

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

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

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- κ B-related pro-inflammatory genes including NLRP3, pro-IL-1 β , 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-1 β 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

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-1 β 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 (A β) 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 A β 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 A β generation [65]. A β peptides released in the extracellular matrix (ECM) aggregate and oligomerize through three-dimensional peptide interactions, leading to A β plaques that occupy the micro-environment of neurons. They affect brain functionality by inducing neurotoxicity or by

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

A β exists as either monomer, unorganized oligomeric structures, or organized fibrillar structures wherein only the A β oligomers and protofibrils induced NLRP3 inflammasome in primary microglia [67–70]. The detection of A β 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 A β 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 A β -induced NLRP3 activation in microglia showed A β phagocytosis as the primary trigger [67]. Microglial A β 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 A β [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 A β clearance [3]. This suggests a critical role of the NLRP3 in orchestrating A β -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 A β to oligomerize and fibrillize 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 A β 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-1 β production [82] whereas, an AD-specific variant of *TREM2* reduced NLRP3 activity [83]. Also, mutations in the microglial *CD33* receptor impairs DAMP sensing and A β phagocytosis in AD [84]. Although, blocking *CD33* with chimeric antibodies showed reduced NLRP3-mediated IL-1 β production in human monocytes, indicating a therapeutic potential [84,85]. Another significant genetic risk is the *APOE* ϵ 4 that impairs APOE-mediated lipid metabolism, and possibly A β phagocytosis leading to increased plaques in AD [86]. APOE4 carrying mouse microglia showed enhanced NLRP3-mediated IL-1 β 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 A β clearance, and rescued the memory deficits in APP/PS1 and TgCRND8 AD mouse models [91,92]. Besides NLRP3, the NF- κ B inhibitor Bay11-7082 also restored kainic acid-induced A β 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.

Table 1. NLRP3 activation in AD

Species	Model	Inflammasome modulation	Molecular intervention	Effects	References
	3* Tg AD mice	Increased NLRP3. Cleaved Caspase-1, IL-1 β	Hexokinase is decreased in AD	Hexokinase dissociation from mitochondria activates the inflammasome	[95]
	5X FAD mice		ASC knockout	IL-1 β 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 A β plaque	BHB, an endogenous anti-inflammatory molecule	Reduced ASC, Caspase-1 cleavage, microgliosis, and A β deposition	[94]
	5X FAD mice	Increased caspase-1, caspase-3, NLRP3, ASC, IL-1 β and IL-18	DJ-1, a regulator of transcription factor Nrf2. DJ-1 overexpression	DJ-1 overexpression reduced hippocampal A β levels, and NLRP3, ASC, caspase-1, IL-1 β , and IL-18 levels by increasing nuclear translocation of Nrf2	[96]
	APP/PS1	Increased cleaved caspase-1, IL-1 β	NLRP3 knockout	Decreased Caspase-1 activation, IL-1 β release, Rescued memory deficits, increased Amyloid phagocytosis	[3]
	APP/PS1	ASC injection increased A β 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-1 β	[90]
	APP/PS1	A systemic challenge with LPS increased A β deposition	NLRP3 knockout	Increased microglial clearance of A β after systemic challenge	[89]
	APP/PS1 and 5X FAD	Increased NLRP3, ASC, Cleaved caspase-1, IL1 β , through increased NF- κ B	N, N'-diacetyl-p-phenylenediamine [DAPPD]; small inhibitor of NLRP3 through its impact on NF- κ B and promotes phagocytosis	Reduced cognitive deficits by increasing microglial phagocytosis and suppressing inflammasome components	[97]
	APP/PS1 mice	A β 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, A β 25-35 mice	IL1 β , NLRP3 increased in the brains due to abnormal autophagy function (LC3 increased and LAMP1 decreased)	TFEB overexpression, lysosomal biogenesis regulator	LC3 decreased and Lamp1 increased, reduced NLRP3, IL1 β , Caspase-1 in vitro	[99]
	APP/PS1 mice, murine microglia and in vivo	Increased IL1 β , TNF, IL-6 mRNA in vivo	MCC950	Reduced microglial inflammasome, enhanced A β phagocytosis, decreased amyloid plaques in vivo, improved cognition	[91]
Mouse	APP23	Increase in NF- κ B, IL-1 β , BDNF	Bay11-7082, NF- κ B inhibitor	Reduced Kainic acid-induced Amyloid propagation and memory deficits in APP23 mice by mitigating inflammasome	[93]

	C57/BL6 injected with A β 1-40, A β induced Retinal degeneration model	IL1 β , 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-1 β production. Protected from A β induced functional loss	[100]
	TgCRND8	NLRP3, ASC, Caspase-1 upregulation	JC-124: a NLRP3 inhibitor	Enhanced A β 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	A β and p-Tau increased	[101]
	A β on BALB/c murine astrocytes	A β 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-1 β	[102]
	A β on Primary microglia	Amyloid β clusters around ASC, inducing toxicity	ASC specks are released, they cross seed with A β in plaques	ASC-binding with A β induced inflammasome activation, Exogenous ASC induced NLRP3 inflammasome in ASC-deficiency, ASC binding reduced A β uptake	[103]
	A β on Primary microglia, in vivo	A β induced NLRP3 upregulation, IL-1 β , through Cathepsin-B release	NLRP3 knockout, ASC knockout, IL1R knockout	Suppressed A β -induced microglial activation	[67]
	A β on Primary microglia	A β 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-1 β	NLRP3 knockout, ASC knockout	Rescues cognitive decline and prevents tau pathology from the spread	[5]
Human	AD patient brain tissues	NLRP3, ASC, Caspase-1 co-localization at A β 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 A β in AD patients			[4]
	AD patient brain tissues	Increased cleaved caspase-1, IL-1 β			[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]
	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 IL1 β	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- κ B-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-1 β 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 NLRP3 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-1 β 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 NLRP3 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-1 β antagonist also rescued

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).

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- α SYN mouse model	Increased NLRP3, ASC, Caspase-1, IL-1 β , 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-1 β , MIF secretion	MCC950, NLRP3 inhibitor in vivo treatment to <i>Atg5</i> knockout mice	TH+ neuronal loss rescued, microglial inflammation reduced	[136]
	MPTP-injected mice	Increased NLRP3, Caspase-1, IL-1 β	MPP+ acts as priming signal for NLRP3, three interventions: NLRP3 knockout; IL1 β antagonist; NLRP3 constitutively active in microglia	NLRP3 knockout and IL1 β antagonist reduced Motor deficits and neuronal loss, whereas over-activation of NLRP3 worsened PD phenotype	[118]
	MPTP-injected mice	Increased NLRP3, Caspase, IL1 β in the olfactory bulb, through TLR2, NF- κ B signaling			[119]
	MPTP-injected mice	Increased NLRP3, IL-1 β , 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-1 β , 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-1 β , 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 NLRP3 is involved in the MPTP model, not NLRP1, NLRP4	[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-1 β	Kaempferol (Ka) promotes ubiquitination of NLRP3, degradation of NLRP3, and reduced the caspase-1, and IL1 β release	Ka prevented neurodegeneration by attenuating the NLRP3 inflammasome cascade	[126]
	MPTP-injected mice, SNCA-injected mice	Increased NLRP3, ASC, Caspase-1, IL-1 β , 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-1 β , NF- κ B signaling	TLR4 knockout, PRR for danger signals	TLR4 deficiency attenuated motor deficits, reduced TH neuron loss, by reducing inflammasome activity	[125]

	MPTP-treated murine astrocytes	Increased NLRP3, Caspase-1, IL1 β	Atp13a2 (Park9), a lysosomal ATPase, deficiency leads to lysosomal dysfunction. Park9 knockout and overexpression	Knockout: Increased NLRP3 and IL1 β release through Cathepsin-B after MPTP in astrocytes; Overexpression: Decreased the effects by MPP+ (MPTP)	[137]
	Paraquat + Maneb induced neurodegeneration	Increased NLRP3, IL1 β , Caspase-1 activity, through NF- κ B	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-1 β	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; IL1 β , Caspase-1, IL-18, through NF- κ B	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]
Hu man	Human monocytes treated with α -Synuclein	NLRP3, Caspase-1, IL-1 β 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-1 β 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-1 β , 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-1 β release	TLR2 neutralizing antibodies, anti- α -Synuclein, and anti-A β antibodies	TLR2 antibodies blocked α -Synuclein-mediated NLRP3 activation, α -Synuclein and A β antibodies increased the activity	[113]
	PD brain tissues	NLRP3 elevated in dopaminergic neurons, NLRP3 immunoreactive neurites	<i>NLRP3</i> ⁹⁷⁹ variant: rs7525979 C-to-T genetic variant of <i>NLRP3</i>	In HEK293 cells, <i>NLRP3</i> SNP rs7525979 reduced the risk of PD by impacting the protein turnover of NLRP3	[135]

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-1 β levels in their spinal cord tissues [145–150]. Similarly, microglial exposure to mutant TDP43 showed NLRP3 inflammasome activation through the NF- κ B 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-1 β 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-1 β 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-1 β -mediated effects in ALS might be redundant [155]. Hence, more studies are needed to dissect the exact role of NLRP3 activation in ALS pathogenesis.

