Mitophagy in Neurodegenerative Diseases: A Survey

Abstract

Mitophagy, the selective autophagic degradation of mitochondria, is essential for maintaining cellular health, particularly in the brain, where its impairment is linked to mitochondrial dysfunction and neurodegenerative diseases such as Alzheimer's, ALS, and Parkinson's. This survey explores the multifaceted role of mitophagy, emphasizing its significance in neuronal health and as a potential therapeutic target. By maintaining mitochondrial quality control and reducing oxidative stress, mitophagy mitigates neuronal damage and disease progression. The paper delves into the genetic and molecular mechanisms underlying mitophagy, highlighting pathways such as PINK1-Parkin and receptor-mediated processes. It also examines the implications of mitophagy impairment in neurodegenerative pathologies, underscoring the need for therapeutic interventions. Current research emphasizes pharmacological and non-pharmacological strategies, including lifestyle modifications and innovative technologies, to enhance mitophagic activity. Challenges remain in translating these insights into clinical practice, particularly in developing reliable biomarkers for early diagnosis and monitoring. Future research should focus on integrating genetic and clinical data to refine predictive models and explore personalized medicine approaches. By advancing our understanding of mitophagy's regulatory mechanisms, this survey aims to pave the way for novel therapeutic strategies that improve health outcomes in neurodegenerative diseases.

1 Introduction

1.1 Mitophagy and Cellular Health

Mitophagy is a selective autophagic process crucial for cellular health, facilitating the removal of damaged mitochondria to preserve mitochondrial function and mitigate excessive reactive oxygen species (ROS) production [1, 2]. This process is vital for metabolic integrity and oxidative stress reduction, which are essential for maintaining cellular homeostasis [3]. In the context of aging and age-related diseases, mitophagy plays a pivotal role in sustaining a functional mitochondrial pool, while mitochondrial DNA (mtDNA) mutations, associated with severe congenital disorders, further emphasize its importance in quality control [4].

In the brain, where neuronal cells exhibit high energy demands and vulnerability to oxidative stress, mitophagy is particularly significant. Neurons rely on mitochondrial function for ATP production; thus, impaired mitophagy can lead to the accumulation of dysfunctional mitochondria, exacerbating neurodegenerative processes [5, 6]. Effective physiological regulation of mitophagy is therefore essential for neuronal health, especially given the substantial energy requirements of these cells [7]. Furthermore, mitophagy has implications in neurodegenerative disease pathology, serving as a potential therapeutic target to enhance neuronal resilience and function by elucidating the molecular mechanisms and signaling pathways involved in mitochondrial elimination [8, 9]. Understanding these pathways is critical for developing strategies to combat neurodegenerative diseases and improve health outcomes [10].

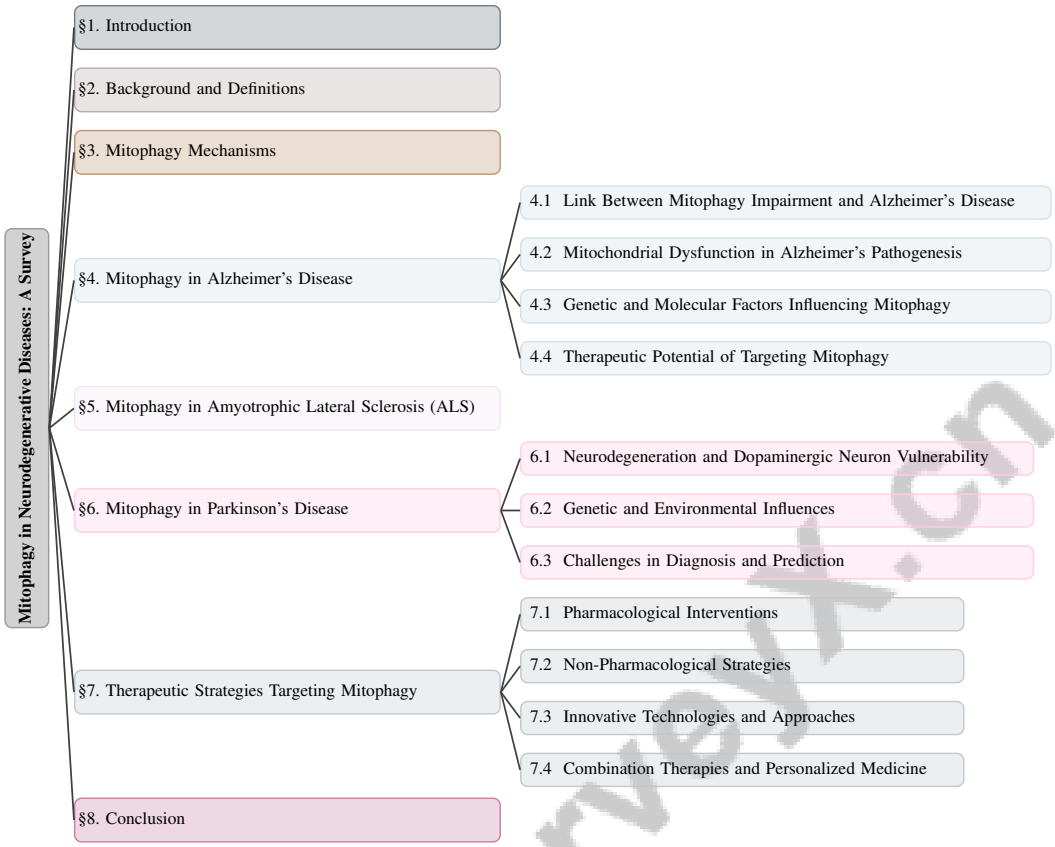

Figure 1: chapter structure

1.2 Link Between Mitophagy Impairment and Neurodegenerative Diseases

Impaired mitophagy is increasingly recognized as a central factor in neurodegenerative disease pathogenesis, where the accumulation of dysfunctional mitochondria leads to cellular dysfunction, synaptic impairments, and cognitive decline. This dysfunction is particularly pronounced in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), where ineffective mitophagy fails to eliminate damaged mitochondria, thereby exacerbating neurodegenerative processes. In Alzheimer's disease, for instance, mitophagy impairment is associated with the accumulation of -amyloid plaques and tau protein aggregates, disrupting cellular functions and promoting neurodegeneration [11].

The interplay between lipid metabolism and mitochondrial quality control is underscored by disruptions in sphingolipid metabolism linked to neurodegenerative diseases [12]. Moreover, mitophagy dysfunction extends beyond neurodegenerative diseases to other age-related disorders, including metabolic diseases and cancer, where mitochondrial quality control is vital for cellular homeostasis. The complexity of brain network dynamics and the multiscale disruptions observed in neurodegenerative diseases highlight the necessity for comprehensive models to understand and address these conditions [13].

Research into lifestyle interventions, such as intermittent fasting and caloric restriction, has revealed potential neuroprotective effects, suggesting strategies that may enhance mitophagy and slow the progression of neurodegenerative diseases [14]. Understanding the intricate connections between mitophagy impairment and neurodegeneration is essential for developing targeted therapeutic strategies against these debilitating diseases [7].

1.3 Structure of the Survey

This survey is meticulously organized to examine the complex role of mitophagy in neurodegenerative diseases, focusing on its implications in Alzheimer's disease, ALS, and Parkinson's disease, while

addressing its dual nature as both protective and potentially harmful. The paper aims to provide a comprehensive understanding of mitophagy and its significance for cellular and neuronal health [15, 10, 16, 17].

The survey begins with an overview of mitophagy, emphasizing its critical role in maintaining cellular homeostasis, particularly in neuronal environments, where efficient clearance of damaged mitochondria is essential for energy metabolism and overall brain health. This process is vital for preventing the accumulation of dysfunctional organelles associated with neurodegenerative diseases such as Alzheimer's and Parkinson's, thereby underscoring the significance of mitophagy in both physiological and pathological contexts [8, 15, 5, 16]. Following this, the discussion shifts to the link between mitophagy impairment and neurodegenerative disease pathogenesis, highlighting the contribution of dysfunctional mitophagy to disease progression.

Subsequent sections provide background definitions and essential explanations of key terms related to mitophagy and mitochondrial dysfunction, laying the groundwork for a detailed exploration of the molecular mechanisms underlying mitophagy, including genetic pathways, ubiquitin-dependent and independent mechanisms, and the PINK1-Parkin pathway.

The survey then delves into the specific roles of mitophagy in Alzheimer's disease, ALS, and Parkinson's disease, analyzing evidence linking mitophagy impairment to these conditions. Each disease-specific section discusses mitochondrial dysfunction, genetic and molecular factors, and the potential for targeting mitophagy as a therapeutic strategy.

