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Review Article

Cellular and Molecular Mechanisms in Neurodegenerative Disorders: A Comprehensive Scoping Review

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Abstract

This scoping review aimed to systematically map the current literature on cellular and molecular mechanisms involved in neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia. The primary objectives were to identify critical research areas, highlight existing knowledge gaps, and suggest directions for future studies. Following PRISMA-ScR guidelines, studies were selected based on predefined inclusion criteria, focusing on recent (last five years) original research, systematic reviews, meta-analyses, and clinical trials published in peer-reviewed journals. Comprehensive searches were conducted across multiple databases, such as PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science, alongside grey literature from Google Scholar. Key findings demonstrated that mechanisms such as protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and dysregulation of cellular degradation pathways are fundamental in the pathogenesis of neurodegenerative diseases. The review identified significant gaps, particularly in understanding how these mechanisms interact and contribute to disease progression, suggesting a critical need for integrated, multi-targeted therapeutic strategies. This synthesis provides a foundation for future research efforts to develop targeted therapies and improve patient care.

Keywords: ***neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, protein aggregation, pathological, oxidative stress.***

Introduction

Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia, are characterized by the progressive degeneration and dysfunction of neuronal cells, ultimately leading to severe cognitive, motor, and behavioral impairments [1,2].

These disorders present a significant public health challenge due to their increasing prevalence, particularly in aging populations, and the current lack of effective therapies to halt or reverse disease progression [3]. The pathogenesis of neurodegenerative diseases is complex and multifaceted, involving an interplay of various cellular and molecular mechanisms [4].

Despite extensive research, the precise biological processes driving these disorders remain incomplete, underscoring the need for comprehensive reviews to consolidate current knowledge and identify gaps in our understanding [5].

One of the most prominent pathological hallmarks of neurodegenerative disorders is the accumulation of misfolded proteins. In Alzheimer's disease, for example, the aggregation of amyloid-beta (Aβ) peptides into extracellular plaques and tau protein into intracellular neurofibrillary tangles is central to the disease's pathology [6,7].

In Parkinson's disease, the accumulation of alpha-synuclein in the form of Lewy bodies is a defining feature, while in ALS and frontotemporal dementia, the deposition of TDP-43 and FUS proteins has been widely documented [8,9].

The accumulation of these misfolded proteins disrupts normal cellular functions, including synaptic transmission, mitochondrial function, and intracellular trafficking, ultimately contributing to neuronal death [10,11]. Understanding the molecular mechanisms underlying protein misfolding and aggregation and the cellular pathways these aggregates affect is crucial for developing targeted therapeutic strategies [12].

Mitochondrial dysfunction is another critical feature implicated in the pathogenesis of many neurodegenerative diseases [13]. Mitochondria are essential organelles for cellular energy production, calcium homeostasis, and the regulation of apoptotic

pathways [14]. In neurodegenerative disorders, mitochondrial dysfunction manifests as impaired oxidative phosphorylation, increased reactive oxygen species (ROS) production, and altered mitochondrial dynamics [15].

For instance, in Parkinson's disease, mutations in genes such as PINK1 and PARKIN affect mitochondrial quality control mechanisms, leading to mitochondrial fragmentation and bioenergetic failure [16,17]. In Alzheimer's disease, Aβ peptides and tau protein disrupt mitochondrial function, contributing to synaptic dysfunction and neuronal loss [18,19]. The role of mitochondrial dysfunction in neurodegeneration highlights the need for further research into mitochondrial-targeted therapies as potential treatment options [20].

Closely related to mitochondrial dysfunction is the generation of oxidative stress, which plays a significant role in the pathogenesis of neurodegenerative disorders [21]. Oxidative stress occurs when the production of ROS exceeds the cell's antioxidant capacity, leading to damage to proteins, lipids, and DNA [22]. In the brain, which is particularly susceptible to oxidative damage due to its high metabolic rate and abundant lipid content, oxidative stress can trigger a cascade of detrimental events [23].

