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# Neuroinflammation and Neurodegeneration: Emerging Insights into Molecular Mechanisms

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**Abstract:**

Neurodegenerative diseases are affecting more people and imposing a greater burden on countries. Scientists have not yet created a drug that cures these diseases completely. This article is written to gain a deeper understanding of neurodegenerative diseases. Microglia, astrocytes and oligodendrocytes cells and significant signalling pathways such as NLRP3 and mitochondria are the major triggers to neuroinflammations. Additionally, four neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis) are discussed through analysis of their symptoms, causes and current treatments. Current treatments still rely on utilising existing methodologies or natural products of green tea to alleviate symptoms. The complexity of these diseases renders single therapy approaches unlikely to be efficacious, necessitating multidisciplinary research to discover more effective intervention strategies. Future research should focus on identifying novel drug targets and developing personalised treatment protocols. Simultaneously, efforts should be made to improve early diagnostic technologies and harness the potential of lifestyle interventions to achieve comprehensive health management from prevention to treatment.

**Keywords:** Neuroscience; Neurodegenerative diseases; Neuroinflammation.

## 1. Introduction

Neurodegenerative diseases (NDDs) encompass various disorders like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). What unites them is the relentless deterioration of nervous system structure and function [1]. As the global population expands rapidly, so does the number of people grapple with these conditions [2]. Projections suggest nearly 153 million individuals could be living with AD alone by 2050 [2]. Despite ongoing scientific efforts to find cures, developing effective therapies remains a long, difficult road, often marked by setbacks

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[2]. These debilitating illnesses place an immense burden on individuals and society due to their progressive nature [1]. The financial toll is staggering; global dementia costs alone are expected to soar nearly tenfold, reaching $9.12 trillion between 2015 and 2050, with similar trends for other NDDs [3]. We now understand that NDDs can trigger neuroinflammation, and conversely, neuroinflammation might kickstart the disease process itself. However, the precise mechanisms linking neuroinflammation to neurodegeneration remain elusive. Research indicates the immune system plays a central role. Initially, immune cells activate to combat neurological threats, but this response can ultimately fuel widespread neuroinflammation, harming the brain [4]. For instance, microglia, the CNS's primary immune cells, release inflammatory factors when activated under disease conditions, contributing to damage [4]. Conditions like AD predominantly affect older adults, typically those over 65 [1]. Key features include the buildup of amyloid-β plaques outside cells and tau tangles inside them, sparking brain inflammation and neuronal death [1]. NDDs such as AD, PD, and ALS are particularly devastating for the elderly, directly causing dementia, disability, loss of independence, and increased mortality. The world's population is aging at an unprecedented rate, with the number of people aged 80 and older set to triple to 426 million between 2020 and 2050 [3]. Aging itself is the primary risk factor for developing these diseases [3]. As we age, accumulating genetic mutations and epigenetic changes gradually disrupt molecular and cellular balance, leading to failures in protein management (proteostasis) and impaired mitochondrial function [3]. In NDDs, this loss of proteostasis critically enables the abnormal accumulation of pathological proteins like amyloid-beta (Aβ), hyperphosphorylated tau, α-synuclein (α-syn), TDP-43, and huntingtin (HTT) [3]. These misfolded proteins then act as triggers, activating glial cells and sparking neuroinflammation alongside other harmful events. The resulting inflammation damages neurons, disrupts neural circuits, and ultimately manifests as various neurodegenerative disorders [3]. Understanding these mechanisms is crucial for identifying new therapeutic targets and precise intervention strategies. Further research into the complex interplay between neurodegeneration and neuroinflammation could help experts pinpoint exactly how inflammation drives disease progression. This knowledge is vital for developing effective treatments to reduce the suffering and mortality these diseases cause, especially among our aging population.