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-1 β through NF- κ B	P2X7 antagonist, Brilliant Blue G (BBG) in vivo	Delayed disease progression through reducing IL-1 β , NF- κ B	[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-1 β expression in spinal cord tissue	Estrogen treatment	Reduced motor deficits, microglial activation, reduced NLRP3, caspase activity, IL-1 β 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-1 β 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-1 β 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-1 β 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-1 β	IL-1 β , Caspase-1 deficient mice	Enhanced survival of G93A-SOD1 mice	[145]
	WT primary microglia exposed to TDP-43	Increased NLRP3, ASC; IL1 β expression, through NF- κ B	SR11302, AP-1 (Activator protein-1) inhibitor	Reduced protein levels of IL-1 β , but not RNA levels of IL-1 β 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-1 β expression in spinal cord post-mortem tissue	NLRP3 is not detected in Iba1+ microglia, but astrocytes		[146]
	ALS patients		Anakinra treatment (IL-1 β antagonist)	No change in disease progression	[155]

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.

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-1 β , 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- κ B through the MyD88/TRAF6 pathway leading to its translocation into the nucleus. NF- κ B 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-1 β , 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-1 β , pro-IL-18, into mature cytokines IL-1 β , 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.

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 ($A\beta$) monomers. The microtubule-stabilizing protein tau in the neuronal axon dissociates from the structure when it is hyperphosphorylated. $A\beta$ 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.

References

1. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol* [Internet]. 2019;15(10):565–81. Available from: <https://doi.org/10.1038/s41582-019-0244-7>
2. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015 Apr;14(4):388–405.
3. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* [Internet]. 2013;493(7434):674–8. Available from: <http://dx.doi.org/10.1038/nature11729>
4. Venegas C, Kumar S, Franklin BS, Dierkes T, Brinkschulte R, Tejera D, et al. Microglia-derived ASC specks cross-seed amyloid- β in Alzheimer's disease. *Nature* [Internet]. 2017;552(7685):355–61. Available from: <https://doi.org/10.1038/nature25158>
5. Ising C, Venegas C, Zhang S, Scheiblich H, Schmidt S V, Vieira-Saecker A, et al. NLRP3 inflammasome activation drives tau pathology. *Nature* [Internet]. 2019;575(7784):669–73. Available from: <https://doi.org/10.1038/s41586-019-1769-z>
6. Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. *Nat Rev Immunol* [Internet]. 2013;13(6):397–411. Available from: <https://doi.org/10.1038/nri3452>
7. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. *Nat Rev Immunol* [Internet]. 2016;16(7):407–20. Available from: <https://doi.org/10.1038/nri.2016.58>
8. Rodrigues TS, de Sá KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, et al. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. *J Exp Med*. 2021 Mar;218(3).
9. Zheng D, Liwinski T, Elinav E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. *Cell Discov* [Internet]. 2020;6(1):36. Available from: <https://doi.org/10.1038/s41421-020-0167-x>
10. Davis BK, Wen H, Ting JP-Y. The inflammasome NLRs in immunity, inflammation, and associated diseases. *Annu Rev Immunol*. 2011;29:707–35.
11. Schroder K, Tschopp J. The inflammasomes. *Cell*. 2010 Mar;140(6):821–32.
12. Martinon F, Burns K, Tschopp J. The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL- β . *Mol Cell* [Internet]. 2002;10(2):417–26. Available from: <https://www.sciencedirect.com/science/article/pii/S1097276502005993>
13. Kaushal V, Dye R, Pakavathkumar P, Foveau B, Flores J, Hyman B, et al. Neuronal NLRP1 inflammasome activation of Caspase-1 coordinately regulates inflammatory interleukin-1-beta production and axonal degeneration-associated Caspase-6 activation. *Cell Death Differ* [Internet]. 2015;22(10):1676–86. Available from: <https://doi.org/10.1038/cdd.2015.16>
14. Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. *Nat Rev Neurosci*. 2018;19(10):610–21.
15. Liu H, Leak RK, Hu X. Neurotransmitter receptors on microglia. Vol. 1, *Stroke and Vascular Neurology*. BMJ Publishing Group; 2016. p. 52–8.

16. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol Immunol* [Internet]. 2021;18(5):1106–21. Available from: <https://doi.org/10.1038/s41423-020-00630-3>
17. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet*. 2001 Nov;29(3):301–5.
18. Swanson K V, Deng M, Ting JP-Y. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol* [Internet]. 2019;19(8):477–89. Available from: <https://doi.org/10.1038/s41577-019-0165-0>
19. Xing Y, Yao X, Li H, Xue G, Guo Q, Yang G, et al. Cutting Edge: TRAF6 Mediates TLR/IL-1R Signaling-Induced Nontranscriptional Priming of the NLRP3 Inflammasome. *J Immunol*. 2017 Sep;199(5):1561–6.
20. Yan Y, Jiang W, Liu L, Wang X, Ding C, Tian Z, et al. Dopamine controls systemic inflammation through inhibition of NLRP3 inflammasome. *Cell*. 2015 Jan;160(1–2):62–73.
21. Py BF, Kim M-S, Vakifahmetoglu-Norberg H, Yuan J. Deubiquitination of NLRP3 by BRCC3 critically regulates inflammasome activity. *Mol Cell*. 2013 Jan;49(2):331–8.
22. Singh M, Kumari B, Yadav UCS. Regulation of oxidized LDL-induced inflammatory process through NLRP3 inflammasome activation by the deubiquitinating enzyme BRCC36. *Inflamm Res* [Internet]. 2019;68(12):999–1010. Available from: <https://doi.org/10.1007/s00011-019-01281-5>
23. Song N, Liu Z-S, Xue W, Bai Z-F, Wang Q-Y, Dai J, et al. NLRP3 Phosphorylation Is an Essential Priming Event for Inflammasome Activation. *Mol Cell*. 2017 Oct;68(1):185-197.e6.
24. Mortimer L, Moreau F, MacDonald JA, Chadee K. NLRP3 inflammasome inhibition is disrupted in a group of auto-inflammatory disease CAPS mutations. *Nat Immunol*. 2016 Oct;17(10):1176–86.
25. Stutz A, Kolbe C-C, Stahl R, Horvath GL, Franklin BS, van Ray O, et al. NLRP3 inflammasome assembly is regulated by phosphorylation of the pyrin domain. *J Exp Med* [Internet]. 2017 May 2;214(6):1725–36. Available from: <https://doi.org/10.1084/jem.20160933>
26. Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. *Cell Death Dis* [Internet]. 2019;10(2):128. Available from: <https://doi.org/10.1038/s41419-019-1413-8>
27. Seok JK, Kang HC, Cho Y-Y, Lee HS, Lee JY. Regulation of the NLRP3 Inflammasome by Post-Translational Modifications and Small Molecules [Internet]. Vol. 11, *Frontiers in Immunology*. 2021. p. 3877. Available from: <https://www.frontiersin.org/article/10.3389/fimmu.2020.618231>
28. Duncan JA, Bergstralh DT, Wang Y, Willingham SB, Ye Z, Zimmermann AG, et al. Cryopyrin/NALP3 binds ATP/dATP, is an ATPase, and requires ATP binding to mediate inflammatory signaling. *Proc Natl Acad Sci* [Internet]. 2007 May 8;104(19):8041 LP – 8046. Available from: <http://www.pnas.org/content/104/19/8041.abstract>
29. Oroz J, Barrera-Vilarmau S, Alfonso C, Rivas G, de Alba E. ASC Pyrin Domain Self-associates and Binds NLRP3 Protein Using Equivalent Binding Interfaces*. *J Biol Chem* [Internet]. 2016;291(37):19487–501. Available from:

- <https://www.sciencedirect.com/science/article/pii/S0021925820360270>
30. Boucher D, Monteleone M, Coll RC, Chen KW, Ross CM, Teo JL, et al. Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity. *J Exp Med*. 2018 Mar;215(3):827–40.
 31. Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. *Nat Rev Neurosci* [Internet]. 2018;19(10):610–21. Available from: <https://doi.org/10.1038/s41583-018-0055-7>
 32. Green JP, Yu S, Martín-Sánchez F, Pelegrin P, Lopez-Castejon G, Lawrence CB, et al. Chloride regulates dynamic NLRP3-dependent ASC oligomerization and inflammasome priming. *Proc Natl Acad Sci U S A*. 2018 Oct;115(40):E9371–80.
 33. Hafner-Bratkovič I, Benčina M, Fitzgerald KA, Golenbock D, Jerala R. NLRP3 inflammasome activation in macrophage cell lines by prion protein fibrils as the source of IL-1 β and neuronal toxicity. *Cell Mol Life Sci*. 2012 Dec;69(24):4215–28.
 34. de Rivero Vaccari JP, Bastien D, Yurcisin G, Pineau I, Dietrich WD, De Koninck Y, et al. P2X4 Receptors Influence Inflammasome Activation after Spinal Cord Injury. *J Neurosci* [Internet]. 2012 Feb 29;32(9):3058 LP – 3066. Available from: <http://www.jneurosci.org/content/32/9/3058.abstract>
 35. He Y, Zeng MY, Yang D, Motro B, Núñez G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. *Nature* [Internet]. 2016;530(7590):354–7. Available from: <https://doi.org/10.1038/nature16959>
 36. Shi H, Wang Y, Li X, Zhan X, Tang M, Fina M, et al. NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. *Nat Immunol* [Internet]. 2016;17(3):250–8. Available from: <https://doi.org/10.1038/ni.3333>
 37. Hafner-Bratkovič I, Sušjan P, Lainšček D, Tapia-Abellán A, Cerović K, Kadunc L, et al. NLRP3 lacking the leucine-rich repeat domain can be fully activated via the canonical inflammasome pathway. *Nat Commun* [Internet]. 2018;9(1):5182. Available from: <https://doi.org/10.1038/s41467-018-07573-4>
 38. Zhang Y, Rong H, Zhang F-X, Wu K, Mu L, Meng J, et al. A Membrane Potential- and Calpain-Dependent Reversal of Caspase-1 Inhibition Regulates Canonical NLRP3 Inflammasome. *Cell Rep* [Internet]. 2018;24(9):2356-2369.e5. Available from: <https://www.sciencedirect.com/science/article/pii/S2211124718312312>
 39. Muñoz-Planillo R, Kuffa P, Martínez-Colón G, Smith BL, Rajendiran TM, Núñez G. K⁺ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity* [Internet]. 2013 Jun 27;38(6):1142–53. Available from: <https://pubmed.ncbi.nlm.nih.gov/23809161>
 40. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *Int J Mol Sci* [Internet]. 2019 Jul 6;20(13):3328. Available from: <https://pubmed.ncbi.nlm.nih.gov/31284572>
 41. Won J-H, Park S, Hong S, Son S, Yu J-W. Rotenone-induced Impairment of Mitochondrial Electron Transport Chain Confers a Selective Priming Signal for NLRP3 Inflammasome Activation*. *J Biol Chem* [Internet]. 2015;290(45):27425–37. Available from: <https://www.sciencedirect.com/science/article/pii/S0021925820495055>
 42. Park S, Won J-H, Hwang I, Hong S, Lee HK, Yu J-W. Defective mitochondrial fission augments NLRP3 inflammasome activation. *Sci Rep* [Internet]. 2015;5(1):15489. Available from: <https://doi.org/10.1038/srep15489>

43. Zhong Z, Liang S, Sanchez-Lopez E, He F, Shalpour S, Lin X-J, et al. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. *Nature*. 2018 Aug;560(7717):198–203.
44. Nakanishi H. Microglial cathepsin B as a key driver of inflammatory brain diseases and brain aging. *Neural Regen Res* [Internet]. 2020 Jan 1;15(1):25–9. Available from: <http://www.nrroonline.org/article.asp?issn=1673-5374>
45. Suzuki T, Kohyama K, Moriyama K, Ozaki M, Hasegawa S, Ueno T, et al. Extracellular ADP augments microglial inflammasome and NF- κ B activation via the P2Y₁₂ receptor. *Eur J Immunol* [Internet]. 2020 Feb 1;50(2):205–19. Available from: <https://doi.org/10.1002/eji.201848013>
46. Chevriaux A, Pilot T, Derangère V, Simonin H, Martine P, Chalmin F, et al. Cathepsin B Is Required for NLRP3 Inflammasome Activation in Macrophages, Through NLRP3 Interaction [Internet]. Vol. 8, *Frontiers in Cell and Developmental Biology* . 2020. p. 167. Available from: <https://www.frontiersin.org/article/10.3389/fcell.2020.00167>
47. Campagno KE, Mitchell CH. The P2X₇ Receptor in Microglial Cells Modulates the Endolysosomal Axis, Autophagy, and Phagocytosis [Internet]. Vol. 15, *Frontiers in Cellular Neuroscience* . 2021. p. 66. Available from: <https://www.frontiersin.org/article/10.3389/fncel.2021.645244>
48. Frank MG, Hershman SA, Weber MD, Watkins LR, Maier SF. Chronic exposure to exogenous glucocorticoids primes microglia to pro-inflammatory stimuli and induces NLRP3 mRNA in the hippocampus. *Psychoneuroendocrinology*. 2014 Feb;40:191–200.
49. Frank MG, Weber MD, Fonken LK, Hershman SA, Watkins LR, Maier SF. The redox state of the alarmin HMGB1 is a pivotal factor in neuroinflammatory and microglial priming: A role for the NLRP3 inflammasome. *Brain Behav Immun*. 2016 Jul;55:215–24.
50. De Filippis L, Halikere A, McGowan H, Moore JC, Tischfield JA, Hart RP, et al. Ethanol-mediated activation of the NLRP3 inflammasome in iPS cells and iPS cells-derived neural progenitor cells. *Mol Brain* [Internet]. 2016;9(1):51. Available from: <https://doi.org/10.1186/s13041-016-0221-7>
51. Zielinski MR, Gerashchenko D, Karpova SA, Konanki V, McCarley RW, Sutterwala FS, et al. The NLRP3 inflammasome modulates sleep and NREM sleep delta power induced by spontaneous wakefulness, sleep deprivation and lipopolysaccharide. *Brain Behav Immun*. 2017 May;62:137–50.
52. Scheiblich H, Schlütter A, Golenbock DT, Latz E, Martinez-Martinez P, Heneka MT. Activation of the NLRP3 inflammasome in microglia: the role of ceramide. *J Neurochem* [Internet]. 2017 Dec 1 [cited 2019 Jan 3];143(5):534–50. Available from: <http://doi.wiley.com/10.1111/jnc.14225>
53. Christ A, Günther P, Lauterbach MAR, Diewell P, Biswas D, Pelka K, et al. Western Diet Triggers NLRP3-Dependent Innate Immune Reprogramming. *Cell*. 2018 Jan;172(1–2):162–175.e14.
54. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science*. 2010 Nov;330(6005):841–5.
55. Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. *Nat Rev Immunol* [Internet]. 2018;18(4):225–42. Available from:

- <https://doi.org/10.1038/nri.2017.125>
56. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci* [Internet]. 2021;24(3):312–25. Available from: <https://doi.org/10.1038/s41593-020-00783-4>
 57. Denes A, Coutts G, Lénárt N, Cruickshank SM, Pelegrin P, Skinner J, et al. AIM2 and NLRC4 inflammasomes contribute with ASC to acute brain injury independently of NLRP3. *Proc Natl Acad Sci* [Internet]. 2015 Mar 16;201419090. Available from: <http://www.pnas.org/content/early/2015/03/13/1419090112.abstract>
 58. Freeman L, Guo H, David CN, Brickey WJ, Jha S, Ting JP-Y. NLR members NLRC4 and NLRP3 mediate sterile inflammasome activation in microglia and astrocytes. *J Exp Med*. 2017 May;214(5):1351–70.
 59. Zhu J, Hu Z, Han X, Wang D, Jiang Q, Ding J, et al. Dopamine D2 receptor restricts astrocytic NLRP3 inflammasome activation via enhancing the interaction of β -arrestin2 and NLRP3. *Cell Death Differ* [Internet]. 2018;25(11):2037–49. Available from: <https://doi.org/10.1038/s41418-018-0127-2>
 60. Ojeda DS, Grasso D, Urquiza J, Till A, Vaccaro MI, Quarleri J. Cell Death Is Counteracted by Mitophagy in HIV-Productively Infected Astrocytes but Is Promoted by Inflammasome Activation Among Non-productively Infected Cells [Internet]. Vol. 9, *Frontiers in Immunology*. 2018. p. 2633. Available from: <https://www.frontiersin.org/article/10.3389/fimmu.2018.02633>
 61. 2021 Alzheimer's disease facts and figures. *Alzheimer's Dement* [Internet]. 2021 Mar 1;17(3):327–406. Available from: <https://doi.org/10.1002/alz.12328>
 62. Hanslik KL, Ulland TK. The Role of Microglia and the Nlrp3 Inflammasome in Alzheimer's Disease. *Front Neurol*. 2020;11:570711.
 63. Guo T, Zhang D, Zeng Y, Huang TY, Xu H, Zhao Y. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. *Mol Neurodegener* [Internet]. 2020;15(1):40. Available from: <https://doi.org/10.1186/s13024-020-00391-7>
 64. Müller UC, Deller T, Korte M. Not just amyloid: physiological functions of the amyloid precursor protein family. *Nat Rev Neurosci* [Internet]. 2017;18(5):281–98. Available from: <https://doi.org/10.1038/nrn.2017.29>
 65. Gratuze M, Leyns CEG, Holtzman DM. New insights into the role of TREM2 in Alzheimer's disease. *Mol Neurodegener* [Internet]. 2018;13(1):66. Available from: <https://doi.org/10.1186/s13024-018-0298-9>
 66. Venegas C, Kumar S, Franklin BS, Dierkes T, Brinkschulte R, Tejera D, et al. Microglia-derived ASC specks cross-seed amyloid- β in Alzheimer's disease. *Nat Publ Gr* [Internet]. 2017 [cited 2019 Jan 4];552. Available from: <http://cyber.sci-hub.tw/MTAuMTAzOC9uYXR1cmUyNTE1OA==/10.1038/nature25158.pdf>
 67. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid- β . *Nat Immunol* [Internet]. 2008;9(8):857–65. Available from: <https://doi.org/10.1038/ni.1636>
 68. Lučiūnaitė A, McManus RM, Jankunec M, Rácz I, Dansokho C, Dalgėdienė I, et al. Soluble A β oligomers and protofibrils induce NLRP3 inflammasome activation in microglia. *J Neurochem* [Internet]. 2020 Dec 1;155(6):650–61. Available from: <https://doi.org/10.1111/jnc.14945>

69. Verma M, Vats A, Taneja V. Toxic species in amyloid disorders: Oligomers or mature fibrils. *Ann Indian Acad Neurol* [Internet]. 2015;18(2):138–45. Available from: <https://pubmed.ncbi.nlm.nih.gov/26019408>
70. Nakanishi A, Kaneko N, Takeda H, Sawasaki T, Morikawa S, Zhou W, et al. Amyloid β directly interacts with NLRP3 to initiate inflammasome activation: identification of an intrinsic NLRP3 ligand in a cell-free system. [cited 2019 Apr 16]; Available from: <https://doi.org/10.1186/s41232-018-0085-6>
71. Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. CD14 and Toll-Like Receptors 2 and 4 Are Required for Fibrillar A β -Stimulated Microglial Activation. *J Neurosci* [Internet]. 2009 Sep 23;29(38):11982 LP – 11992. Available from: <http://www.jneurosci.org/content/29/38/11982.abstract>
72. Liu S, Liu Y, Hao W, Wolf L, Kiliaan AJ, Penke B, et al. TLR2 Is a Primary Receptor for Alzheimer's Amyloid β Peptide To Trigger Neuroinflammatory Activation. *J Immunol* [Internet]. 2012 Feb 1;188(3):1098 LP – 1107. Available from: <http://www.jimmunol.org/content/188/3/1098.abstract>
73. De S, Wirthensohn DC, Flagmeier P, Hughes C, Aprile FA, Ruggeri FS, et al. Different soluble aggregates of A β 42 can give rise to cellular toxicity through different mechanisms. *Nat Commun* [Internet]. 2019;10(1):1541. Available from: <https://doi.org/10.1038/s41467-019-09477-3>
74. Facci L, Barbierato M, Zusso M, Skaper SD, Giusti P. Serum amyloid A primes microglia for ATP-dependent interleukin-1 β release. *J Neuroinflammation* [Internet]. 2018;15(1):164. Available from: <https://doi.org/10.1186/s12974-018-1205-6>
75. Fu W, Vukojevic V, Patel A, Soudy R, MacTavish D, Westaway D, et al. Role of microglial amylin receptors in mediating beta amyloid (A β)-induced inflammation. *J Neuroinflammation* [Internet]. 2017;14(1):199. Available from: <https://doi.org/10.1186/s12974-017-0972-9>
76. Huang Y, Happonen KE, Burrola PG, O'Connor C, Hah N, Huang L, et al. Microglia use TAM receptors to detect and engulf amyloid β plaques. *Nat Immunol* [Internet]. 2021;22(5):586–94. Available from: <https://doi.org/10.1038/s41590-021-00913-5>
77. Franklin BS, Bossaller L, De Nardo D, Ratter JM, Stutz A, Engels G, et al. The adaptor ASC has extracellular and “prionoid” activities that propagate inflammation. *Nat Immunol* [Internet]. 2014;15(8):727–37. Available from: <https://doi.org/10.1038/ni.2913>
78. Barbier P, Zejneli O, Martinho M, Lasorsa A, Belle V, Smet-Nocca C, et al. Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects [Internet]. Vol. 11, *Frontiers in Aging Neuroscience*. 2019. p. 204. Available from: <https://www.frontiersin.org/article/10.3389/fnagi.2019.00204>
79. Arnsten AFT, Datta D, Del Tredici K, Braak H. Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. *Alzheimer's Dement* [Internet]. 2021 Jan 1;17(1):115–24. Available from: <https://doi.org/10.1002/alz.12192>
80. Stancu I-C, Cremers N, Vanrusselt H, Couturier J, Vanoosthuyse A, Kessels S, et al. Aggregated Tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. *Acta Neuropathol*. 2019 Apr;137(4):599–617.
81. Busche MA, Hyman BT. Synergy between amyloid- β and tau in Alzheimer's disease. *Nat Neurosci* [Internet]. 2020;23(10):1183–93. Available from:

<https://doi.org/10.1038/s41593-020-0687-6>

82. Garcia-Reitboeck P, Phillips A, Piers TM, Villegas-Llerena C, Butler M, Mallach A, et al. Human Induced Pluripotent Stem Cell-Derived Microglia-Like Cells Harboring TREM2 Missense Mutations Show Specific Deficits in Phagocytosis. *Cell Rep* [Internet]. 2018;24(9):2300–11. Available from: <https://www.sciencedirect.com/science/article/pii/S2211124718312270>
83. Cosker K, Mallach A, Limaye J, Piers TM, Staddon J, Neame SJ, et al. Microglial signalling pathway deficits associated with the patient derived R47H TREM2 variants linked to AD indicate inability to activate inflammasome. *Sci Rep*. 2021 Jun;11(1):13316.
84. Zhao L. CD33 in Alzheimer's Disease – Biology, Pathogenesis, and Therapeutics: A Mini-Review. *Gerontology* [Internet]. 2019;65(4):323–31. Available from: <https://www.karger.com/DOI/10.1159/000492596>
85. Basiorka AA, McGraw KL, Eksioglu EA, Chen X, Johnson J, Zhang L, et al. The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. *Blood*. 2016 Dec;128(25):2960–75.
86. Yamazaki Y, Zhao N, Caulfield TR, Liu C-C, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat Rev Neurol* [Internet]. 2019;15(9):501–18. Available from: <https://doi.org/10.1038/s41582-019-0228-7>
87. Wong MY, Lewis M, Doherty JJ, Shi Y, Cashikar AG, Amelanchik A, et al. 25-Hydroxycholesterol amplifies microglial IL-1 β production in an apoE isoform-dependent manner. *J Neuroinflammation* [Internet]. 2020;17(1):192. Available from: <https://doi.org/10.1186/s12974-020-01869-3>
88. Couturier J, Stancu I-C, Schakman O, Pierrot N, Huaux F, Kienlen-Campard P, et al. Activation of phagocytic activity in astrocytes by reduced expression of the inflammasome component ASC and its implication in a mouse model of Alzheimer disease. *J Neuroinflammation*. 2016 Jan;13:20.
89. Tejera D, Mercan D, Sanchez-Caro JM, Hanan M, Greenberg D, Soreq H, et al. Systemic inflammation impairs microglial A β clearance through NLRP3 inflammasome. *EMBO J*. 2019 Sep;38(17):e101064.
90. Martin E, Amar M, Dalle C, Youssef I, Boucher C, Le Duigou C, et al. New role of P2X7 receptor in an Alzheimer's disease mouse model. *Mol Psychiatry*. 2019 Jan;24(1):108–25.
91. Lonnemann N, Hosseini S, Marchetti C, Skouras DB, Stefanoni D, D'Alessandro A, et al. The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci* [Internet]. 2020 Dec 15;117(50):32145 LP – 32154. Available from: <http://www.pnas.org/content/117/50/32145.abstract>
92. Yin J, Zhao F, Chojnacki JE, Fulp J, Klein WL, Zhang S, et al. NLRP3 Inflammasome Inhibitor Ameliorates Amyloid Pathology in a Mouse Model of Alzheimer's Disease. *Mol Neurobiol*. 2018 Mar;55(3):1977–87.
93. Ruan Y, Qiu X, Lv Y-D, Dong D, Wu X-J, Zhu J, et al. Kainic acid Induces production and aggregation of amyloid β -protein and memory deficits by activating inflammasomes in NLRP3- and NF- κ B-stimulated pathways. *Aging (Albany NY)* [Internet]. 2019 Jun 10;11(11):3795–810. Available from: <https://pubmed.ncbi.nlm.nih.gov/31182681>

94. Shippy DC, Wilhelm C, Viharkumar PA, Raife TJ, Ulland TK. β -Hydroxybutyrate inhibits inflammasome activation to attenuate Alzheimer's disease pathology. *J Neuroinflammation* [Internet]. 2020;17(1):280. Available from: <https://doi.org/10.1186/s12974-020-01948-5>
95. Han S, He Z, Jacob C, Hu X, Liang X, Xiao W, et al. Effect of Increased IL-1 β on Expression of HK in Alzheimer's Disease. Vol. 22, *International Journal of Molecular Sciences* . 2021.
96. Cheng L, Zhang W. DJ-1 affects oxidative stress and pyroptosis in hippocampal neurons of Alzheimer's disease mouse model by regulating the Nrf2 pathway. *Exp Ther Med*. 2021 Jun;21(6):557.
97. Park MH, Lee M, Nam G, Kim M, Kang J, Choi BJ, et al. N,N'-diacetyl-p-phenylenediamine restores microglial phagocytosis and improves cognitive defects in Alzheimer's disease transgenic mice. *Proc Natl Acad Sci* [Internet]. 2019 Nov 19;116(47):23426 LP – 23436. Available from: <http://www.pnas.org/content/116/47/23426.abstract>
98. Rivers-Auty J, Tapia VS, White CS, Daniels MJD, Drinkall S, Kennedy PT, et al. Zinc Status Alters Alzheimer's Disease Progression through NLRP3-Dependent Inflammation. *J Neurosci*. 2021 Mar;41(13):3025–38.
99. Zhou W, Xiao D, Zhao Y, Tan B, Long Z, Yu L, et al. Enhanced Autolysosomal Function Ameliorates the Inflammatory Response Mediated by the NLRP3 Inflammasome in Alzheimer's Disease [Internet]. Vol. 13, *Frontiers in Aging Neuroscience* . 2021. p. 46. Available from: <https://www.frontiersin.org/article/10.3389/fnagi.2021.629891>
100. Chen J, Sun J, Hu Y, Wan X, Wang Y, Gao M, et al. MicroRNA-191-5p ameliorates amyloid- β 1-40-mediated retinal pigment epithelium cell injury by suppressing the NLRP3 inflammasome pathway. *FASEB J* [Internet]. 2021 Apr 1;35(4):e21184. Available from: <https://doi.org/10.1096/fj.202000645RR>
101. Silva DF, Candeias E, Esteves AR, Magalhães JD, Ferreira IL, Nunes-Costa D, et al. Microbial BMAA elicits mitochondrial dysfunction, innate immunity activation, and Alzheimer's disease features in cortical neurons. *J Neuroinflammation* [Internet]. 2020;17(1):332. Available from: <https://doi.org/10.1186/s12974-020-02004-y>
102. Ebrahimi T, Rust M, Kaiser SN, Slowik A, Beyer C, Koczulla AR, et al. α 1-antitrypsin mitigates NLRP3-inflammasome activation in amyloid β 1–42-stimulated murine astrocytes. *J Neuroinflammation* [Internet]. 2018;15(1):282. Available from: <https://doi.org/10.1186/s12974-018-1319-x>
103. Friker LL, Scheiblich H, Hochheiser I V, Brinkschulte R, Riedel D, Latz E, et al. β -Amyloid Clustering around ASC Fibrils Boosts Its Toxicity in Microglia. *Cell Rep*. 2020 Mar;30(11):3743-3754.e6.
104. Wang H-M, Zhang T, Huang J-K, Xiang J-Y, Chen J-J, Fu J-L, et al. Edaravone Attenuates the Proinflammatory Response in Amyloid- β -Treated Microglia by Inhibiting NLRP3 Inflammasome-Mediated IL-1 β Secretion. *Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol*. 2017;43(3):1113–25.
105. Ahmed ME, Iyer S, Thangavel R, Kempuraj D, Selvakumar GP, Raikwar SP, et al. Co-Localization of Glia Maturation Factor with NLRP3 Inflammasome and Autophagosome Markers in Human Alzheimer's Disease Brain. *J Alzheimers Dis*. 2017;60(3):1143–60.

