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MITOCHONDRIAL DYSFUNCTION IN DISEASE: PATHOGENIC MECHANISMS AND NOVEL THERAPIES

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ABSTRACT

Mitochondria serve as vital cellular components with functions extending far beyond ATP generation, encompassing calcium homeostasis, oxidative balance, and programmed cell death regulation. Their malfunction contributes to a wide spectrum of disorders spanning neurological (Alzheimer's, Parkinson's), metabolic (diabetes), cardiac, liver, and cancerous conditions. Shared disease mechanisms include disrupted energy production, oxidative stress, impaired organelle dynamics, and persistent mtDNA damage. In neurological degeneration, mitochondrial impairment initiates and worsens protein aggregation pathologies, whereas in metabolic diseases it promotes insulin insensitivity and fat deposition. Malignant cells hijack mitochondrial adaptability to support growth and treatment evasion. Current therapies primarily address symptoms, though innovative approaches show potential: mitochondria-specific antioxidants (MitoQ), dynamics regulators (DRP1 blockers), mitophagy stimulators, and genetic interventions. Emerging techniques include mitochondrial transfer and nanoparticle-based delivery systems. Non-pharmacological approaches like physical activity positively influence mitochondrial performance. Critical obstacles involve enhancing drug targeting precision, reducing unintended effects, and improving clinical applicability. Future priorities should emphasize establishing robust biomarkers, creating standardized disease databases, and advancing tailored treatment protocols. Deciphering mitochondrial disease mechanisms holds revolutionary promise for managing chronic illnesses, connecting basic science with therapeutic implementation.

KEYWORDS

Mitochondria, Oxidative Stress, Mitochondrial Dynamics, Neurodegenerative Diseases, Metabolic Disorders, Cancer Therapy, Mitochondrial-Targeted Treatments, Personalized Medicine

CITATION

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Introduction

Mitochondria, commonly known as the cell's powerhouse, play a vital role in energy metabolism, redox balance, calcium signaling, and programmed cell death. In addition to these well-established functions, growing evidence highlights their participation in intricate signaling networks and the regulation of gene expression, underscoring their importance in preserving cellular stability and overall health [1], [2]. Dysfunctional mitochondria contribute to a wide array of human diseases, including genetic primary mitochondrial disorders as well as secondary mitochondrial impairments involved in cancer, neurodegenerative diseases, metabolic disorders, cardiovascular conditions, and autoimmune diseases [3], [4], [5], [6], [7], [8]. Mitochondrial diseases exhibit remarkable genetic and clinical diversity. Mutations can arise in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA), and the intricate interaction between these two genomes influences disease manifestation and progression [7], [9], [10]. The involvement of both genomes creates substantial diagnostic, prognostic, and therapeutic challenges. Although the mitochondrial genome produces just 13 polypeptides, all crucial for oxidative phosphorylation (OXPHOS), most mitochondrial proteins originate from nuclear genes, further complicating disease modeling and genetic counseling [2], [11]. Emerging epidemiological data indicate mitochondrial disorders may affect approximately 1 in 4,300 people, suggesting they are more common than once believed [12], [13]. Mitochondrial disorders are particularly severe because they affect multiple organ systems and often manifest in childhood, although adult-onset forms are being recognized more frequently [14], [15]. These disorders frequently present with myopathy, encephalopathy, cardiomyopathy, and endocrinopathies, whose symptoms overlap with those of prevalent chronic diseases, making accurate diagnosis challenging [12], [14], [16], [17]. Mitochondrial dysfunction can arise from various pathological mechanisms, including defects in OXPHOS complexes, abnormal mitochondrial dynamics (impaired fission and fusion), disrupted mitophagy, excessive reactive oxygen species production, or faulty mitochondrial biogenesis [18], [19], [20], [21]. Such impairments compromise energy

