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# Inflammasome activation in neurodegenerative diseases

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## Abstract

About ten million people are diagnosed with dementia annually since they experience difficulties in memory and thinking abilities. Because of the late diagnosis, most of the neurodegenerative diseases that causes dementia are difficult to treat. This is due to the increased severity of the disease with time, where neuroinflammation plays a key role. When scientists started investigating beyond neurons to address neurodegenerative diseases, they found high activation of immune cells in the brains of these patients, specifically microglia. Molecular sensors within these microglia, such as the NLRP3 inflammasome, are activated by signals that represent the hallmarks of these neurodegenerative diseases. Here, we first summarize the two activation steps of NLRP3 inflammasome activation. Furthermore, we discuss the key factors that contribute to NLRP3 inflammasome activation in the different neuroinflammatory diseases, like Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS). The prominent NLRP3 inflammasome triggers include Amyloid β and tau oligomers in AD, α-Synuclein in PD, and SOD1 and TDP43 in ALS. NLRP3 inhibitor treatment has shown promising results in several preclinical mouse models of AD, PD, and ALS. Finally, we postulate that current understandings underpin the potential for NLRP3 inhibitors as a therapeutic target in these diseases.

## Keywords

Neuroinflammation, Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis

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## 1. Introduction

Being the sole matter contributing to the collective wonders of human intelligence and consciousness, the human brain is strikingly compact and fragile. This fatty organ has been facing novel threats ever since mankind has enhanced our longevity through scientific research. Indeed, every change to the course of a natural process is subject to a bittersweet result, in particular, the increasing prevalence of neurodegenerative diseases in the aging population [1]. In 2019, neurodegenerative diseases were recorded worldwide as the seventh most common cause of death (WHO, 2019). Hence, understanding the mechanisms behind neurodegenerative processes is key to identify therapeutic targets against these diseases. Recently, it was concluded that neuroinflammation in response to degenerative processes in the brain acts like a double-edged sword, which exacerbates the disease progression [2]. Several studies have shown that neuroinflammation in the brain is primarily mediated by special inflammatory molecules called "inflammasomes" within the glial cells of the brain [3–5]. Hence, this review aims to address the current understanding of inflammasome biology and its specific implications, particularly the role of NLRP3 inflammasome on neurodegenerative diseases.

## 2. Inflammasome

### 2.1. Inflammasomes - an overview

The immune system of the human body is remarkable. For instance, it offers defense mechanisms through vaccines in the current Covid-19 pandemic [6–8]. Any immune cell is equipped with the innate defense mechanism to detect and respond to exogenous harms and stress. It achieves this through its pattern recognition receptors (PRRs), which recognize and detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These PRRs exist in a wide variety and are localized at various compartments of the cell (for example, Toll-like receptors (TLRs) in the membrane, absent in melanoma-2 (AIM2) in the cytosol) [9]. The NLR (Nod-like receptor) and AIM2 classes of PRRs are known to form inflammasome complexes following a damage signal [9–11].

The term "inflammasome" refers to the supramolecular-multiprotein structures that are exclusively formed in the cytoplasm of activated immune cells, which leads to a pro-inflammatory response cascade [12]. To date, the well-described NLR family inflammasome sensors are the NLRP1 (NLR and pyrin-domain containing 1), NLRP3, NLRP6, NLRP7, NLRP12, and NLRC4 (NLR and CARD-domain containing 4). The AIM2 family of sensors is AIM2 and Interferon-gamma inducible protein 16 (IFI16), both containing a PYHIN (pyrin and HIN domain-containing protein) domain. The ultimate goal of these inflammasome

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complexes is to recruit and activate inflammatory proteases called caspases, mainly caspase-1 [6,9]. This protease is generated in the inactive form as pro-Caspase-1 that contains three domains: a CARD (caspase recruitment domain), p10, and p20 functional protease subunits. CARD-containing inflammasomes NLRP1 and NLRC4 can recruit caspases directly [7,13], whereas others require an adaptor called apoptosis-associated speck-like protein containing a CARD (ASC) [14]. A brief overview of these sensors and their effectors is described in Fig. 1.

An exhaustive compilation of activation and regulatory mechanisms for every inflammasome is reviewed elsewhere [7,9]. This review restricts the scope within the NLRP3 inflammasome and its implications in neurodegenerative diseases. The NLRP3 activation leads to the release of inflammatory mediators and ultimately pyroptosis, a lytic cell death [9,15,16]. In diseases underlying inflammation, the inflammasome activation worsens the disease progression through a pro-inflammatory chain reaction.

### 2.2. NLRP3 inflammasome - a closer look:

Formerly called cryopyrin and NALP3, the NLRP3 is one of the molecules that have been extensively studied in the context of inflammatory diseases. A gain of function mutation of this gene deemed the patients towards a severe inflammatory disease (cryopyrin-associated autoinflammatory syndrome) [17,18]. Being a part of the NLR family of inflammasome sensors, the NLRP3 contains a sensory domain called the NACHT, which is interspaced between an amino-terminal pyrin domain (PYD) and carboxy-terminal leucine-rich repeats (LRR) (Fig.1). Under physiological conditions, the functional NACHT domain is auto-inhibited through the folding of the LRR domain of NLRP3 thereby preventing oligomerization [18].

The complete activation of the NLRP3 inflammasome is a two-step process (Fig. 2). Initially, the NLRP3 inflammasome is primed by PAMPs/DAMPs recognition through the PRRs (TLRs and NLRs). PRR activation triggers MyD88 and TRAF6 signaling, which converge onto the activation and transcription of NF-κB-related pro-inflammatory genes including NLRP3, pro-IL-1β, pro-IL-18, Gasdermin-D, and pro-Caspase-1 [18,19]. Priming also helps in the licensing of the auto-inhibited NLRP3 to a functional form. This is mediated through several enzymes that execute post-translational modifications (PTM) on the NLRP3. Briefly, multiple factors activate ubiquitinases (MARCH7) [20], deubiquitinases (BRCC3, BRCC36) [21,22], kinases (JNK1, PKA) [23,24], and phosphatases (PP2A) [25] that act at specific sites at NLRP3 leading to its activation or suppression [18,26] (Fig 2). An exhaustive list of NLRP3

PTMs is reviewed elsewhere [26,27]. Future studies are needed to investigate the regulation of NLRP3 PTMs in neurodegenerative disease phenotype.

Once activated, key PTMs of NLRP3 render the oligomerization of multiple NLRP3 proteins in the cytosol via the ATPase activity of the exposed NACHT domain (Fig. 2) [18,28]. The PYD of the ASC adaptor self-associates and binds with the PYD of NLRP3 through homotypic interactions [29]. Additionally, ASC oligomerization leads to a helical-fibrillar assembly called ASC specks. This exposes structurally organized CARD domains that attract CARD-containing pro-Caspase-1 [18,30,31]. This scaffold juxtaposes the proteolytic sites of pro-caspase-1 leading to auto-cleavage into active Caspase-1 p20 and p10 subunits [30]. The majority of activating mechanisms are triggered through the by-products of destabilization in cellular homeostasis, which are broadly characterized as ionic disturbances, mitochondrial dysfunction, and lysosomal destabilization (Fig. 2) [18,26]. For instance, a sudden ionic efflux of $K^+$ and $Cl^-$, and an influx of $Na^+$ and $Ca^{2+}$ ions in the cells via pore-forming toxins and proteins result in membrane depolarization and swelling of the cell thereby activating inflammasomes [26,32,33].

In general, potassium efflux primarily involves pore-forming proteins like Gasdermin-D, Pannexin-1, two-pore domain weak inwardly rectifying $K^+$ channel 2 (TWIK2), the purinergic ion-channel P2X7 receptor, and pore-forming toxin Nigericin. Potassium depletion from the cells triggered an intrinsic sensory kinase NEK7 (NIMA-related kinase 7) that binds with the LRR domain of NLRP3 and results in caspase-1-mediated IL-1β production (Fig. 2) [34–37]. Conversely, a high extracellular potassium level was sufficient to destabilize the membrane potential and inhibit the NLRP3 inflammasome [38]. Interestingly, this dependency on potassium levels is specific to NLRP3 inflammasome, since these effects were not observed in AIM2 and NLRC4 inflammasome [39,40].

