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The Consequences of Mitochondrial DNA Mutation on Neurodegenerative Diseases

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Abstract:

Mitochondrial DNA (mtDNA) mutations have been more and more embraced as key determinants in the pathogenesis of a range of neurodegenerative disorders, most notably Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS). Situated close to the electron transport chain, without the protection of histones, and with lower potential for repair, mtDNA is more susceptible to mutation than nuclear DNA. These mtDNA mutations, like large-scale deletions and point mutations, undermine oxidative phosphorylation by compromising the electron transport chain, reducing ATP generation and augmenting ROS production. The consequent energy deficit and oxidative stress severely deteriorate neuronal function and viability. In addition, mtDNA mutations negatively affect mitochondrial dynamics—deteriorating the delicate equilibrium of fission and fusion—and impair mitophagy, the critical process for the removal of defective mitochondria. These dysfunctions also sustain a vicious cycle of mitochondrial stress, leading to apoptotic cell death and the release of mitochondrial DAMPs (damage-associated molecular patterns) that trigger chronic neuroinflammation through pathways like NLRP3 inflammasome and cGAS-STING. This review integrates robust experimental and clinical evidence that connects mtDNA alterations with underlying neurodegenerative mechanisms and emphasizes the importance of addressing mitochondrial health in therapeutic strategies. Promising advances such as the use of mitochondrial antioxidants (e.g., MitoQ, CoQ10), new gene editing technologies (e.g., mitoTALENs, CRISPR), and mitophagy-inducing therapies offer a window of opportunity for the development of effective, disease-modifying therapies. With the prevalence of neurodegenerative diseases still increasing, an improved understanding of mtDNA-mediated mitochondrial dysfunction has the potential to revolutionize early diagnosis, prognosis, and therapeutic intervention in these disabling disorders.

Keywords: Mitochondrial DNA, Neurodegeneration, Oxidative Phosphorylation, Reactive Oxygen Species, Mitophagy, Neuroinflammation.

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1. INTRODUCTION

Mitochondria play a central role in cellular energy balance, especially in energy-demanding metabolic tissues such as the brain [1]. The rest of the organelles lack an immediate genome because mitochondria have their own genetic information mtDNA —containing genes that code essential proteins responsible for oxidative phosphorylation (OXPHOS), a process for ATP production [2]. This unique circular DNA is highly susceptible to mutations due to its sensitivity to reactive oxygen species (ROS), lack of protective histones, and limited repair pathways. These mutations can disrupt the integrity and function of the electron transport chain, which would compromise ATP production and increase oxidative stress. Therefore, neurons that rely on mitochondrial energy for synaptic transmission and survival are particularly vulnerable to mitochondrial dysfunction [3].

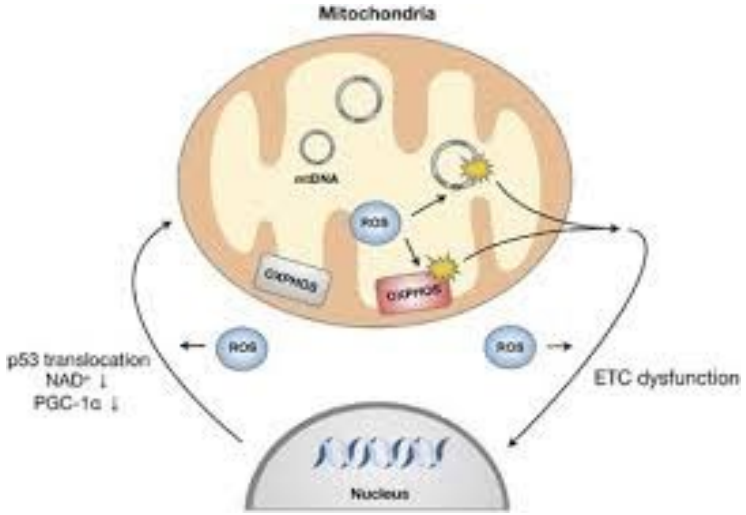

Figure 1: Mitochondrial Dysfunction and ROS Generation Pathway [4]

Recent advances in neuropathology and neurogenetics have conclusively implicated mtDNA mutations in a spectrum of neurodegenerative diseases. AD, PD, HD, and ALS all exhibit typical features of mitochondrial dysfunction, including impaired bioenergetics, increased ROS production, and dysregulated mitochondrial dynamics. In the majority of cases, mtDNA deletions or point mutations are accountable for triggering and sustaining neuronal degeneration. Exploring these correlations provides valuable insight into the mechanistic underpinning of these diseases as well as potentially creates new avenues for therapy to treat mitochondrial stability and function [5].