production, increase oxidative damage, and induce inflammation, collectively leading to progressive cellular and tissue deterioration [3], [4], [22]. Additionally, impaired mitochondrial function contributes to altered immune regulation and inflammasome activation, especially in neurodegenerative and autoimmune disorders [20], [23], [24], [25]. A major obstacle in treating mitochondrial diseases is the lack of specific therapies. Existing approaches mainly focus on supportive and symptomatic care, frequently using compounds like coenzyme Q10, L-carnitine, and antioxidants, though their effectiveness remains modest [5], [26], [27]. Nevertheless, emerging developments in gene therapy, mitochondrial replacement strategies, and drugs that modulate mitochondrial functions have demonstrated potential [28], [29], [30], [31]. Current research is actively exploring novel treatments designed to boost mitochondrial biogenesis, regulate mitochondrial dynamics, and repair mtDNA defects through ongoing clinical trials [29], [32], [33], [34]. The development of mitochondrial disease registries has been crucial for progress in both clinical care and research. These repositories systematically gather standardized clinical and genetic data, aiding long-term studies and improving clinical trial planning [7], [35]. Existing mitochondrial disease registries differ in their organization, data reliability, and availability, underscoring the necessity for standardization and global cooperation to maximize their effectiveness [7], [35], [36]. This thesis investigates mitochondrial dysfunction in specific disease models, examines its molecular basis, and assesses novel therapeutic strategies. Combining fundamental research, clinical findings, and translational approaches, the study offers a thorough analysis of current knowledge and outlines future perspectives for treating mitochondrial disorders

Material and methods

We performed an extensive literature review through PubMed and Google Scholar to examine studies investigating mitochondrial dysfunction's involvement in disease development, clinical presentation, and treatment. Our search incorporated key terms including: mitochondrial dysfunction, oxidative phosphorylation, mtDNA mutations, mitochondrial dynamics, bioenergetics, metabolic disorders, neurodegeneration, cardiomyopathy, mitophagy, reactive oxygen species, mitochondrial-targeted therapy, gene therapy, and mitochondrial transplantation. The analysis was restricted to English-language, open-access peer-reviewed publications from 2005 to 2025. We evaluated both observational and experimental studies, prioritizing mechanistic investigations, clinical trials, and systematic reviews. This methodology allowed for a thorough assessment of current knowledge regarding mitochondrial dysfunction's molecular basis and the analysis of novel mitochondria-focused treatments for diverse diseases.

Structure and Functions of Mitochondria

Mitochondria are organelles enclosed by two membranes that serve as crucial regulators of cellular energy production and metabolic balance. Their primary known role involves generating adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), a process facilitated by the electron transport chain (ETC) located within the inner mitochondrial membrane [7], [8], In addition to ATP synthesis, mitochondria control various cellular processes such as calcium signaling, reactive oxygen species production, programmed cell death, and immune system activation [8], [14], [18]. [9]. Mitochondria contain four distinct structural components: the outer mitochondrial membrane (OMM), intermembrane space, inner mitochondrial membrane (IMM), and matrix. The IMM forms characteristic cristae folds that expand its surface area to enhance metabolic activity [2], [15]. Mitochondria contain circular mitochondrial DNA (mtDNA) that encodes critical subunits of the electron transport chain, while the majority of mitochondrial proteins are nuclear-encoded and transported into the organelle after translation [2], [9]. Reactive oxygen species (ROS), natural byproducts of electron transport, function as signaling mediators at normal levels but promote oxidative damage when excessively accumulated [5], [13]. Mitochondria exhibit constant structural remodeling through fission and fusion events, regulated by key proteins like DRP1, MFN1/2, and OPA1, which maintain proper organelle distribution, quality assurance, and functional responsiveness to cellular demands [10], [17]. Impairment of these dynamic processes may result in the buildup of defective mitochondria and has been associated with neurodegenerative disorders, cardiovascular conditions, and metabolic pathologies [10], [14], [33]. Mitophagy, a specialized autophagic process, facilitates the removal of impaired mitochondria, thereby inhibiting the release of inflammatory mediators and cell death signals [7], [12], [21]. Impaired mitophagy contributes to elevated cellular stress and persistent inflammation in various disorders, particularly Parkinson's and Alzheimer's diseases [10], [12], [16]. Mitochondria also significantly contribute to immune system modulation. Their constituents, including mtDNA and N-formyl peptides, function as damage-associated molecular patterns (DAMPs) that trigger innate immune responses through pathways such as TLR9 and the

NLRP3 inflammasome [19], [24], [25]. In summary, mitochondria serve as master regulators that extend beyond energy production to critically influence cell survival, inflammatory responses, and cellular signaling. A thorough comprehension of their architecture and biological roles is fundamental for investigating their involvement in diverse disease mechanisms.