Finally, the survey explores current and emerging therapeutic strategies aimed at enhancing mitophagy, encompassing pharmacological interventions, lifestyle modifications, and innovative technologies. The paper concludes with a detailed summary of its key findings, emphasizing the critical role of mitophagy in neuroprotection. It highlights that effective mitophagy not only prevents the accumulation of damaged mitochondria, supporting neuronal health, but also suggests that therapeutic strategies aimed at enhancing this process could provide promising avenues for treating various neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, as well as mitigating acute brain injuries such as stroke and traumatic brain injury [15, 18, 5, 16].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Key Definitions and Concepts

Mitophagy is a selective autophagic process vital for degrading defective mitochondria, preserving mitochondrial quality control and cellular homeostasis [10]. It prevents mitochondrial dysfunction, which can impair ATP production and ROS regulation, leading to cellular damage [19]. The mechanisms of mitophagy include both ubiquitin-dependent and independent pathways, highlighting their evolutionary importance [10].

Mitochondrial dysfunction is a key factor in neurodegenerative diseases, such as Alzheimer's, where it contributes to -amyloid and tau protein accumulation, influencing disease pathogenesis [20]. The mitochondrial network's dynamics, involving mitophagy and mtDNA copy number control, reflect complex regulatory mechanisms [4].

Neurodegeneration, marked by progressive neuronal degeneration, is central to diseases like Alzheimer's, Parkinson's, and ALS [10]. This degeneration arises from intricate genetic, molecular, and environmental interactions, requiring advanced techniques for understanding disease mechanisms. Metabolomics, assessing small molecule metabolites, alongside biomarkers, is crucial for indicating Alzheimer's progression [20].

Sphingolipid metabolism is essential for synthesizing sphingolipids, critical for cell membrane integrity and signaling. Disruptions in this metabolism are linked to neurodegenerative diseases, emphasizing its cellular importance [21].

Neuroprotection involves strategies to preserve neuronal structure and function, often through neurogenesis and signaling pathways mitigating neurodegeneration. Understanding these concepts is crucial for exploring mitophagy mechanisms and implications in neurodegenerative diseases, aiding therapeutic development [10].

2.2 Mitochondrial Function and Dysfunction

Mitochondria are essential organelles generating ATP through oxidative phosphorylation, providing energy for cellular activities [6]. Beyond energy production, they regulate metabolic homeostasis, calcium signaling, and apoptosis, crucial for cellular health [7]. Efficient removal of damaged mitochondria via mitophagy is critical for maintaining mitochondrial integrity and metabolic balance, vital for neuronal survival [10].

Mitochondrial dysfunction, characterized by impaired ATP production and increased ROS, poses significant threats to cellular health, contributing to damage and death [6]. In neurodegenerative diseases, such dysfunction exacerbates synaptic failure and neuronal loss, accelerating disease progression [7]. In Alzheimer's, mitochondrial dysfunction correlates with -amyloid and tau protein tangles, key disease features [20].

The regulation of mitophagy and its impact on disease progression underscore the importance of understanding mitochondrial dynamics and quality control. Alterations in amino acid and lipid metabolism, observed in aging and Alzheimer's, further highlight mitochondrial dysfunction's consequences on cellular health [20]. Identifying crucial features amid correlated data remains a challenge, necessitating advanced feature selection methods for reliable insights [21].

Research into mitophagy stages, including initiation, receptor involvement, and downstream effects, offers a framework for investigating mitochondrial dysfunction's impact on cellular health [10]. Understanding these interactions is essential for developing therapeutic strategies to mitigate mitochondrial dysfunction and improve health outcomes across diseases.

In recent years, the study of mitophagy has gained significant attention due to its critical role in maintaining mitochondrial quality control and cellular homeostasis. Understanding the various mechanisms involved in mitophagy is essential for elucidating its implications in aging and disease, as well as identifying potential therapeutic targets. Figure 2 illustrates the hierarchical categorization of mitophagy mechanisms, detailing genetic and molecular mechanisms, ubiquitin-dependent and independent pathways, the PINK1-Parkin pathway, receptor-mediated mitophagy, and the role of mitophagy adaptors and regulatory proteins. Each category within the figure explores key processes and interactions that are vital for the effective functioning of mitophagy, thereby enriching our understanding of its complex regulatory networks.

3 Mitophagy Mechanisms

3.1 Genetic and Molecular Mechanisms

Mitophagy regulation is a complex interplay of genetic and molecular mechanisms critical for mitochondrial quality control and cellular homeostasis, especially in aging and disease [3]. Central to this process are mitochondrial cargo receptors that activate signaling pathways in response to cellular stress, facilitating the selective degradation of damaged mitochondria via PINK1-Parkin dependent and independent pathways [1, 22]. The PINK1-Parkin pathway involves PINK1 accumulation on the outer mitochondrial membrane of dysfunctional mitochondria, recruiting and activating Parkin, an E3 ubiquitin ligase, which ubiquitinates mitochondrial surface proteins for degradation [18]. Other mechanisms, such as BNIP3, NIX-mediated mitophagy, and FUNDC1 involvement, are also vital [18].

Theoretical frameworks emphasize mitophagy's role in cellular homeostasis and its implications for aging and disease [3]. Computational models, such as multi-scale stochastic models, explore mitophagy dynamics and its impact on cellular processes, particularly in astrocyte networks affected by neurodegenerative conditions like Alzheimer's disease [23, 24]. Categorizing mitophagy adaptors and their regulatory mechanisms provides insights into their diverse roles in modulating mitophagic activity, essential for addressing challenges associated with mitophagy impairment [2, 16]. Integrating genomic, epigenomic, transcriptional, and phenotypic data reveals causal pathways from genetic variants to Alzheimer's disease, highlighting complex connections between genetic factors and mitophagy [14].

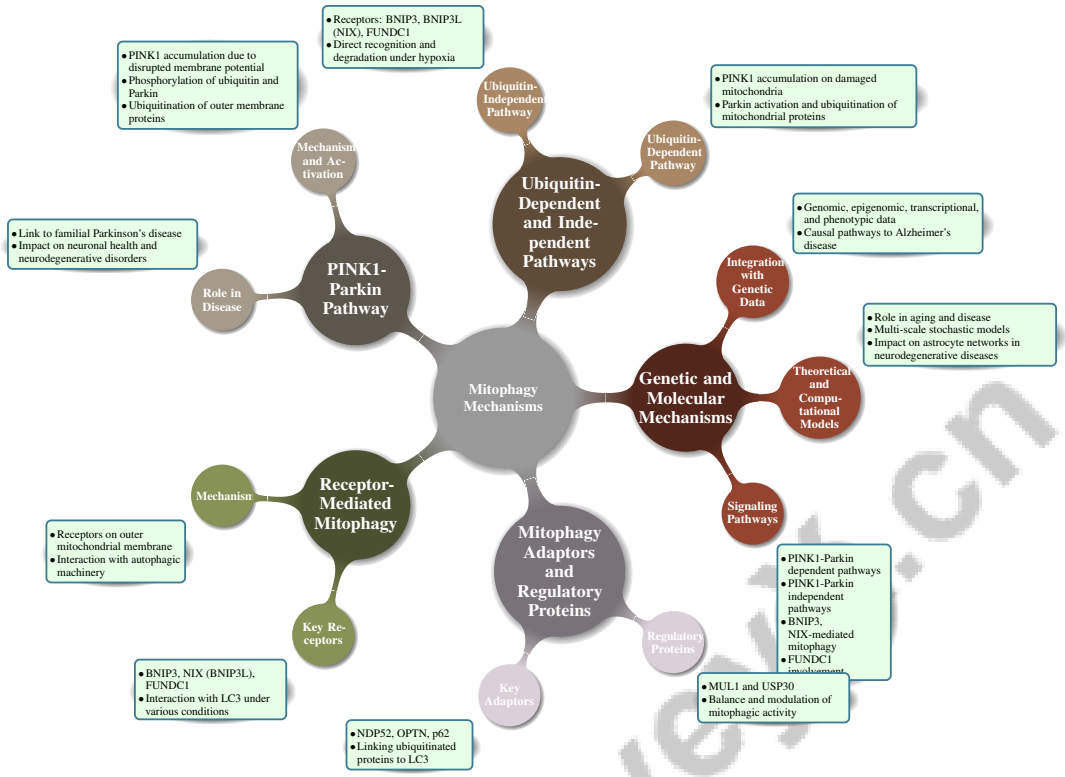

Figure 2: This figure illustrates the hierarchical categorization of mitophagy mechanisms, detailing genetic and molecular mechanisms, ubiquitin-dependent and independent pathways, the PINK1-Parkin pathway, receptor-mediated mitophagy, and the role of mitophagy adaptors and regulatory proteins. Each category explores key processes and interactions essential for mitochondrial quality control and cellular homeostasis, with implications for aging, disease, and potential therapeutic targets.

