IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

Targeting the NLRP3 Inflammasome in Neurodegeneration: Mechanisms, Therapeutics, and Translational Challenges

[1*]Rudra Pratap Singh, [2]Arun Kumar Sahu, [3]Anish Chandy, [4] Dr. Dheeraj Kumar Ahirwar

[1]M. Pharmacy Student, [2]Assistant Professor (Pharmacology), [3]Associate Professor (Pharmaceutics), [4]Professor (Pharmacognosy) & Principal

[1]Department of Pharmacology,

[1]School of Pharmacy, Chouksey Engineering College, Bilaspur, Chhattisgarh, India 495004

Corresponding author*

1. Rudra Pratap Singh

(Research Scholar)

Department of Pharmacology,

School of Pharmacy, Chouksey Engineering College,

Bilaspur, Chhattisgarh, India 495004

Abstract

Neuroinflammation is increasingly recognized as an important contributor to the progression of neurodegenerative disorders, where persistent activation of glial cells can promote neuronal dysfunction and loss. Among the pathways involved, the NLRP3 inflammasome has emerged as a key regulator of innate immune responses in the central nervous system. Unlike pathways activated by a single stimulus, NLRP3 responds to a broad range of cellular disturbances, including potassium efflux, calcium imbalance, mitochondrial dysfunction, reactive oxygen species generation, lysosomal damage, and metabolic stress. Its activation leads to assembly of the NLRP3–ASC inflammasome, followed by caspase-1 activation and maturation of interleukin-1β and interleukin-18. Sustained activation of this pathway can reinforce inflammatory signaling and contribute to an environment that is detrimental to neuronal survival. This review examines the molecular mechanisms underlying NLRP3 activation in the central nervous system and discusses its therapeutic relevance in neurodegenerative disease. Although several NLRP3-targeting approaches have produced encouraging results in preclinical models, their translation to clinical settings remains challenging. Important obstacles include patient and disease-stage heterogeneity, uncertainty regarding the optimal timing of intervention, limited availability of reliable pathway-specific biomarkers, difficulties in achieving effective drug exposure in the brain, and differences between experimental models and human pathology. Emerging strategies involving precision medicine, biomarker-guided patient selection, rational combination therapies, and humanized disease models may help address these limitations. Overall, NLRP3 represents a promising therapeutic target, but successful translation will depend on a clearer understanding of disease context, appropriate patient selection, and the development of therapies that modulate neuroinflammation without compromising essential immune functions.

Keywords: NLRP3 inflammasome; neuroinflammation; neurodegeneration; microglia; neuroinflammatory signaling; IL-1β; IL-18; inflammasome inhibitors; precision medicine; biomarkers.

1. Introduction

1.1 Neuroinflammation as a Core Driver

Historically, the central nervous system (CNS) was viewed as "immune-privileged" sanctuary separated from the periphery by the blood-brain barrier (BBB), but it is now understood to be an immunologically active microenvironment in which innate immune responses are crucial for regulating neuronal survival, synaptic remodeling and homeostasis [1]. For decades, the presence of reactive microglia and astrogliosis around deposits of misfolded proteins, such as extracellular amyloid-β (Aβ) plaques in Alzheimer's disease (AD) or Lewy bodies enriched in α-synuclein in Parkinson's disease (PD), was believed to be a secondary, reactive epiphenomenon. This paradigm has been refined by human genetic, transcriptomic, neuropathological, and functional studies indicating that neuroinflammatory processes can emerge early and persist during neurodegenerative disease progression. Genetic Determinants Sterile, Sustained Reactivity the Self-Amplifying Circuit GWAS have identified disease-associated variants in major innate immune and phagocytic genes (such as TREM2, CD33, APOE, CR1, and LRRK2), indicating that innate immune alterations alone can be sufficient to initiate or promote neurodegeneration. Unlike peripheral host-defense inflammation that resolves rapidly after pathogen clearance, CNS neuroinflammation in chronic degenerative diseases is mostly sterile, triggered by damage-associated molecular patterns (DAMPs) and intrinsic cellular stress [2]. Chronic microglial and astrocytic activation can alter phagocytic, metabolic, and inflammatory functions, potentially reduce effective aggregate clearance while sustain inflammatory signaling. This ongoing immune response impairs synaptic plasticity, damages adjacent axons and leads to breakdown of the blood-brain barrier, fueling a progressive neurotoxic loop.

1.2 Inflammasome Superfamily in the CNS

At the heart of this sterile innate immune activation are inflammasomes, high-molecular-weight multi-protein complexes that serve as intracellular sensors of cellular stress, tissue damage and homeostatic disruption [3]. Upon detection of specific ligands, these cytosolic platforms nucleate and recruit the adapter protein ASC (apoptosis-associated speck-like protein containing a CARD) and activate inflammatory pro-caspases (mainly pro-caspase-1) [4]. Activated caspase-1 cleaves the inactive precursors pro-IL-1β and pro-IL-18 to produce mature bioactive cytokines and simultaneously cleaves Gasdermin D (GSDMD) to produce an N-terminal fragment (GSDMD^Nterm) that oligomerizes to form lytic pores in the plasma membrane to drive an inflammatory mode of programd cell death called pyroptosis. Within the CNS, distinct inflammasome complexes are distributed across specific cell types (Table 1) [5].