Mechanisms of Mitochondrial Dysfunction in Diseases

Mitochondria are vital organelles that sustain cellular energy balance primarily through oxidative phosphorylation-mediated ATP synthesis, while also controlling metabolic processes, ROS production, programmed cell death, and signal transduction. The growing understanding of mitochondrial dysfunction – characterized by compromised organelle activity – reveals its significant role in the development of diverse chronic and neurodegenerative disorders [2], [7], [8], [9]. A major pathway of mitochondrial dysfunction stems from impaired electron transport chain (ETC) complexes, resulting in diminished oxidative phosphorylation efficiency and subsequent ATP production deficits. These energy impairments prove especially damaging in highly metabolic tissues including skeletal muscle, nervous tissue, and cardiac muscle [2], [6], [28]. Disruptions in ETC function additionally drive overproduction of reactive oxygen species, causing oxidative injury to mitochondrial components including proteins, lipids, and mtDNA, creating a self-perpetuating cycle that worsens mitochondrial deterioration [5], [20], [37]. Elevated ROS levels induce oxidative stress, marked by disproportionate reactive oxygen species production relative to antioxidant protection. This mitochondrial oxidative stress severely damages mtDNA, which is particularly vulnerable because of its close location to the ETC and insufficient DNA repair capacity. The buildup of mtDNA mutations and oxidative damage worsens mitochondrial dysfunction, significantly contributing to disease development in conditions like diabetes, neurodegenerative diseases, and cardiovascular pathologies [5], [9], [19], [20], [38]. Mitochondrial fission and fusion processes are essential for preserving mitochondrial health and activity. These dynamic mechanisms facilitate the sharing of mitochondrial contents, isolation of impaired components, and control of mitochondrial degradation through mitophagy. When disrupted, they lead to abnormal mitochondrial morphology (either excessive fragmentation or fusion), compromised quality control, and buildup of defective organelles. Such disturbances in mitochondrial dynamics contribute significantly to multiple neurodegenerative and metabolic disorders [7], [10], [12], [21]. A key feature of mitochondrial dysfunction involves the progressive accumulation of mtDNA mutations and deletions. Unlike nuclear DNA, mtDNA is present in numerous copies per cell and follows maternal inheritance patterns. These mtDNA mutations interfere with the production of mitochondrial-encoded ETC subunits, resulting in compromised respiratory chain activity. The heteroplasmic distribution of mtDNA mutations accounts for variations in clinical manifestation and tissue-specific pathology, significantly influencing both classical mitochondrial disorders and age-associated conditions [4], [9], [35]. Additionally, impaired mitochondria may discharge damage-associated molecular patterns (DAMPs), such as mtDNA segments, into the cytosol or extracellular environment. These mitochondrial-derived DAMPs activate innate immunity pathways, fostering persistent inflammation characteristic of autoimmune disorders, inflammatory conditions, neurodegenerative diseases, and metabolic dysregulation [19], [24], [25]. To summarize, mitochondrial dysfunction results from multiple interconnected mechanisms including deficient energy generation, oxidative damage, disrupted organelle dynamics, mtDNA defects, and inflammatory signaling. Together, these pathological processes contribute fundamentally to the development of numerous chronic and neurodegenerative disorders, positioning mitochondria as a key focus for novel treatment approaches.

Mitochondrial Dysfunction in Alzheimer's Disease

Mitochondrial dysfunction has been identified as a fundamental and early pathological feature in Alzheimer's disease (AD), intricately linked with amyloid β (Aβ) deposition, tau abnormalities, oxidative damage, and energy failure. Even during preclinical stages, neurons in susceptible brain areas like the hippocampus and cortex exhibit compromised mitochondrial function, characterized by decreased complexes I and IV activity in the electron transport chain, leading to both ATP deficiency and elevated ROS production [9], [39], [40], [41], [42], [43]. This bioenergetic impairment both disrupts synaptic activity and exacerbates oxidative injury to cellular components including lipids, proteins, and mtDNA, establishing a self-reinforcing cycle of cellular damage [39], [44]. Oligomeric Aβ species enter mitochondria through outer membrane translocases, where they bind critical proteins including ABAD and cyclophilin D, inducing permeability transition pore formation and loss of membrane potential. These events lead to cytochrome c release, activation of apoptosis, and additional ROS generation [45]. Simultaneously, Aβ disrupts axonal mitochondrial