1.1. Background and Context

Mitochondria are essential organelles that supply energy to the cell via oxidative phosphorylation (OXPHOS), a process that is dependent on the intact function of the mtDNA. While nuclear DNA is a huge, linear genome, mtDNA is a small, circular genome that includes genes for 13 significant

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proteins of the electron transfer chain, together with 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs) for mitochondrial protein synthesis [6]. This mtDNA plays a vital role in sustaining neuronal energy metabolism and cellular homeostasis. Neurons, with their great metabolic demands and reliance on mitochondrial ATP production, are particularly sensitive to mitochondrial dysfunction. Even minimal mutations or deletions in mtDNA can disrupt ATP production and enhance reactive oxygen species (ROS) production, leading to oxidative stress, calcium dysregulation, and eventual neuronal apoptosis. In addition, mtDNA is more susceptible to damage than nuclear DNA due to its close proximity to the electron transfer chain, absence of protective histones, and restricted repair capabilities. Such mtDNA mutations are maternally inherited or accumulate with age and increasingly blamed for the etiology of several neurodegenerative disorders [7].

1.2. Objectives of the Review

The main aim of this review is to thoroughly review the effects of mtDNA mutations in the etiology of neurodegenerative disorders. The review emphasizes:

- To examine how mtDNA mutations lead to mitochondrial dysfunction in neurons [8].
- To explore the role of mtDNA alterations in Alzheimer's, Parkinson's, Huntington's disease, and ALS.
- To discuss the impact of mtDNA mutations on bioenergetics, oxidative stress, and mitochondrial dynamics.
- To evaluate current and emerging diagnostic and therapeutic strategies targeting mitochondrial dysfunction.

1.3. Importance of the Topic

The worldwide increase of neurodegenerative disorders, especially in elderly populations, constitutes a mounting problem for health care systems, since today's treatments primarily intervene to suppress symptoms but not disease evolution [9]. The comprehension of mtDNA mutations in the molecular basis of such diseases provides a hopeful avenue toward early diagnosis, increased understanding of disease mechanisms, and targeted therapy. Because mitochondrial dysfunction is a shared etiology across so many neurodegenerative diseases, discovering how mtDNA mutations propel cellular decline is of scientific significance and clinical relevance. Progress in mitochondrial genetics and therapeutics promises to revolutionize treatment strategies, providing hope for interventions that can alter disease course and improve patient quality of life [10].

2. mtDNA MUTATIONS IN NEURODEGENERATIVE DISEASES

mtDNA is vital in neuronal function since it encodes for the major components of the oxidative phosphorylation system critical in the production of ATP. In neurodegenerative conditions like Alzheimer's, Parkinson's, Huntington's, and ALS, mtDNA deletions

and mutations compromise mitochondrial function, resulting in energy deficiency, production of excessive reactive oxygen species (ROS), and neuronal degeneration. In Alzheimer's, mtDNA deletions inhibit cytochrome c oxidase function, whereas in Parkinson's, mtDNA and nuclear gene mutation-induced complex I deficiency inhibits mitophagy. HD demonstrates secondary mtDNA damage that synergizes with nuclear HTT mutations [11]. In ALS, mitochondrial fragmentation and impaired ETC activity resulting from mtDNA mutations and oxidative stress are responsible for motor neuron degeneration. Together, these disorders demonstrate how impaired mtDNA integrity deranges neuronal survival and metabolism and point to mitochondria as a unitary pathologic target throughout neurodegenerative disorders.