Table 1. Major inflammasome sensors implicated in CNS inflammation

Inflammasome	Principal CNS cell types	Representative stimuli	Major pathological contexts	Evidence level	Reference
NLRP3	Microglia; astrocytes; neurons; infiltrating macrophages	Extracellular ATP; K^+ efflux; mitochondrial dysfunction/mtROS; lysosomal damage; amyloid-β; α-synuclein; cellular stress	Alzheimer's disease; Parkinson's disease; ALS/FTD; Huntington's disease; stroke; traumatic brain injury; neuroinflammation	Experimental; human evidence emerging	6
NLRP1	Neurons; microglia; astrocytes	Cellular stress; proteotoxic stress; metabolic disturbances; pathogen-associated signals	Neuronal injury; traumatic brain injury; stroke; neurodegenerative and neuroinflammatory disorders	Experimental; human evidence emerging	7
NLRC4	Microglia; macrophages; infiltrating myeloid cells	Bacterial flagellin; type III secretion system components; microbial-associated signals	CNS infection; neuroinflammation; spinal cord injury and other inflammatory CNS conditions	Experimental; human evidence limited/emerging	8
AIM2	Microglia; neurons; astrocytes; infiltrating immune cells	Cytosolic double-stranded DNA; damaged nuclear/mitochondrial DNA; cellular injury	Neuroinflammation; stroke; traumatic CNS injury; neurodegenerative conditions	Experimental; human evidence emerging	9
Pyrin	Myeloid cells; microglia/macrophage populations	RhoA inactivation; bacterial toxins; cytoskeletal perturbation	Autoinflammatory inflammation; infection-associated inflammation; potential CNS inflammatory responses	Experimental/emerging in CNS	10

1.3 NLRP3: Architecture, Priming, and Two-Signal Activation Paradigm

The NLRP3 sensor is a member of the nucleotide-binding oligomerization domain and leucine-rich repeat-containing (NLR) family of proteins. NLRP3 comprises three principal domains: an N-terminal pyrin domain (PYD), a central NACHT domain with ATPase activity, and a C-terminal leucine-rich repeat (LRR) domain [11]. These domains coordinate autoinhibition, conformational rearrangement, oligomerization, and interaction with the adaptor ASC. The C-terminal LRR domain contributes to the autoinhibited conformation of NLRP3 under resting conditions (Figure 1) [12].

The Two-Signal Activation Model

Under basal conditions, microglial expression of both NLRP3 and pro-IL-β is kept below the threshold necessary for complex nucleation. Classically, NLRP3 activation is described as requiring a priming step followed by an activation step, although the molecular requirements can vary with stimulus and cellular context [13].

Signal 1: Priming (Transcriptional & Post-Translational)

Transcriptional Upregulation, extracellular ligands (e.g., systemic lipopolysaccharide, TNF-α/IL-1β cytokines, or early soluble DAMPs) are recognized by cell-surface pattern recognition receptors (for example, TLR2, TLR4) or cytokine receptors. This activates the NF-kB pathway and translocates p50/p65 heterodimers to the nucleus to drive transcription of NLRP3, IL1B and IL18. Fast Post-Translational Modifications (PTMs) are priming also works non-transcriptionally within minutes [14]. De-ubiquitination (by enzymes such as BRCC3) and key phosphorylation/dephosphorylation events (e.g. JNK1-mediated phosphorylation of the NLRP3 NACHT-LRR linker) license NLRP3, relieving auto-inhibition and priming it for assembly.