trafficking and alters fission-fusion equilibrium, producing abnormally fragmented organelles with compromised functionality [9], [40], [41], [43], [45], [46]. Hyperphosphorylated tau plays an equally vital role by impairing microtubule stability, which hinders mitochondrial transport to synapses and worsens localized energy shortages. Additionally, tau abnormalities dysregulate mitochondrial dynamics, promoting excessive fission while reducing fusion, thereby decreasing membrane potential and increasing ROS generation - collectively accelerating neurodegeneration [39], [40], [45]. In AD, the critical quality control process of mitophagy becomes impaired. Under physiological conditions, the PINK1/Parkin pathway ensures selective removal of defective mitochondria, but in AD this clearance mechanism fails, resulting in accumulated damaged organelles, persistent oxidative stress, and progressive synaptic dysfunction [39], [40], [41], [43], [44], [45]. Both Aβ and tau pathologies correlate with decreased levels or function of mitophagy-associated proteins, demonstrating the connection between protein homeostasis and mitochondrial clearance. Additionally, AD brains exhibit progressive mtDNA damage through somatic mutations, deletions, and deficient repair systems, which compromise mtDNA stability. This reduces production of mitochondrial-encoded ETC subunits and worsens energy deficits [9], [39], [40], [42], [43], [44], [45], [46], [47], [48]. Such genetic deterioration supports the mitochondrial cascade hypothesis, suggesting mitochondrial dysfunction may occur early and actively drive the development of both Aβ and tau pathologies [9]. Mitochondria emerge not as passive observers but as active instigators in AD pathogenesis. Their pivotal involvement orchestrates multiple pathological processes - from impaired glucose utilization and calcium imbalance to neuroinflammation and synaptic dysfunction - directly connecting energy failure to characteristic neurodegenerative changes [43]. With mitochondria identified as potential treatment targets, investigators have developed approaches to improve mitochondrial function. While conventional antioxidants (vitamins E/C) demonstrate variable effectiveness, mitochondria-specific compounds like MitoQ and SS-31 show more promise in experimental studies by reducing oxidative damage, maintaining ETC activity, and protecting membrane stability [41], [42], [44]. Pharmacological activation of PINK1/Parkin-mediated mitophagy or stimulation of mitochondrial biogenesis through PGC-1α upregulation has demonstrated potential for improving mitochondrial quality control in experimental models [41], [42], [45]. Non-pharmacological approaches including regular aerobic activity, dietary restriction, and antioxidant supplementation have shown efficacy in boosting mitochondrial performance, lowering oxidative damage, and enhancing cognitive function in both animal studies and limited human trials [41], [44], [45]. Current mitochondrial-targeted therapeutic approaches highlight the importance of precision medicine—considering individual metabolic characteristics, sex differences, and genetic factors like APOE ε4 status—along with cell-specific strategies due to varying metabolic demands between neurons and glial cells [42]. Although most mitochondria-focused treatments haven't yet achieved clinical breakthroughs, combining mitochondrial repair approaches with anti-amyloid/tau agents, metabolic interventions, and anti-inflammatory drugs presents a potentially effective multipronged approach to slow AD progression. The interplay of energy deficits, oxidative damage, abnormal organelle dynamics, defective mitophagy, and mtDNA deterioration establishes mitochondria as central players in Alzheimer's pathology. Understanding these mechanisms provides both fundamental knowledge about disease processes and numerous opportunities for developing novel therapies that enhance mitochondrial function and modify disease course.

Mitochondrial Dysfunction in Metabolic and Cardiovascular Diseases

Mitochondrial impairment is fundamentally involved in the development of various metabolic and cardiovascular diseases, particularly type 2 diabetes (T2D), dyslipidemia, atherosclerosis, and cardiac dysfunction. These conditions are interconnected through common pathological pathways involving oxidative damage, disrupted energy production, and persistent low-grade inflammation, all originating from mitochondrial disturbances. Specifically in T2D, mitochondrial dysfunction simultaneously drives both peripheral insulin resistance and pancreatic β-cell dysfunction. Within muscle tissue, diminished mitochondrial oxidative function reduces fatty acid metabolism, leading to lipid buildup within muscle cells and worsening insulin sensitivity [26], [29]. Mitochondria control glucose-dependent insulin secretion in pancreatic β-cells through ATP production. Impaired mitochondrial activity results in insufficient insulin output, promoting elevated blood glucose levels [3], [16]. Mitochondrial dysfunction also contributes to diabetes-related complications including kidney disease and heart muscle damage. Excessive mitochondrial ROS generation worsens oxidative damage and harms mtDNA, creating a cycle of progressive functional decline [49]. Excessive mitochondrial fragmentation coupled with impaired mitophagy results in the buildup of defective organelles, worsening metabolic dysfunction [11]. Mitochondrial impairment plays a key role in dyslipidemia