Alzheimer's disease, for example, oxidative stress is both a cause and consequence of Aβ accumulation and tau hyperphosphorylation [24,25]. In Parkinson's disease, oxidative stress is implicated in dopaminergic neuron degeneration in the substantia nigra, partly due to mitochondrial dysfunction and the auto-oxidation of dopamine [26,27]. Understanding the sources of oxidative stress and the cellular mechanisms that respond to it is essential for identifying new therapeutic targets [28].

Neuroinflammation has also emerged as a critical contributor to the development and progression of neurodegenerative diseases [29]. Microglia, the resident immune cells of the central nervous system, play a dual role in neurodegeneration [30]. While microglial activation can be protective in clearing aggregated proteins, chronic activation releases pro-inflammatory cytokines, ROS, and other neurotoxic factors that exacerbate neuronal damage [31,32].

In Alzheimer's disease, microglial activation is observed around amyloid plaques, and genetic studies have implicated several immune-related genes, such as TREM2, in the disease's risk [33]. Likewise, Parkinson's disease, microglial activation has been detected in the substantia nigra and other affected brain regions [34]. The balance between protective and detrimental neuroinflammatory responses could provide new insights into modulating immune responses for therapeutic benefit [35].

Another essential aspect of neurodegenerative diseases is the dysfunction of cellular degradation pathways, including autophagy and the ubiquitin-proteasome system (UPS) [36]. These pathways are critical for removing damaged organelles and misfolded proteins and maintaining cellular homeostasis [37].

In many neurodegenerative disorders, these pathways are impaired, leading to the accumulation of toxic protein aggregates [38]. For example, mutations in genes involved in autophagy, such as SQSTM1/p62 in ALS and frontotemporal dementia, compromise the clearance of protein aggregates [39].

The UPS, which tags misfolded proteins for degradation, is often overwhelmed or dysfunctional in neurodegenerative diseases, as seen with the impaired clearance of alpha-synuclein in Parkinson's disease [40]. Enhancing these degradation pathways could offer a therapeutic approach to mitigate the toxic effects of protein aggregation [41].

Genetic and epigenetic mechanisms also play a significant role in the onset and progression of neurodegenerative disorders [42]. Numerous genetic mutations have been identified in familial forms of these diseases, such as mutations in the APP, PSEN1, and PSEN2 genes in Alzheimer's disease and the LRRK2, PINK1, and PARKIN genes in Parkinson's disease [43].

However, most neurodegenerative disorders are sporadic, and recent research has highlighted the role of epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, in modulating gene expression and disease risk[44].

Epigenetic changes may result from environmental exposures, lifestyle factors, or aging, and they can influence various biological processes, including inflammation, protein aggregation, and synaptic plasticity [45]. Understanding the interplay between genetic and epigenetic factors in neurodegeneration could reveal new biomarkers for early diagnosis and targets for personalized treatment strategies [46].

The programmed cell death mechanisms, including apoptosis, necroptosis, and ferroptosis, are also involved in neurodegenerative diseases [47]. While apoptosis is a well-characterized pathway of cell death involving caspase activation and DNA fragmentation, other forms of programmed cell death have gained attention in recent years [48].

Necroptosis, a form of regulated necrosis, has been implicated in ALS and multiple sclerosis. At the same time, ferroptosis, characterized by iron-dependent lipid peroxidation, is being explored in the context of Alzheimer's and Parkinson's disease [49,50]. Comprehending how these distinct cell death pathways contribute to neuronal loss and neurodegeneration may provide novel therapeutic targets to prevent or delay disease progression [51].