Secondly, mitochondrial dysfunction elicits signals that activate the NLRP3. For instance, rotenone impaired mitochondria, leading to reactive oxygen species (ROS) generation and NLRP3 inflammasome activation (Fig. 2) [41]. Similarly, aberrant mitophagy and inhibition of mitochondrial fission through drp-1 (fission protein) knockout activate and enhance NLRP3 assembly [42]. Interestingly, oxidized mitochondrial DNA (mtDNA) produced in response to TLR-signaling also activates the NLRP3 inflammasome [43].

Lysosomal destabilization is caused by abnormal phagocytosis of foreign particulates or host-derived protein aggregates. This results in the release of lysosome-resident protein Cathepsin-B into the cytosol, a NLRP3 inflammasome activator [18,44]. For example, the

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purinergic receptors P2X7 and P2Y12 signaling caused lysosomal leakage and subsequent rise in cathepsin B [45–47].

Additionally, there are numerous other external activation cues including stress, metabolism disorder, alcohol exposure, western diet, and aging that activate the NLRP3 inflammasome and IL-1β production [48–53].

## 3. NLRP3 activation in neurodegenerative diseases

The brain is composed of two types of cells: functional cells -neurons, and supporting cells - glia or neuroglia. Neuroglia are further classified based on their origin as neuroepithelial-derived cells: oligodendrocytes, astrocytes, oligodendrocyte progenitor cells, and ependymal cells; and yolk sac-derived myeloid cells: microglia [54–56]. Inflammasomes are well-established in immune cells and due to their origin, it was thought that only microglia was responsible for inflammasome activation in the brain. However, recent studies have shown that inflammasome activation is prominent in microglia, astrocytes, and neurons suggesting a synergistic role of multiple cell types in inflammasome activation [13,57–60]. We will now discuss in detail the role of NLRP3 activation in each of the neurodegenerative diseases Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (Fig. 3).

### 3.1. NLRP3 activation in Alzheimer's disease (AD)

AD is one of the leading causes of dementia, which is a collective phenotype characterized by difficulties with memory, language, and cognition [61]. The symptoms of AD are prominent only after 20 years of disease onset making it difficult to treat or cure [61,62]. The key pathologies observed are AD is β-amyloid (Aβ) plaques, neurofibrillary tau tangles (NFT), gliosis, and neuronal loss [63].

The two primary hypotheses postulated for AD are the amyloidogenic and the tau hypothesis. The amyloidogenic hypothesis is based on the amyloid precursor protein (APP), a transmembrane protein specific to the cells of nervous tissue. APP is involved in axonal guidance and synaptic plasticity under physiological conditions [2,64]. The enzymes β-secretase-1 and γ-secretase cleave APP into insoluble Aβ fragments that span 37-42 amino acids in length [2]. Genome-wide association studies in AD patients have identified mutations in *APP* and the γ-secretase subunits (*PSEN1,2)* that accelerate Aβ generation [65]. Aβ peptides released in the extracellular matrix (ECM) aggregate and oligomerize through three-dimensional peptide interactions, leading to Aβ plaques that occupy the micro-environment of neurons. They affect brain functionality by inducing neurotoxicity or by

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initiating an inflammatory cascade through the inflammasome activation in microglia, astrocytes, and neurons [3,66].

Aβ exists as either monomer, unorganized oligomeric structures, or organized fibrillar structures wherein only the Aβ oligomers and protofibrils induced NLRP3 inflammasome in primary microglia [67–70]. The detection of Aβ is primarily mediated through several TLRs and other receptors [2,71–73]. Interestingly, the TLR2/4 also detects a non-pathological form of amyloid, serum amyloid A (SAA), that circulates in the AD and multiple sclerosis patient brains and potentially prime the microglia for inflammasome activation [74]. Besides the designated PRRs, there also exist the amylin receptors that sense Aβ and activate the NLRP3 inflammasome in human and murine microglia. Amylin antagonist (AC253) treatment on an Alzheimer's mouse model ameliorates the inflammatory markers and senile plaques observed in the controls [75].

Interestingly, the first report on Aβ-induced NLRP3 activation in microglia showed Aβ phagocytosis as the primary trigger [67]. Microglial Aβ phagocytosis, maybe through the TAM receptors (Tyro-3, MerTK, Axl), leads to lysosomal damage due to a drop in acidification and enlargement of lysosomes resulting in the release of cathepsin B into cytosol that activates NLRP3 [67,76] (Fig. 2).

It is essential to understand the physiological implications of NLRP3 activation in AD patients. An increased level of caspase-1 was found in the brains of patients with mild cognitive impairment and AD, supporting the neuroinflammatory cascade of Aβ [3,5]. Conversely, deletion of the *NLRP3* and *ASC* genes in a double mutant AD mouse model (APP/PS1 mice) rescued their spatial memory deficits by enhancing Aβ clearance [3]. This suggests a critical role of the NLRP3 in orchestrating Aβ-induced memory deficits. This may be because inflammasome-activated cells release ASC specks, that activate the NLRP3 inflammasome in surrounding microglia by damaging their lysosomes after being ingested [77]. This was confirmed in another study where intrahippocampal injection of exogenous ASC specks in APP/PS1 mice led to an accelerated spread of the disease in these mice [4]. Here, ASC-specks act as nucleation sites for Aβ to oligomerize and fibrilize leading to disease progression [4]. Taken together, the NLRP3-ASC axis is instrumental in driving the pathological spread of AD by the amyloid cascade.

The tau hypothesis on the other hand considers the microtubule-stabilizing protein tau as the initiator. Axons within neurons are structurally supported by cytoskeletal elements called microtubules wherein phosphorylated-tau maintains the structural integrity of α-tubulin and β-tubulin [78]. Abnormal activation of specific kinases like protein kinase A (PKA), CamKII-α,

and GSK3-β hyperphosphorylate tau, leading to axonal destabilization and formation of neurofibrillary tau tangles (NFT) inside neurons [5,79]. This leads to neuronal dysfunction and subsequent apoptosis leading to tau release and inflammasome activation in the surrounding cells. Non-fibrillar tau actively released by dying neurons activate the NLRP3 inflammasome in microglia leading to chronic neuroinflammation in tauopathies [5].

Recently, it is accepted that the amyloid cascade acts upstream to tau-induced pathology in AD and they both act synergistically in contributing towards disease progression. The Aβ and tau activation is a vicious cycle of events that needs simultaneous attention [5,80,81]. Besides neuronal proteins, recent genomic studies have identified AD-associated novel risk factors like genetic variants of *TREM2* and *CD33*. However, the role of the TREM2 and CD33 receptors in regulating NLRP3 is not completely established. In human iPSC-derived microglia, missense mutations of *TREM2* did not affect IL-1β production [82] whereas, an AD-specific variant of TREM2 reduced NLRP3 activity [83]. Also, mutations in the microglial CD33 receptor impairs DAMP sensing and Aβ phagocytosis in AD [84]. Although, blocking CD33 with chimeric antibodies showed reduced NLRP3-mediated IL-1β production in human monocytes, indicating a therapeutic potential [84,85]. Another significant genetic risk is the *APOE ε4* that impairs APOE-mediated lipid metabolism, and possibly Aβ phagocytosis leading to increased plaques in AD [86]. APOE4 carrying mouse microglia showed enhanced NLRP3-mediated IL-1β production with LPS and cholesterol stimulation [87]. Hence, NLRP3 might be an indispensable protein to target in the therapeutic search against AD.

NLRP3 modulations were designed in AD mouse models to check their role in disease progression. Genetic deletion of NLRP3, ASC, P2X7 receptor rescued the cognitive phenotype of not only APP/PS1 mice but also other models like 5X FAD mice and Tau22 mice [3,5,66,88–90]. It is noteworthy that some interventions are not entirely NLRP3-specific (ASC, P2X7) indicating that the protective effects could be due to overlap from other inflammasomes. Similarly, treatment with NLRP3 inhibitors MCC950, DAAPD, and JC-124 reduced microglial activation, enhanced Aβ clearance, and rescued the memory deficits in APP/PS1 and TgCRND8 AD mouse models [91,92]. Besides NLRP3, the NF-κB inhibitor Bay11-7082 also restored kainic acid-induced Aβ pathology in APP23 mice [93]. The endogenous anti-inflammatory molecule β-hydroxybutyrate (BHB), released under fasting conditions was decreased in AD patient brain and blood. Treatment with BHB in 5XFAD mice ameliorated the cognitive deficits by suppressing the NLRP3 activity [94]. A selected list of studies describing NLRP3 inflammasome in AD is summarized in table 1.