and atherosclerotic plaque development by inducing vascular inflammation. The transformation of macrophages into foam cells is facilitated by oxLDL-induced mitochondrial damage in both macrophages and endothelial cells, triggering the secretion of inflammatory mediators [49], [50]. Impaired mitochondrial fatty acid β-oxidation contributes to lipid deposition within arterial walls and exacerbates systemic lipid abnormalities [51]. Mitochondrial dysfunction serves as a central pathological mechanism in heart failure. Cardiac deterioration is characterized by diminished ATP production, elevated ROS generation, and defective calcium regulation - all indicative of compromised mitochondrial function [28], [33]. Alterations in mitochondrial biogenesis, fission-fusion balance, and autophagic clearance collectively drive the gradual decline in cardiac muscle cell performance [16], [23]. Emerging therapeutic approaches focus on improving mitochondrial quality control and energy metabolism. Compounds including mitochondria-targeted antioxidants (like MitoQ) and regulators of fission-fusion dynamics (such as DRP1 inhibitors) demonstrate potential for enhancing mitochondrial performance and slowing pathological progression [1]. Lifestyle interventions like physical activity and dietary restriction improve mitochondrial function and stimulate biogenesis, providing non-drug approaches with whole-body metabolic advantages [21]. Mitochondrial dysfunction emerges as a unifying feature across metabolic and cardiovascular diseases, revealing its foundational pathological importance. Developing interventions to address these mitochondrial defects may create a shared therapeutic platform for managing diverse chronic conditions.

Mitochondrial Dysfunction in Liver Diseases

Mitochondria serve as vital metabolic hubs in hepatocytes, orchestrating not only energy production but also lipid metabolism, ammonia detoxification, oxidative stress management, and cell death/inflammation signaling. Impairments in these multifaceted functions play a fundamental role in developing liver pathologies such as NAFLD, NASH, ALD, and HCC [37], [52]. Mitochondrial impairment develops early in NAFLD pathogenesis and is closely associated with liver fat accumulation. When hepatocytes experience lipid overload, mitochondrial fatty acid breakdown capacity is exceeded, resulting in partial oxidation and elevated ROS production. This oxidative damage affects mtDNA and mitochondrial proteins, reduces ATP synthesis, and triggers stress pathways. During progression to NASH, structural changes occur - including enhanced fission, reduced fusion, and faulty mitophagy - which sustain oxidative damage, promote cell death, and drive inflammatory responses [24], [37]. Mitochondrial dysfunction further compromises hepatic lipid metabolism. Under physiological conditions, PPARα and AMPK maintain fatty acid oxidation, but their reduced activity in liver disease worsens lipid buildup. This lipotoxic environment sustains mitochondrial damage, creating a self-amplifying cycle of metabolic dysfunction [53]. Mitochondria also play pivotal roles in driving inflammatory responses and cellular demise. When impaired, they release mtDNA and cardiolipin into the cytoplasm, activating TLR-mediated pathways and inflammasomes. This inflammation recruits additional immune cells, exacerbating hepatic injury. Concurrently, prolonged calcium overload and permeability transition pore opening induce hepatocyte apoptosis and necrosis - key pathological mechanisms in both NASH and ALD progression [24], [52]. In alcoholic liver disease, ethanol metabolism similarly leads to excessive ROS and reduced mitochondrial antioxidant capacity. Prolonged alcohol consumption disrupts mitochondrial protein transport, weakens energy production, and causes organelle swelling along with mtDNA loss, culminating in hepatocyte destruction. These effects combine with inflammatory and fibrotic responses to worsen liver damage [24]. Hepatocellular carcinoma develops from chronic mitochondrial dysfunction, with tumor cells displaying distinct mitochondrial adaptations. These include shifted dynamics favoring fragmentation, metabolic reprogramming to aerobic glycolysis for survival in low-oxygen conditions, and evasion of quality control mechanisms like mitophagy and apoptosis - all enabling tumor growth and treatment resistance [20]. Understanding mitochondria's central role in liver disease pathogenesis reveals novel treatment possibilities. Current investigations explore approaches to boost mitochondrial regeneration, improve damaged organelle clearance, reactivate AMPK/PPARα signaling, and reduce oxidative stress. Innovative methods like mitochondrial transfer or precision delivery of mtDNA repair tools show potential, though still in preliminary research phases [52], [53]. Mitochondria serve as more than just power generators in liver cells - they are master regulators of cellular health and destiny. Their malfunction both triggers and exacerbates metabolic disturbances, inflammatory responses, and cancerous transformations in the liver, establishing them as essential therapeutic targets for chronic liver conditions.