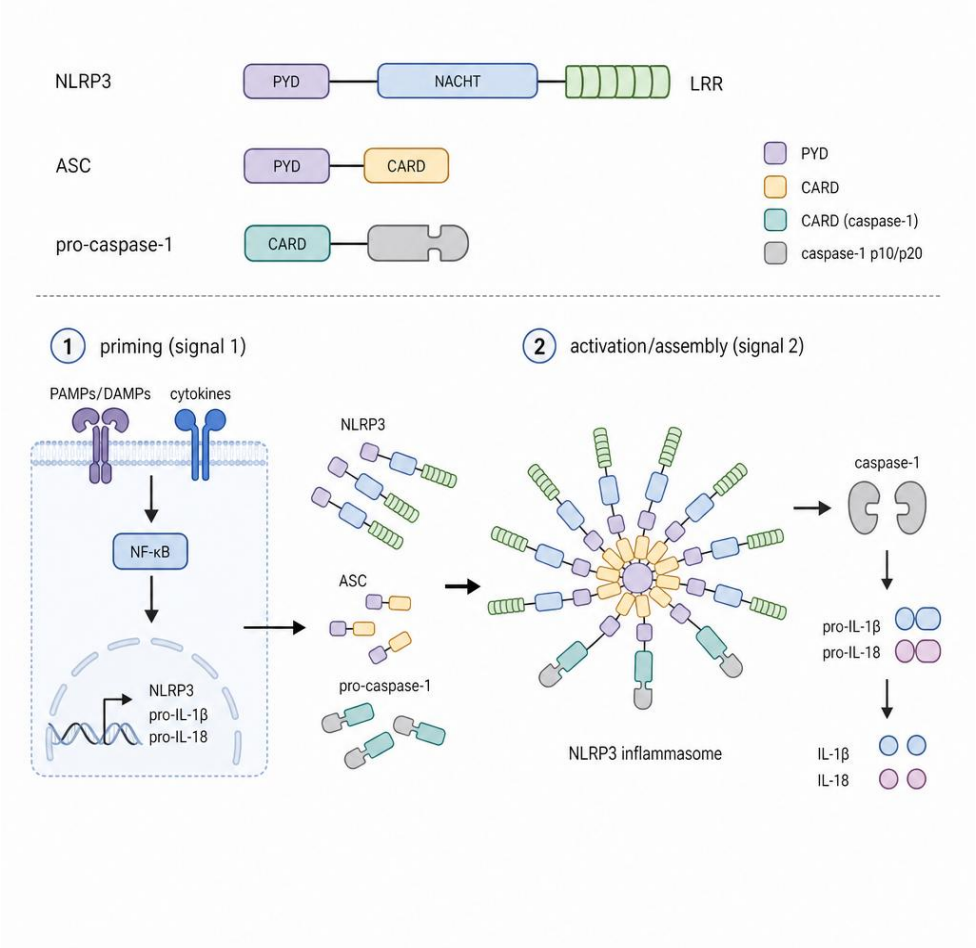

Figure 1. NLRP3 inflammasome architecture and activation in the CNS
Schematic showing NLRP3 domains (PYD, NACHT, LRR), ASC (PYD and CARD), pro-caspase-1, and the two-signal activation paradigm: priming through NF-κB followed by activation/assembly.

Signal 2: Activation (Assembly & Catalysis)

The primed complex is triggered by diverse neurodegenerative stress inputs. Potassium (K^+) Efflux by triggered by the binding of extracellular ATP (released from dying neurons) to purinergic P2X7 receptors or by structural membrane perturbations. Lysosomal destabilization uptake of crystalline or fibrillar aggregates (Aβ fibrils, α-synuclein, hyperphosphorylated tau or TDP-43) induces physical rupture of lysosomes and release of Cathepsin B and other hydrolases into the cytosol [15]. Mitochondrial Dysfunction & mtROS which damaged mitochondria accumulate due to impaired mitophagy, leading to the production of excess reactive oxygen species (mtROS) and the leakage of oxidized mitochondrial DNA (ox-mtDNA) into the cytoplasm. These inputs point to the basic structural interaction of NEK7 (NIMA-related kinase 7) with the NACHT domain of primed NLRP3 [16]. NEK7 acts as a molecular switch to induce a conformational change in NLRP3 to allow oligomerization into a wheel-like disk. The clustered PYD domains of NLRP3 nucleate ASC into insoluble macromolecular filaments (ASC speck) [17]. ASC recruit's pro-caspase-1 by homotypic CARD-CARD interactions, leading to proximity-induced auto-cleavage into active p20 and p10 subunits. Activation

of caspase-1 cleaves pro-IL-1 β and pro-IL-18 to their mature forms and cleaves GSDMD to initiate pyroptosis [18].

2. Molecular Mechanisms of NLRP3 Activation in the CNS

The NLRP3 inflammasome is a cytosolic signaling complex linking aberrations in cellular homeostasis to the processing of inflammatory cytokines and pyroptotic cell death. The core components include sensor NLRP3, adaptor apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1[19]. In the central nervous system (CNS), NLRP3 is most strongly associated with microglia, although activation has also been observed in astrocytes, infiltrating myeloid cells, and, in some disease states, other neural cell types. Protein aggregates, extracellular ATP, ionic imbalance, mitochondrial injury, lysosomal damage and metabolic stress can promote NLRP3 signaling [20]. Instead of directly binding all of these chemically diverse stimuli, NLRP3 is believed to sense the convergent cellular disturbances that they induce.

Chronic activation of this pathway may be particularly detrimental in neurodegenerative diseases. Aggregated amyloid-beta, alpha-synuclein and tau species, damaged myelin and molecules released from injured neurons can prime or activate glial NLRP3 [21]. The subsequent IL-1beta/IL-18 signaling and pyroptotic membrane damage could further augment microglial reactivity, attract peripheral immune cells, alter neuronal and glial function and generate further damage-associated molecular patterns (DAMPs) [22]. Thus, NLRP3 may participate in a feed-forward cycle linking proteotoxic stress, neuroinflammation, and progressive neuronal damage.

2.1 Priming (Signal 1): NF-kappaB Transcriptional Upregulation and Post-Translational Priming

The classical model describes NLRP3 activation as a priming phase followed by an activation phase, although additional stimulus- and cell-type-specific regulatory mechanisms have been recognized [23]. Pattern-recognition receptors and cytokine receptors recognize microbial or endogenous inflammatory signals in priming. Activation of toll-like receptors, particularly TLR2 and TLR4, or receptors for tumor necrosis factor and IL-1 results in MyD88- or TRIF-dependent signaling and activates IKK complex. IKK-mediated degradation of IkappaB facilitates NF-kappaB translocation into the nucleus [24]. NF-kappaB induces the transcription of NLRP3 and IL1B. In many cell types pro-IL-18 is constitutively expressed and thus transcriptional priming is usually less marked. Candidate priming stimuli in the CNS are protein aggregates, extracellular DAMPs, microbial products and cytokines released by reactive glia or infiltrative leukocytes. Priming is more than a transcriptional event [25]. It also rapidly post-translationally prepares the activation competence of pre-existing NLRP3. Phosphorylation/dephosphorylation, ubiquitination/deubiquitination, SUMOylation, acetylation and other modifications can modulate stability, localization, conformation and interaction of NLRP3 with regulatory proteins. These modifications can keep NLRP3 in an autoinhibited state, or promote its transition to an assembly-competent state, depending on the residue and cellular context [26]. Priming also changes cellular metabolism, mitochondrial activity and organelle trafficking, thereby influencing the threshold for subsequent inflammasome activation. This distinction has potential therapeutic implications. While NF-kappaB suppression may decrease NLRP3 and pro-IL-1beta expression, it can also block widespread immune and cell-survival pathways [27]. Conversely, targeting a specific priming-related post-translational modification could theoretically reduce pathological inflammasome activity while preserving other NF-kappaB-dependent functions. However, the identity and functional consequences of these modifications are stimulus-, cell type and experimental model dependent and findings from peripheral macrophages should not be automatically translated to microglia or other cells of the CNS.