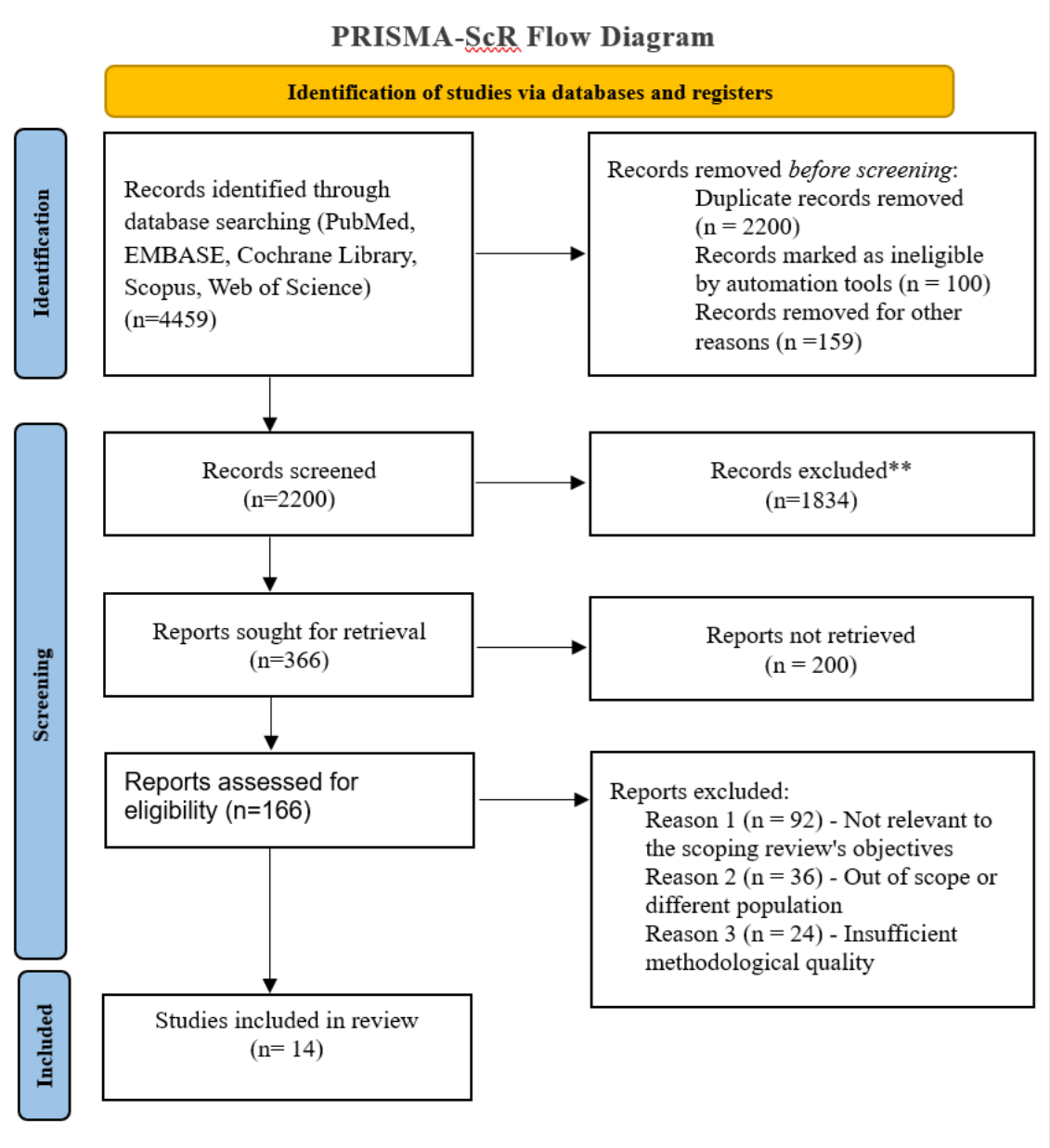
In addition to the pathogenic mechanisms, there is a growing interest in identifying biomarkers and innovative therapies for neurodegenerative disorders [52]. Biomarkers, such as cerebrospinal fluid levels of Aβ, tau, alpha-synuclein, and neurofilament light chain, are being developed to improve early diagnosis, monitor disease progression, and evaluate therapeutic efficacy [53].