3.2 Ubiquitin-Dependent and Independent Pathways

Mitophagy encompasses ubiquitin-dependent and independent pathways, each crucial for mitochondrial quality control and cellular homeostasis. The ubiquitin-dependent PINK1/Parkin pathway involves PINK1 accumulation on the outer mitochondrial membrane of damaged mitochondria, recruiting and activating Parkin, leading to the ubiquitination of mitochondrial proteins for degradation, preserving mitochondrial integrity during stress [8, 22, 7]. Ubiquitin-independent mechanisms involve receptors like BNIP3, BNIP3L (NIX), and FUNDC1, which facilitate direct recognition and degradation of damaged mitochondria, particularly under hypoxia [7, 1, 8, 6, 9].

As illustrated in Figure 3, the hierarchical classification of mitophagy pathways highlights both the ubiquitin-dependent and independent mechanisms, emphasizing their roles in mitochondrial quality control and their implications in various diseases. The interplay between various adaptors and signaling pathways complicates mitophagy regulation, affecting roles in different cellular contexts, including cancer [2]. Integrating genetic and omics data highlights causal pathways linking genetic variants to diseases, emphasizing intricate connections between genetic factors and mitophagy [14]. Understanding both ubiquitin-dependent and independent pathways is essential for elucidating mitochondrial quality control mechanisms, impacting cellular health and disease outcomes, and opening avenues for therapeutic interventions targeting these processes in neurodegenerative disorders and cancer [8, 7, 2, 9].

3.3 PINK1-Parkin Pathway

The PINK1-Parkin pathway is pivotal in mitophagy regulation, eliminating damaged mitochondria to preserve mitochondrial integrity, optimize energy metabolism, and ensure cellular homeostasis.

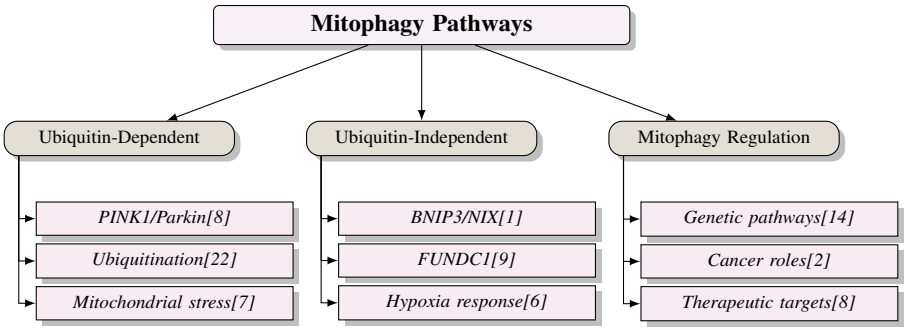

Figure 3: This figure illustrates the hierarchical classification of mitophagy pathways, highlighting the ubiquitin-dependent and independent mechanisms, and their roles in mitochondrial quality control and disease implications.

Its impairment can lead to dysfunctional mitochondria accumulation, contributing to diseases like neurodegenerative disorders [8, 7]. Activation occurs when mitochondrial membrane potential is disrupted, leading to PINK1 accumulation, initiating mitophagy by phosphorylating ubiquitin and Parkin, recruiting Parkin to mitochondria, where it ubiquitinates outer membrane proteins for degradation via the autophagosome-lysosome pathway [2].

This pathway is critical for mitophagy and plays a significant role in neurodegenerative disease pathogenesis. Mutations in PINK1 and Parkin genes are linked to familial Parkinson's disease, highlighting this pathway's importance in neuronal health [1]. Loss of function in these proteins impairs mitophagy, leading to dysfunctional mitochondria, increased oxidative stress, and neuronal death, typical of neurodegenerative disorders [15].

Research into the PINK1-Parkin pathway reveals potential therapeutic targets for enhancing mitophagy and mitigating mitochondrial dysfunction in neurodegenerative diseases. Understanding this pathway's molecular mechanisms can lead to strategies for enhancing or inhibiting its activity, promising interventions to slow disease progression associated with mitochondrial dysfunction, such as cancer, where impaired mitophagy contributes to metabolic reprogramming and increased disease susceptibility [8, 2].

3.4 Receptor-Mediated Mitophagy

Receptor-mediated mitophagy, independent of the ubiquitin-proteasome system, facilitates the selective degradation of damaged mitochondria, maintaining mitochondrial quality and energy metabolism, especially in neurodegenerative diseases and cellular stress responses. This process involves specific receptors on the outer mitochondrial membrane that interact with autophagic machinery to sequester and degrade dysfunctional mitochondria. Key receptors like BNIP3, NIX (BNIP3L), and FUNDC1 interact with LC3, promoting mitophagy under various conditions [8, 15, 16, 1].

BNIP3 and NIX, upregulated under hypoxia, interact with LC3 through LIR motifs, promoting the engulfment of damaged mitochondria by autophagosomes, crucial in erythrocyte maturation and cardiac stress responses [15]. FUNDC1, involved in hypoxia-induced mitophagy, undergoes phosphorylation events regulating its interaction with LC3, highlighting receptor-mediated mitophagy's complexity and its importance in adapting to cellular changes [18].

Receptor-mediated mitophagy pathways underscore mechanisms for maintaining mitochondrial quality control, offering potential therapeutic targets for diseases characterized by mitochondrial dysfunction. Understanding receptor-mediated mitophagy regulation is crucial for developing strategies to mitigate mitochondrial-related pathologies and improve cellular health [2].

3.5 Mitophagy Adaptors and Regulatory Proteins

Mitophagy adaptors and regulatory proteins are crucial for executing mitophagy, ensuring mitochondrial quality control and cellular homeostasis. These proteins facilitate the recognition, sequestration, and degradation of damaged mitochondria by interacting with mitochondrial and autophagic machinery. Key adaptors like NDP52, OPTN, and p62 link ubiquitinated mitochondrial proteins to LC3,

essential for selective degradation, maintaining mitochondrial quality control and energy homeostasis, crucial in preventing neurodegenerative diseases [7, 15, 8, 3, 16].

NDP52 and OPTN are significant in the PINK1-Parkin pathway, recognizing ubiquitinated proteins on mitochondria and recruiting LC3 to initiate autophagosome formation, crucial for selective autophagic degradation [15]. p62, also known as sequestosome 1, links ubiquitinated proteins to autophagic machinery and participates in signaling pathways regulating cellular stress responses [15].

Regulatory proteins like MUL1 and USP30 modulate mitophagy. MUL1 ubiquitinates mitochondrial proteins independently of Parkin, while USP30 counteracts Parkin-mediated ubiquitination, serving as a negative mitophagy regulator. The balance between these enzymes is critical for fine-tuning mitophagic activity and mitochondrial turnover [1, 15].

The dynamic interplay between mitophagy adaptors and regulatory proteins highlights mitochondrial quality control mechanisms' complexity. These proteins mediate mitophagy specificity and efficiency by facilitating dysfunctional mitochondria degradation while integrating signals from diverse cellular pathways, ensuring cellular homeostasis and adaptation to physiological or pathological conditions [8, 2, 9]. Understanding these proteins provides insights into potential therapeutic targets for diseases associated with mitochondrial dysfunction, such as neurodegenerative disorders, where enhancing mitophagy could alleviate symptoms and improve cellular health.

4 Mitophagy in Alzheimer's Disease

4.1 Link Between Mitophagy Impairment and Alzheimer's Disease

Mitophagy impairment is closely associated with Alzheimer's disease (AD) pathogenesis, characterized by neuronal loss, memory deficits, and cognitive decline. Central to AD are amyloid-beta plaques and tau tangles, exacerbated by mitochondrial dysfunction and oxidative stress due to defective mitophagy [25]. Failure to clear damaged mitochondria increases reactive oxygen species (ROS), furthering synaptic dysfunction and neuronal degeneration [26]. Genetic studies highlight key AD-associated genes, emphasizing the genetic basis of mitophagy impairment [19]. This genetic complexity complicates early diagnosis and treatment, particularly in Mild Cognitive Impairment (MCI), where distinguishing AD from other dementias is challenging [19]. The role of matrix metalloproteinases (MMPs) in AD underscores the need for treatments targeting mitophagy-related molecular mechanisms. Enhancing mitophagy offers a potential therapeutic strategy to counteract mitochondrial dysfunction and cognitive decline [25], with lifestyle interventions potentially boosting mitophagic activity and promoting neuroprotection [26]. Advances in neuroimaging and multi-omics have enriched understanding of cognitively impaired individuals, leading to innovative diagnostic frameworks. A comprehensive grasp of mitophagy-related processes is crucial for pre-symptomatic diagnosis and potential interventions, focusing on genetic and molecular factors influencing mitophagic pathways [19].