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## Table 1. NLRP3 activation in AD

| Species | Model | Inflammasome modulation | Molecular intervention | Effects | References |
|---|---|---|---|---|---|
| | 3* Tg AD mice | Increased NLRP3. Cleaved Caspase-1, IL-1β | Hexokinase is decreased in AD | Hexokinase dissociation from mitochondria activates the inflammasome | [95] |
| | 5X FAD mice | | ASC knockout | IL-1β release in astrocytes is ASC dependent (in vitro), Improved cognition in 5X FAD mice | [88] |
| | 5X FAD mice | ASC, Caspase-1 activity and Microgliosis. Increased Aβ plaque | BHB, an endogenous anti-inflammatory molecule | Reduced ASC, Caspase-1 cleavage, microgliosis, and Aβ deposition | [94] |
| | 5X FAD mice | Increased caspase-1, caspase-3, NLRP3, ASC, IL-1β and IL-18 | DJ-1, a regulator of transcription factor Nrf2. DJ-1 overexpression | DJ-1 overexpression reduced hippocampal Aβ levels, and NLRP3, ASC, caspase-1, IL-1β, and IL-18 levels by increasing nuclear translocation of Nrf2 | [96] |
| | APP/PS1 | Increased cleaved caspase-1, IL-1β | NLRP3 knockout | Decreased Caspase-1 activation, IL-1β release, Rescued memory deficits, increased Amyloid phagocytosis | [3] |
| | APP/PS1 | ASC injection increased Aβ pathology | ASC knockout | APP/PS1 brain homogenate injection in ASC knockout APP/PS1 mice did not alter disease progression | [4] |
| | APP/PS1 | P2X7 receptor upregulation | P2X7 knockout | Reduced cognitive impairment and synaptic dysfunction; effects independent of IL-1β | [90] |
| | APP/PS1 | A systemic challenge with LPS increased Aβ deposition | NLRP3 knockout | Increased microglial clearance of Aβ after systemic challenge | [89] |
| | APP/PS1 and 5X FAD | Increased NLRP3, ASC, Cleaved caspase-1, IL1β, through increased NF-κB | N, N′-diacetyl-p-phenylenediamine [DAPPD]; small inhibitor of NLRP3 through its impact on NF-κB and promotes phagocytosis | Reduced cognitive deficits by increasing microglial phagocytosis and suppressing inflammasome components | [97] |
| | APP/PS1 mice | Aβ plaques, memory deficits | Zn deficiency/supplementation; Zn inhibits NLRP3 inflammasome activation, deficiency activates it | Zn deficiency accelerates AD progression, supplementation rescues memory deficits by inhibiting NLRP3 | [98] |
| | APP/PS1 mice, Aβ 25-35 mice | IL1β, NLRP3 increased in the brains due to abnormal autolysosome function (LC3 increased and LAMP1 decreased | TFEB overexpression, lysosomal biogenesis regulator | LC3 decreased and Lamp1 increased, reduced NLRP3, IL1β, Caspase-1 in vitro | [99] |
| | APP/PS1 mice, murine microglia and in vivo | Increased IL1β, TNF, IL-6 mRNA in vivo | MCC950 | Reduced microglial inflammasome, enhanced Aβ phagocytosis, decreased amyloid plaques in vivo, improved cognition | [91] |
| Mouse | APP23 | Increase in NF-κB, IL-1β, BDNF | Bay11-7082, NF-kB inhibitor | Reduced Kainic acid-induced Amyloid propagation and memory deficits in APP23 mice by mitigating inflammasome | [93] |

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|---|---|---|---|---|---|
| | C57/BL6 injected with Aβ 1-40, Aβ induced Retinal degeneration model | IL1β, NLRP3, ASC, Caspase-1 increased | C/EBP, a positive regulator of NLRP3. miR-191-5p silences the c/EBP | Knockdown of E/CBP inhibited NLRP3 expression and IL-1β production. Protected from Aβ induced functional loss | [100] |
| | TgCRND8 | NLRP3, ASC, Caspase-1 upregulation | JC-124: a NLRP3 inhibitor | Enhanced Aβ clearance; reduced microglial activation; increased synaptophysin; reduced oxidative stress | [92] |
| | β-N-Methylamino-L-alanine (BMAA), a microbial toxin in sAD, treated on neurons | | BMAA-induced mitochondrial dysfunction and cardiolipin exposure | Aβ and p-Tau increased | [101] |
| | Aβ on BALB/c murine astrocytes | Aβ induced NLRP3 upregulation, but not ASC | MCC950 and α-antitrypsin (protease inhibitor) | MCC950 reduced caspase-1 activity, AT1 acts as an NLRP3 inflammasome inhibitor and suppress IL-1β | [102] |
| | Aβ on Primary microglia | Amyloid β clusters around ASC, inducing toxicity | ASC specks are released, they cross seed with Aβ in plaques | ASC-binding with Aβ induced inflammasome activation, Exogenous ASC induced NLRP3 inflammasome in ASC-deficiency, ASC binding reduced Aβ uptake | [103] |
| | Aβ on Primary microglia , in vivo | Aβ induced NLRP3 upregulation, IL-1β, through Cathepsin-B release | NLRP3 knockout, ASC knockout, IL1R knockout | Suppressed Aβ-induced microglial activation | [67] |
| | Aβ on Primary microglia | Aβ induced ROS accumulation and NLRP3 activation | Edaravone (3-methyl-1-phenyl-2-pyrazoline-5-one, EDA, Fig. 1), a free radical scavenger | EDA reduced mitochondrial depolarization, suppressed ROS, and increased SOD-2 | [104] |
| | Tau22 mice | Increased cleaved caspase-1, IL-1β | NLRP3 knockout, ASC knockout | Rescues cognitive decline and prevents tau pathology from the spread | [5] |
| | AD patient brain tissues | NLRP3, ASC, Caspase-1 co-localization at Aβ plaques | GMF: Glial maturation factor (endogenous) | GMF is released in response to dysfunctional autophagosomes; Increases ROS and activates NLRP3, ASC, Caspase-1 | [105] |
| | AD patient brain tissues | Increased cleaved caspase-1 | | | [3] |
| | AD patient brain tissues | ASC-bound Aβ in AD patients | | | [4] |
| | AD patient brain tissues | Increased cleaved caspase-1, IL-1β | | | [5] |
| | AD patient brain tissues | Increased neuronal NLRP3 expression | Neurexin3 (NRXN3) rs8019381 SNP; important for synaptic regulation | Reduced NRXN3 correlated with increased inflammasome components | [106] |
| | AD patient brain and blood | β hydroxybutyrate decreased | BHB endogenous anti-inflammatory molecule | | [94] |
| | AD patient serum | miR-223-3p downregulated in serum | miR-223-3p is a negative regulator of NLRP3 | | [107] |
| Human | AD Patients | Zinc supplementation reduced AD prevalence | Zn is a negative regulator of NLRP3 inflammasome | | [98] |

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| | | | | | |
|---|---|---|---|---|---|
| | SH-APP neurons and CHME microglia | Increased caspase-1 and IL1β | CRID3, Withaferin-A plant extract | Inhibited inflammasome activity | [108] |

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### 3.2. NLRP3 activation in Parkinson's disease (PD)

Parkinson's disease is characterized by motor-associated deficits including rest tremor, bradykinesia, postural instability caused by the degeneration of the neurons in the brain stem. The pathophysiology for this disease has converged into dopaminergic neuronal loss in substantia nigra and α-Synuclein misfolding and aggregation within Lewy bodies inside neurons [109–111]. PD is majorly associated with α-Synuclein aggregation, which is encoded by the gene *SNCA (PARK1)*. The mutant form of α-Synuclein assembles into β-pleated sheets and is misfolded into protein aggregates. Recent studies have shown that α-Synuclein aggregates can both prime and activate the NLRP3 inflammasome pathway [112,113]. α-Synuclein initiated both TLR2-NF-κB-mediated priming as well as activation through TLR5 signaling, lysosome destabilization, and mitochondrial damage [112–114].