## 2. Molecular Mechanisms of Neuroinflammation

Neuroinflammation is the state of having an inflammatory response within the brain. Microglia are the central nervous system's resident immune cells and key players in neuroinflammation as well. Microglia release several pro-inflammatory and cytotoxic mediators to quickly react to changes in the brain's internal environment, causing neuroinflammation and neurodegeneration. There is variation in the initiation of activation depending on cell type, sensor, stimulus and patter recognition. Transcription factrs, such as NF-b have been reported to control the expression of inflammasome elements including NLRP3 thus modulating the assembly and activity of inflammsome [4]. In addition, inflammasomes' function is also regulated by their post-translational modifications such as: phosphorylation, ubiquitination, acetylation, alkylation S-nitrosylation and S-glutathionylation. These changes regulate the stability, structure, interaction and subcellular distribution of inflammasome components which act to control the activation even in a repressed form of the inflammasome [4]. Protein–protein interactions may be implicated in modifying the assembly and activation of inflammasomes. Adapter proteins, for example those like ASC may promote localization of the components of the inflammasome while repressor proteins may inhibit this process [4]. In pathologic state, microglia would be activated and evolving to pro-inflammatory phenotype release inflammatory modulators [4]. These activating substances will then activate astrocytes in which they lose their normal homeostatic roles and release neurotoxic factors under certain conditions. Intense lines of research revealed that astrocytes can assume two different reactive phenotypes: A1 and A2 [5]. The A1 phenotype is neurotoxic and drives the death of neurons and oligodendrocytes, while the A2 phenotype has beneficial roles [5]. A1 astrocytes can mediate the immune cell infiltration into the CNS through expressing neurotoxins, complement components and chemokines. This leads to more neuro-inflammation and neuronal injury [4]. Oligodendrocytes are nearly the only myelinating glia in the CNS. Oligodendrocytes produce "myelin sheath" that coats the nerves and aids in fast conduction of impulses in the CNS. Demyelination and oligodendrocyte loss are prominent in neurodegenerative diseases [6]. NLRP3 is the representative sensor of the innate immune system [7]. NLRP3 is distinguished by its ability to recognize not just the incursion of foreign pathogens but also internal damage that occurs to cells [7]. NLRP3 inflammasome controls microglia activation and pro-inflammatory cytokines production. NLRP3 acts as a vital molecular bridge of innate immunity and neurodegeneration, which regulates the microglial activation and inflam-

matory cytokines release [8]. The activation of NLRP3 is caused by the upstream signals, including K+ and Cl efflux, mitochondrial damage, cathepsin B release, reactive ROS and mtDNA. NLRP3 preferentially binds to NEK7, and after inflammasome is activated, the NEK7-NLRP3 binding intensifies to form an oligomerization between NEK7 and NLRP3. Aggregation of NLRP3 causes oligomerised state and subsequent ASC recruitment through PYD-PYD interaction being the primary step towards procaspase-1 recruitment thereby bringing out protein complex formation referred to as NLRP3 inflammasome. The proinflammatory cytokines IL-1 and IL-18 mature following the cleavage of procaspase-1 by NLRP3 inflammasome activation [8]. Mitochondria are found in the matrix and consist of diverse proteins some copy numbers encoded by mtDNA (mito named DNA) [9]. Mitochondria provide the energy. Mitochondria also serve as a reservoir for Ca2+ required in cellular signal pathways, particularly cell growth and generate multiple biosynthetic intermediates necessary for autophagy and apoptosis. Thus, mitochondrial dysfunction causes a wide range of diseases such as neurodegenerative disorders. Studies are increasingly showing that mitochondrial dysfunction enhances NLRP3 inflammasome activation, leading to local or systemic inflammation. NLRP3 inflammasome activation is suppressed by autophagy and enhanced by ROS. Upon detection of the mitochondrial defective status, NLRP3 inflammasome is activated to enhance inflammation that aggravates multiple organ failure from mitochondrial injury. It has been reported that mitochondrial impairment expands the microglial NLRP3 inflammasome-mediated pro-inflammatory cycle, although enhancing neurodegenerative mechanisms in DA neurons. Hence, mitochondria impairment in NLRP3 inflammasome driven neuroinflammation is pertinent in PD [9].