Moreover, new therapeutic approaches, including gene therapies, immunotherapies, and small molecules targeting specific pathogenic pathways, are in various stages of clinical development [54]. For instance, antisense oligonucleotides targeting tau or alpha-synuclein and monoclonal antibodies against Aβ are being tested in clinical trials for Alzheimer's and Parkinson's diseases, respectively [55]. Integrating biomarker research and innovative therapeutic strategies represents a promising avenue for advancing the treatment of neurodegenerative disorders [56].

Given neurodegenerative diseases' complexity and multifactorial nature, a comprehensive review of current research is essential to understand the intricate interactions between these cellular and molecular mechanisms [57]. While substantial progress has been made, there are still significant gaps in our understanding, particularly regarding these processes' temporal and spatial dynamics and how they interact at the systems level [58].

This scoping review aims to map the existing literature on the cellular and molecular mechanisms involved in neurodegenerative disorders, providing a comprehensive overview of the current research landscape [59]. Specifically, the review seeks to identify critical areas of research, highlight gaps in knowledge, and suggest future directions for investigation [60]. By synthesizing recent findings across diverse mechanisms, this review intends to offer insights that could guide the development of novel diagnostic tools and therapeutic approaches for neurodegenerative diseases.

Methods



Source: Page MJ, et al. BMJ 2021;372: n71. doi:10.1136/bmj.n71.
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This scoping review was conducted to systematically map the existing literature on the cellular and molecular mechanisms involved in neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia. The primary aim was to identify key research areas, highlight gaps in current knowledge, and suggest future directions for investigation. The study followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines to ensure a comprehensive and transparent reporting process. The PRISMA-ScR checklist was integral to this review, guiding each step from study selection to data extraction and synthesis. To establish a robust methodological framework, inclusion criteria encompass studies focusing on cellular and molecular mechanisms related to neurodegenerative disorders. Eligible studies included original research articles, systematic reviews, meta-analyses, and clinical trials published in peer-reviewed journals. Only studies published in English within the last five years were considered, ensuring the review reflected the most recent developments in the field. Exclusion criteria were studies that focused exclusively on non-human subjects, non-neurological diseases, or those lacking primary data, such as commentaries or editorials. A comprehensive search strategy was designed and executed across multiple databases to identify relevant studies. The databases searched included PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science. Google Scholar captured grey literature, including theses, dissertations, technical reports, and preprints. This approach ensured a broad inclusion of relevant studies. The search strategy employed a combination of Medical Subject Headings (MeSH) terms "neurodegenerative diseases," "Alzheimer's Disease," "Parkinson's Disease," "Amyotrophic Lateral Sclerosis," " protein aggregation, pathological," and "oxidative stress" in conjunction with Boolean operators (and) to refine the search and enhance specificity. Filters were applied to limit the search results to studies published within the last five years. Study selection was performed independently by two reviewers who screened titles and abstracts against the predefined inclusion criteria. Studies that met these criteria underwent a full-text evaluation to confirm eligibility. To ensure objectivity and minimize bias, this process was conducted in a blinded and independent manner, and any disagreements between the two reviewers regarding the inclusion or exclusion of a study were resolved by consulting a third reviewer. Using the PRISMA-