Besides *PARK1* genetic mutations, PD is associated with autosomal dominant variants of *LRRK2* (kinase regulating vesicular trafficking), and autosomal recessive variants of *PINK1* (mitochondrial kinase), *PRKN* (E3 ubiquitin-protein ligase), and *DJ-1* (oxidative stress sensor and protease) [115]. Interestingly, DJ-1 overexpression suppressed NLRP3 activity in AD mice [96], while its knockdown enhanced neuroinflammation in a PD mouse model by disrupting Nrf2/Trx1 axis [116]. Besides, recent GWAS studies revealed novel risk genes associated with PD like *TMEM175* (lysosomal potassium channel) and *GBA* (Glucosylceramidase) indicating the role of reduced potassium currents and lysosomal damage in PD [111,117]. It may be inferred that familial and sporadic cases of PD patients have mitochondrial and lysosomal damage leading to the activation of inflammasomes.

Oxidative stress is regarded as one of the key causative factors in PD. Several mouse studies employed the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which induces irreversible damage to dopaminergic neurons in the substantia nigra [118–120]. Glial cells convert MPTP to $MPP^+$ cation that mimics dopamine leading to accumulation in mitochondria of dopaminergic neurons and complex I dysfunction [121]. Mitochondrial complex I is essential for generating ATP and vanquishing free radicals. Its disability leads to mitochondrial dysfunction and increases oxidative stress in the cell. Subsequently, the mitochondrial complex I inhibitor Rotenone and Paraquat became toxins to induce PD in mice for studying the pathophysiology [122–124].

Mitochondrial destabilization is one of the important activating signals for the NLRP3 inflammasome (Fig. 2). The reactive oxygen species and cardiolipin released due to mitochondrial destabilization lead to the activation of NLRP3 via PTM of the protein. It is

well-documented that the levels of NLRP3 and other inflammasome components including cleaved-caspase-1, ASC, IL-1β are increased in mice injected with MPTP, rotenone, and paraquat [118–120,122,125–128]. Besides, other mouse models of PD also showed increased NLRP3 activity [112,129,130]. A recent study on MPTP mice revealed that only NLRP3 inflammasome is activated, but not NLRP1, NLRC4, AIM2, indicating the relevance of NLRP3 inhibition in PD pathogenesis [131]. However, a PD-associated protein LRRK2 deficiency impaired NLRC4 inflammasome assembly after bacterial stimuli, revealing the role of LRRK2 in other inflammasome activation [132]. In contrast, overexpression of another PD-associated protein PINK1 reduced NLRP3 activity by increasing mitophagy in vivo [133].

In humans, α-synuclein activated NLPR3 inflammasome in peripheral blood mononuclear cells, through TLR signaling, ROS production, and cathepsin B release [134]. Similarly, an increased NLRP3 activation, caspase-1 cleavage, and IL-1β production were documented in brain tissues from PD patients and iPSC-derived microglia-like cells showing the critical role of NLRP3 in promoting PD [112,113,130,135]. Additionally, the plasma levels of miRNA miR-188-3p, a negative regulator of NLRP3 expression, were lower in PD patients suggesting an unregulated inflammasome activity [127]. In line with this, a genetic variant of NLRP3 that impacts its protein turnover was associated with a reduced risk of PD [135]. Hence, multiple studies investigated the impact of NLRP3 inflammasome modulation on PD pathology.

In 2018, Gordon and colleagues tested the NLRP3 inhibitor MCC950 in vivo in several mouse models of PD and found promising results [130]. Inhibition of the NLRP3 rescued dopaminergic neuronal loss and improved their motor functions regardless of the PD model [130]. Another study showed that deletion of NLRP3 and treatment with MCC950 prevented the α-synuclein-mediated inflammasome activation in mouse primary microglia and bone-marrow-derived macrophages [112]. This was also confirmed in vivo wherein MPTP-induced PD pathology was suppressed in NLRP3 knockout mice by reducing microglial recruitment and activation [118]. Similarly, dopaminergic neuronal loss and motor deficits were rescued by repressing NLRP3 expression through silencing RNA siNLRP3 and micro RNA miR-188-3p injection in MPTP mice [127,129]. It is key to note that other models of PD like the mitopark mice that lack mitochondrial DNA maintenance and AtgKO mice that have abnormal lysosomal activity also showed promising effects after MCC950 treatment [130,136]. Hence, PD pathogenesis involves multiple factors that converge into NLPR3 activation and inflammasome signaling.

Besides NLRP3, several studies have also tested its downstream and upstream effectors that might impact PD pathogenesis. Negative regulation of other inflammasome components by genetic deletion of ASC, Caspase-1, and treatment with IL-1β antagonist also rescued

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the functional loss in PD models [112,118]. Other indirect targets to suppress the NLRP3 signaling are the PRRs that recognize the α-synuclein. Anti-TLR2 antibodies blocked α-synuclein-mediated NLRP3 activation in human iPSC-derived microglia-like cells [113]. Similarly, genetic deletion of TLR4, integrin CD11b, and a downstream Fyn kinase for the receptor CD36 also suppressed the PD pathology in α-synuclein and MPTP mouse models [112,124,125]. However, these models are not NLRP3-specific and may interfere with the effects of other inflammasomes as well. Nevertheless, reducing the mtROS by treating with Hydrox, a free radical scavenger, suppressed NLRP3 activation and MPTP-induced neurodegeneration in mice [123]. Together, these finding strongly supports the involvement of NLRP3 activation in Parkinson's disease (Table 2).

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## Table 2. NLRP3 activation in PD

| Species | Model | Inflammasome modulation | Molecular intervention | Effects | References |
|---|---|---|---|---|---|
| Mouse | 6-OHDA(hydroxydopamine)-mice; α-synuclein and Mitopark mice | Increased NLRP3, Caspase-1, ASC | Oral MCC950, NLRP3 inhibitor | Prevents inflammasome activation in the brain, protects against dopaminergic degeneration, prevents alpha-synuclein pathology | [130] |
| | α-synuclein treated microglia, AAV-αSYN mouse model | Increased NLRP3, ASC, Caspase-1, IL-1β, TNF | Fyn kinase, a downstream effector of CD36 receptor, NLRP3, ASC. Caspase-1, Fyn deficiency | NLRP3, ASC, Caspase-1 deficiency prevents α-synuclein-induced inflammasome, microglial activation in vivo | [112] |
| | ATG-5 (Autophagy-5) deletion, shows PD motor deficits | Increased NLRP3 activation, Caspase, IL-1β, MIF secretion | MCC950, NLRP3 inhibitor in vivo treatment to *Atg5* knockout mice | TH+ neuronal loss rescued, microglial inflammation reduced | [136] |
| | MPTP-injected mice | Increased NLRP3, Caspase-1, IL-1β | $MPP^+$ acts as priming signal for NLRP3, three interventions: NLRP3 knockout; IL1β antagonist; NLRP3 constitutively active in microglia | NLRP3 knockout and IL1β antagonist reduced Motor deficits and neuronal loss, whereas over-activation of NLRP3 worsened PD phenotype | [118] |
| | MPTP-injected mice | Increased NLRP3, Caspase, IL1β in the olfactory bulb, through TLR2, NF-κB signaling | | | [119] |
| | MPTP-injected mice | Increased NLRP3, IL-1β, Caspase-1, Gasdermin-D | Flavanoid Baicalein treatment has anti-inflammatory effects | Rescued motor deficits, reduced TH neuronal loss, reduced inflammasome activation in vivo | [120] |
| | MPTP-injected mice | Increased NLRP3, ASC, Caspase-1, serum IL-1β, IL-18, IL-6, TNF | miR-188-3p-(repress NLRP3, CDK5), enriched within exosomes, injected in MPTP mice | Rescued motor deficits, TH neuron loss, through suppressing NLRP3, ASC, caspase-1 and serum IL-1β, IL-18, IL-6, and TNF; effects reversed with NLRP3 overexpression | [127] |
| | MPTP-injected mice | NLRP3 upregulation in Nigro-striatal region | MCC950 treatment | Rescued motor deficits, reduced dopaminergic neuronal degeneration, glial activation in MPTP mice: Only NLPR3 is involved in the MPTP model, not NLPR1, NLRC4 | [131] |
| | MPTP-injected mice (acute and chronic) | Increased NLRP3 | siNLRP3 wrapped in lentivirus: tail vein injection in vivo | Prevents NLRP3 activation in the brain, and rescues TH neuron loss | [129] |
| | MPTP-injected mice, SNCA PD model | Increased NLRP1, NLRP3, Caspase-1, IL-1β | Kaempferol (Ka) promotes ubiquitination of NLRP3, degradation of NLRP3, and reduced the caspase-1, and IL1β release | Ka prevented neurodegeneration by attenuating the NLRP3 inflammasome cascade | [126] |
| | MPTP-injected mice, SNCA-injected mice | Increased NLRP3, ASC, Caspase-1, IL-1β, TNF | Serum/ glucocorticoid related kinase 1 (SGK1), inhibition using (GSK-650394); silencing using shSGK1 AAV9 | Rescued motor deficits, through reducing inflammasome components and senescence in vivo | [128] |
| | MPTP-Probenecid injected mice | Increased NLRP1, NLRP3, Caspase-1, IL-1β, NF-κB signaling | TLR4 knockout, PRR for danger signals | TLR4 deficiency attenuated motor deficits, reduced TH neuron loss, by reducing inflammasome activity | [125] |