2.1. Mitochondrial DNA and Neuronal Function

mtDNA is a compact, double-stranded circular genome localized within the mitochondria, independent of the nuclear genome, and is passed down maternally. It contains 13 critical protein subunits of the oxidative phosphorylation (OXPHOS) complexes. These proteins are a crucial component of electron transport chain (ETC

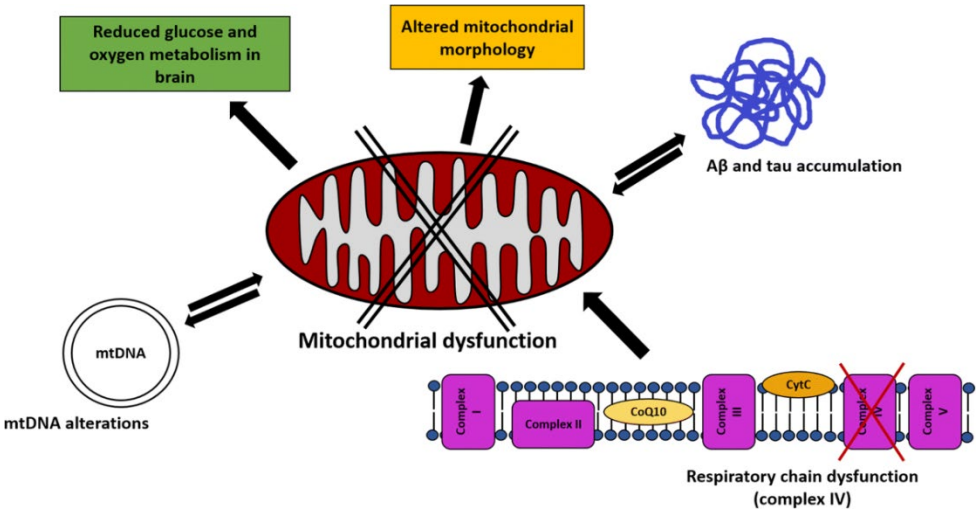

Figure 2: Mitochondrial Dysfunction in Neurodegeneration[12]

function, a series of protein complexes located in the inner mitochondrial membrane and tasked with adenosine triphosphate (ATP) synthesis, the cell's main energy currency. In high-energy-demand cells like neurons, mitochondrial proficiency is necessary to maintain ionic gradients, neurotransmission, and cellular viability.

Due to their post-mitotic status and ongoing requirement for energy, neurons are highly dependent on intact mitochondrial function. Any interference with the expression

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2.2. or replication of mtDNA—e.g., deletions, point mutations, or copy number reductions—can drastically interfere with ATP production. This energy deficit is often accompanied by enhanced generation of ROS, a byproduct of impaired electron transport and electron leakage from dysfunctional ETC complexes. Excess ROS not only leads to oxidative damage to lipids, proteins, and nucleic acids, but also initiates mitochondrial permeability transition, disturbs calcium buffering, and activates apoptotic pathways [11]. These cascades lead to cellular degeneration, synaptic impairment, and finally neuronal death—characteristics of several neurodegenerative disorders.

Alzheimer's Disease and mtDNA Mutations

AD is the most prevalent condition of dementia, and accumulating evidence points to mitochondrial dysfunction as an important cause. Research has identified elevated mtDNA deletions, including the well-documented "common deletion" of 4977 base pairs, in hippocampus and other areas of AD brains. The deletions interfere with cytochrome c oxidase (COX) activity, resulting in defective synaptic transmission and energy failure. In addition, mtDNA point mutations may change ETC component structure and function, heighten oxidative stress, and increase amyloid-beta plaque formation.

Cybrid (cytoplasmic hybrid) models, in which patient AD mtDNA is imported into mtDNA-depleted cell lines, have demonstrated that mtDNA can alone cause AD-like phenotypes, such as reduced ATP content, enhanced ROS generation, and changes in tau phosphorylation. These observations highlight the direct impact of mtDNA mutations on AD disease beyond simple secondary effects [12].

- **Methodological Strengths and Weaknesses:**
  - **Strengths:** Numerous research studies make use of patient-derived brain tissues and use high-resolution molecular methods including polymerase chain reaction (PCR), long-range PCR, quantitative PCR, and next-generation sequencing (NGS), which facilitate accurate mutation identification.
  - **Limitations:** The primary weakness is the unavailability of longitudinal cohort data for determining causality. Secondarily, most studies do not measure heteroplasmy — the ratio of mutant to wild-type mtDNA — which is responsible for the phenotypic expression of mtDNA mutations [13].