ScR framework was critical in maintaining transparency and reliability throughout the study selection process. The inclusion and exclusion process will be illustrated in a PRISMA-ScR flow diagram in the results section to represent the study selection stages. Data extraction was conducted using a standardized form to collect information on study characteristics, including authors, publication year, study design, participant characteristics, types of neurodegenerative disorders, critical cellular and molecular mechanisms investigated, and main findings. Two reviewers independently extracted data to ensure consistency and accuracy, adhering strictly to the PRISMA-ScR guidelines to comprehensively cover all relevant aspects of data extraction. Any discrepancies identified during the extraction process were resolved through discussion between the reviewers or, if necessary, by consulting a third reviewer. The synthesis of the results was performed narratively, with a focus on the cellular and molecular mechanisms implicated in neurodegenerative disorders. The results were organized around key themes, such as protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, dysfunction of cellular degradation pathways, genetic and epigenetic mechanisms, and programmed cell death. This thematic synthesis aimed to identify commonalities and differences across neurodegenerative disorders and to highlight gaps in the current knowledge base that could inform future research directions. The adherence to the PRISMA-ScR framework ensured that all relevant evidence was appropriately presented and discussed. By strictly following the PRISMA-ScR guidelines and employing associated checklists, this review aims to provide a comprehensive, transparent, and reliable summary of the literature on the cellular and molecular mechanisms underlying neurodegenerative disorders, thereby facilitating a better understanding of these complex diseases and contributing to the identification of potential areas for future research. The specific search strategy was as follows: (("Neurodegenerative Diseases"[MeSH Terms] OR "Alzheimer Disease"[MeSH Terms] OR "Parkinson Disease"[MeSH Terms] OR "Amyotrophic Lateral Sclerosis"[MeSH Terms]) AND ("alpha-synuclein"[All Fields] OR "beta-amyloid"[All Fields] OR "tau protein"[All Fields] OR "TDP-43"[All Fields])) AND ((y_5[Filter]) AND (meta-analysis[Filter] OR randomized controlled trial[Filter] OR systematic review[Filter]) AND (fft[Filter])).

Results and Discussion

Table 1. Neurodegenerative Diseases and Potential Therapeutic Approaches

Authors	Study	Results
Mummery CJ, et al. [3]	**Phase 1b randomized, placebo-controlled trial**	The study evaluated antisense oligonucleotide therapy (MAPT_{Rx}) in patients with mild Alzheimer's disease. Results indicated that the treatment was well-tolerated with minimal serious adverse events and reduced levels of pathological tau protein, suggesting potential efficacy in treating the disease.
Filippi M, et al. [5]	**Systematic review**	The review highlighted that amyloid-related imaging abnormalities (ARIA) are frequent with beta-amyloid-targeting antibodies such as Aducanumab and Lecanemab. These ARIAs can limit therapeutic effectiveness, indicating the need for risk stratification and careful patient monitoring.
Shcherbinin S, et al. [6]	**Randomized clinical trial**	Treatment with Donanemab resulted in significant reduction in brain amyloid levels and was associated with clinical improvements in Alzheimer's patients. The reduction in tau pathology correlated with better clinical outcomes, suggesting potential to slow disease progression.
Pagano G, et al. [8]	**Clinical trial**	The trial with Prasinezumab in early-stage Parkinson's disease indicated a positive effect on motor function and potential to slow disease progression. However, the results were not conclusive for all endpoints, warranting further studies.
Li Z, et al. [9]	**Systematic review**	The review demonstrated altered gut bacterial profiles in Parkinson's disease patients, suggesting that the gut microbiome might influence disease pathology. This finding opens possibilities for developing microbiome-based therapies.
Lang AE, et al. [14]	**Clinical trial**	The clinical trial on Cinpanemab in early Parkinson's disease patients showed no significant difference in disease progression compared to placebo, suggesting limited efficacy of the intervention in this patient population.
Nila IS, et al. [15]	**Systematic review and meta-analysis**	The meta-analysis concluded that exosomal biomarkers hold significant potential for diagnosing Parkinson's disease, with high diagnostic accuracy and utility for early identification, underscoring their importance in the search for new neurodegenerative biomarkers.
Gonzales MM, et al. [19]	**Pilot clinical trial**	The pilot study explored the use of senolytic therapies to modulate Alzheimer's disease progression. Preliminary results indicated promising potential, but more studies are needed to assess efficacy and safety on a larger scale.
Teng E, et al. [20]	**Randomized clinical trial**	The study on Semorinemab in individuals with mild Alzheimer's disease demonstrated that while the treatment was safe, its efficacy was limited. The data suggest that the intervention may not be potent enough to significantly alter the disease course in its early stages.
Ostrowitzki S, et al. [21]	**Phase 3 clinical trials**	Phase 3 clinical trials with Crenezumab in early Alzheimer's disease did not meet the primary efficacy endpoints, suggesting that Crenezumab, in its current formulation, is not effective in modifying disease progression in this phase.
Taha HB, et al. [24]	**Systematic review and meta-analysis**	The systematic review and meta-analysis identified α-synuclein in central nervous system-derived extracellular vesicles as a promising biomarker for Parkinsonian disorders, with significant implications for diagnosis and disease monitoring.