4.2 Mitochondrial Dysfunction in Alzheimer's Pathogenesis

Mitochondrial dysfunction plays a pivotal role in Alzheimer's disease (AD) pathogenesis, contributing to beta-amyloid and tau aggregations, hallmark features of the disease [27]. These aggregates disrupt mitochondrial function, impair energy metabolism, and increase oxidative stress, exacerbating neuronal damage and synaptic dysfunction [28]. The complexity of AD's biological mechanisms and overlapping symptoms with other dementias pose challenges for early diagnosis and effective treatment [29]. Integrating quantitative MRI with deep learning has enhanced diagnostic models, providing insights into disease progression and therapeutic targets [30]. MMPs' dual role in AD pathogenesis, degrading amyloid-beta while contributing to neuroinflammation and blood-brain barrier disruption, highlights the need for targeted interventions addressing mitochondrial dysfunction [31]. Understanding genetic variability's impact on mitochondrial function is crucial for early biomarkers and targeted interventions [28]. Redescription mining reveals novel insights into associations between clinical and biological attributes, emphasizing AD's multifactorial nature [32]. A comprehensive understanding of mitochondrial dysfunction mechanisms is essential for developing strategies to alleviate AD's effects and enhance patient outcomes by addressing mitochondrial abnormalities and mitophagy impairments [25, 16, 26].

4.3 Genetic and Molecular Factors Influencing Mitophagy

Genetic and molecular factors significantly modulate mitophagy in Alzheimer's disease (AD), influencing disease progression and pathogenesis. AD's genetic landscape includes familial and sporadic forms, with mutations in genes like PINK1 and Parkin affecting mitophagy regulation and mitochondrial quality control, leading to defective clearance of damaged mitochondria and exacerbating oxidative stress [26]. Genetic influences extend to plasma membrane lipid rafts, essential for brain plasticity and memory, disrupted in AD. The ApoE 4 allele is linked to increased AD risk and earlier onset, affecting lipid metabolism and mitochondrial function, underscoring the importance of lipid homeostasis in mitophagic activity [33]. Molecular pathways involving amyloid-beta, tau dynamics, oxidative stress, and calcium homeostasis are integral to mitophagy regulation in AD. Amyloid-beta and tau aggregates impair mitochondrial function and disrupt calcium signaling, increasing oxidative stress and compromising mitophagy [34]. Advanced methodologies, like integrating GWAS with expression data, identify causal AD-associated genes, enhancing understanding of genetic influences on mitophagy and disease progression [35]. Despite advancements, challenges persist in developing effective diagnostic tools and therapies due to AD's heterogeneity [28]. Redescription mining techniques offer promising avenues for exploring clinical and biological associations [32]. A comprehensive understanding of these mechanisms is essential for devising therapeutic strategies to enhance mitophagic activity and mitigate AD's impact on neuronal health.

4.4 Therapeutic Potential of Targeting Mitophagy

Targeting mitophagy offers a promising therapeutic strategy for Alzheimer's disease (AD) by addressing mitochondrial dysfunction and enhancing neuronal health. Enhancing mitophagy is crucial for maintaining mitochondrial quality control and cellular homeostasis, mitigating neurodegenerative processes in AD. Metabolomic biomarkers emerge as diagnostic tools or therapeutic targets, emphasizing metabolomics integration into therapeutic strategies [20]. Advanced computational approaches, like the MINDSETS framework integrating MRI radiomics, clinical assessments, and genetic data, provide comprehensive diagnostic tools for AD and vascular dementia, enhancing early diagnosis and treatment planning [11]. Ensemble feature selection with clustering shows promise in identifying stable biomarkers, enhancing therapeutic target identification [21]. Innovative therapies, including stem cell therapy and photobiomodulation, potentially replace lost neurons and enhance neurogenesis, offering novel treatment avenues [36]. Integrating computational models like ScAtt offers insights into AD's molecular mechanisms and potential early detection avenues [37]. Proposed joint models for improving predictive and personalized strategies in neurodegenerative diseases show potential, particularly without reliable reference time points [13]. Future research should elucidate interactions among neurobiological factors and explore new therapeutic avenues based on these insights [34]. Advancing understanding of mitophagy's molecular mechanisms and regulatory pathways can develop strategies to enhance mitophagic activity, offering hope for diseases previously deemed incurable [3].

5 Mitophagy in Amyotrophic Lateral Sclerosis (ALS)

Investigating amyotrophic lateral sclerosis (ALS) requires an in-depth analysis of cellular mechanisms underpinning disease progression. Mitophagy, vital for mitochondrial integrity and neuronal health, plays a significant role in ALS pathogenesis. This section highlights mitophagy's contributions to ALS, focusing on its impact on neurodegeneration and the relationship between mitochondrial dysfunction and motor neuron survival, thereby providing a basis for interventions aimed at enhancing mitophagic processes in ALS patients.

5.1 Role of Mitophagy in ALS Pathogenesis

Mitophagy dysfunction, crucial for neuronal health via the removal of damaged mitochondria, is intricately linked to ALS pathogenesis [15]. ALS is characterized by motor neuron degeneration, beginning with localized muscle weakness and often leading to paralysis [38]. Impaired clearance of defective mitochondria exacerbates oxidative stress and cellular damage, promoting motor neuron degeneration. A key aspect of ALS is the misfolding and aggregation of mutant superoxide dismutase 1 (SOD1), inducing neurodegenerative effects [39]. The phenotypic heterogeneity of ALS, with varying upper and lower motor neuron involvement, complicates its pathophysiology and treatment

[40]. Furthermore, defective lipid metabolism, particularly in mSOD1 mice, underscores ALS's multifaceted nature [41].

Research has identified various genetic mutations associated with ALS, illuminating its biological underpinnings and potential therapeutic targets [40]. However, the lack of effective biomarkers complicates timely diagnosis and treatment, adversely affecting patient outcomes [42]. The correlation dimension of ALS time series data, being less than four, implies non-chaotic behavior, impacting disease progression modeling [43]. Efforts to estimate treatment effects using observational data from clinical registries highlight the challenges in developing effective therapies [44]. The rapid progression of neurodegenerative changes and ALS heterogeneity pose significant obstacles to obtaining reliable functional measures, necessitating advanced methodologies for accurate assessment and intervention.

Understanding mitophagy's role in ALS pathogenesis is crucial for developing targeted interventions that enhance mitochondrial quality control and mitigate motor neuron degeneration. Addressing mitophagy impairment mechanisms can pave the way for novel therapeutic strategies aimed at improving ALS patient outcomes. Personalized survival predictions based on clinical, cognitive, and genetic data offer promising avenues for tailoring interventions to individual needs [45].

5.2 Lipid Metabolism and Proteinopathy in ALS

The interplay between lipid metabolism and proteinopathy significantly influences mitophagy in ALS, a neurodegenerative disorder marked by motor neuron degeneration. Altered lipid metabolism in ALS can adversely affect mitochondrial function, leading to the accumulation of toxic lipid species that contribute to oxidative stress and impaired mitophagy, increasing neuronal vulnerability [41]. ALS's genetic complexity, encompassing oligogenic and polygenic factors, complicates therapeutic target identification, as these variations impact lipid metabolism and mitochondrial dynamics [40].

Proteinopathy, characterized by the misfolding and aggregation of proteins such as TDP-43 and SOD1, plays a critical role in ALS pathogenesis. These aggregates disrupt cellular homeostasis by interfering with essential processes, including mitophagy, leading to dysfunctional mitochondria and heightened neuronal susceptibility to damage [39]. ALS's multifactorial nature, involving genetic and environmental components, necessitates a comprehensive approach to understanding and addressing its underlying mechanisms [38].