## 3. The Role of Neuroinflammation in Neurodegenerative Diseases

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are neurodegenerative disorders with different etiologies. Individuals with AD may present with mental and memory impairments, cognitive decline, and personality changes [1]. The neuropathological hallmarks of AD are the deposition of amyloid plaques, accumulation of neurofibrillary tangles, and cerebral amyloid angiopathy, along with significant glial activation and pronounced neuronal and synaptic degeneration [10]. The amyloid accumulation hypothesis suggests that an imbalance between protein synthesis and degradation drives AD pathogenesis [10]. Physiologically, amyloid precursor protein is cleaved by αand β-secretases to produce Aβ peptides that may follow amyloidogenic pathways under abnormal conditions. In AD, aberrant amyloid precursor protein processing leads to the disproportionate overproduction of Aβ42 relative to Aβ40, the latter of which is deposited as extracellular senile plaques [10]. However, the presence of Aβ plaques alone does not characterize the complexity of AD pathogenesis, as many individuals with severe amyloid deposition have no associated cognitive impairment, suggesting additional pathological determinants [10]. Various recent treatment strategies now target mitochondrial resilience to combat the heterogeneous AD pathology [10]. Mitochondrial resilience has emerged as a valid therapeutic target for early intervention for AD, based on the recognition that mitochondrial dysfunction is a major component of AD pathology, including oxidative stress-related respiratory chain failure, impaired mitochondrial biogenesis, and mtDNA mutations [10]. Early mitochondrial dysfunction correlates with augmented Aβ production and accumulation, suggesting that targeting mitochondrial resilience in the early stages of the disease is crucial. Various strategies aimed at promoting mitochondrial function have yielded promising results in preclinical research, including the development of mitochondria-targeted antioxidants, modulation of mitochondrial biogenesis by activation of PGC-1α, and inhibition of aberrant mitochondrial fission [10]. PD increases the risk of premature death in affected individuals by reducing motor function and elicited symptoms, such as bradykinesia, resting tremor, postural instability, and rigidity [1]. The molecular pathogenesis of PD remains multifactorial and complex, involving genetic, environmental, and cellular components. Mutations in several genes, LRRK2, SNCA, and PINK1, have been implicated in PD pathogenesis by genetic studies [11]. Moreover, the convergence of data indicates that mitochondrial damage, oxidative stress, and defective protein quality control result in dopaminergic neuronal death in PD [11]. Mitochondrial dysfunction leads to increased production of reactive oxygen species that cause cellular damage, triggering apoptosis pathways, and neuroinflammation [11]. Furthermore, α-synuclein accumulation into Lewy bodies is a pathological hallmark, and its toxic gain-of-function is proposed to accelerate neurodegeneration via proteotoxicity and synaptic impairment. Although much has been gained, the molecular mechanisms underlying the development and propagation of PD remain unknown [11]. Several clinically validated natural compounds are used for the treatment of PD [11]. Caffeine was shown to rescue neurons from dopaminergic injury [12]. Caffeine is also antioxidant in nature, which can abolish oxidative stress, the primary etiology