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| | | | | | |
|---|---|---|---|---|---|
| | MPTP-treated murine astrocytes | Increased NLRP3, Caspase-1, IL1β | Atp13a2 (Park9), a lysosomal ATPase, deficiency leads to lysosomal dysfunction. Park9 knockout and overexpression | Knockout: Increased NLRP3 and IL1β release through Cathepsin-B after MPTP in astrocytes; Overexpression: Decreased the effects by MPP+ (MPTP) | [137] |
| | Paraquat + Maneb induced neurodegeneration | Increased NLRP3, IL1β, Caspase-1 activity, through NF-κB | Integrin CD11b deletion, Glybenclamide (A sulfonylurea inhibitor of NLRP3) | CD11b deletion reduced the activation of NLRP3 inflammasome in vivo; Glybenclamide also reduced P+M -mediated LC neurodegeneration in mice, reduced α-synuclein aggregation | [124] |
| | Rotenone, tebufenpyrad treated microglia and mice | Increased NLRP3, Caspase-1,IL-1β | Mt complex I inhibitors: Rotenone and tebufenpyrad induced structural changes to microglia, Increased mitochondrial superoxide, through Cathepsin-B | Conditioned medium from rotenone treated microglia induced neurodegeneration in neurons | [122] |
| | Rotenone-treated mice | Increased NLRP3, ASC; IL1β, Caspase-1, IL-18, through NF-κB | Hydrox (Hydroxytyrosol, free radical evacuation, and anti-inflammatory effects | Rescued motor deficits, reduced TH neuronal loss, reduced α-synuclein aggregation, reduced inflammasome activation in vivo | [123] |
| | Intra-gastric rotenone-treated mice | Increased NLRP3, cleaved caspase-1 in striatal tissues | NLRP3 knockout mice | Reduced microglial activation, TH neuronal loss | [138] |
| Human | Human monocytes treated with α-Synuclein | NLRP3, Caspase-1, IL-1β release | Monomeric α-synuclein is not capable of activating inflammasome, α-synuclein fibrils activate through TLR2, ROS production, and Cathepsin B release | | [134] |
| | PD brain tissues | Increased NLRP3, Caspase-1, ASC | | | [130] |
| | PD brain tissues | Elevated Caspase-1, IL-1β in Substantia nigral tissues | | | [112] |
| | PD brain tissues, Plasma | Elevated NLRP3, ASC in tissues, Elevated NLRP3 in plasma associated with PD | Extracellular vesicles in Plasma | Ex Vesicles contain active inflammasome components like cleaved caspase-1, IL-1β, Gasdermin-D, NLRP3, ASC | [139] |
| | PD plasma | Elevated IL-18 | microRNA (miR)-188-3p, represses NLRP3 and CDK5 | Reduced in PD patients, correlated with an increased IL-18 | [127] |
| | hiPSC-Derived Microglia-like cells treated with α-Synuclein oligomers | NLRP3 activation, mitochondrial ROS generation, IL-1β release | TLR2 neutralizing antibodies, anti-α-Synuclein, and anti-Aβ antibodies | TLR2 antibodies blocked α-Synuclein-mediated NLRP3 activation, α-Synuclein and Aβ antibodies increased the activity | [113] |
| | PD brain tissues | NLRP3 elevated in dopaminergic neurons, NLRP3 immunoreactive neurites | *NLRP3*$^{979}$ variant: rs7525979 C-to-T genetic variant of *NLRP3* | In HEK293 cells, *NLRP3* SNP rs7525979 reduced the risk of PD by impacting the protein turnover of NLRP3 | [135] |

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### 3.3. NLRP3 activation in Amyotrophic lateral sclerosis

ALS is a motor neuron-specific degenerative disease, that results in motor deficits accompanied by behavioral and cognitive loss during the disease progression [140,141]. The exact pathophysiology for ALS is loosely described, although key genetic variants are identified as a predictive factor for this disease. At least 25 main genes that associate with ALS prevalence were identified, whose mutations primarily lead to disruption in these tasks of the cell: mitochondrial maintenance, autophagy, and nucleic acid maintenance [140]. In particular, mutations in the genes SOD1 (Superoxide dismutase), TAR-DNA binding protein 43 (TDP43), the hexanucleotide repeat (G4C2) expansions in the chromosome 9 open reading frame 72 (C9orf72), fused in sarcoma (FUS), and TANK-binding kinase-1 (TBK-1) are the leading factors for ALS [141]. Protein aggregates of SOD1, TDP43, and FUS have been identified in the brains of both ALS patients with and without the corresponding mutations implicating that they are one of the common features observed in the ALS spectrum [142].

SOD1 (Superoxide dismutase) is an antioxidant enzyme that helps scavenge the reactive oxygen species (superoxide anion) that accumulates within the cell during respiration. Naturally, mutant and functionally defective SOD1 aggregate in the mitochondria and impact protein import for proper functioning, while it increases the concentration of reactive oxygen species in the cell [143]. TDP43 preferentially binds to mitochondrial complex 1 mRNA leading to localization of TDP3 in mitochondria and subsequent disruption in ATP generation [144]. Besides disrupting the electron transport chain, aggregates of SOD1 and TDP43 also destabilize the vesicular transport mechanisms thereby promoting lysosomal destabilization [140]. Hence, it is seemingly inevitable to circumvent the NLRP3 activation in ALS disease progression.

The widely used ALS mouse model is the mice expressing the mutant SOD1 and these mice also exhibited an increased NLRP3 activation, ASC speck formation, and IL-1β levels in their spinal cord tissues [145–150]. Similarly, microglial exposure to mutant TDP43 showed NLRP3 inflammasome activation through the NF-κB pathway [151]. In humans, ALS patients had increased levels of NLRP3 products in their serum, specifically the cytokine IL-18 [150,152]. Additionally, post mortem spinal cord tissues also showed an upregulation of NLRP3, ASC, Caspase-1, and IL-1β in ALS patients confirming the NLRP3 activation [146]. Hence, several studies tried to ameliorate the ALS pathology by modulating the NLRP3 pathway.

Caspase-1 and IL-1β deficiency in SOD1 mutant mice rescued the ALS motor deficits and encouraged other modes of NLRP3 modulation [145]. NLRP3 inhibition through MCC950 treatment and estrogen treatment also rescued the phenotype in these transgenic mice through reduced microglial activation [148–150]. However, the permeability of MCC950 through the blood-brain barrier is not efficient, leading to NLRP3 inhibition in the peripheral immune cells as well. MCC950 treatment also decreased the lifespan of these SOD1 mutant mice suggesting a potential side-effect of cell type unspecificity. Additionally, a study detected no NLRP3 in Iba1+ cells [146] whereas another study detected it in CD11b+ cells [148] in the spinal cord tissues of SOD1 mice. This is in contrast with AD and PD where Iba1+ microglia show NLRP3 activation. As discussed in the recent review [153], peripheral immune cells might also play a role in inflammation along with microglia in neurodegenerative diseases.