2.2 Triggering (Signal 2) and Structural Assembly

A second signal following priming induces activation and assembly of NLRP3. NLRP3 contains an N-terminal pyrin domain, a central NACHT domain that has ATPase activity and C-terminal leucine-rich repeats. Current models suggest that activation releases NLRP3 from an autoinhibited conformation, enables nucleotide-dependent conformational rearrangement and promotes oligomerization [28]. The resulting NLRP3 platform nucleates polymerization of ASC and recruitment of caspase-1. While many stimuli activate this pathway, no one upstream event explains all experimental contexts. Among them, the most well-established common mechanism is potassium efflux, with calcium signaling, mitochondrial dysfunction, reactive oxygen species and lysosomal injury as interlinked or context-dependent contributors (Figure 2) [29].

Potassium efflux, calcium fluxes, and mitochondrial dysfunction

A decrease in intracellular K+ is a key permissive event for NLRP3 activation. The P2X7 purinergic receptor is activated by extracellular ATP and induces K+ loss via cation fluxes. Other stimuli, such as pore-forming toxins or damage to the membrane, might also cause a similar ionic imbalance [30]. Low intracellular K+ supports the interaction of NLRP3 with NEK7, a kinase-associated protein that plays a structural role in inflammasome activation downstream of K+ efflux. NEK7 binding promotes NLRP3 oligomerization, but the exact dependence on NEK7 may vary depending on the priming condition and cellular context [31].

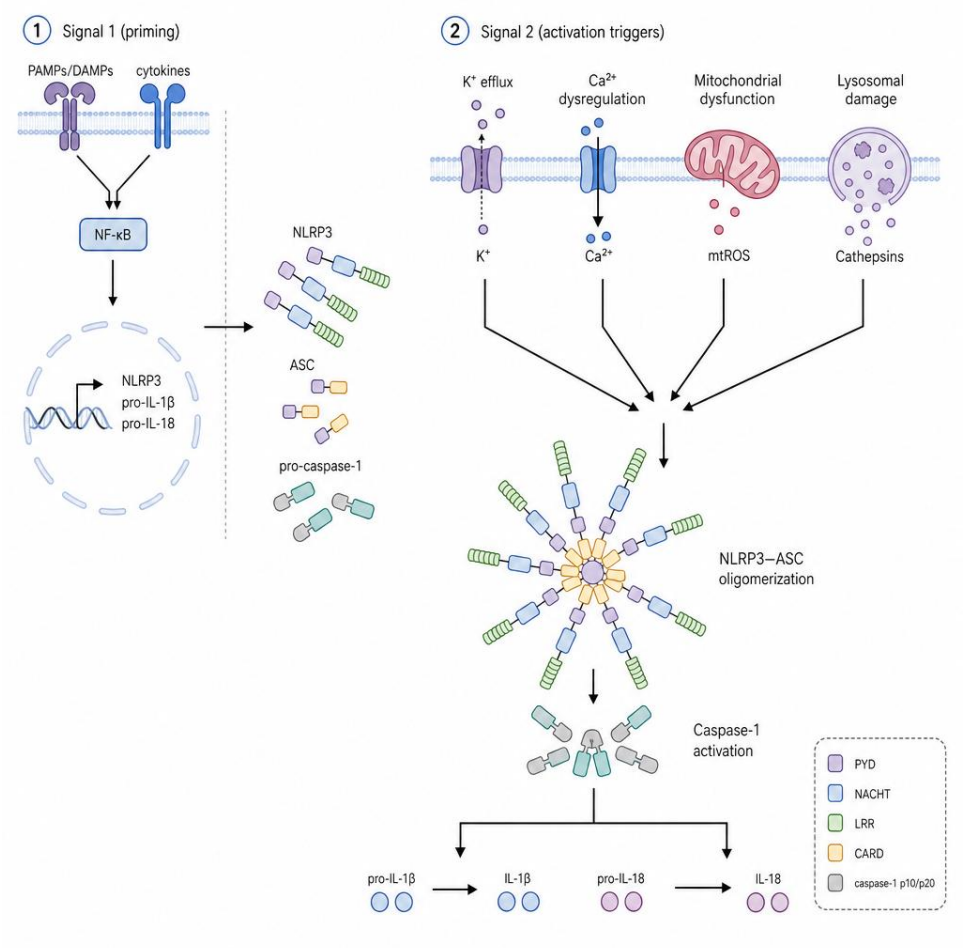

Figure 2. Molecular mechanisms of NLRP3 activation in CNS cells
Integrated schematic illustrating major Signal-2 triggers, including K^+ efflux, Ca^{2+} dysregulation, mitochondrial dysfunction/mtROS, lysosomal damage and cathepsin release, leading to NLRP3–ASC oligomerization and caspase-1 activation.