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of PD. Caffeine can also rescue dopaminergic neurons by activating antioxidant pathways, like Nrf2-Keap1 and peroxisome proliferator-activated receptor-gamma coactivator 1α/ (PGC1α) [12]. Caffeine could activate the Nrf2-keap1 and PGC1α signaling pathways, thereby inducing the production of new mitochondria, stabilizing a redox balance, and increasing cell proliferation [12]. Moreover, consumption of green tea enhanced antioxidant enzymes catalase and SOD and reduced protein and lipid oxidation in PD patients [12]. Green tea consumption reduces oxidative stress, thereby protecting the body from oxidative stress-related diseases. Clinical trials show, PD patients who drank three cups of green tea per day for three months and had 550 g of polyphenols reduced oxidative damage and saw a significant rise in their antioxidant level [12]. ALS is a rare disease, with incidence rates ranging from 0.5 to 3.6 per 100,000 individuals worldwide. ALS is usually sporadic, possibly due to an interaction of environmental and genetic factors. However, in about 5–10% of the cases, ALS becomes familial, and of these cases, about 70% are associated with gene mutations in the Superoxide dismutase 1 gene, Chromosome 9 open reading frame 72 [13]. ALS is a severe neurodegenerative disorder, which ultimately leads to respiratory failure and causing paralysis, followed by mortality [1]. Patients with ALS often have dysphagia and difficulty in managing secretions. A 30% increase in mortality accompanies every 5% decrease in weight among nutritionally compromised ALS patients, leading to a cumulative sevenfold increase in mortality risk. Initial dysphagia management involves several measures, such as dietary advice, food and liquid texture modification, prescribing high-caloric diets, teaching feeding and swallowing to patient and caregiver, and the use of postural modifications [13]. Maneuvers such as the chin-tuck maneuver, where the neck is flexed forward during swallowing, are also used to protect the airway [13]. HD is an autosomal dominant neurodegenerative disorder resulting from CAG repeat expansion within the huntingtin gene with expression of mutant huntingtin [14]. HD is clinically characterized by cognitive deficits, abnormal movements, and psychiatric disturbances [1]. Pathological changes are evident early in the caudate nucleus in vivo, with degeneration of the GABAergic medium spiny neurons of the striatum a hallmark of HD [14]. Extensive neurodegeneration is evident post-mortem [14]. Clinically, HD presents with a triad of motor impairment, which is chorea, cognitive impairment, and neuropsychiatric. In addition to increased irritability, perseverations, and depression, apathy is very common in HD [14]. Iron plays a critical role in HD by amplifying oxidative stress and neural damage, particularly by interacting with mHTT [15]. However, in HD, mHTT disrupts transcription, mitochondrial function, and lipid metabolism, facilitating ferroptosis by increasing ACSL4 expression, decreasing GPX4 activity, and dysregulated iron homeostasis through TFR1 and ferroportin [15]. The involvement of ferroptosis in HD is an exciting avenue for both the elucidation of disease mechanisms and the development of new therapies [15]. Ferroptosis is a regulated neuronal death triggered by lipid oxidation and iron dysregulation, playing a role in neurodegeneration [15]. Researching it could identify new therapeutic targets. Modulating strategies against ferroptosis, for example, the use of selective inducers or inhibitors, holds the potential to delay or arrest HD progression [15].

## 4. Conclusion

This review provides an overview of recent developments on the molecular mechanism of neuroinflammation and attendant neurodegenerative disorders. This review presents an overview of the neurodegenerative diseases and their relationship with neuroinflammation. Firstly, we describe how various cells talk to each other and the damages of NLRP3 known of mitochondrial dysfunction that ultimately contribute to neuro inflammation. It discusses specifically about the four common neurodegenerative diseases of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis by covering their symptoms etiology and treatments. In short, the neuroinflammation is a collection of multi-link coupling network. Up to now all these treatments can only ease symptoms of such neurodegenerative diseases partially. Not a single cure that allow patients to fully recover from NDs has been found due to the complexity of NDs. In the light of current situation, the accurate typing and early treatment might be the key to any new break through. A more thorough understanding of the mechanisms of neurodegenerative diseases can help researchers identify effective treatments as soon as possible, reaching and curing a greater number of people with neurodegenerative diseases. The limitations in the earlier trials and their studies still exist. In the future inflammation endotype-based adaptive clinical trials can be used by scientists. Scientists can also use AI to help gather statistical data, which is good in case they need to figure out a model.

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