2.3. Parkinson's Disease and Mitochondrial Dysfunction

PD is a chronic, progressive neurodegenerative condition mainly defined by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to motor manifestations like tremors, rigidity, bradykinesia, and postural instability. Among the many causative factors, mitochondrial dysfunction has

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always been found to be a primary pathological feature of PD. Particularly, dysfunction of complex I within the mitochondrial electron transport chain is often reported. Mutations within mtDNA-encoded NADH dehydrogenase (ND) subunit genes functionally impair activity of complex I and consequently lower the production of ATP while augmenting the yield of reactive oxygen species (ROS). This bioenergetic dysfunction and oxidative load are majorly responsible for the neuronal damage and death, especially in high-energy-demand neurons, like those of the substantia nigra.

Post-mortem examinations of brains of PD patients have shown an elevation of mtDNA deletions and dramatically lower mtDNA copy number in affected tissues. These data imply deterioration of mitochondrial genomic integrity as a disease-promoting factor. In addition, familial PD associated with mutations in nuclear genes, including PINK1, Parkin, and DJ-1, also shed light on mitochondrial implication [14]. These genes play key roles in mitochondrial quality control, especially in mitochondrial processes such as mitophagy, which disposes of faulty mitochondria. When these genes are mutated or defective, excessive accumulation of defective mitochondria is related with higher oxidative stress, disrupted calcium management, and finally apoptosis. The interaction between the nuclear-encoded and mitochondrial-encoded genes thus underlines the significance of mitochondrial upkeep in the maintenance of neuronal health and points to the essential role played by mtDNA stability in the pathophysiology of PD.

2.4. Huntington's Disease and Oxidative Phosphorylation Deficits

HD is a genetic neurodegenerative disorder caused by the amplification of CAG repeats within the HTT gene. Although the primary mutation occurs in nuclear DNA, mitochondrial impairment has been identified as a significant secondary reason for disease advancement. HD neurons are prone to having reduced mitochondrial membrane potential, fragmentation of mitochondrial networks, and impaired calcium buffering [15].

There is proof that mtDNA in HD neurons is under more oxidative stress and deletions that further impair the mitochondrial respiratory function. These alterations disrupt neuronal metabolism, enhance excitotoxicity, and result in cognitive impairment and motor dysfunction. While not causal, mtDNA mutations in HD have the effect of amplifying the pathological effect of the initial genetic mutation.

Table 1: Studies on Mitochondrial Dysfunction in Aging and Neurodegeneration

Authors	Study	Focus Area	Method	Findings

Klein et al. (2021) [14]	mtDNA quantity and quality in AD brains	mtDNA copy number and integrity in Alzheimerâ€™s disease	Postmortem brain tissue analysis	AD brains showed reduced mtDNA copy number and fragmentation linked to neuronal loss
Lawless et al. (2020) [15]	Prevalence of mtDNA mutations with aging	Somatic mtDNA mutations and bioenergetic failure	Literature review and theoretical synthesis	Accumulation and expansion of mtDNA mutations may contribute to age-related disease
Li et al. (2019) [16]	Mathematical modeling of age-related mtDNA mutations	Distribution and diversity of mtDNA variants in aging	Mathematical simulation and modeling	Model explained how small changes in mutation dynamics alter mtDNA diversity over time
Lin et al. (2022) [17]	mtDAMPs and neuroinflammation in neurodegeneration	Neuroinflammation mediated by mitochondrial damage signals	Experimental and mechanistic review	mtDNA and other components act as DAMPs, triggering chronic inflammation in the brain
Monzio Compagnoni et al. (2020) [18]	Role of mitochondria in AD and PD pathogenesis	Mitochondrial dysfunction in neurodegenerative disease mechanisms	Review of cellular, animal, and human studies	Mitochondrial dysfunction was both a driver and result of neurodegenerative disease progression

3. PATHOGENIC MECHANISMS OF MTDNA MUTATIONS

mtDNA mutations are becoming more recognized as being at the center of pathogenesis of numerous neurodegenerative diseases and metabolic disorders. Unlike nuclear DNA, mtDNA is more susceptible to mutation since it is more proximal to the electron transport chain (ETC), lacks protective histones, and contains limited repair mechanisms. The pathogenic action of mtDNA mutations is primarily mediated through a variety of interrelated cellular and biochemical events, which have the potential to disrupt energy metabolism, increase oxidative stress, upset calcium homeostasis, and trigger apoptotic pathways [19].