The initiation and progression of mitophagy are vital for mitochondrial quality control, particularly in ALS, where motor neurons are susceptible to metabolic and proteotoxic stress. Current research aims to elucidate the stages of autophagy and mitophagy, including autophagosome formation, transport, and lysosomal fusion, to better understand their roles in ALS pathogenesis. These insights are crucial for developing targeted therapeutic strategies that enhance mitophagic activity and mitigate the adverse effects of lipid metabolism and proteinopathy in ALS [42].

Moreover, the limited availability of discriminative features in MRI data presents challenges for existing deep learning models, hindering accurate detection of brain activation changes and disease progression in ALS patients. Advanced methodologies, such as longitudinal surface-based spatial Bayesian models, offer promising avenues for improving the detection and monitoring of ALS-related changes over time, providing valuable insights into the disease's progression and potential therapeutic interventions [44].

5.3 Challenges in ALS Research and Therapeutic Development

Researching ALS and developing therapies targeting mitophagy are challenging due to the disease's complexity and heterogeneity. A primary difficulty is the absence of definitive diagnostic tests, complicating early and accurate diagnosis and delaying intervention [46]. The heterogeneity of ALS presentations, manifesting in diverse clinical forms with varying progression rates and symptomatology, further complicates research efforts [40]. This diversity is mirrored in the underlying biological processes, which remain poorly understood, making targeted therapy development challenging [40].

A significant challenge in ALS research is elucidating the mechanisms of disease onset and progression. Ongoing debates regarding whether ALS is triggered locally with subsequent spread or arises from simultaneous decay across multiple sites complicate effective therapeutic strategy development [38]. Unclear pathogenic mechanisms, including genetic and environmental risk factors, hinder the identification of reliable biomarkers for early diagnosis and monitoring of disease progression.

Current research methods face limitations in addressing metabolic shifts and their implications in ALS pathology. The interplay between lipid metabolism and proteinopathy, along with the non-chaotic behavior observed in ALS time series data, presents challenges in developing accurate predictive models for disease intervention. Additionally, excluding treatment variables, such as riluzole, from predictive models limits their accuracy and clinical applicability [45].

Future research should focus on refining models of SOD1 misfolding and aggregation, exploring additional mutations, and elucidating mechanisms of neuroanatomic propagation. Addressing the non-randomized nature of clinical interventions, such as PEG insertion, and overcoming issues related to censoring and missing data are critical for advancing ALS research and therapeutic development [44]. A comprehensive approach integrating genetic, environmental, and clinical data is essential for overcoming these challenges and improving outcomes for individuals with ALS.

6 Mitophagy in Parkinson's Disease

6.1 Neurodegeneration and Dopaminergic Neuron Vulnerability

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, with impaired mitophagy playing a pivotal role. This impairment leads to dysfunctional mitochondria and elevated oxidative stress, exacerbating neuronal damage [47]. The reliance on calcium channels for pacemaking in dopaminergic neurons increases their susceptibility to mitochondrial dysfunction, thereby accelerating neurodegeneration [47].

The clinical variability of PD complicates treatment development, as disease presentation and progression differ significantly [48]. Despite numerous trials, effective disease-modifying treatments are lacking, underscoring the need for novel strategies targeting PD's underlying mechanisms [49]. Current therapies often focus on symptomatic relief but can exacerbate neurodegeneration, particularly in energy-deficient states [50].

Advancements in diagnostic models, such as the 3DCNN + LSTM, have shown promise, achieving a Macro Averaged OVR AUC of 91.9% in predicting PD progression [51]. Innovative methods like analyzing computer keyboard interactions for motor sign detection offer frequent, objective assessments, enhancing early detection and management [52].

Challenges remain in predicting PD progression using longitudinal data, such as MDS-UPDRS scores [53]. The insufficient dopamine release in the basal ganglia due to SNc neuron degeneration highlights the need for strategies to improve mitochondrial quality control and mitigate neurodegeneration [50]. Integrating advanced computational models, including LSTM-based approaches for FOG detection, demonstrates potential for improved diagnostic tools [54]. Addressing PD's diagnostic and treatment challenges can lead to personalized interventions, enhancing patient outcomes and quality of life.

6.2 Genetic and Environmental Influences

Parkinson's disease (PD) pathogenesis involves a complex interplay of genetic and environmental factors influencing mitophagy and neurodegeneration. Genetic studies have identified numerous variants, including a rare coding non-synonymous SNP in the DZIP1 gene, linked to late-onset sporadic PD, suggesting deviations in cellular expression programs may underlie sporadic PD [55, 56]. However, most research has focused on European populations, highlighting a need for broader genetic studies across diverse groups. These genetic predispositions emphasize the importance of understanding mitophagy's molecular mechanisms in PD.

Environmental influences, such as toxin exposure and lifestyle, significantly affect mitophagy and PD risk. Demographic factors, including age, sex, race/ethnicity, and socioeconomic status, shape individual susceptibility [57]. Toxins like pesticides and heavy metals are linked to mitochondrial dysfunction, exacerbating neurodegenerative changes [57]. The interaction between genetic and environmental factors is further complicated by the relationship between lipids and -synuclein, a key protein in PD pathology. Dysregulated lipid metabolism can influence -synuclein aggregation, impacting mitophagy and contributing to neurodegeneration [58]. Mechanistic models accounting for endogenous processes facilitating Parkinsonian damage spread are needed [59].

PD symptom variability and the lack of robust biomarkers pose challenges in identifying distinct subtypes and predicting disease trajectories [60]. Advanced approaches integrating clinical and genetic

data may aid in identifying these subtypes, paving the way for personalized therapeutic strategies [61]. Theoretical perspectives draw parallels between PD and conditions involving mitochondrial dysfunction and systemic inflammation, such as spaceflight-induced changes [62]. Innovative diagnostic approaches, like using ANN to analyze speech measurements, leverage distinct speech patterns for objective assessments [63]. This understanding highlights the need to explore genetic and environmental factors influencing mitophagy in PD, contributing to targeted interventions addressing the disease's mechanisms.

6.3 Challenges in Diagnosis and Prediction

Diagnosing and predicting Parkinson's disease (PD) involves complexities, particularly concerning mitophagy and its regulatory pathways. A major challenge is PD's late-stage diagnosis, typically after significant neurodegeneration, limiting therapeutic intervention potential [64]. Reliance on clinical symptoms often leads to overlap with other neurodegenerative conditions, complicating accurate diagnosis and increasing misdiagnosis risk [65].

Developing reliable biomarkers for early detection is crucial, yet existing methods are often costly and inaccessible, limiting clinical application [65]. Advanced computational models using deep learning have shown promise in enhancing diagnostic accuracy and sensitivity, serving as potential early detection tools [54]. However, integrating complex, multidimensional data to predict disease trajectories and identify PD subtypes remains challenging [61].

Innovative diagnostic methods, such as analyzing computer keyboard interactions to detect motor signs, offer potential for frequent, non-invasive PD symptom monitoring, particularly in early stages [52]. ANN trained on biomedical voice measurements demonstrate high classification accuracy, suggesting potential as non-invasive diagnostic tools [63]. However, relying solely on voice data may not capture all relevant clinical features, emphasizing the need for comprehensive diagnostic strategies integrating multiple data sources [66].

Another challenge is the conflicting evidence on levodopa's neuroprotective versus neurotoxic effects and the unclear mechanisms underlying these effects [50]. This uncertainty complicates treatment decisions and underscores the need for a deeper understanding of PD's pathophysiological mechanisms, including calcium signaling and mitochondrial dysfunction roles in neuronal death [47].

The variability and unpredictability of PD symptoms, combined with the need for improved biomarkers and diagnostic tools, highlight the importance of ongoing research and innovation. Addressing challenges in PD and dementia can significantly enhance diagnostic accuracy and facilitate earlier detection, vital for improving patient management and treatment outcomes. Innovations such as objective biomarkers, precision medicine approaches, and multi-omics integration with neuroimaging are essential for refining diagnostic methodologies and identifying disease-modifying therapies to slow or halt disease progression [49, 11].

7 Therapeutic Strategies Targeting Mitophagy

Category	Feature	Method
Pharmacological Interventions	Neurodegenerative Diagnostics	LSTM-FOG[54]
Innovative Technologies and Approaches	Data-Driven Analysis	SMC[67], RWR[68]
	Healthcare Diagnostics	EAM[69], nQi[52]
	Dynamic Feature Selection	EFSDT[12]
Combination Therapies and Personalized Medicine	Targeted Therapeutic Strategies	SMI[31]
	Genetic and Molecular Analysis	TWAS[35], LMA[41]
	Data-Driven Analytical Methods	CIF-PEG[44]

Table 1: Summary of methods employed in various therapeutic strategies targeting mitophagy in neurodegenerative diseases. The table categorizes the methods into pharmacological interventions, innovative technologies and approaches, and combination therapies and personalized medicine, highlighting specific features and techniques used in each category.