Disorders of intracellular Ca2+ have also been implicated, via Ca2+ entry, release from endoplasmic-reticulum stores, impaired mitochondrial buffering, and signaling at organelle contact sites. However, the universality of the requirement of Ca2+ elevation is still in debate. Otherwise, enhanced mitochondrial stress, membrane remodeling, or K+ efflux may indirectly promote NLRP3 activation via calcium dysregulation. Another major point of convergence is mitochondrial damage [32]. Loss of membrane potential, impaired electron transport, defective mitophagy and altered mitochondrial dynamics can lead to increased mitochondrial reactive oxygen species (mtROS) and release of mitochondrial DNA, cardiolipin or other mitochondrial DAMPs. These signals may favor NLRP3 recruitment and activation, and impaired mitophagy may lead to accumulation of damaged mitochondria [33]. In neurodegenerative diseases, which often involve mitochondrial dysfunction and defective proteostasis, this mechanism could connect neuronal or glial metabolic stress to sustained innate immune activation. However, mtROS should be considered as an important amplifier and not as an obligatory trigger in all NLRP3 activating conditions [34].

Lysosomal destabilization and cathepsin release

Microglia can phagocytose particulate and aggregated material and deliver it to lysosomes. Lysosomal swelling, membrane permeabilization and leakage of luminal contents into the cytosol may occur due to poorly degradable cargo, such as fibrillar protein assemblies or crystalline material [35]. NLRP3 activation has been associated with cytosolic release of cathepsins, especially cathepsin B. Lysosomal injury can also result in ionic imbalance, ROS production, mitochondrial dysfunction and loss of degradative capacity. This pathway is particularly relevant to neurodegeneration, as microglia constantly phagocytose extracellular aggregates and cellular debris [36]. When lysosomal processing becomes insufficient to efficiently handle aggregated or particulate material, lysosomal stress may contribute to inflammasome activation and amplify inflammatory signaling. Inhibition or deletion of individual cathepsins, however, has variable effects in different experimental systems and cathepsin release is therefore unlikely to represent the sole universal molecular switch. Lysosomal rupture is therefore best viewed as a network level danger signal converging with ionic and mitochondrial stress [37].

NLRP3-ASC speck formation and pro-caspase-1 recruitment

In active NLRP3 oligomers, the pyrin domains are exposed and interact homotypically with the pyrin domain of ASC. ASC then polymerizes into filaments that aggregate to form a large perinuclear structure known as the ASC speck. ASC has a caspase recruitment domain that binds to the corresponding domain in pro-caspase-1, bringing together many molecules of pro-caspase-1 [38]. Their proximity enables autoproteolytic processing and the formation of catalytically active caspase-1. ASC specks are not just microscopic markers of inflammasome activation. They offer a signal amplifying platform and, upon release from damaged cells, may persist extracellularly, be taken up by neighboring phagocytes and possibly interact with pathological protein assemblies. These observations support a potential role of inflammasome particles in the spatial propagation of inflammation in degenerating neural tissue [39]. At the same time, ASC speck abundance does not always directly correlate with cytokine secretion or cell death, and therefore should not be used as the sole measure of pathway activity.

2.3 Effector Execution

Proteolytic maturation of IL-1beta and IL-18

Active caspase-1 cleaves cytosolic pro-IL-1beta and pro-IL-18 to their mature, biologically active forms IL-1 beta causes endothelial activation, chemokine production, leukocyte recruitment and reactive changes of glial cells. Chronic IL-1beta signaling in the CNS may affect synaptic function, neuronal excitability, blood-brain barrier integrity and neuroimmune communication. IL-18 promotes inflammatory signaling and can augment IFN-γ production, but its effects are contingent on the responding cell population and tissue environment [40].

Neither cytokine has a classical secretory signal peptide. Thus, their release relies largely on unconventional secretory mechanisms, in particular by pores formed by gasdermin D, although secretion by viable cells and gasdermin-independent release can also happen in specific contexts. Therefore, inflammasome activation has linked but separable effects of cytokine maturation and cell lysis [41].

GSDMD cleavage, pore formation, and pyroptosis in glial cells

Caspase-1 cleaves gasdermin D (GSDMD) at the junction between its N- and C-terminal domains. This processing relieves autoinhibition of the pore forming N terminal fragment. GSDMD N-terminal fragments oligomerize in the plasma membrane, forming pores that allow ion movement and the release of mature IL-1beta and IL-18 [42]. Viable cells can release cytokines by membrane-repair mechanisms to counteract limited pore formation. When pore burden exceeds repair capacity, water influx, cellular swelling, membrane rupture and pyroptotic cell death occur.

Pyroptosis in microglia may result in the rapid release of cytokines, ASC particles and ATP, as well as intracellular proteins and other DAMPs that can activate neighboring glia, potentially exacerbating neuronal injury [43]. Astrocytic inflammasome responses have also been reported, but they vary greatly in magnitude and molecular composition between species, brain regions, culture systems and disease models. Claims of neuronal NLRP3-dependent pyroptosis should be approached with special care as neurons may express other inflammasome sensors and death pathways. Furthermore, showing increased NLRP3, cleaved caspase-1, GSDMD fragments, or terminal membrane permeability alone does not establish a full causal pathway [44]. Ideally, pyroptosis should be established by genetic or selective pharmacological intervention at multiple nodes in the pathway (Figure3).