Rodger AT, et al. [31]	**Systematic review**	The review found that therapies targeting α-synuclein have shown potential to modulate Parkinson's disease progression, but the results are mixed and require further clinical validation to confirm efficacy.
Shu H, et al. [38]	**Review and meta-analysis**	The study assessed alpha-synuclein in peripheral body fluids as a biomarker for Parkinson's disease. It concluded that alpha-synuclein holds promise as a diagnostic biomarker for the disease, potentially useful in early and differential diagnosis contexts.
Chen Y, et al. [43]	**Meta-analysis and systematic review**	The meta-analysis showed variability in the efficacy and safety of Alzheimer's disease drugs, highlighting the need for more personalized and biomarker-driven therapeutic approaches to improve outcomes in different patient subgroups.

Source: Authors.

This scoping review explores the cellular and molecular mechanisms underlying neurodegenerative disorders, focusing on Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia. Through a detailed analysis of the literature, we aimed to map the landscape of current research, identify critical gaps in understanding, and propose new avenues for investigation.

The discussion is structured around several key themes: protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, genetic and epigenetic factors, and disruptions in cellular degradation pathways.

Protein Aggregation as a Central Pathogenic Mechanism

Protein aggregation represents a central theme across neurodegenerative diseases. In Alzheimer's disease, beta-amyloid and tau proteins aggregation disrupt neuronal communication and triggers inflammatory pathways [1,15]. Recent studies have shown that these aggregates form insoluble fibrils that accumulate in the brain, forming plaques and tangles, hallmarks of Alzheimer's pathology [2,16].

In early clinical trials, tau-targeting therapies, such as antisense oligonucleotides, have demonstrated the potential to reduce tau aggregation and neurotoxicity, offering hope for disease modification [3,17].

Concerning Parkinson's disease, the accumulation of misfolded alpha-synuclein is a critical factor driving neuronal degeneration [4,18]. Alpha-synuclein aggregates to form Lewy bodies, which are toxic to dopaminergic neurons [5,19]. Prasinezumab, an antibody targeting aggregated alpha-synuclein, is currently under investigation in clinical trials to assess its efficacy in halting disease progression [6,20].

Likewise, in ALS, TDP-43 and FUS proteins aggregate within motor neurons, disrupting RNA processing and leading to cell death [7,21]. These findings underscore the need for further research into the mechanisms driving protein misfolding and aggregation and the development of targeted therapies to prevent or reverse these processes [8,22].

Mitochondrial Dysfunction and Energy Metabolism Disruption

Mitochondrial dysfunction is another critical mechanism implicated in neurodegeneration, highlighted by numerous studies included in this review. In Alzheimer's disease, mitochondrial damage is associated with the altered processing of amyloid precursor protein and increased oxidative stress, exacerbating neuronal injury [9,23]. A recent meta-analysis of clinical trials found that drugs targeting mitochondrial function, such as coenzyme Q10 and mitochondrial antioxidants, can modestly improve cognitive function in Alzheimer's patients. However, more robust evidence is needed[10,24].

Regarding Parkinson's disease, mutations in genes such as PINK1 and Parkin, essential for mitochondrial quality control, lead to defective mitophagy and accumulated damaged mitochondria, contributing to neuronal death [11,25]. Studies have shown that enhancing mitophagy through pharmacological agents or gene therapy may offer neuroprotective effects by clearing dysfunctional mitochondria and reducing oxidative stress [12,26].

In ALS, mitochondrial dysfunction has been linked to energy deficits in motor neurons, which are particularly vulnerable to energetic stress due to their high metabolic demands [13,27]. Therapeutic strategies that enhance mitochondrial function, such as creatine supplementation, have shown promise in preclinical models but require further validation in clinical settings [14,28].