The advancement in understanding mitophagy has underscored its pivotal role in cellular homeostasis and its potential therapeutic implications for neurodegenerative diseases. Table 1 provides a comprehensive overview of the diverse methods applied in therapeutic strategies targeting mitophagy, categorizing them into pharmacological interventions, innovative technologies, and combination

therapies within the context of neurodegenerative diseases. This section examines both pharmacological and non-pharmacological interventions aimed at enhancing mitophagy, offering potential improvements in outcomes for various neurodegenerative disorders.

7.1 Pharmacological Interventions

Pharmacological strategies targeting mitophagy offer promising avenues for treating neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). These interventions aim to bolster mitophagic pathways, ensuring mitochondrial quality control, reducing oxidative stress, and promoting neuronal health [10]. Investigational compounds such as Urolithin A, Nicotinamide riboside, and Metformin are currently under clinical evaluation for their mitophagy-stimulating effects [26].

In PD, while traditional dopaminergic therapies remain prevalent, novel approaches are emerging. Deep learning models utilizing retinal imagery have shown potential for early PD diagnosis, enhancing patient outcomes [65]. Additionally, LSTM methods that capture long-term gait patterns offer improved diagnostic capabilities [54].

For ALS, high-fat dietary strategies have been suggested to improve lipid metabolism and clinical outcomes [41], highlighting the multifaceted nature of therapeutic approaches targeting metabolic pathways in neurodegenerative diseases.

In AD, selective inhibition of matrix metalloproteinases (MMPs) presents a novel therapeutic approach, focusing on specific MMPs implicated in the disease while preserving those with protective roles [31]. These strategies underscore the potential of pharmacological agents that modulate specific molecular pathways in neurodegeneration.

Exploring pharmacological agents that enhance mitophagy is crucial for advancing therapeutic options across age-related diseases [10]. By focusing on mitophagy-targeting compounds, research can develop improved treatment strategies addressing the underlying mechanisms of neurodegenerative diseases, thus enhancing the quality of life for affected individuals.

7.2 Non-Pharmacological Strategies

Non-pharmacological strategies, particularly lifestyle modifications, have gained prominence for their potential to enhance mitophagy and slow neurodegenerative disease progression. Exercise is a key intervention, with evidence suggesting its ability to mitigate PD medication side effects, improve efficacy, and enhance quality of life [70]. Regular physical activity supports mitochondrial biogenesis and function, promoting neuronal health and delaying disease progression.

Dietary interventions play a significant role in mitophagy regulation, selectively degrading damaged mitochondria to enhance cellular health and potentially mitigate age-related diseases [10, 2, 3]. Caloric restriction and intermittent fasting activate autophagic pathways, including mitophagy, promoting cellular homeostasis and reducing oxidative stress. These dietary strategies may mimic the benefits of exercise on mitochondrial function, offering complementary advantages for enhancing mitophagic activity.

Cognitive and social engagement activities are also crucial for maintaining cognitive function and slowing neurodegenerative processes. Mentally stimulating activities and social connections can enhance brain health by promoting optimal mitochondrial function. Research indicates that impaired mitophagy is linked to various age-related chronic diseases, including neurodegenerative disorders, and that interventions like exercise and nutrition can effectively activate mitophagy, potentially mitigating health risks [10, 71, 22, 5].

The potential of non-pharmacological strategies lies in their ability to provide holistic, accessible approaches to disease management, complementing pharmacological interventions. By promoting healthy lifestyle choices—regular physical activity, balanced nutrition, and cognitive engagement—individuals can significantly improve their overall well-being and resilience against neurodegenerative diseases like AD. This highlights the need to integrate these strategies into comprehensive care plans, especially as the prevalence of dementia is expected to rise dramatically in the coming decades [72, 29, 71, 73, 11].

7.3 Innovative Technologies and Approaches

Innovative technologies are reshaping therapeutic strategies targeting mitophagy, particularly in neurodegenerative diseases like PD. The integration of diverse data sources and advanced machine learning techniques offers promising avenues for enhancing mitophagic pathways and improving disease outcomes. The Random Walk with Restart algorithm, for instance, systematically evaluates and prioritizes drug-disease associations, demonstrating its potential in drug repurposing for PD [68].

In diagnostics, smartphone data assessing PD symptoms represents a significant advancement. Utilizing data from walking, voice, tapping, and memory tests provides a comprehensive diagnosis, illustrating the potential of mobile health technologies in PD management [69]. Additionally, ensemble regression algorithms effectively distinguish early PD patients from controls based on key hold times, showcasing innovative diagnostic tools [52].

The application of deep learning techniques in analyzing large-scale datasets, such as the UK Biobank's fundus images, emphasizes the importance of high-quality data in enhancing predictive accuracy and identifying potential therapeutic targets [65]. Ensemble feature selection methods that adaptively select thresholds based on data characteristics improve feature stability and predictive accuracy, offering robust solutions for feature extraction and analysis [12].

Advancements in imaging technologies, such as semi-supervised multi-view clustering (SMC) techniques, enhance feature extraction from MRI data through dimensionality reduction via Linear Discriminant Analysis (LDA). This integration of multi-view data provides a comprehensive understanding of disease mechanisms and potential interventions [67].

Future research should continue to explore the effects of exercise on nonmotor symptoms in PD and establish standardized exercise protocols, as exercise shows promise in mitigating disease progression and enhancing mitophagic activity [70]. By leveraging innovative technologies, research can advance towards more effective, personalized interventions targeting the underlying mechanisms of neurodegenerative diseases, ultimately improving patient outcomes and quality of life.

7.4 Combination Therapies and Personalized Medicine

The integration of combination therapies and personalized medicine offers a promising avenue for targeting mitophagy in neurodegenerative diseases by tailoring interventions to individual genetic and environmental profiles. In AD, the potential for combination therapies underscores the need to validate identified genes and explore their roles in disease progression, suggesting that personalized medicine approaches could enhance therapeutic efficacy [35]. Future research should optimize therapeutic candidates for enhancing mitophagy and investigate the potential of lifestyle interventions alongside pharmacological approaches [26].

In PD, exploring genetic risk factors and their biological implications is crucial for developing targeted therapies. Improved patient stratification, better preclinical models, and objective measures for target engagement are essential for identifying effective disease-modifying therapies [49]. Additionally, the relationship between calcium signaling and mitochondrial function in dopaminergic neurons presents a therapeutic target warranting further investigation [47].

The potential for combination therapies extends to the selective inhibition of matrix metalloproteinases (MMPs), which can reduce neuroinflammation and amyloid-beta accumulation without disrupting their physiological roles [31]. This approach emphasizes the importance of integrating pharmacological and lifestyle interventions for optimal therapeutic outcomes.

Future research should focus on personalized medicine approaches, integrating pharmacological and lifestyle interventions, and exploring the role of biomarkers in understanding disease mechanisms [29]. The survey evaluates potential therapeutic targets arising from the understanding of mitophagy processes, underscoring the significance of personalized approaches in improving patient outcomes [7].

By assessing the potential of combination therapies and personalized medicine, research can progress towards more effective, individualized interventions targeting mitophagy, ultimately enhancing patient outcomes in neurodegenerative diseases. Integrating personalized approaches with innovative technologies and combination therapies offers a comprehensive strategy for addressing the complex pathophysiology of these conditions, paving the way for improved therapeutic efficacy and patient

care. Future research should refine targeted therapies to selectively enhance beneficial mitophagy while minimizing risks [15]. Manipulating mitochondrial network states and mitophagy rates may have therapeutic implications for managing mitochondrial diseases and promoting healthy aging [4]. In ALS, compensating for lipid metabolism disturbances could inform personalized medicine approaches targeting metabolic pathways [41]. Additionally, collecting data on PEG usage and confounders in prospective observational studies, along with exploring joint modeling of propensity scores with outcome and missing data models, could refine therapeutic strategies [44]. Future research could also refine computational models to include more detailed biological processes, explore additional therapeutic interventions, and validate findings with experimental data [50].

8 Conclusion

This survey underscores the pivotal role of mitophagy in maintaining neuronal health and its potential as a therapeutic avenue for neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis. By ensuring mitochondrial quality control, mitophagy prevents the buildup of dysfunctional mitochondria, thereby reducing oxidative stress and neuronal damage. Understanding the intricacies of mitophagy not only aids in developing therapeutic strategies for neurodegenerative diseases but also extends to conditions like cancer, highlighting its broader significance in cellular homeostasis.