Similarly, the role of the P2X7 purinergic receptors in ALS is debatable since its inhibition improved motor functions in SOD1 mice [147]. However, another study showed no increase in P2X7 receptors in SOD1 mice tissues and could not rescue the phenotype using the P2X7 antagonist [154]. They attribute this contrasting evidence to a gender-based difference in the regulation of P2X7 receptors in SOD1 mice. In humans, a mini-clinical trial with IL-1 receptor antagonist anakinra treatment did not impact the disease progression in ALS patients, suggesting that the IL-1β-mediated effects in ALS might be redundant [155]. Hence, more studies are needed to dissect the exact role of NLRP3 activation in ALS pathogenesis.

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## Table 3. NLRP3 activation in ALS

| Species | Model | Inflammasome modulation | Molecular intervention | Effects | References |
|---|---|---|---|---|---|
| Mouse | B6.Cg-Tg(SOD1-G93A)1Gur/J: SOD1G93A ALS mice | Increased IL-1β through NF-κB | P2X7 antagonist, Brilliant Blue G (BBG) in vivo | Delayed disease progression through reducing IL-1β, NF-kB | [147] |
| | B6.Cg-Tg(SOD1-G93A)1Gur/J: SOD1G93A ALS Mice | Had no increased P2X7 receptors | P2X7 antagonist, Brilliant Blue G (BBG) in vivo | Showed no difference in motor neuron loss, microgliosis, P2X7 receptor levels: differed from Apolloni et al. [147], through gender-based deviations | [154] |
| | B6.Cg-Tg(SOD1-G93A)1Gur/J: SOD1G93A ALS Mice | Increased NLRP3, ASC, cleaved Caspase-1 and IL-1β expression in spinal cord tissue | Estrogen treatment | Reduced motor deficits, microglial activation, reduced NLRP3, caspase activity, IL-1β production | [149] |
| | B6.Cg-Tg(SOD1-G93A)1Gur/J: SOD1G93A ALS Mice | Upregulated NLRP3 in skeletal muscles; correlated with increased longevity in mice | MCC950, NLRP3 inhibitor | Reduced longevity in G93A-SOD1 mice, a dual role for NLRP3 | [150] |
| | B6/SJL-Tg(SOD1*G93A)1Gur/J: SOD1G93A ALS mice | Increased NLRP3, ASC, cleaved Caspase-1 and IL-1β expression in spinal cord tissue | Primary astrocytes are shown as the main source of NLRP3, not microglia | | [146] |
| | B6-Cg-Tg (SOD1-G93A) 1Gur/J: SOD1G93A ALS mice, TDP43 ALS mice | Increased NLRP3, ASC, cleaved Caspase-1 and IL-1β expression in microglia and astrocytes in vivo | MCC950, NLRP3 inhibitor; AP-DC, a ROS inhibitor; A438079, P2X7 receptor inhibitor | Reduced SOD1G93A, TDP-43-induced NLRP3 activation, and IL-1β production | [148] |
| | WT primary microglia exposed to mutant G93A-SOD1, B6/SJL-Tg(SOD1*G93A)1Gur/J: SOD1G93A ALS mice | Increased cleaved caspase-1 and IL-1β | IL-1β, Caspase-1 deficient mice | Enhanced survival of G93A-SOD1 mice | [145] |
| | WT primary microglia exposed to TDP-43 | Increased NLRP3, ASC; IL1β expression, through NF-kB | SR11302, AP-1 (Activator protein-1) inhibitor | Reduced protein levels of IL-1β, but not RNA levels of IL-1β and other inflammasome components | [151] |
| Human | ALS patient blood sample | Upregulated NLRP3 | | | [150] |
| | ALS patients | Increased serum IL-18, IL-18BP | | | [152] |
| | ALS patients | Increased NLRP3, ASC, cleaved Caspase-1 and IL-1β expression in spinal cord post-mortem tissue | NLRP3 is not detected in Iba1+ microglia, but astrocytes | | [146] |
| | ALS patients | | Anakinra treatment (IL-1β antagonist) | No change in disease progression | [155] |

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## 4. Conclusion

The NLRP3 inflammasome activation is a necessary evil. Its sole purpose is to prepare and defend against threats by initiating a pro-inflammatory cascade. However, the NLRP3 activation loops into a vicious cycle of activation and inducing cell death in neurodegenerative diseases. It is ironic that NLRP3 ultimately becomes the one thing that it swore to destroy: Threat! In this review, we have presented several recent findings supporting this fact and multiple studies that showed a reversal of disease phenotype by inhibiting or modulating NLRP3. Hence, it is worthwhile to design clinical trials that use therapeutic strategies against the NLRP3 pathway for AD and PD.

## 5. Summary

- The aging population faces the threat of incurable neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, and many others, which have ongoing inflammatory processes that worsen the disease.
- Neuroinflammation in these diseases is primarily orchestrated by the NLRP3 inflammasome in microglia.
- Key pathological forms of proteins that activate NLRP3 include but are not limited to Amyloid β, tau in AD, α synuclein in PD, and SOD1, TDP43 in ALS.
- Activation of NLRP3 is a two-step process: priming through TLR signaling and gene transcription, and licensing through secondary signals like potassium efflux, lysosomal cathepsin-B, and mitochondrial ROS among others.
- NLRP3 inhibitor MCC950 treatment in mouse models of AD and PD has improved memory, cognitive, and motor functions in these mice, indicating the potential of NLRP3 inhibitors as therapeutic strategies.

## 6. Competing Interests

M.T.H. belongs to the advisory board of IFM Therapeutics and Alector and is editor of the Journal of Neurochemistry. K.A.R. declares no competing interests associated with the manuscript.

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## 9. Author Contribution

All authors wrote, reviewed, and edited the manuscript.

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## Figure Legends

**Figure 1. An overview of the inflammasome**. Pathogen-associated molecular patterns (PAMPs) from external bacteria, viruses, and fungi or damage-associated molecular patterns (DAMPs) from the host are sensed and activate the inflammasome. The inflammasome Human NLRP1 and NLRC4 contains a CARD domain that recruits pro-Caspase-1 through homotypic interactions. Other inflammasomes like NLRP3, NLRP6, NLRP7, and AIM2/IFI16 do not contain the CARD domain and require the adaptor protein ASC to recruit pro-caspase-1. Successful recruitment of pro-caspase-1 and oligomerization leads to inflammasome assembly which results in activation of caspase-1. When active, caspase-1 proteolytically converts precursor proteins into pro-inflammatory cytokines like IL-1β, IL-18 through Gasdermin-D pores. This pro-inflammatory outburst leads to cell death called pyroptosis and spreads information to neighboring cells to prepare for the threat.

**Figure 2. NLRP3 inflammasome activation mechanism.** The NLRP3 inflammasome is activated in a two-step process. The first step is priming, where the PAMPs or DAMPs including Amyloid-β, Tau, α-Synuclein, etc. are sensed by the Toll-like receptors (TLRs) in the membrane. TLR signaling results in the activation of NF-κB through the MyD88/TRAF6 pathway leading to its translocation into the nucleus. NF-κB binds to pro-inflammatory genes and results in the production of NLRP3, ASC, Pro-Caspase-1, and also the precursor forms of cytokines pro-IL-1β, pro-IL-18, and Gasdermin-D. When produced, NLRP3 exists in auto-inhibited form and is only activated through the second step called licensing or activation. Post-translational modification (PTMs) on NLRP3 by phosphatase PP2A, kinase JNK1, and deubiquitinases BRCC2, BRCC36 facilitates its activation, whereas ubiquitinase MARCH7 and kinase PKA inactivates it. The activation is achieved through three ways: (i) ionic imbalances by potassium and chloride ion efflux or sodium and calcium ion influx; (ii) mitochondrial dysfunction by reduced fission or abnormal electron transport chain leading to reactive oxygen species (ROS) build-up and cardiolipin release; (iii) lysosomal dysfunction by phagocytosis of abnormal protein aggregates of Amyloid-β, Tau, and α-synuclein leading to cathepsin-B release. These cues are received by NLRP3 and initiate oligomerization of the inflammasome complex leading to the cleavage of caspase-1. Active caspase-1 cleaves the precursor forms of cytokines pro-IL-1β, pro-IL-18, into mature cytokines IL-1β, IL-18 that are released by the pores formed on the membrane by cleaved Gasdermin-D. This a burst of pro-inflammatory cytokines to signal surrounding cells and the cell dies by pyroptosis.