106. Hishimoto A, Pletnikova O, Lang DL, Troncoso JC, Egan JM, Liu Q-R. Neurexin 3 transmembrane and soluble isoform expression and splicing haplotype are associated with neuron inflammasome and Alzheimer's disease. *Alzheimers Res Ther* [Internet]. 2019;11(1):28. Available from: <https://doi.org/10.1186/s13195-019-0475-2>
107. Mancuso R, Agostini S, Hernis A, Zanzottera M, Bianchi A, Clerici M. Circulatory miR-223-3p Discriminates Between Parkinson's and Alzheimer's Patients. *Sci Rep* [Internet]. 2019;9(1):9393. Available from: <https://doi.org/10.1038/s41598-019-45687-x>
108. Atluri VSR, Tiwari S, Rodriguez M, Kaushik A, Yndart A, Kolishetti N, et al. Inhibition of Amyloid-Beta Production, Associated Neuroinflammation, and Histone Deacetylase 2-Mediated Epigenetic Modifications Prevent Neuropathology in Alzheimer's Disease in vitro Model. *Front Aging Neurosci*. 2019;11:342.
109. Karabiyik C, Lee MJ, Rubinsztein DC. Autophagy impairment in Parkinson's disease. Lane JD, Korolchuk VI, Murray JT, editors. *Essays Biochem* [Internet]. 2017 Dec 12;61(6):711–20. Available from: <https://doi.org/10.1042/EBC20170023>
110. Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. *J Neurol Neurosurg & Psychiatry* [Internet]. 2020 Aug 1;91(8):795 LP – 808. Available from: <http://jnnp.bmj.com/content/91/8/795.abstract>
111. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Prim* [Internet]. 2021;7(1):47. Available from: <https://doi.org/10.1038/s41572-021-00280-3>
112. Panicker N, Sarkar S, Harischandra DS, Neal M, Kam T-I, Jin H, et al. Fyn kinase regulates misfolded α -synuclein uptake and NLRP3 inflammasome activation in microglia. *J Exp Med*. 2019 Jun;216(6):1411–30.
113. Trudler D, Nazor KL, Eisele YS, Grabauskas T, Dolatabadi N, Parker J, et al. Soluble α -synuclein-antibody complexes activate the NLRP3 inflammasome in hiPSC-derived microglia. *Proc Natl Acad Sci U S A*. 2021 Apr;118(15).
114. Scheiblich H, Bousset L, Schwartz S, Griep A, Latz E, Melki R, et al. Microglial NLRP3 Inflammasome Activation upon TLR2 and TLR5 Ligation by Distinct α -Synuclein Assemblies. *J Immunol*. 2021 Sep;
115. Billingsley KJ, Bandres-Ciga S, Saez-Atienzar S, Singleton AB. Genetic risk factors in Parkinson's disease. *Cell Tissue Res* [Internet]. 2018;373(1):9–20. Available from: <https://doi.org/10.1007/s00441-018-2817-y>
116. Ji Y-J, Wang H-L, Yin B-L, Ren X-Y. Down-regulation of DJ-1 Augments Neuroinflammation via Nrf2/Trx1/NLRP3 Axis in MPTP-induced Parkinson's Disease Mouse Model. *Neuroscience*. 2020 Aug;442:253–63.
117. Chia R, Sabir MS, Bandres-Ciga S, Saez-Atienzar S, Reynolds RH, Gustavsson E, et al. Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. *Nat Genet* [Internet]. 2021;53(3):294–303. Available from: <https://doi.org/10.1038/s41588-021-00785-3>
118. Lee E, Hwang I, Park S, Hong S, Hwang B, Cho Y, et al. MPTP-driven NLRP3 inflammasome activation in microglia plays a central role in dopaminergic neurodegeneration. *Cell Death Differ* [Internet]. 2019;26(2):213–28. Available from: <https://doi.org/10.1038/s41418-018-0124-5>
119. Chen Y, Zhang Q, Shao Q, Wang S, Yuan Y, Chen N, et al. NLRP3 inflammasome pathway is involved in olfactory bulb pathological alteration induced by MPTP. *Acta*

- Pharmacol Sin [Internet]. 2019;40(8):991–8. Available from: <https://doi.org/10.1038/s41401-018-0209-1>
120. Rui W, Li S, Xiao H, Xiao M, Shi J. Baicalein Attenuates Neuroinflammation by Inhibiting NLRP3/caspase-1/GSDMD Pathway in MPTP Induced Mice Model of Parkinson's Disease. *Int J Neuropsychopharmacol*. 2020 Aug;23(11):762–73.
 121. Langston JW. The MPTP Story. *J Parkinsons Dis*. 2017;7:S11–9.
 122. Sarkar S, Malovic E, Harishchandra DS, Ghaisas S, Panicker N, Charli A, et al. Mitochondrial impairment in microglia amplifies NLRP3 inflammasome proinflammatory signaling in cell culture and animal models of Parkinson's disease. *npj Park Dis* [Internet]. 2017;3(1):30. Available from: <https://doi.org/10.1038/s41531-017-0032-2>
 123. Siracusa R, Scuto M, Fusco R, Trovato A, Ontario ML, Crea R, et al. Anti-inflammatory and Anti-oxidant Activity of Hidrox® in Rotenone-Induced Parkinson's Disease in Mice. Vol. 9, *Antioxidants*. 2020.
 124. Hou L, Qu X, Qiu X, Huang R, Zhao X, Wang Q. Integrin CD11b mediates locus coeruleus noradrenergic neurodegeneration in a mouse Parkinson's disease model. *J Neuroinflammation* [Internet]. 2020;17(1):148. Available from: <https://doi.org/10.1186/s12974-020-01823-3>
 125. Shao Q, Chen Y, Li F, Wang S, Zhang X, Yuan Y, et al. TLR4 deficiency has a protective effect in the MPTP/probenecid mouse model of Parkinson's disease. *Acta Pharmacol Sin* [Internet]. 2019;40(12):1503–12. Available from: <https://doi.org/10.1038/s41401-019-0280-2>
 126. Han X, Sun S, Sun Y, Song Q, Zhu J, Song N, et al. Small molecule-driven NLRP3 inflammation inhibition via interplay between ubiquitination and autophagy: implications for Parkinson disease. *Autophagy* [Internet]. 2019 Nov 2;15(11):1860–81. Available from: <https://doi.org/10.1080/15548627.2019.1596481>
 127. Li Q, Wang Z, Xing H, Wang Y, Guo Y. Exosomes derived from miR-188-3p-modified adipose-derived mesenchymal stem cells protect Parkinson's disease. *Mol Ther - Nucleic Acids* [Internet]. 2021;23:1334–44. Available from: <https://www.sciencedirect.com/science/article/pii/S2162253121000226>
 128. Kwon O-C, Song J-J, Yang Y, Kim S-H, Kim JY, Seok M-J, et al. SGK1 inhibition in glia ameliorates pathologies and symptoms in Parkinson disease animal models. *EMBO Mol Med* [Internet]. 2021 Apr 9;13(4):e13076. Available from: <https://doi.org/10.15252/emmm.202013076>
 129. Qiao C, Zhang Q, Jiang Q, Zhang T, Chen M, Fan Y, et al. Inhibition of the hepatic Nlrp3 protects dopaminergic neurons via attenuating systemic inflammation in a MPTP/p mouse model of Parkinson's disease. *J Neuroinflammation* [Internet]. 2018;15(1):193. Available from: <https://doi.org/10.1186/s12974-018-1236-z>
 130. Gordon R, Albornoz EA, Christie DC, Langley MR, Kumar V, Mantovani S, et al. Inflammasome inhibition prevents α -synuclein pathology and dopaminergic neurodegeneration in mice. *Sci Transl Med*. 2018 Oct;10(465).
 131. Huang S, Chen Z, Fan B, Chen Y, Zhou L, Jiang B, et al. A selective NLRP3 inflammasome inhibitor attenuates behavioral deficits and neuroinflammation in a mouse model of Parkinson's disease. *J Neuroimmunol* [Internet]. 2021 May 15;354. Available from: <https://doi.org/10.1016/j.jneuroim.2021.577543>
 132. Liu W, Liu X, Li Y, Zhao J, Liu Z, Hu Z, et al. LRRK2 promotes the activation of

- NLRC4 inflammasome during *Salmonella Typhimurium* infection. *J Exp Med*. 2017 Oct;214(10):3051–66.
133. Xu Y, Tang Y, Lu J, Zhang W, Zhu Y, Zhang S, et al. PINK1-mediated mitophagy protects against hepatic ischemia/reperfusion injury by restraining NLRP3 inflammasome activation. *Free Radic Biol Med*. 2020 Nov;160:871–86.
 134. Codolo G, Plotegher N, Pozzobon T, Brucale M, Tessari I, Bubacco L, et al. Triggering of Inflammasome by Aggregated α -Synuclein, an Inflammatory Response in Synucleinopathies. *PLoS One* [Internet]. 2013 Jan 31;8(1):e55375. Available from: <https://doi.org/10.1371/journal.pone.0055375>
 135. von Herrmann KM, Salas LA, Martinez EM, Young AL, Howard JM, Feldman MS, et al. NLRP3 expression in mesencephalic neurons and characterization of a rare NLRP3 polymorphism associated with decreased risk of Parkinson's disease. *NPJ Park Dis*. 2018;4:24.
 136. Cheng J, Liao Y, Dong Y, Hu H, Yang N, Kong X, et al. Microglial autophagy defect causes parkinson disease-like symptoms by accelerating inflammasome activation in mice. *Autophagy* [Internet]. 2020 Dec 1;16(12):2193–205. Available from: <https://doi.org/10.1080/15548627.2020.1719723>
 137. Qiao C, Yin N, Gu H-Y, Zhu J-L, Ding J-H, Lu M, et al. Atp13a2 Deficiency Aggravates Astrocyte-Mediated Neuroinflammation via NLRP3 Inflammasome Activation. *CNS Neurosci Ther* [Internet]. 2016 Jun 1;22(6):451–60. Available from: <https://doi.org/10.1111/cns.12514>
 138. Martinez EM, Young AL, Patankar YR, Berwin BL, Wang L, von Herrmann KM, et al. Editor's Highlight: Nlrp3 Is Required for Inflammatory Changes and Nigral Cell Loss Resulting From Chronic Intragastric Rotenone Exposure in Mice. *Toxicol Sci*. 2017 Sep;159(1):64–75.
 139. Anderson FL, von Herrmann KM, Andrew AS, Kuras YI, Young AL, Scherzer CR, et al. Plasma-borne indicators of inflammasome activity in Parkinson's disease patients. *npj Park Dis* [Internet]. 2021;7(1):2. Available from: <https://doi.org/10.1038/s41531-020-00147-6>
 140. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. *Nat Rev Dis Prim* [Internet]. 2017;3(1):17071. Available from: <https://doi.org/10.1038/nrdp.2017.71>
 141. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. *Eur J Neurol* [Internet]. 2020 Oct 1;27(10):1918–29. Available from: <https://doi.org/10.1111/ene.14393>
 142. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*. 2006 Oct;314(5796):130–3.
 143. Higgins CMJ, Jung C, Xu Z. ALS-associated mutant SOD1G93A causes mitochondrial vacuolation by expansion of the intermembrane space and by involvement of SOD1 aggregation and peroxisomes. *BMC Neurosci*. 2003 Jul;4:16.
 144. Wang W, Wang L, Lu J, Siedlak SL, Fujioka H, Liang J, et al. The inhibition of TDP-43 mitochondrial localization blocks its neuronal toxicity. *Nat Med* [Internet]. 2016;22(8):869–78. Available from: <https://doi.org/10.1038/nm.4130>
 145. Meissner F, Molawi K, Zychlinsky A. Mutant superoxide dismutase 1-induced IL-1 β accelerates ALS pathogenesis. *Proc Natl Acad Sci* [Internet]. 2010 Jun