Despite the promising nature of strategies targeting mitophagy, their clinical application faces significant hurdles. The development of reliable biomarkers is crucial for early diagnosis, monitoring disease progression, and evaluating therapeutic effectiveness. The integration of genetic and clinical data can refine predictive models, offering a comprehensive view of disease dynamics. Data-driven approaches, such as ensemble feature selection, are instrumental in identifying stable biomarkers, particularly in Alzheimer's research.

Innovative diagnostic methods, including machine learning applications, have shown promise in enhancing the diagnostic precision for Parkinson's disease, achieving notable sensitivity and specificity. The modulation of mitophagy and the creation of therapies targeting specific mitophagic pathways represent promising areas for future exploration.

Future research should aim to broaden genetic studies across diverse populations, enhance predictive models through the integration of genetic and clinical data, and explore the functional impacts of genetic variations. Longitudinal studies are vital for evaluating the impact of lifestyle interventions, such as exercise and caloric restriction, on cognitive health and their potential to boost mitophagic activity. Moreover, the risk of excessive mitophagy leading to cell death highlights the need for a balanced therapeutic approach.

Enhancing mitophagy emerges as a promising strategy for tackling age-related diseases, with ongoing clinical trials playing a critical role in validating these approaches. By addressing the challenges associated with mitophagy impairment and deepening our understanding of its regulatory mechanisms, research can pave the way for innovative therapeutic strategies that improve health outcomes in neurodegenerative diseases. Future efforts should focus on expanding datasets, refining models, and exploring advanced deep learning techniques to enhance diagnostic accuracy and robustness.

References

[1] Logan P Poole and Kay F Macleod. Mitophagy in tumorigenesis and metastasis. *Cellular and molecular life sciences*, 78:3817–3851, 2021.

[2] Lauren E Drake, Maya Z Springer, Logan P Poole, Casey J Kim, and Kay F Macleod. Expanding perspectives on the significance of mitophagy in cancer. In *Seminars in cancer biology*, volume 47, pages 110–124. Elsevier, 2017.

[3] Daniela Bakula and Morten Scheibye-Knudsen. Mitophaging: mitophagy in aging and disease. *Frontiers in cell and developmental biology*, 8:239, 2020.

[4] Juvid Aryaman, Charlotte Bowles, Nick S. Jones, and Iain G. Johnston. Mitochondrial network state scales mtdna genetic dynamics, 2019.

[5] Guofeng Lou, Konstantinos Palikaras, Sofie Lautrup, Morten Scheibye-Knudsen, Nektarios Tavernarakis, and Evandro F Fang. Mitophagy and neuroprotection. *Trends in molecular medicine*, 26(1):8–20, 2020.

[6] Jee-Hyun Um and Jeanho Yun. Emerging role of mitophagy in human diseases and physiology. *BMB reports*, 50(6):299, 2017.

[7] University of dundee.

[8] Konstantinos Palikaras, Eirini Lionaki, and Nektarios Tavernarakis. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. *Nature cell biology*, 20(9):1013–1022, 2018.

[9] Shouliang Wang, Haijiao Long, Lianjie Hou, Baorong Feng, Zihong Ma, Ying Wu, Yu Zeng, Jiahao Cai, Da-wei Zhang, and Guojun Zhao. The mitophagy pathway and its implications in human diseases. *Signal transduction and targeted therapy*, 8(1):304, 2023.

[10] Guo Chen, Guido Kroemer, and Oliver Kepp. Mitophagy: an emerging role in aging and age-associated diseases. *Frontiers in cell and developmental biology*, 8:200, 2020.

[11] Salma Hassan, Dawlat Akaila, Maryam Arjemandi, Vijay Papineni, and Mohammad Yaqub. Mindsets: Multi-omics integration with neuroimaging for dementia subtyping and effective temporal study, 2024.

[12] Annette Spooner, Gelareh Mohammadi, Perminder S. Sachdev, Henry Brodaty, and Arcot Sowmya. Ensemble feature selection with data-driven thresholding for alzheimer's disease biomarker discovery, 2022.

[13] Juliette Ortholand, Nicolas Gensollen, Stanley Durrleman, and Sophie Tezenas du Montcel. Joint model with latent disease age: overcoming the need for reference time, 2024.

[14] Zixin Hu, Rong Jiao, Jiucun Wang, Panpan Wang, Yun Zhu, Jinying Zhao, Phil De Jager, David A Bennett, Li Jin, and Momiao Xiong. Shared causal paths underlying alzheimer's dementia and type 2 diabetes, 2019.

[15] Lijun Zhang, Lei Dai, and Deyuan Li. Mitophagy in neurological disorders. *Journal of neuroinflammation*, 18(1):297, 2021.

[16] Elayne M Fivenson, Sofie Lautrup, Nuo Sun, Morten Scheibye-Knudsen, Tinna Stevnsner, Hilde Nilsen, Vilhelm A Bohr, and Evandro F Fang. Mitophagy in neurodegeneration and aging. *Neurochemistry international*, 109:202–209, 2017.

[17] Chantell S Evans and Erika LF Holzbaur. Autophagy and mitophagy in als. *Neurobiology of disease*, 122:35–40, 2019.

[18] Ruiqiao Guan, Wei Zou, Xiaohong Dai, Xueping Yu, Hao Liu, Qiuxin Chen, and Wei Teng. Mitophagy, a potential therapeutic target for stroke. *Journal of biomedical science*, 25:1–16, 2018.

[19] Athanasios Alexiou and Panayiotis Vlamos. Evidence for early identification of alzheimer's disease, 2012.

[20] Yiming Li and Yuan Luo. Metabolomics of aging and alzheimer's disease: From single-omics to multi-omics, 2022.

[21] Annette Spooner, Gelareh Mohammadi, Perminder S. Sachdev, Henry Brodaty, and Arcot Sowmya. Ensemble feature selection with clustering for analysis of high-dimensional, correlated clinical data in the search for alzheimer's disease biomarkers, 2022.

[22] Review article.

[23] Michael Taynnan Barros, Walisson Silva, and Carlos Danilo Miranda Regis. The multi-scale impact of the alzheimer's disease in the topology diversity of astrocytes molecular communications nanonetworks, 2018.

[24] Hina Shaheen and Roderick Melnik. Brain network dynamics and multiscale modelling of neurodegenerative disorders: A review, 2024.

[25] Jangampalli Adi Pradeepkiran and P Hemachandra Reddy. Defective mitophagy in alzheimer's disease. *Ageing Research Reviews*, 64:101191, 2020.

[26] Arnaud Mary, Fanny Eysert, Frédéric Checler, and Mounia Chami. Mitophagy in alzheimer's disease: Molecular defects and therapeutic approaches. *Molecular psychiatry*, 28(1):202–216, 2023.

[27] Michiel Bertsch, Bruno Franchi, Maria Carla Tesi, and Andrea Tosin. Microscopic and macroscopic models for the onset and progression of alzheimer's disease, 2017.

[28] Enze Xu, Jingwen Zhang, Jiadi Li, Qianqian Song, Defu Yang, Guorong Wu, and Minghan Chen. Pathology steered stratification network for subtype identification in alzheimer's disease, 2023.

[29] Philip Scheltens, Bart De Strooper, Miia Kivipelto, Henne Holstege, Gael Chételat, Charlotte E Teunissen, Jeffrey Cummings, and Wiesje M van der Flier. Alzheimer's disease. *The Lancet*, 397(10284):1577–1590, 2021.

[30] Christian Tinauer, Anna Damulina, Maximilian Sackl, Martin Soellradl, Reduan Achtibat, Maximilian Dreyer, Frederik Pahde, Sebastian Lapuschkin, Reinhold Schmidt, Stefan Ropele, Wojciech Samek, and Christian Langkammer. Explainable concept mappings of mri: Revealing the mechanisms underlying deep learning-based brain disease classification, 2024.

[31] Pauline Zipfel, Christophe Rochais, Kévin Baranger, Santiago Rivera, and Patrick Dallemagne. Matrix metalloproteinases as new targets in alzheimer's disease: Opportunities and challenges, 2021.

[32] Matej Mihelčić, Goran Šimić, Mirjana Babić Leko, Nada Lavrač, Sašo Džeroski, and Tomislav Šmuc. Using redescription mining to relate clinical and biological characteristics of cognitively impaired and alzheimer's disease patients, 2017.

[33] Ari Rappoport. A lipid rafts theory of alzheimer's disease, 2024.