3.1 Impaired Oxidative Phosphorylation and ATP Deficiency

One of the most direct and severe consequences of pathogenic mtDNA

mutations is the disruption of oxidative phosphorylation (OXPHOS), the essential biochemical process by which mitochondria produce adenosine triphosphate (ATP)—the energy source of major importance for cellular functions. mtDNA is also involved in the coding of some of the electron transport chain (ETC) subunits, i.e., those belonging to complexes I, III, IV, and V. Mutations in genes lead to impaired assembly or functioning of the ETC complexes, which cause impaired electron transfer down the chain. This disturbance not only reduces the efficiency of proton pumping through the inner mitochondrial membrane but also results in a decreased electrochemical gradient that is critical for ATP synthesis via ATP synthase (complex V).

As a result, cells experience a dramatic loss of ATP synthesis, which is especially catastrophic in energy-hungry tissues such as the brain and skeletal muscle. Neurons particularly rely heavily on ATP to maintain ionic gradients, fuel synaptic transmission, and enable axonal transport. In neurons, insufficient energy causes compromised neurotransmission, synaptic collapse, and compromised plasticity—significant causes of cognitive and motor dysfunction observed in neurodegenerative disorders [20]. Apart from this, the defective electron transport mechanism increases the leakage of electrons, which combine with molecular oxygen to generate reactive oxygen species (ROS). The secondary oxidative stress not only damages cellular components but also aggravates mitochondrial dysfunction, creating a vicious circle that increases neuronal damage and cell death. Hence, mtDNA mutation-mediated ATP deficiency lies at the forefront of mitochondrial pathophysiology and is a force behind the initiation of a number of neurodegenerative diseases.

3.1. Enhanced Production of Reactive Oxygen Species (ROS)

Defective units of the electron transport chain (ETC) complexes I and III, caused by mtDNA mutations, are primary contributors to electron leak during oxidative phosphorylation. Under normal conditions, electrons are efficiently transferred through the ETC to molecular oxygen, resulting in the formation of water. Yet, when the function of ETC is interrupted by structural and functional impairment in complex subunits coded by abnormal mtDNA, electrons leave the pathway ahead of time and are oxidized by molecular oxygen to yield reactive oxygen species (ROS), including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) [21].

This overproduction of ROS overpowers the antioxidant defense systems of the cell, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, resulting in oxidative stress. ROS easily target cellular macromolecules—mitochondrial membrane lipids (causing lipid peroxidation), proteins (denaturation and enzyme deactivation), and nucleic acids both nuclear and mitochondrial. Most importantly, mtDNA itself becomes a targeted site of damage caused by ROS, as it is positioned very close to where ROS are formed in the vicinity of the inner

mitochondrial membrane and does not receive protective histones and effective mechanisms of repair. This damage even further disrupts the integrity and replication of mtDNA, making ETC worse and setting a self-reinforcing vicious circle of mitochondrial genome instability and oxidative stress.

With time, chronic ROS load results in ultrastructural changes including mitochondrial swelling, disruption of cristae, and opening of permeability transition pores. These ultrastructural changes lead to the efflux of pro-apoptotic proteins like cytochrome c into the cytosol, initiating pathways of programmed cell death. ROS-induced damage also initiates inflammatory signaling cascades and causes neuroinflammation through microglial activation and cytokine secretion [22].

3.1Mitochondrial Genome Instability and Heteroplasmy

One of the characteristics of mtDNA mutations is heteroplasmy, in which both mutated and normal mtDNA exist in a cell. When the fraction of mutated mtDNA exceeds a certain threshold (usually 60–90%), mitochondrial function is greatly compromised—a process referred to as the "threshold effect." Also, mtDNA is inherited maternally and undergoes replicative segregation during cell division, which leads to heterogeneous mutation loads between tissues and over time. This unequal distribution is the cause of the tissue-specific and progressive characteristics of most mitochondrial diseases.