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**Figure 3. NLRP3 activation in neurodegenerative diseases. A.** In Alzheimer's disease (AD), the amyloid precursor protein (APP) in the cell membrane is cleaved by mutated β-secretase and γ-secretase to produce soluble Amyloid-β (Aβ) monomers. The microtubule-stabilizing protein tau in the neuronal axon dissociates from the structure when it is hyper-phosphorylated. Aβ and Phosphorylated tau (p-tau) monomers are released in AD, which when aggregated form amyloid plaques and neurofibrillary tangles respectively. These protein aggregates activate the TLR2/4 signaling and damage the lysosome after phagocytosis leading to NLRP3 activation in AD. **B.** In Parkinson's disease (PD), a mutation in the synapse-associated protein α-Synuclein leads to its aggregation and formation of Lewy bodies in neurons. Aggregates of α-Synuclein also activate TLR2/4 signaling and damage the lysosomes leading to NLRP3 activation in PD. **C.** In Amyotrophic lateral sclerosis (ALS), a mutation in antioxidant enzyme superoxide dismutase (SOD1) leads to increased superoxide anion (reactive oxygen species ROS) and also the aggregation of SOD1 proteins. An RNA/DNA regulating protein called TAR DNA binding protein 43 (TDP43) is also involved in the pathogenesis of ALS. Mutations in TDP43, hyperphosphorylation, or ubiquitination of this protein causes aggregation. Mutant SOD1 along with mutant TDP43 activates NLRP3 through TLR2/4 signaling, lysosomal damage, and ROS generation in ALS.

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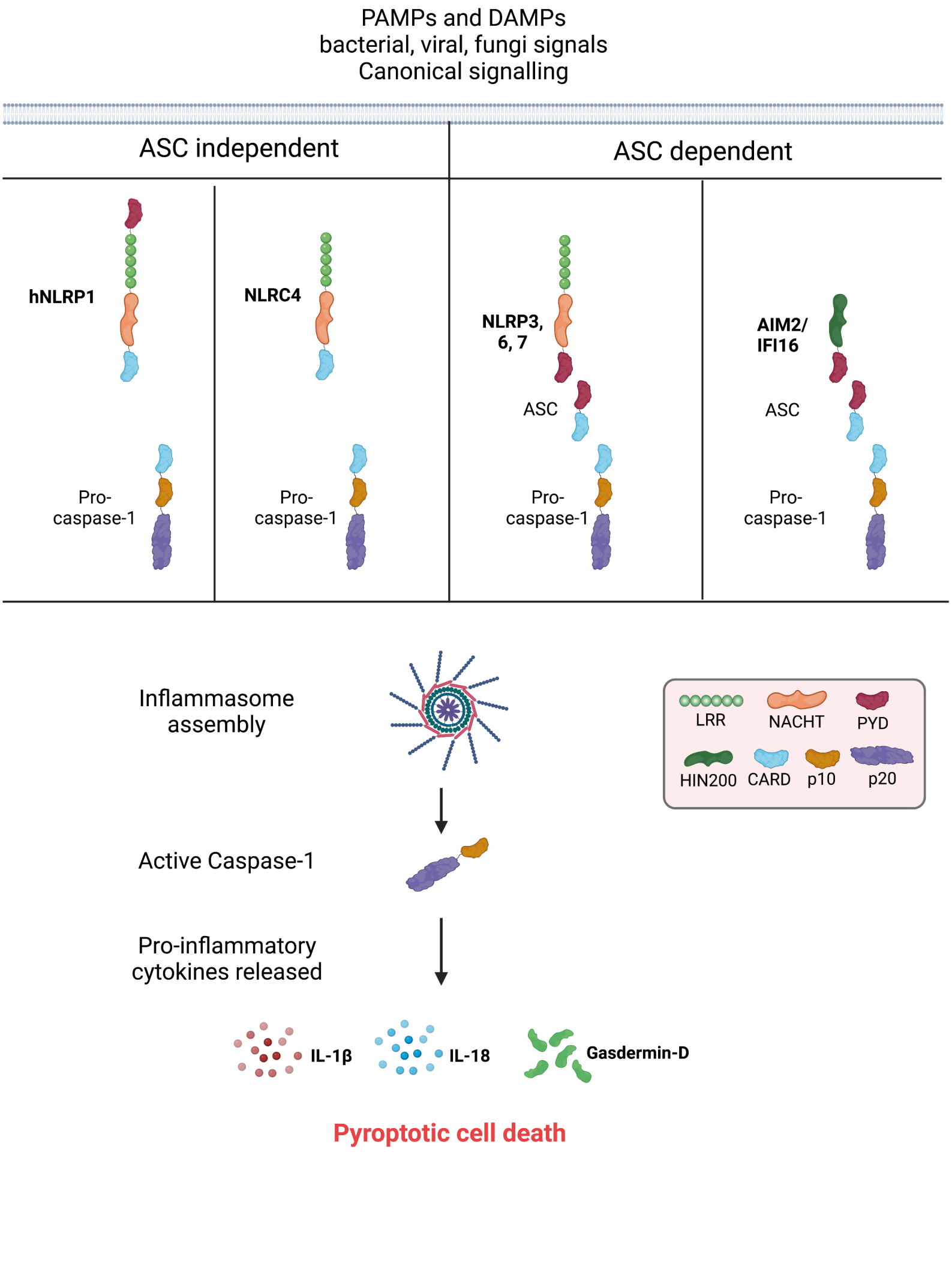
Figure 1.


PAMPs and DAMPs
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ASC dependent
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NLRC4
NLRP3, 6, 7
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ASC
ASC
Pro-caspase-1
Pro-caspase-1
Pro-caspase-1
Pro-caspase-1
Inflammasome assembly
LRR
NACHT
PYD
HIN200
CARD
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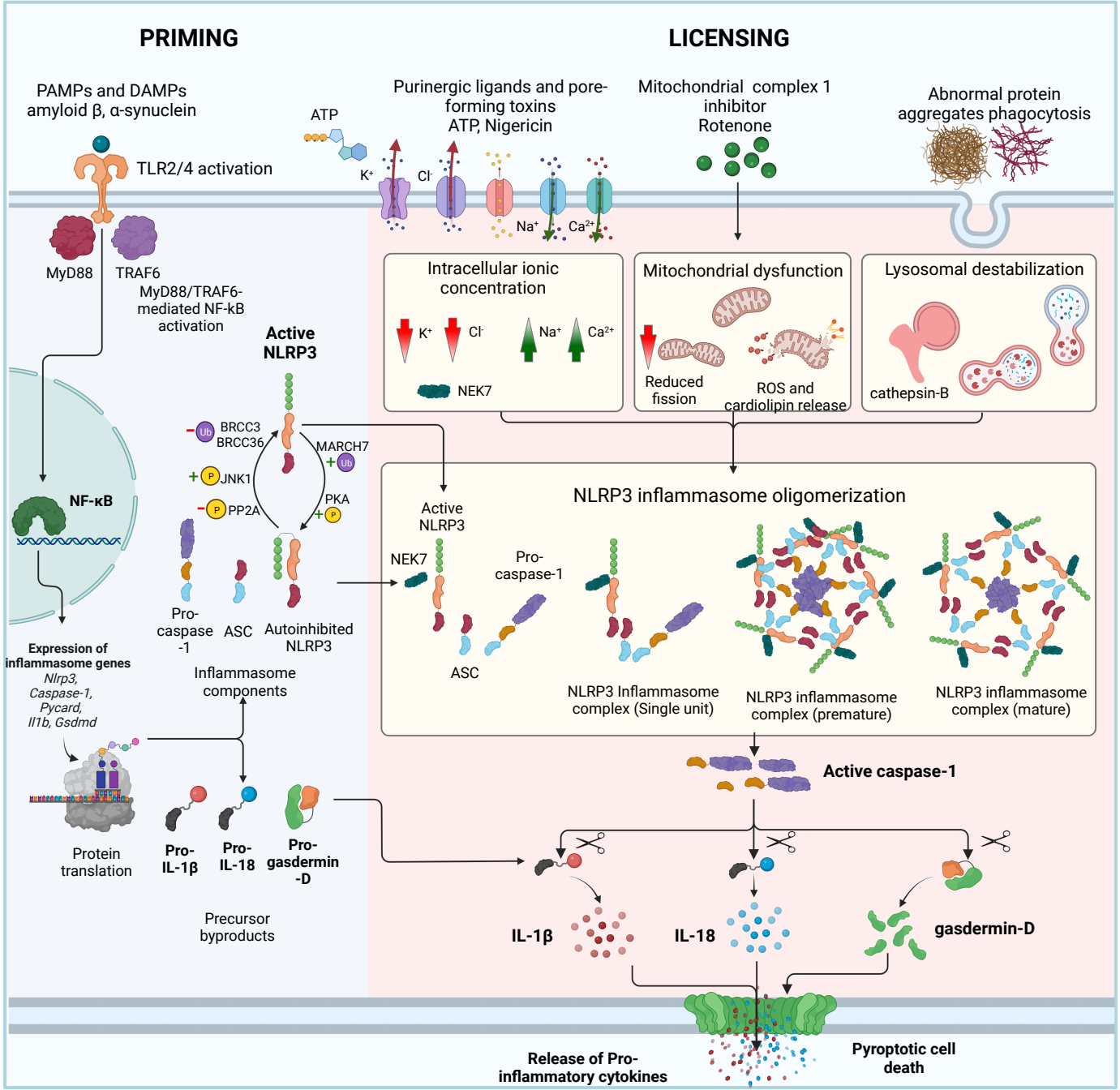
p20
Active Caspase-1
Pro-inflammatory cytokines released
IL-1β
IL-18
Gasdermin-D
Pyroptotic cell death