Mitochondrial Dysfunction in Cancer

Mitochondria significantly contribute to cancer initiation and advancement by modulating energy metabolism, oxidative stress responses, apoptosis control, and metabolic communication. Their dysregulation has become recognized as a fundamental characteristic of cancer, affecting virtually all stages of tumor development. At the molecular level, mitochondrial abnormalities facilitate cancerous changes by controlling energy metabolism, biomolecule production, and cell death evasion. Additionally, ROS generation, mtDNA defects, and altered organelle dynamics enhance cancerous features and drive genetic instability [7]. Cancer-associated mtDNA mutations frequently disrupt electron transport chain activity, causing elevated ROS levels and metabolic adaptation. Such changes promote tumor cell viability in low-oxygen environments, affect competitive cellular selection, and regulate cancer advancement [10]. Mitochondria act as key regulators of apoptosis, controlling cell death pathways through membrane potential changes and cytochrome c release. Malignant cells often acquire strategies to bypass this apoptotic control, enhancing their ability to resist treatments [17]. Mitochondria additionally regulate cell cycle progression and cellular senescence, directly linking their impairment to cancer development [18]. Cancer cells characteristically rewire mitochondrial metabolism to support biosynthetic demands. Although the Warburg effect demonstrates preferential glycolysis, numerous malignancies maintain active mitochondria that utilize OXPHOS for both energy generation and biomolecule synthesis [13]. Mitochondria undergo dynamic adaptation to meet the metabolic and anabolic requirements of cancer cells. Certain malignancies, especially those with stem-like properties, develop dependence on oxidative phosphorylation ("OXPHOS addiction"), making them vulnerable to mitochondrial-targeting drugs [19]. Metabolic adaptations in mitochondria further enhance cancer cell resilience to treatments and stress conditions, especially in hypoxic tumor regions with limited blood supply [15]. Increased mitochondrial biogenesis or modified TCA cycle activity can promote cancer cell resistance to both chemotherapeutic agents and radiation treatment [6]. Mitochondria participate directly in cancer-related signaling, particularly through ROS generation that functions as a secondary messenger to activate key pathways including MAPK, NF-κB, and PI3K/AKT [14]. Mitochondria-derived reactive oxygen species maintain HIF-1α stability, promoting blood vessel formation, glycolytic metabolism, and cancer spread, especially in oxygen-deprived tumors [30]. Additionally, mitochondrial metabolites such as succinate and fumarate can suppress prolyl hydroxylases, enhancing HIF-1α stabilization and promoting the pseudohypoxic condition seen in numerous cancers. Mitochondria also influence the PI3K/AKT/mTOR pathway via energy-sensing mechanisms and AMPK-mediated feedback loops, aiding tumor proliferation and metabolic adaptation [28]. Due to their critical role in cancer biology, mitochondria have become promising therapeutic targets. Approaches involve impairing mitochondrial respiration, increasing mitochondrial ROS, or activating mitochondrial-dependent apoptosis. Complex I inhibitors, like metformin, have demonstrated potential in preclinical and clinical research [54]. Alternative strategies seek to disrupt mitochondrial metabolism specifically in cancer cells by inhibiting enzymes critical for glutaminolysis, fatty acid oxidation, or redox balance [51]. Researchers are also investigating mitophagy—the targeted removal of dysfunctional mitochondria—as a potential treatment strategy. Controlling mitophagy through drugs could enhance tumor sensitivity to chemotherapy or reduce the buildup of mitochondria that promote cancer cell survival [49]. A more comprehensive approach integrates mitochondrial-directed treatments with standard therapies to improve effectiveness and counteract drug resistance [9]. Mitochondrial impairment further promotes metastasis and therapy resistance. During epithelial-mesenchymal transition (EMT), tumor cells exhibit increased mitochondrial adaptability, facilitating survival in varied microenvironments and colonization of distant sites [5]. Additionally, changes in mitochondrial dynamics and redox signaling enhance the survival of circulating tumor cells and support metastatic spread. Resistance to therapy is further driven by mitochondrial-based detoxification mechanisms, shifts in apoptotic sensitivity, and metabolic reprogramming [12]. Notably, mitochondria also play a role in immunotherapy response. Cancer cells with impaired mitochondrial function or modified ROS production might avoid immune surveillance or inhibit T-cell function [11]. Emerging research is identifying new mitochondrial roles and clinically significant biomarkers. Multi-omics approaches have uncovered distinct mitochondrial profiles that could predict outcomes or direct tailored treatments [16]. Investigational compounds directed at mitochondrial DNA repair, metabolic pathways, or biogenesis are currently being explored. Additionally, innovative diagnostic and treatment methods, including mitochondrial-specific imaging probes and nanoparticle-based drug delivery systems, are enhancing the clinical applications of mitochondrial-targeted cancer therapies [53]. Future research will focus on elucidating the relationship between mitochondrial dynamics and the tumor microenvironment, while incorporating mitochondrial-directed treatments into combination therapy approaches [24]. In summary, mitochondria play a crucial role

