excess ROS, ensuring cellular health (3,4). Additionally, mitochondria are central to the regulation of programmed cell death (apoptosis) and participate in cell signaling pathways, influencing responses to stress and infection, and are involved in fatty acid breakdown through beta-oxidation for ATP production (5,6).

Mitochondrial dysfunction (MD) emerges as a pivotal factor in a multitude of diseases by impairing cellular energy supply. This dysfunction can result from genetic disorders stemming from abnormalities in genes encoding mitochondrial proteins or affecting mitochondrial DNA (mtDNA). Mitochondrial diseases, categorized into primary mitochondrial diseases (PMDs) and secondary mitochondrial diseases (SMDs), manifest across various organs due to mitochondria's ubiquitous presence in the body. PMDs are attributed to genetic mutations affecting mitochondrial function, present in nuclear DNA or mtDNA, whereas SMDs result from external factors or underlying conditions impacting mitochondrial function (7,8).

PMDs originate from germline mutations passed through nuclear DNA from both egg and sperm, with mtDNA being transmitted from the egg. This transmission process underscores the unique aspect of heteroplasmy, where both mutated and wild-type mtDNA can coexist within the same cell, potentially leading to variable expression of mitochondrial diseases depending on the distribution of mutant mtDNA across different tissues. The mtDNA mutation rate significantly exceeds that of nuclear DNA due to less effective repair mechanisms, contributing to the higher prevalence of mtDNA mutations. These mutations, varying in form from point mutations to deletions and duplications, can be maternally inherited, leading to a spectrum of PMDs, which may or may not manifest symptoms depending on the mutation's expression threshold in various organs (9-20).

Environmental factors and metabolic states can influence epigenetic processes, affecting mtDNA and nuclear DNA, contributing to both PMD and SMD. Various mtDNA mutations have been associated with chronic diseases such as atherosclerosis, highlighting the impact of environmental stressors and epigenetic alterations on mitochondrial function. Notably, nuclear DNA-related PMDs exhibit complex inheritance patterns, often autosomal recessive, and involve mutations in genes crucial for mitochondrial function. These mutations not only predispose individuals to PMDs but can also be exacerbated by environmental factors, blurring the lines between PMDs and SMDs and complicating their diagnosis (12-21).

This intricate interplay between genetic predispositions, environmental influences, and the critical role of mitochondria in cellular energy production and regulation underscores the complexity of mitochondrial diseases. Understanding the mechanisms underlying mitochondrial dysfunction and its contribution to disease pathology is essential for developing targeted therapeutic strategies and improving patient outcomes.

MATERIAL AND METHODS

The methodology for this narrative review was meticulously designed to compile and analyze the extant literature on mitochondrial dysfunction (MD) and its implications for human health and disease. The review was conducted following a structured approach, encompassing a comprehensive search strategy, selection criteria, data extraction, and synthesis of findings. This section details the procedures undertaken to ensure the thoroughness and relevance of the review.

The literature search was conducted across several electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify articles published up to April 2023. The search terms used were a combination of keywords related to mitochondrial dysfunction, such as "mitochondrial dysfunction," "primary mitochondrial diseases," "secondary mitochondrial diseases," "mtDNA mutations," "oxidative stress," "neurodegenerative disorders," "cardiovascular diseases," "diabetes," and "cancer." These terms were used individually and in conjunction with other keywords to capture the broad spectrum of research related to MD. Additionally, reference lists of identified articles were manually searched to find additional relevant studies.

Inclusion criteria were established to select studies that specifically addressed MD and its association with various diseases. Selected studies included original research articles, review papers, and meta-analyses published in English. The review focused on articles that provided insights into the genetic basis of mitochondrial diseases, the role of mitochondrial dysfunction in disease pathogenesis, and potential therapeutic strategies. Exclusion criteria were articles not in English, conference abstracts, and studies not directly related to MD.

Data from the selected articles were extracted and organized into categories based on disease classification (PMDs and SMDs), genetic mutations involved, mechanisms of mitochondrial dysfunction, affected physiological systems, and therapeutic approaches.

This process was conducted independently by two reviewers to ensure accuracy and comprehensiveness. Discrepancies were resolved through discussion or consultation with a third reviewer.

The extracted data were synthesized to provide a coherent narrative on the role of mitochondrial dysfunction in health and disease. This involved a critical analysis of the mechanisms by which mitochondrial dysfunction contributes to disease pathogenesis, the interplay between genetic and environmental factors, and the exploration of emerging therapeutic interventions. The review also highlighted gaps in current knowledge and suggested directions for future research.