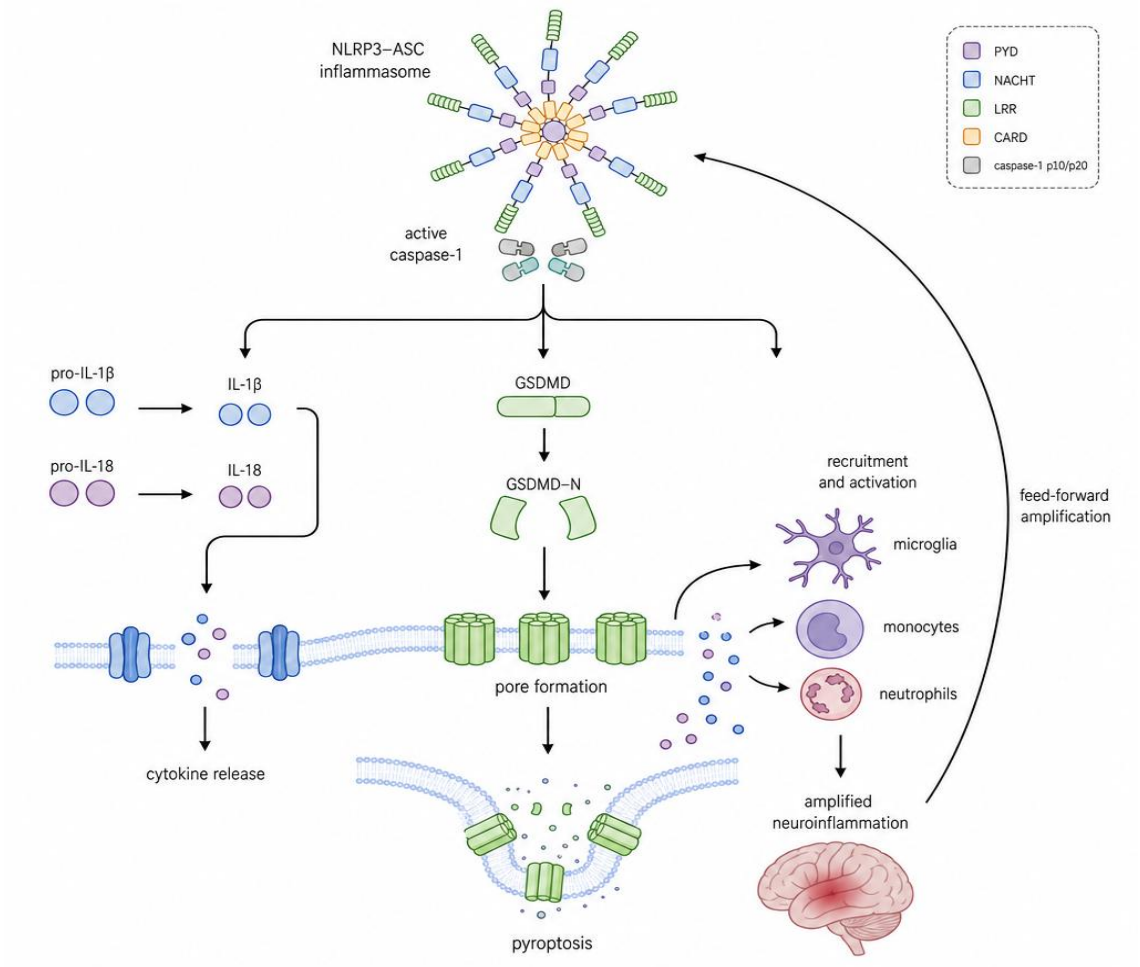

Figure 3. NLRP3 inflammasome effector pathways and pyroptosis
Diagram depicting caspase-1-mediated maturation of IL-1β and IL-18, GSDMD cleavage, pore formation, pyroptosis, cytokine release, and subsequent amplification of neuroinflammation.

Table 2. Evidence linking NLRP3 activation to major neurodegenerative and neuroinflammatory disorders

Disease	Pathological trigger	NLRP3-activating mechanism	Principal cell type	Downstream consequences	Evidence level / major limitation	Reference
Alzheimer's disease (AD)	Aβ oligomers/fibrils; pathological tau; cellular debris	Aβ/tau uptake → lysosomal destabilization and cathepsin release; mitochondrial dysfunction, ROS and ionic stress → NLRP3–ASC assembly → caspase-1 activation	Microglia; astrocytes; other glial cells	IL-1β/IL-18 maturation, GSDMD-mediated pyroptosis, sustained microglial activation, synaptic and neuronal dysfunction	Strong experimental + human pathological evidence; human causal/therapeutic evidence remains limited. Post-mortem and biomarker studies support inflammasome activation, but association does not establish that NLRP3 is a primary driver or that inhibition alters clinical progression.	45
Parkinson's disease (PD)	α-Synuclein oligomers/fibrils; mitochondrial dysfunction; oxidative stress	α-Synuclein uptake → endolysosomal injury; mitochondrial stress/mtROS and altered mitochondrial DNA → NLRP3 activation in inflammatory microglia	Microglia; astrocytes; infiltrating myeloid cells	IL-1β/IL-18 release, pyroptotic signaling, oxidative/inflammatory injury and dopaminergic neuronal dysfunction	Strong experimental + emerging human evidence; clinical disease-modifying efficacy unproven. Human studies support inflammatory/NLRP3-associated changes, but direct CNS target engagement and clinical benefit require further validation.	46
Amyotrophic lateral sclerosis (ALS)	Misfolded/aggregated SOD1; TDP-43 pathology; neuronal injury	TDP-43/SOD1-associated DAMP signaling, NF-κB priming, lysosomal/mitochondrial stress and K^+/P2X7-associated signaling → NLRP3 activation	Microglia; astrocytes; infiltrating monocytes/macrophages	IL-1β/IL-18 signaling, GSDMD cleavage/pyroptosis, motor-neuron injury and amplification of spinal neuroinflammation	Strong experimental evidence + emerging human evidence; causality remains uncertain. Much of the mechanistic evidence derives from transgenic and cellular models; human studies are limited by disease heterogeneity and difficulty	47