- 22;201002396. Available from:
<http://www.pnas.org/content/early/2010/06/21/1002396107.abstract>
146. Johann S, Heitzer M, Kanagaratnam M, Goswami A, Rizo T, Weis J, et al. NLRP3 inflammasome is expressed by astrocytes in the SOD1 mouse model of ALS and in human sporadic ALS patients. *Glia*. 2015 Dec;63(12):2260–73.
 147. Apolloni S, Amadio S, Parisi C, Matteucci A, Potenza RL, Armida M, et al. Spinal cord pathology is ameliorated by P2X7 antagonism in a SOD1-mutant mouse model of amyotrophic lateral sclerosis. *Dis Model Mech* [Internet]. 2014/07/18. 2014 Sep;7(9):1101–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/25038061>
 148. Deora V, Lee JD, Albornoz EA, McAlary L, Jagaraj CJ, Robertson AAB, et al. The microglial NLRP3 inflammasome is activated by amyotrophic lateral sclerosis proteins. *Glia*. 2020 Feb;68(2):407–21.
 149. Heitzer M, Kaiser S, Kanagaratnam M, Zendedel A, Hartmann P, Beyer C, et al. Administration of 17 β -Estradiol Improves Motoneuron Survival and Down-regulates Inflammasome Activation in Male SOD1(G93A) ALS Mice. *Mol Neurobiol* [Internet]. 2017;54(10):8429–43. Available from: <https://doi.org/10.1007/s12035-016-0322-4>
 150. Moreno-García L, Miana-Mena FJ, Moreno-Martínez L, de la Torre M, Lunetta C, Tarlarini C, et al. Inflammasome in ALS Skeletal Muscle: NLRP3 as a Potential Biomarker. Vol. 22, *International Journal of Molecular Sciences* . 2021.
 151. Zhao W, Beers DR, Bell S, Wang J, Wen S, Baloh RH, et al. TDP-43 activates microglia through NF- κ B and NLRP3 inflammasome. *Exp Neurol*. 2015 Nov;273:24–35.
 152. Italiani P, Carlesi C, Giungato P, Puxeddu I, Borroni B, Bossù P, et al. Evaluating the levels of interleukin-1 family cytokines in sporadic amyotrophic lateral sclerosis. *J Neuroinflammation* [Internet]. 2014;11(1):94. Available from: <https://doi.org/10.1186/1742-2094-11-94>
 153. Bettcher BM, Tansey MG, Dorothee G, Heneka MT. Peripheral and central immune system crosstalk in Alzheimer disease — a research prospectus. *Nat Rev Neurol* [Internet]. 2021; Available from: <https://doi.org/10.1038/s41582-021-00549-x>
 154. Bartlett R, Sluyter V, Watson D, Sluyter R, Yerbury JJ. P2X7 antagonism using Brilliant Blue G reduces body weight loss and prolongs survival in female SOD1(G93A) amyotrophic lateral sclerosis mice. *PeerJ*. 2017;5:e3064.
 155. Maier A, Deigendesch N, Müller K, Weishaupt JH, Krannich A, Röhle R, et al. Interleukin-1 Antagonist Anakinra in Amyotrophic Lateral Sclerosis--A Pilot Study. *PLoS One*. 2015;10(10):e0139684.

Figure 1.