not just in cancer cell metabolism and survival, but also in driving oncogenic signaling, treatment resistance, and metastatic capacity. Addressing mitochondrial dysfunction represents a significant opportunity for developing advanced cancer treatments, with current research revealing novel approaches for therapeutic implementation.

Therapeutic Strategies Targeting Mitochondria and Future Directions

Mitochondria have become attractive therapeutic targets owing to their critical involvement in cellular metabolism, redox regulation, programmed cell death, and immune modulation. This has led to the creation of treatments targeting mitochondrial abnormalities, especially in cancer and chronic conditions. One strategy employs pharmacological agents, including electron transport chain inhibitors. Complex I blockers have demonstrated promising antitumor activity by disrupting oxidative phosphorylation and creating energy deficits in cancer cells [54]. Other approaches focus on metabolic interventions that impair glutamine metabolism, fatty acid breakdown, or mitochondrial generation, aiming to specifically disrupt cancer cells' adaptive metabolic capabilities [51]. Reactive oxygen species (ROS) exhibit a dual function—while elevated mitochondrial ROS levels can drive disease progression, they may also be exploited to trigger programmed cell death in specific cancers, rendering both antioxidant and pro-oxidant compounds potentially valuable for treatment [9]. Mitochondria also play a significant role in critical cancer-related signaling pathways. Their control over HIF-1α and mTOR, which mediate cellular responses to hypoxia and nutrient deprivation, positions them as strategic targets for therapy. Through altering mitochondrial function and reactive oxygen species generation, these pathways can be adjusted to suppress cancer growth [30]. Mitochondria also play a role in immune system recognition and response, impacting the effectiveness of immunotherapies including checkpoint blockade. Their metabolic condition influences T-cell activation and longevity, making them a key factor in determining immunotherapy outcomes [11]. An additional promising approach focuses on regulating mitophagy – the targeted removal of defective mitochondria. Activating mitophagy mechanisms like PINK1/Parkin or BNIP3/NIX can reduce the buildup of malfunctioning organelles, especially in neurodegenerative diseases and cancer, where defective mitophagy drives pathology [49]. Similarly, mutations in mitochondrial DNA—which impair oxidative phosphorylation and drive cancer development or degenerative conditions—have emerged as focal points for genetic interventions. Although editing mitochondrial genes presents technical difficulties, progress with tools such as DddA-based cytosine base editors and mitochondria-specific zinc-finger nucleases provides potential strategies for repairing disease-causing mtDNA variants [10], [24], [55]. Cutting-edge advances have significantly broadened treatment possibilities. Nanoscale delivery systems now allow direct mitochondrial drug targeting through specialized peptides or engineered nanoparticles capable of traversing both mitochondrial membranes and releasing therapeutics with precise localization. This approach enhances treatment effectiveness while reducing systemic side effects, currently being studied in both oncological and neurodegeneration research [33]. Emerging cell-based treatments now include mitochondrial approaches, particularly mitochondrial replacement or transfer methods designed to revive metabolic function in damaged tissues through the introduction of healthy donor mitochondria. While still in experimental stages, these techniques are under investigation for conditions including cardiac ischemia, traumatic brain injury, and mitochondrial muscle disorders [4]. Progress in diagnostic tools and biomarker identification has accelerated the development of mitochondrial-focused precision medicine. Novel mitochondrial biomarkers, including distinct mtDNA mutations or metabolic profiles, now enable prediction of disease susceptibility and treatment efficacy, facilitating tailored therapeutic approaches [16]. Innovative approaches such as single-cell metabolic profiling and precise oxygen consumption measurements allow comprehensive mitochondrial characterization, and extracellular mtDNA shows promise as a minimally invasive biomarker [3], [32]. Mitochondrial impairment extends beyond cancer, serving as a key factor in neurodegenerative and metabolic conditions. In disorders like Alzheimer's and Parkinson's disease, faulty mitochondrial processes, impaired mitochondrial recycling, and persistent oxidative damage drive neuronal deterioration. Likewise, in metabolic disorders including type 2 diabetes and obesity, defective mitochondria promote insulin insensitivity, fat buildup, and chronic inflammatory responses [6], [18]. Consequently, approaches first designed for cancer treatment are being adapted to address mitochondrial dysfunction in these disorders. Novel technologies also offer potential to revolutionize mitochondrial therapies. Creating artificial mitochondria, mitochondrial mimics, or synthetic vesicles capable of performing mitochondrial functions could eventually enable replacement of severely impaired organelles. Mitochondrial engineering techniques that modify cellular metabolism or repair mtDNA defects are emerging as promising future treatments [12], [56]. These advanced approaches represent a significant transition, from managing