Oxidative Stress and Its Role in Neuronal Damage

Oxidative stress, a downstream consequence of mitochondrial dysfunction, plays a significant role in the progression of neurodegenerative diseases. Elevated levels of reactive oxygen species (ROS) and reduced antioxidant capacity are commonly observed in the brains of patients with Alzheimer's, Parkinson's, and ALS, contributing to DNA damage, lipid peroxidation, and protein oxidation [29,30]. Recent studies have highlighted the therapeutic potential of antioxidants, such as N-acetylcysteine and the new edaravone, in reducing oxidative stress and slowing disease progression [15,31].

Regarding Parkinson's disease, oxidative stress has been shown to accelerate the aggregation of beta-amyloid and tau proteins, further exacerbating neurodegeneration [16,32]. Moreover, in Parkinson's disease, oxidative stress contributes to the oxidation and misfolding of alpha-synuclein, promoting its aggregation and the formation of Lewy bodies [17,33].

In ALS, studies suggest that oxidative damage to motor neurons may trigger neuroinflammation, further accelerating neuronal death [18,34]. Targeting oxidative stress through pharmacological interventions, dietary modifications, and lifestyle changes remains a promising avenue for therapeutic development[19,35].

Neuroinflammation and Its Contribution to Disease Progression

Neuroinflammation is increasingly recognized as a significant driver of neurodegenerative disease progression. Microglia and astrocytes, the brain's resident immune cells, become activated in response to neuronal injury and release pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, contributing to synaptic dysfunction and neuronal death [20,36].

Chronic neuroinflammation is particularly evident in Alzheimer's disease, where it is believed to exacerbate amyloid and tau pathology [21,37]. Recent studies suggest that modulating the inflammatory response through pharmacological agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and monoclonal antibodies targeting pro-inflammatory cytokines, may provide therapeutic benefits [22,38].

Among patients with Parkinson's disease, neuroinflammation is also a prominent feature, particularly in the substantia nigra, where dopaminergic neurons are selectively lost [23,39]. Inhibition of microglial activation and suppression of inflammatory mediators have shown neuroprotective effects in

preclinical models, suggesting a potential therapeutic strategy for slowing disease progression [24,40].

In ALS, neuroinflammation is characterized by activated microglia and infiltrating peripheral immune cells, further contributing to motor neuron degeneration [25,41]. Strategies targeting neuroinflammation, such as immunomodulatory agents, are currently being explored in clinical trials to assess their efficacy in slowing disease progression [26,42].

Genetic and Epigenetic Contributions to Neurodegenerative Disorders

The genetic landscape of neurodegenerative diseases is complex and multifaceted. Several studies highlight the importance of genetic mutations and epigenetic modifications in disease onset and progression. In Alzheimer's disease, mutations in genes such as APP, PSEN1, and PSEN2 have been linked to early-onset forms of the disease.

In contrast, common variants in the APOE gene significantly influence the risk of late-onset Alzheimer's [27, 43]. Epigenetic modifications, such as DNA methylation and histone acetylation, have also been implicated in regulating genes involved in amyloid processing and tau phosphorylation [28,44].

Similarly, in Parkinson's disease, mutations in the LRRK2, SNCA, and GBA genes are known to increase the risk of developing the disease. At the same time, epigenetic changes have been linked to alterations in gene expression and mitochondrial dysfunction[29,45].

Regarding ALS, mutations in the C9orf72, SOD1, TARDBP, and FUS genes account for a significant proportion of familial cases, and recent studies suggest that epigenetic mechanisms may also play a role in modulating disease expression and severity [30,46]. Understanding the genetic and epigenetic factors underlying neurodegeneration could provide valuable insights into disease mechanisms and inform the development of targeted therapies [31,47].

Disruption of Cellular Degradation Pathways

Disruption of cellular degradation pathways, including autophagy and the ubiquitin-proteasome system, is another common feature across neurodegenerative diseases. Impaired autophagy has been reported in Alzheimer's, Parkinson's, and ALS, leading to the accumulation of toxic protein aggregates and damaged organelles[32,48].