3.2. Defective Calcium Homeostasis

Mitochondria are key players in intracellular calcium buffering. Pathogenic mutations in mtDNA interfere with calcium uptake and storage processes, causing elevated cytosolic calcium concentrations. This dysregulation has the capacity to trigger proteases, nucleases, and other calcium-sensitive enzymes, which participate in cellular injury. Moreover, mitochondrial permeability transition pores (mPTPs) may open due to calcium overload, leading to mitochondrial membrane potential loss and apoptosis activation [23].

3.3. Disruption of Mitochondrial Dynamics and Mitophagy

Mitochondria are unstable organelles that continuously fuse and divide to maintain their shape, redistribute mitochondrial material, and adapt to cellular demands. Fusion allows for the merging of contents of the mitochondria, which helps dilute the defective components and maintain mtDNA stability, while fission allows for segregation and removal of defective portions. This dynamic balance is significant in cellular homeostasis, particularly in high-energy demand neurons. But mutations in mtDNA can disrupt such mechanisms by damaging the structure and function of mitochondria. It is also added to by nuclear gene defects such as PINK1 and Parkin that regulate mitophagy—autophagic degradation of abnormal mitochondria. Defective in this mechanism, abnormal mitochondria are not properly eliminated from the cell and end up accumulating within the cell.

The buildup of abnormal mitochondria contributes to faulty bioenergetics, excessive rates of production of reactive oxygen species (ROS), disrupted calcium signaling, and pro-apoptotic pathway activation. This aggregate mitochondrial stress triggers a cascade of cell damage, most notably in neurons with high energy requirements and reliance on mitochondria. Abnormal mitophagy and mitochondrial dynamics have been explicitly linked to producing various neurodegenerative conditions, including PD, AD, and ALS. In these disorders, defects in mitochondrial turnover drive synaptic dysfunction, axonal degeneration, and final neuronal death. Therefore, the regulation of mitochondrial fission, fusion, and mitophagy is required to maintain neuronal health, and disruption in these mechanisms by mtDNA mutations is a primary mechanism of neurodegeneration [24].

3.4. Activation of Apoptotic and Inflammatory Pathways

Mutations in mtDNA lead to chronic mitochondrial dysfunction and induce intrinsic apoptotic signaling pathways, resulting in programmed cell death. Highly damaged mitochondria become depolarized and release cytochrome c into the cytosol, which associates with Apaf-1 and pro-caspase-9 and forms the apoptosome complex. This results in a caspase activation cascade, particularly caspase-3, resulting in the sequential destruction of cellular components. This is especially ill for neurons, which are highly sensitive to mitochondrial stress and lack good regenerative capacity. The progressive neuronal loss via apoptosis is a feature of neurodegenerative diseases such as Alzheimer's, Parkinson's, and HD [25].

Other than cell death, also accountable for chronic inflammation are dysfunctional mitochondria. Mitochondrial injury may lead to the release of mtDNA, cardiolipin, and other danger-associated molecular patterns (DAMPs) into the cytoplasm or extracellularly. These molecules stimulate innate immune sensors, with specific stimulation of the NLRP3 inflammasome and cGAS-STING pathway, which stimulate pro-inflammatory cytokine production, such as IL-1β and type I interferons. This pathogen-independent sterile inflammation results in chronic tissue damage and contributes to both autoimmune and neurodegenerative diseases. In the brain, chronic neuroinflammation not only amplifies neuronal loss but also compromises synaptic communication and hastens cognitive deterioration, again highlighting the double role of mitochondrial dysfunction in both apoptotic and inflammatory neurodegenerative mechanisms.

4. DISCUSSION

The review emphasizes that mtDNA mutations are at the centre of neurodegenerative diseases through interference with energy generation, leading to enhanced oxidative stress, and inducing neuroinflammation [26]. Mutations are not mere secondary but could actually start disease, positioning mitochondria as a prime therapeutic target. However, loopholes such as sparse longitudinal information and

unresolved heteroplasmy necessitate sophisticated in vivo models and personalized strategies in future studies.