					demonstrating cell-specific NLRP3 activity.	
Frontotemporal dementia (FTD)	TDP-43 mislocalization/aggregation; neuronal injury	TDP-43-associated innate immune activation, mitochondrial/lysosomal stress and inflammatory priming may promote NLRP3 signaling	Microglia; astrocytes; neurons under pathological conditions	Pro-inflammatory cytokine signaling, pyroptotic pathways and potential amplification of neurodegeneration	Experimental evidence emerging; human NLRP3-specific evidence limited. TDP-43–NLRP3 links are better established mechanistically in ALS-related models than in FTD patients; disease heterogeneity is an important limitation.	48
Huntington's disease (HD)	Mutant huntingtin (mHTT); polyglutamine aggregates; neuronal debris	mHTT-associated inflammatory priming, impaired autophagy/lysosomal clearance and lysosomal stress → NLRP3 activation	Microglia/macrophage populations; vulnerable striatal neuronal environment	IL-1β-mediated inflammatory signaling, excitotoxic stress, microglial activation and neuronal dysfunction	Predominantly experimental/preclinical; human evidence emerging or limited. Evidence supports inflammatory and NLRP3-associated mechanisms in models, but direct demonstration of pathogenic NLRP3 activation in human HD remains comparatively limited.	49
Multiple sclerosis (MS)	Myelin debris; ATP/DAMPs; oxidative and mitochondrial stress; adaptive immune infiltration	Inflammatory priming plus ATP/P2X7 signaling, ionic disturbance and cellular stress → NLRP3 activation	Microglia; infiltrating macrophages/monocytes; astrocytes	IL-1β/IL-18 signaling, pyroptotic responses, demyelination, BBB dysfunction and chronic neuroinflammation	Experimental + human inflammatory/pathological evidence; NLRP3-specific clinical causality remains uncertain. NLRP3-associated signaling is reported in CNS and immune compartments, but its relative contribution versus other inflammatory pathways is difficult to isolate.	50
Neurovascular cognitive impairment /	Ischemia/hypoxia; vascular injury; BBB disruption;	Cellular injury → ATP/P2X7 signaling, K^+ efflux,	Microglia; infiltrating myeloid cells;	IL-1β/IL-18 release, pyroptosis, BBB dysfunction, neurovascular	Strong experimental evidence; human evidence limited/emerging.	51

cerebrovascular disease	ATP/DAMP release; oxidative stress	mitochondrial dysfunction and ROS → NLRP3 activation	endothelial/neurovascular cells	inflammation and secondary neuronal injury	NLRP3 activation is well supported in experimental stroke/vascular-injury models, but human studies often measure downstream inflammatory markers rather than direct CNS-specific NLRP3 activation.	

2.4 Non-Canonical and Alternative NLRP3 Pathways

In humans, caspase-4, caspase-5, and in mice, caspase-11 directly sense cytosolic lipopolysaccharide and activate the non-canonical inflammasome pathway. These inflammatory caspases bind intracellular LPS, oligomerize and cleave GSDMD. GSDMD pores induce pyroptosis and K+ efflux Secondary activation of canonical NLRP3-ASC-caspase-1 complex. Thus, caspase-4/5/11 can directly mediate GSDMD-dependent membrane permeabilization, but generally require downstream NLRP3 and caspase-1 for efficient maturation of IL-1beta and IL-18. Other molecular interactions could boost the association between caspase-11 and NLRP3.

Alternative NLRP3 activation is a separate response that is most evident in primary human monocytes [53]. In this regard, extracellular LPS via TLR4 can promote NLRP3-ASC-caspase-1-dependent IL-1beta processing without the need for a classical second stimulus. This response differs from classical activation in that it can occur without extensive K+ efflux, robust ASC speck formation or rapid pyroptosis, and has been linked to a TLR4-TRIF-RIPK1-FADD-caspase-8 signaling axis [54]. Other TLRs and regulatory proteins may mediate similar responses, depending on the monocyte population and stimulus. Importantly, alternative activation is not the same as the caspase-4/5/11-dependent non-canonical pathway.

3. Cellular Landscape: NLRP3 Regulation Across CNS Cell Types

The pathogenesis of the NLRP3 inflammasome is not uniformly distributed in the central nervous system. Rather, it operates in a compartmentalized cellular network that includes brain-resident myeloid cells, macroglia, parenchymal neurons, and infiltrating peripheral leukocytes. Cell-type-specific transcriptional wiring, activation thresholds and proximity to neuropathological lesions determine phenotypic consequences of NLRP3 assembly [55].

3.1 Microglia: Primary Sensor, Phenotypic Shifting, and Spatial Clustering

Microglia are the principal resident innate immune cells of the CNS and represent a major cellular compartment in which NLRP3 signaling has been investigated [56].

Phenotypic Transitions: Homeostatic vs. DAM/MGnD

Single-cell RNA sequencing (scRNA-seq) has broken the classical M1/M2 dichotomy and has shown that microglia undergo transcriptional reprogramming in neurodegenerative state. Homeostatic Signature Suppression is homeostatic checkpoint markers (such as P2ry12, Tmem119, Cx3cr1, and Hexb) preserve quiescent microglia with low baseline NLRP3 activity. DAM/MGnD State Acquisition [57]. Microglia, when exposed to protein aggregates (Aβ, α-synuclein, or pathological tau), induce a TREM2–APOE-dependent transcriptional pathway, adopting Disease-Associated Microglia (DAM) or Microglial Neurodegenerative (MGnD) states. Experimental studies have reported early-stage microglial responses associated with phagocytic handling of pathological aggregates of toxic fibrils in early-stage DAM (Stage 1, TREM2-

independent) but transition into late-stage DAM (Stage 2, TREM2-dependent) or chronically stalled MGnD cells coincided with sustained Nlrp3, Casp1, and Il1b transcriptional upregulation [58]. Chronic aggregate overload and lysosomal rupture induce NLRP3 assembly, which converts microglial function from neuroprotective clearance to neurotoxic cytokine secretion.