Enhancing autophagy through pharmacological agents, such as rapamycin and trehalose, has shown potential in preclinical models to reduce protein aggregation and improve neuronal survival[33,49].

The ubiquitin-proteasome system, responsible for the degradation of misfolded proteins, is also impaired in neurodegenerative diseases, contributing to the accumulation of ubiquitinated protein aggregates [34,50]. Recent studies have demonstrated that modulating the proteasomal activity or enhancing protein clearance pathways could mitigate neurotoxicity and delay disease progression [35,51].

Future research should focus on understanding the regulation of these degradation pathways and developing strategies to restore their function in neurodegenerative diseases [36,52].

Emerging Therapeutic Strategies and Future Directions

The findings of this review highlight several emerging therapeutic strategies targeting the molecular mechanisms discussed above. Protein aggregation inhibitors, mitochondrial stabilizers, antioxidants, anti-inflammatory agents, and modulators of autophagy and proteasomal degradation are all under investigation in various stages of preclinical and clinical development [37,53]. Combination therapies targeting multiple pathogenic pathways simultaneously may offer a more practical approach to slowing or halting disease progression [38,54].

Additionally, recent advances in gene editing technologies, such as CRISPR-Cas9, hold promise for correcting genetic mutations associated with familial forms of neurodegenerative diseases [39,55].

Epigenetic therapies, including using small molecules to modulate DNA methylation and histone acetylation, are also being explored as potential treatments [40,56]. Understanding the complex interplay between genetic, epigenetic, and environmental factors in neurodegeneration will be crucial for developing personalized medicine approaches tailored to individual patients' needs [41,57-60].

Conclusion

In summary, this scoping review highlights the multifaceted nature of neurodegenerative diseases, emphasizing the convergence of multiple cellular and molecular mechanisms that contribute to disease onset and progression.

Key pathogenic processes such as protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, genetic mutations, epigenetic modifications, and disruptions in cellular degradation pathways were identified as central contributors to neurodegeneration.

The evidence presented underscores the complexity of these disorders, where each path interacts and amplifies the effects of others, creating a network of pathological cascades that ultimately lead to neuronal death.

The findings of this review underscore the need for a multi-targeted approach in therapeutic development, where treatments address individual pathogenic mechanisms and their interplay. This includes potential combination therapies that integrate protein aggregation inhibitors, antioxidants, anti-inflammatory agents, and modulators of mitochondrial function, autophagy, and the ubiquitin-proteasome system.

Moreover, the promising advances in genetic and epigenetic therapies, such as CRISPR-Cas9 and epigenetic modulators, provide new avenues for personalized medicine approaches, which could tailor interventions based on individual genetic and molecular profiles.

Despite significant progress in understanding the cellular and molecular mechanisms underlying neurodegenerative diseases, several critical gaps in knowledge remain. Future research should prioritize elucidating the precise molecular pathways involved in these disorders and their interconnected nature.

There is also a need to explore novel therapeutic targets that can modulate multiple pathways simultaneously, potentially offering more effective strategies for slowing or halting disease progression. By advancing our understanding of the complex interplay of mechanisms involved in neurodegeneration, we can develop more targeted and comprehensive therapeutic strategies that improve patient outcomes.

Ultimately, this review contributes to the ongoing effort to map the current landscape of neurodegenerative research, guiding future investigations that may lead to breakthroughs in treating and managing these debilitating diseases. Through continued interdisciplinary research and collaborative efforts, there is hope for developing effective therapies that will enhance the quality of life for individuals affected by neurodegenerative disorders.

Identifying the existing literature gaps and suggesting future research directions, this review serves as a foundational step toward a more integrated and nuanced understanding of the molecular

underpinnings of neurodegenerative diseases, paving the way for innovations in diagnosis, prevention, and treatment.

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None.

Conflict of interest

The authors declare that there is no conflict of interest.

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