4.1. Interpretation and Analysis of Findings

The cumulative evidence in this review highlights the key role of mtDNA mutations in the pathophysiology of neurodegenerative disorders [27]. From Alzheimer's to Parkinson's to HD to ALS, one observes a continuity of pathology that cuts across each: compromised mitochondrial bioenergetics due to mtDNA deletions, point mutations, or decreased copy numbers. These alterations impair oxidative phosphorylation (OXPHOS), reducing ATP yield and increasing electron leakage within the electron transport chain (ETC), particularly at complexes I and III. This promotes the excessive production of reactive oxygen species (ROS), initiating a cascade of cellular damage including lipid peroxidation, protein denaturation, and further mtDNA damage—initiating a self-perpetuating cycle of oxidative stress and mitochondrial instability . Furthermore, these are compounded by nuclear gene dysfunctions such as in PINK1 and Parkin, which disrupt mitophagy and allow dysfunctional mitochondria to accumulate, particularly in neurons where energy demands and mitochondrial dependence are unusually high.

4.2. Implications and Significance

These results have important clinical and therapeutic implications. First, they disclose mitochondrial dysfunction as a central, potentially initiating process rather than as a downstream event in neurodegeneration. mtDNA and other mitochondrial constituents' release into the cytoplasm triggers innate immune mechanisms such as NLRP3 inflammasome and cGAS-STING, connecting mitochondrial dysfunction to chronic neuroinflammation—another prime driver of disease progression. This double function of mtDNA mutations in metabolic collapse and immune activation renders mitochondria a reconciling and highly actionable treatment target. Treatments that seek to augment mitochondrial function—CoQ10 supplementation, MitoQ, antioxidants, and methods to salvage mitophagy—have promise to slow neurodegeneration. Additionally, sophisticated tools such as mitochondrial gene editing (e.g., mitoTALENs, zinc-finger nucleases, and derivatives of CRISPR) are revealing promising pathways to directly correct mtDNA mutations [28].

4.3. Gaps and Future Research Directions

Despite significant advances, a number of gaps in research persist which preclude translation to clinical utility. Most published studies are cross-sectional or post-mortem, without longitudinal understanding of when and how mtDNA mutations cause their pathogenic impact[29]. In addition, heteroplasmy, where mutated and wild-type mtDNA are present within cells, is infrequently measured or modeled correctly, yet has a significant bearing upon phenotype expression. Present disease models usually are not able to reflect this heterogeneity,

particularly tissue-specific thresholds of mutation for clinical outcome. There is a pressing requirement for non-invasive, mtDNA-derived biomarkers that will help in early diagnosis, prognosis, and monitoring of treatment. In the future, research needs to be aimed at creating in vivo models with exact mtDNA manipulation abilities, studying mitochondrial dynamics as a function of time, and creating patient-tailored therapies considering mtDNA heterogeneity and nuclear-mitochondrial communication. An inter-disciplinary approach integrating genomics, molecular neuroscience, and bioenergetics will be crucial to completely untangle the function of mtDNA mutations and create meaningful interventions for neurodegenerative diseases [30].

5. CONCLUSION

This review highlights the central impact of mtDNA mutations as critical drivers in the etiology and pathogenesis of severe neurodegenerative disorders like AD, PD, HD, and ALS. These mutations impair the mitochondrial electron transport chain, disturb oxidative phosphorylation, reduce ATP synthesis, and cause excessive generation of reactive oxygen species (ROS), leading to oxidative stress, calcium homeostasis impairment, and activation of apoptosis. Additionally, mtDNA mutations are involved in mitochondrial dynamics imbalance and dysfunctional mitophagy, further promoting cellular stress and neuronal degeneration. Release of mitochondrial constituents like mtDNA into the cytoplasm also initiates inflammatory signaling through the NLRP3 inflammasome and cGAS-STING pathways, connecting mitochondrial dysfunction with chronic neuroinflammation—a hallmark of neurodegeneration. This review emphasizes the essentiality of early detection, biomarker identification, and therapeutic strategy design to restore mitochondrial integrity and function. The way forward should include designing strong in vivo models that realistically replicate heteroplasmy and tissue-specific loads of mtDNA, as well as personalized therapies through specific mitochondrial gene editing or pharmacological resurfacing. Overcoming these hurdles holds out the possibility of slowing down, or even reversing, neurodegenerative mechanisms, promising once again new hopes for therapeutic gains in treating these disabling diseases.

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