symptoms to addressing core organelle dysfunction through repair and regeneration. While mitochondrial medicine progresses, it must overcome key obstacles such as delivery limitations, safety considerations, and ethical implications, especially regarding heritable mtDNA modifications. However, deepening insights into mitochondrial mechanisms, combined with technological advances, establish mitochondria as central targets for innovative treatments spanning diverse medical fields.

Conclusions

Mitochondrial impairment has emerged as a key contributor to diverse human pathologies, spanning neurodegenerative conditions, metabolic disturbances, cardiovascular ailments, hepatic disorders, and malignancies. This review underscores mitochondria's pivotal roles in cellular energy metabolism, redox regulation, and signaling networks, while detailing how their dysregulation drives disease progression. The intricate relationship between nuclear and mitochondrial DNA, combined with disruptions in oxidative phosphorylation, organelle dynamics, quality control mechanisms, and ROS production, explains the varied clinical manifestations of mitochondrial diseases. In neurodegenerative pathologies like Alzheimer's disease, mitochondrial deficits occur early and amplify characteristic features including amyloid-β deposition and tau pathology. Bioenergetic collapse, oxidative damage, and impaired mitochondrial clearance mechanisms lead to synaptic failure and neuronal degeneration, establishing mitochondria as prime therapeutic targets. Experimental approaches such as mitochondrial-targeted antioxidants, mitophagy enhancers, and behavioral modifications show encouraging results in animal studies, though human applications prove more complex. Metabolic and cardiovascular disorders similarly stem from mitochondrial failure, where diminished oxidative capacity, lipid overload, and persistent inflammatory signaling drive insulin dysfunction, diabetes-related tissue damage, and cardiac impairment. Investigational treatments focusing on mitochondrial generation, dynamics regulation, and oxidative stress mitigation are underway, with compounds like MitoQ and dynamics modulators showing preliminary efficacy. Hepatic conditions including NAFLD, ALD, and HCC progress through mitochondrial-mediated pathways involving fat-induced toxicity, oxidative injury, and defective organelle recycling. Pharmacological and genetic strategies to revive mitochondrial performance may provide innovative treatments for liver diseases. Cancer cells strategically manipulate mitochondrial adaptability to meet energy needs, evade cell death, and survive challenging conditions. mtDNA alterations, metabolic shifts, and redox signaling promote tumor development, spread, and treatment resistance. Emerging anticancer approaches seek to exploit mitochondrial vulnerabilities through ETC disruption and metabolic pathway inhibition. The field of mitochondrial medicine is advancing rapidly, with gene editing technologies, organelle transfer techniques, and targeted delivery systems opening new therapeutic possibilities. Persistent challenges include optimizing drug specificity, minimizing side effects, and developing individualized treatment protocols. Ultimately, mitochondria serve as critical hubs in disease pathways, offering valuable targets for mechanistic understanding and therapeutic innovation. Future efforts should focus on standardizing disease classification systems, improving targeted interventions, and employing comprehensive omics analyses to identify biomarkers and refine treatments. Integrating fundamental discoveries with clinical applications will advance interventions capable of restoring mitochondrial health across multiple disease states.

Disclosure

Author's contribution

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