Figure 2.


PRIMING
LICENSING
PAMPs and DAMPs
amyloid β, α-synuclein
TLR2/4 activation
MyD88
TRAF6
MyD88/TRAF6-mediated NF-kB activation
ATP
K+
Cl-
Na+
Ca2+
Purinergic ligands and pore-forming toxins
ATP, Nigericin
Mitochondrial complex 1 inhibitor
Rotenone
Abnormal protein aggregates phagocytosis
Intracellular ionic concentration
NEK7
Mitochondrial dysfunction
Reduced fission
ROS and cardiolipin release
Lysosomal destabilization
cathepsin-B
Active NLRP3
BRCC3
BRCC36
JNK1
PP2A
MARCH7
PKA
Pro-caspase -1
ASC
Autoinhibited NLRP3
NF-κB
Expression of inflammasome genes
Nlrp3, Caspase-1, Pycard, Il1b, Gsdmd
Inflammasome components
NLRP3 inflammasome oligomerization
Active NLRP3
NEK7
Pro-caspase-1
ASC
NLRP3 Inflammasome complex (Single unit)
NLRP3 inflammasome complex (premature)
NLRP3 inflammasome complex (mature)
Active caspase-1
Protein translation
Pro-IL-1β
Pro-IL-18
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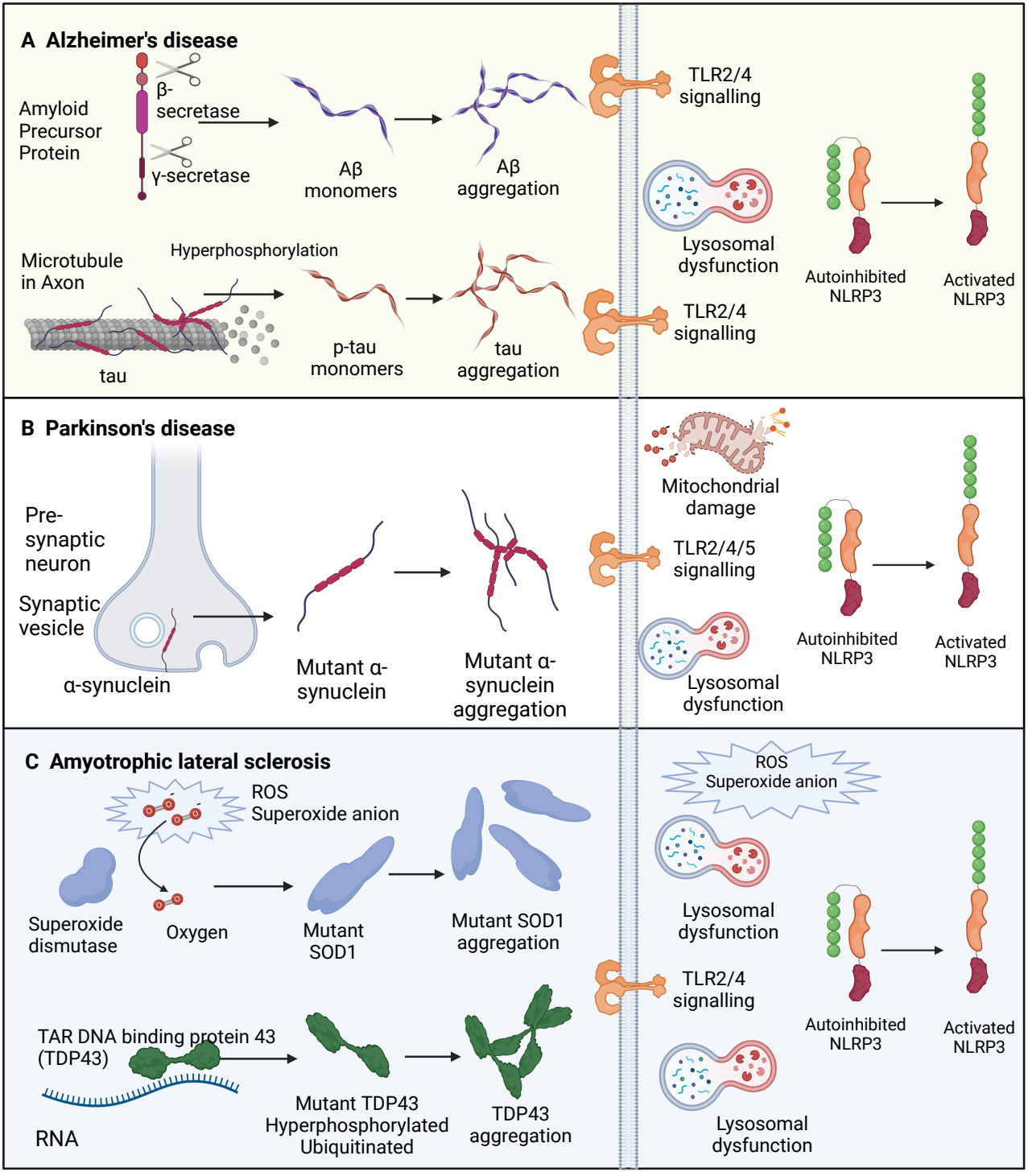
Precursor byproducts
IL-1β
IL-18
gasdermin-D
Release of Pro-inflammatory cytokines
Pyroptotic cell death

Figure 3.


A Alzheimer's disease
Amyloid Precursor Protein
β-secretase
γ-secretase
Aβ monomers
Aβ aggregation
TLR2/4 signalling
Lysosomal dysfunction
Autoinhibited NLRP3
Activated NLRP3
Microtubule in Axon
Hyperphosphorylation
tau
p-tau monomers
tau aggregation
TLR2/4 signalling
B Parkinson's disease
Pre-synaptic neuron
Synaptic vesicle
α-synuclein
Mutant α-synuclein
Mutant α-synuclein aggregation
Mitochondrial damage
TLR2/4/5 signalling
Lysosomal dysfunction
Autoinhibited NLRP3
Activated NLRP3
C Amyotrophic lateral sclerosis
ROS
Superoxide anion
Superoxide dismutase
Oxygen
Mutant SOD1
Mutant SOD1 aggregation
TAR DNA binding protein 43 (TDP43)
RNA
Mutant TDP43
Hyperphosphorylated
Ubiquitinated
TDP43 aggregation
ROS
Superoxide anion
Lysosomal dysfunction
TLR2/4 signalling
Lysosomal dysfunction
Autoinhibited NLRP3
Activated NLRP3