[34] Alfredo Sanabria-Castro, Ileana Alvarado-Echeverría, and Cecilia Monge-Bonilla. Molecular pathogenesis of alzheimer's disease: an update. *Annals of neurosciences*, 24(1):46–54, 2017.

[35] Sicheng Hao, Rui Wang, Yu Zhang, and Hui Zhan. Prediction of alzheimer's disease-associated genes by integration of gwas summary data and expression data, 2018.

[36] Michael A DeTure and Dennis W Dickson. The neuropathological diagnosis of alzheimer's disease. *Molecular neurodegeneration*, 14(1):32, 2019.

[37] Xiaoxia Liu, Robert R Butler III au2, Prashnna K Gyawali, Frank M Longo, and Zihuai He. Scatt: an attention based architecture to analyze alzheimer's disease at cell type level from single-cell rna-sequencing data, 2024.

[38] Steven A. Frank. Puzzles in modern biology. iv. neurodegeneration, localized origin and widespread decay, 2016.

[39] Sagar D. Khare, Feng Ding, and Nikolay V. Dokholyan. Folding of cu, zn superoxide dismutase and familial amyotrophic lateral sclerosis, 2003.

[40] Leslie I Grad, Guy A Rouleau, John Ravits, and Neil R Cashman. Clinical spectrum of amyotrophic lateral sclerosis (als). *Cold Spring Harbor perspectives in medicine*, 7(8):a024117, 2017.

[41] A. Fergani, H. Oudart, J. L. Gonzalez De Aguilar, B. Fricker, F. René, J. F. Hocquette, V. Meininger, L. Dupuis, and J. P. Loeffler. Increased peripheral lipid clearance in an animal model of amyotrophic lateral sclerosis, 2007.

[42] Katherine E Irwin, Udit Sheth, Philip C Wong, and Tania F Gendron. Fluid biomarkers for amyotrophic lateral sclerosis: a review. *Molecular neurodegeneration*, 19(1):9, 2024.

[43] Farshad Merrikh-Bayat. Time series analysis of parkinson's disease, huntington's disease and amyotrophic lateral sclerosis, 2013.

[44] Pallavi Mishra-Kalyani, Brent A. Johnson, Jonathan D. Glass, and Qi Long. Estimating the effect of peg in als patients using observational data subject to censoring by death and missing outcomes, 2019.

[45] Henk-Jan Westeneng, Thomas PA Debray, Anne E Visser, Ruben PA van Eijk, James PK Rooney, Andrea Calvo, Sarah Martin, Christopher J McDermott, Alexander G Thompson, Susana Pinto, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *The Lancet Neurology*, 17(5):423–433, 2018.

[46] Michael A Van Es, Orla Hardiman, Adriano Chio, Ammar Al-Chalabi, R Jeroen Pasterkamp, Jan H Veldink, and Leonard H Van den Berg. Amyotrophic lateral sclerosis. *The Lancet*, 390(10107):2084–2098, 2017.

[47] D James Surmeier, Paul T Schumacker, Jaime D Guzman, Ema Ilijic, Ben Yang, and Enrico Zampese. Calcium and parkinson's disease. *Biochemical and biophysical research communications*, 483(4):1013–1019, 2017.

[48] Bastiaan R Bloem, Michael S Okun, and Christine Klein. Parkinson's disease. *The Lancet*, 397(10291):2284–2303, 2021.

[49] Nirosen Vijiaratnam, Tanya Simuni, Oliver Bandmann, Huw R Morris, and Thomas Foltynie. Progress towards therapies for disease modification in parkinson's disease. *The Lancet Neurology*, 20(7):559–572, 2021.

[50] Vignayanandam R. Muddapu, Karthik Vijayakumar, Keerthiga Ramakrishnan, and V Srinivasa Chakravarthy. A computational model of levodopa-induced toxicity in substantia nigra pars compacta in parkinson's disease, 2020.

[51] Maria Frasca, Davide La Torre, Gabriella Pravettoni, and Ilaria Cutica. Predicting parkinson's disease evolution using deep learning, 2024.

[52] L. Giancardo, A. Sánchez-Ferro, T. Arroyo-Gallego, I. Butterworth, C. S. Mendoza, P. Montero, M. Matarazzo, A. Obeso, M. L. Gray, and San José Estépar. Computer keyboard interaction as an indicator of early parkinson's disease, 2016.

[53] Abhinav Roy, Bhavesh Gyanchandani, Aditya Oza, and Abhishek Sharma. Advancing parkinson's disease progression prediction: Comparing long short-term memory networks and kolmogorov-arnold networks, 2024.

[54] Aqib Nazir Mir, Iqra Nissar, Mumtaz Ahmed, Sarfaraz Masood, and Danish Raza Rizvi. Parkinson's disease diagnosis through deep learning: A novel lstm-based approach for freezing of gait detection, 2024.

[55] Cornelis Blauwendraat, Mike A Nalls, and Andrew B Singleton. The genetic architecture of parkinson's disease. *The Lancet Neurology*, 19(2):170–178, 2020.

[56] A. X. C. N. Valente, J. H. Shin, A. Sarkar, and Y. Gao. Rare coding snp in dzip1 gene associated with late-onset sporadic parkinson's disease, 2011.

[57] Yoav Ben-Shlomo, Sirwan Darweesh, Jorge Llibre-Guerra, Connie Marras, Marta San Luciano, and Caroline Tanner. The epidemiology of parkinson's disease. *The Lancet*, 403(10423):283–292, 2024.

[58] Saranna Fanning, Dennis Selkoe, and Ulf Dettmer. Parkinson's disease: proteinopathy or lipidopathy? *NPJ Parkinson's disease*, 6(1):3, 2020.

[59] Míriam R. García, Mathieu Cloutier, and Peter Wellstead. A reaction-diffusion model for the progression of parkinson's disease, 2017.

[60] Elliot Burghardt, Daniel Sewell, and Joseph Cavanaugh. Identification of parkinson's disease subtypes with divisive hierarchical bayesian clustering for longitudinal and time-to-event data, 2023.

[61] Sanjukta Krishnagopal, Rainer Von Coelln, Lisa M. Shulman, and Michelle Girvan. Identifying and predicting parkinson's disease subtypes through trajectory clustering via bipartite networks, 2019.

[62] Nilufar Ali, Afshin Beheshti, and Greg Hampikian. Unveiling parkinson's disease-like changes triggered by spaceflight, 2024.

[63] Pooja Chandrashekar. Mathematically modeling the gpe/stn neuronal cluster to account for parkinsonian tremor and developing a novel method to accurately diagnose parkinson's disease using speech measurements and an artificial neural network, 2014.

[64] Werner Poewe, Klaus Seppi, Caroline M Tanner, Glenda M Halliday, Patrik Brundin, Jens Volkmann, Anette-Eleonore Schrag, and Anthony E Lang. Parkinson disease. *Nature reviews Disease primers*, 3(1):1–21, 2017.

[65] Charlie Tran, Kai Shen, Kang Liu, Akshay Ashok, Adolfo Ramirez-Zamora, Jinghua Chen, Yulin Li, and Ruogu Fang. Deep learning predicts prevalent and incident parkinson's disease from uk biobank fundus imaging, 2024.

[66] María Teresa García-Ordás, José Alberto Benítez-Andrades, Jose Aveleira-Mata, José-Manuel Alija-Pérez, and Carmen Benavides. Determining the severity of parkinson's disease in patients using a multi task neural network, 2024.

[67] Xiaobo Zhang, Donghai Zhai, Yan Yang, Yiling Zhang, and Chunlin Wang. A novel semi-supervised multi-view clustering framework for screening parkinson's disease, 2020.

[68] Pratham Kankariya, Rachita Rode, Kevin Mudaliar, and Pranali Hatode. Drug repurposing for parkinson's disease using random walk with restart algorithm and the parkinson's disease ontology database, 2024.

[69] Patrick Schwab and Walter Karlen. Phonemd: Learning to diagnose parkinson's disease from smartphone data, 2018.

[70] Xiaojiao Xu, Zhenfa Fu, and Weidong Le. Exercise and parkinson's disease. *International review of neurobiology*, 147:45–74, 2019.

[71] Eric Mayor. Neurotrophic effects of intermittent fasting, calorie restriction and exercise: A review and annotated bibliography, 2023.

[72] Ankur Patel, Grishma joshi, and Rupali Ugile. Stem cell therapy for alzheimer's disease, 2016.

[73] Joachim Enengl and Peter Dungel. neverforget - photobiomodulation against alzheimer's disease: A systematic review, 2019.

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