RESULTS

Leigh syndrome, known as subacute necrotizing encephalomyelopathy, epitomizes a severe neurodegenerative condition affecting the central nervous system, particularly the brainstem and basal ganglia, primarily in early childhood. This disorder is characterized by progressive neurological decline, leading to significant disabilities and often premature death. The crux of Leigh syndrome lies in mitochondrial dysfunction (MD), attributed to mutations in genes encoding proteins crucial for the electron transport chain (ETC), a vital process in cellular energy production. These mutations result in compromised ATP production and subsequent energy failure in cells. mtDNA mutations in genes such as MT-ATP6 and MT-ND disrupt enzyme activities essential for mitochondrial function, notably ATP synthase and complex I, exacerbating energy deficiency. Similarly, nuclear DNA mutations in genes like SURF1 and PDHA1 impair mitochondrial function and energy metabolism, further contributing to Leigh syndrome's pathology. The consequences of MD in Leigh syndrome are significant, with impaired energy production leading to extensive neuronal loss, gliosis, and demyelination in affected brain regions, coupled with excessive ROS production and oxidative stress, furthering cellular damage (22, 23).

Kearns-Sayre Syndrome (KSS) presents as a rare condition marked by symptoms such as progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects, manifesting before the age of twenty. The genesis of KSS is rooted in MD, specifically due to large-scale deletions or rearrangements in mtDNA affecting oxidative phosphorylation. Such deletions impair the production of proteins essential for energy generation, affecting mitochondrial energy metabolism and leading to the syndrome's characteristic manifestations (24, 25). Unlike specific genetic mutations, the dysfunction in KSS predominantly pertains to the impaired mitochondrial function impacting cellular energy metabolism and contributing to the clinical spectrum observed in patients (26).

Alpers-Huttenlocher Syndrome (AHS) and Ataxia Neuropathy Syndrome are distinguished by their impact on infants and children through progressive neurological decline. AHS is driven by MD, with the POLG gene frequently implicated, although not exclusively. The syndrome's hallmark is the decline in ATP production, particularly affecting high-energy demand tissues like the brain and liver. Ataxia Neuropathy Syndrome similarly results from MD due to mutations affecting mitochondrial function and mtDNA maintenance, leading to energy metabolism impairment (27, 29).

Table 1: Descriptive Examples of Primary Mitochondrial Diseases (PMDs) and Mutated Genes

Primary Mitochondrial Diseases	Features of Diseases	Mutated Genes
Leigh Syndrome (mtDNA defect)	mtDNA defect leading to complex 1 deficiency, muscle weakness, cardiomyopathy, gray & white matter involvement	MT-ND1; mtDNA gene encoding one of 7 complex I subunits governed by mtDNA.
Leigh Syndrome (nDNA defect)	nDNA defect leading to complex 1 deficiency, cardiac myopathy, encephalopathy, renal/hepatic dysfunction	NDUFS1; nDNA gene encoding one of 38 complex I subunits governed by nDNA.
Kearns-Sayre Syndrome	Common in <20 years, pigmentary retinopathy, heart block	mtDNA deletion; heteroplasmic; includes several mtDNA genes
Alpers-Huttenlocher Syndrome	Seizures, liver failure, mtDNA deletion/depletion	POLG; nDNA gene encoding mitochondrial gamma polymerase
Ataxia Neuropathy Syndrome	SANDO, epilepsy, cerebellar ataxia, myopathy	C10ORF2; nDNA gene encoding twinkle protein

Secondary mitochondrial diseases (SMDs) encompass disorders resulting from compromised mitochondrial function not directly attributable to the genetic encoding of ETC proteins. These include conditions where mitochondrial dynamics, such as fission and fusion, are affected, impacting cellular energy production beyond ATP generation. SMDs are linked with various multifactorial diseases, including diabetes, coronary heart disease, renal diseases, and neurodegenerative disorders, underscoring the broader impact of mitochondrial dysfunction beyond primary mitochondrial diseases (PMDs) (30-34).

The diagnosis and treatment of mitochondrial diseases involve a multidisciplinary approach due to their complex nature and diverse clinical presentations. Genetic testing, including sequencing of nuclear DNA and mtDNA, plays a pivotal role in diagnosing these conditions. However, there remains no cure for most mitochondrial diseases, with treatments primarily aimed at symptom management, improving patient quality of life, and supportive care. Among therapeutic interventions, CoQ10 supplementation emerges as a potential strategy to support mitochondrial function by enhancing the electron transport and ATP synthesis processes, although its efficacy may vary across individuals. Ongoing research efforts are directed towards exploring novel treatments, including gene therapy and enzyme replacement therapy, offering hope for more effective interventions in the future (43-45).