PAMPs and DAMPs
bacterial, viral, fungi signals
Canonical signalling

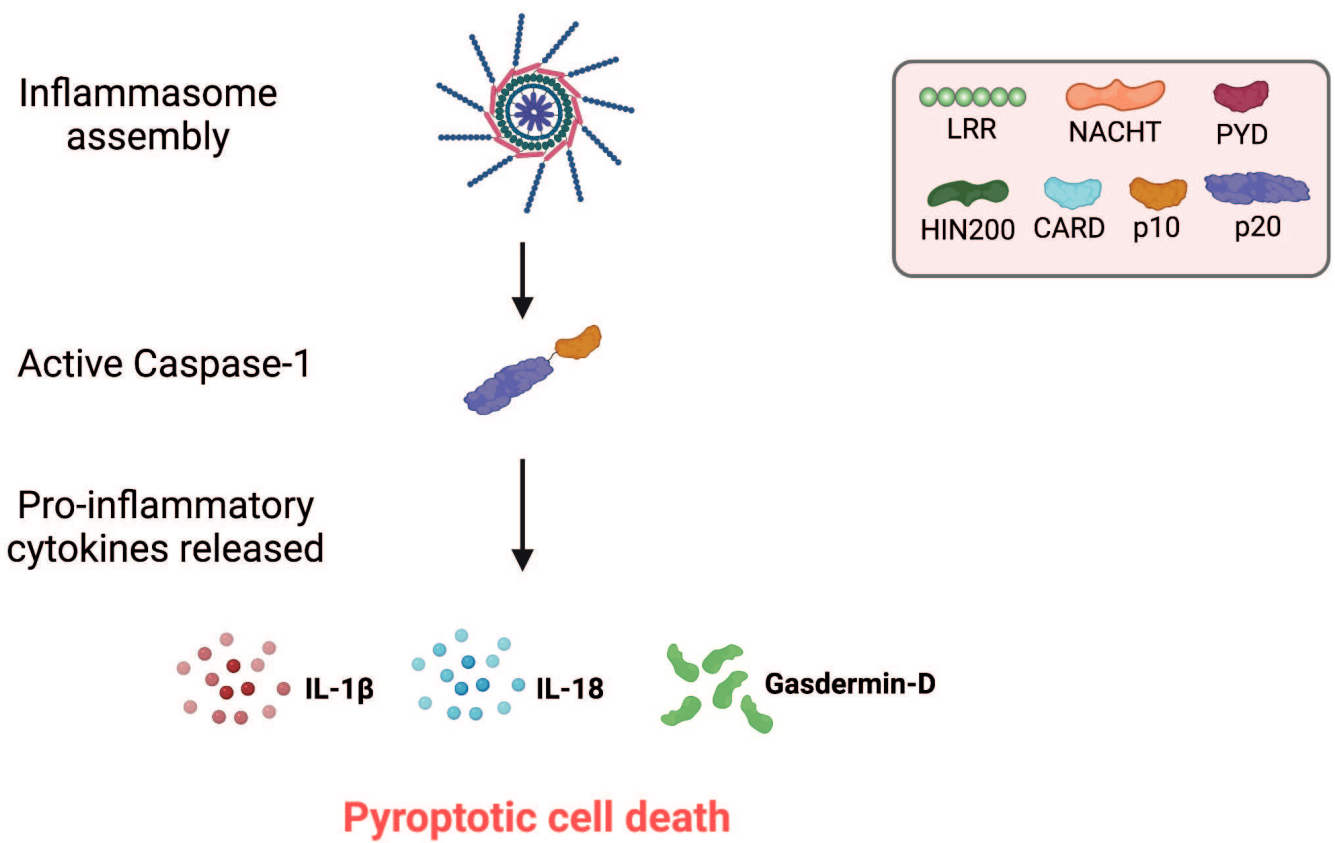
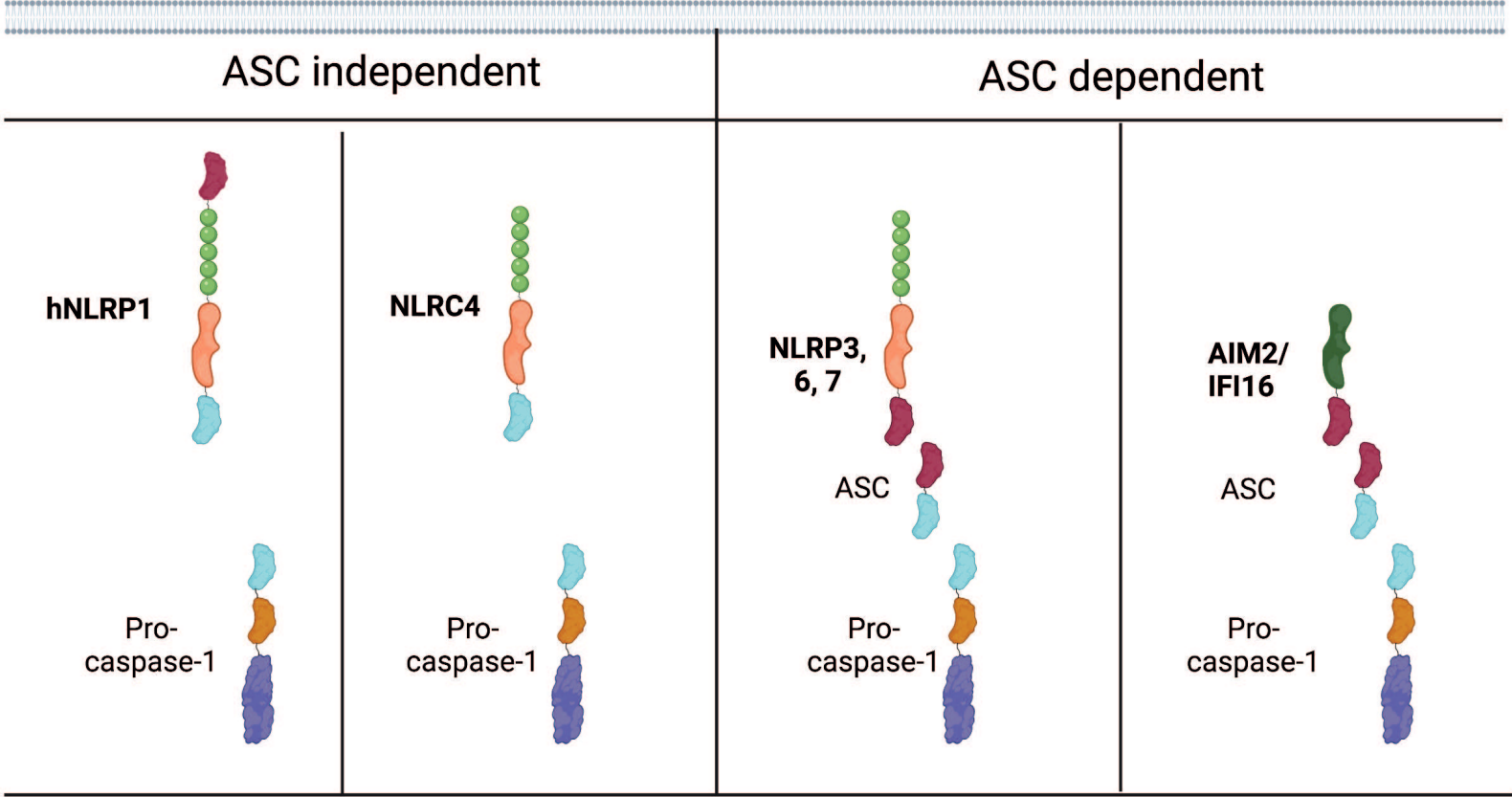


Figure 2.

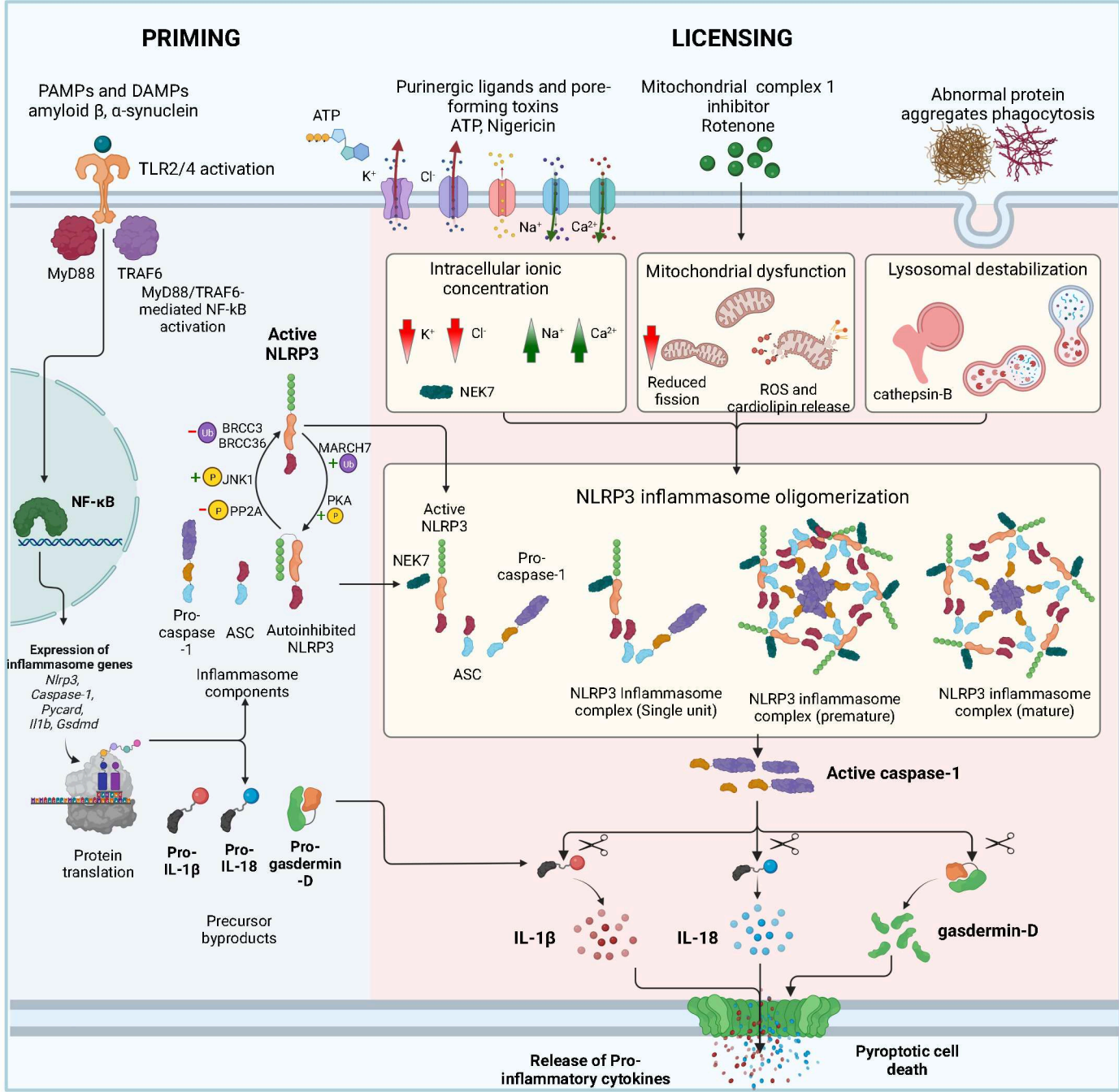


Figure 3.