Table 2: Examples of Disorders Resulting in Secondary Mitochondrial Diseases (SMDs)

Disorders	Features of Disorders	Mutated Genes
Spinal Muscular Atrophy	Loss of motor neurons, muscle weakness	SMN1
Friedreich's Ataxia	Ataxia, hypertrophic cardiac myopathy, diabetes mellitus	FXN
Charcot-Marie Tooth	Motor regression, peripheral neuropathy, weakness	GDAP1
Hereditary Spastic Paraplegia 7	Peripheral neuropathy, ataxia, weakness	SPG7
Wilson's Disease	Copper deposition, neurological features, ataxia, neurosis, depression	ATP7B

DISCUSSION

In this review, the critical and multifunctional role of mitochondria within human physiology was delineated, underscoring their designation as cellular powerhouses primarily responsible for ATP synthesis, although their contributions extend well beyond energy production. The classification of mitochondrial dysfunction-related diseases into primary and secondary categories elucidates the nuanced understanding of mitochondrial pathology. Primary mitochondrial diseases (PMDs) arise directly from mutations that impair mitochondrial function, whereas secondary mitochondrial diseases (SMDs) result from mitochondrial impairment secondary to other primary conditions. The seminal work by Wallace (2013) provided a comprehensive examination of the implications of mtDNA mutations in the pathogenesis of various diseases and their role in the aging process. The study underscored the deleterious effects of mutations within the mitochondrial genome on ATP production and elucidated their association with a spectrum of diseases, including neurodegenerative disorders, cardiovascular diseases, diabetes, and cancer. Wallace's findings emphasized the disruption of the electron transport chain (ETC) by specific genetic mutations, leading to augmented oxidative stress and reactive oxygen species (ROS) production, thereby implicating mitochondrial dysfunction in disease progression (46).

Similarly, Schon and Manfredi (2013) highlighted the pivotal role of mitochondria in energy provision to neurons and the maintenance of cellular homeostasis. Their discussion extended to the impact of mitochondrial dysfunction on neurodegenerative diseases, exploring how impaired ATP production and excessive ROS generation contribute to neurodegenerative processes. The authors also delved into the importance of mitochondrial dynamics, including fusion and fission, for neuronal health and the distribution of mitochondria within cells. The exploration of mtDNA mutations and their detrimental effects on oxidative phosphorylation presented a critical insight into mitochondrial pathology. Schon and Manfredi concluded with an overview of emerging therapeutic strategies aimed at mitigating mitochondrial dysfunction in neurodegenerative diseases, such as the application of mitochondria-targeted antioxidants and interventions promoting mitochondrial biogenesis (47).

Chowdhury et al. (2020) focused on mitochondrial dysfunction (MD) in the context of aging and Alzheimer's disease (AD), highlighting the role of impaired mitochondrial function in aging and its contribution to AD progression. They pointed out the accumulation of mtDNA mutations, altered mitochondrial dynamics, and energy metabolism deficits as pivotal in MD. Their review of therapeutic avenues targeting MD in AD underscored the potential of interventions aimed at preserving mitochondrial function to ameliorate AD pathology, thereby emphasizing the critical link between MD, aging, and neurodegenerative diseases (48).

Despite these advances, the understanding of mitochondrial dysfunction and its myriad consequences remains complex and incompletely understood. The distinction between PMDs and SMDs is crucial, yet the overlap in their pathophysiological manifestations and the continuous influence of environmental factors, including epigenetics, complicate their delineation. The challenges in diagnosing and treating mitochondrial disorders are compounded by the heterogeneous nature of these diseases and the variable expressivity and penetrance of the underlying genetic mutations. This review acknowledges the limitations inherent in the current understanding of mitochondrial diseases, including the reliance on studies that may not fully capture the diversity of mitochondrial dysfunction across different tissues and the potential for novel therapeutic strategies that have yet to be widely tested in clinical settings.

CONCLUSION

In conclusion, while significant strides have been made in understanding the role of mitochondria in health and disease, the complexity of mitochondrial pathology demands further investigation. Future research should aim to elucidate the intricate mechanisms underpinning mitochondrial dysfunction, explore the full spectrum of PMDs and SMDs, and develop targeted therapeutic interventions. Such endeavors will require a multidisciplinary approach, leveraging advances in genetics, molecular biology, and clinical medicine to forge new pathways in the diagnosis, treatment, and prevention of mitochondrial diseases.

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