Spatial Clustering Around Pathological Foci

High-resolution immunohistochemistry reveals tight clustering of NLRP3- and ASC-positive microglia in the spatial vicinity of the peri-plaque niche in Alzheimer's disease and in the vicinity of α-synuclein-rich Lewy neurites in Parkinson's disease. This is a specific pathological assertion and needs direct evidence. This burst releases intact insoluble macromolecular ASC specks into the extracellular space. Extracellular ASC specks have been proposed to persist after inflammasome activation and may interact with pathological protein assemblies, potentially contributing to propagation of inflammatory or proteopathic signals. However, the extent to which ASC specks directly drive pathological protein aggregation in human neurodegenerative disease remains uncertain [59].

3.2 Astrocytes: Microglial Cross-Talk, Secondary Activation, and BBB Breakdown

This numerical/general anatomical claim should have an appropriate human neuroanatomical source. Resting astrocytes have lower baseline expression of the entire NLRP3-ASC-Caspase-1 axis compared to microglia, but they are secondary amplification hubs and structural effectors of neurovascular decline [60].

The Microglial-Astrocyte Inflammasome Axis

Astrocytes are primed and activated downstream of microglial pyroptosis via a defined paracrine signaling loop.

Microglia-derived inflammatory mediators, including IL-1β, TNF-α, and complement-associated signals, can induce reactive astrocytic states with altered inflammatory and homeostatic functions. The historically used A1/A2 classification is increasingly viewed as an oversimplification of astrocyte heterogeneity. Reactive astrocytes may exhibit reduced expression or altered function of homeostatic pathways involved in glutamate and potassium regulation [61].

Compromise of the Blood-Brain Barrier (BBB)

Astrocytes form the structural foundation of the BBB through specialized end-feet that ensheath the cerebral microvasculature. End-Feet Detachment & Aquaporin-4 Dysregulation: Astrocytic NLRP3 activation and microglial IL-β exposure impair polarized anchoring of Aquaporin-4 (AQP4) water channels to dystroglycan complexes at the perivascular end-feet, impairing glymphatic fluid transport and waste clearance. Induction of Matrix Metalloproteinase (MMP) Inflammasome signaling causes astrocytes to secrete MMP-2 and MMP-9. These proteases digest basement membrane proteins (laminin, fibronectin and type IV collagen) and degrade endothelial tight junction complexes (claudin-5, occludin and ZO-1) resulting in an increase in vascular permeability [62].

3.3 Neurons and Oligodendrocytes: Intrinsic Signaling vs. Bystander Toxicity

In neuroimmunology, a long-standing debate has been whether mature neurons and myelinating oligodendrocytes build functional NLRP3 complexes or are merely collateral victims

Neurons: Intrinsic Sensors vs. Cytokine Targets

Dominance of NLRP1: Cortical and hippocampal neurons express low levels of NLRP3 in the absence of pathology. NLRP1 has been more clearly implicated than NLRP3 in several neuronal inflammasome responses, which initiates neuronal pyroptosis in response to metabolic stress, double-stranded RNA, and direct proteolytic cleavage by viral proteases or calpains. Inducible Neuronal NLRP3: Neurons can up-regulate NLRP3 transcripts during severe, protracted proteotoxic stress. Activation of neuronal caspase-1

results in cleavage of intracellular tau at specific residues (e.g., Asp421) to generate aggregation-prone truncated tau fragments that accelerate neurofibrillary tangle maturation. Neurons are mainly affected by non-cell-autonomous damage [63]. Microglia/astrocyte-derived IL-β binds to neuronal IL-1R1 located at post-synaptic densities. This binding causes the hyperactivation of the p38 MAPK and JNK pathways that initiate the endocytosis of AMPA and NMDA receptor subunits, resulting in the collapse of long-term potentiation (LTP), pruning of spines, and ultimately excitotoxic death.

Oligodendrocytes and Myelin Vulnerability

Mature oligodendrocytes possess a poor transcriptional machinery for the de novo assembly of the NLRP3 core and are therefore inefficient to execute autonomous, canonical pyroptotic cascades. However, oligodendrocytes are highly sensitive to extracellular IL-1®, IL-18 and reactive oxygen species (ROS). Exposure to IL-18 suppresses remyelination by inhibiting differentiation of oligodendrocyte precursor cells (OPCs) into mature myelinating glia [64]. Concurrently, high levels of peroxynitrite and microglia-derived cytokines promote secondary caspase-3-dependent apoptosis of mature oligodendrocytes, thereby accelerating white matter rarefaction and axonal conduction block.

3.4 Peripheral Immune Infiltration: Leukocyte Migration Across the Compromised BBB

Chronic neurodegeneration is characterized by progressive breakdown of the neurovascular unit, which allows peripheral myeloid cells to infiltrate the CNS parenchyma (Table 3) (Figure 4).

Table 3. Peripheral Immune Cell Infiltration and Their Roles in CNS NLRP3 Cascades

Cell Type	Primary Chemokine Receptors	Infiltration Mechanism	Role in CNS NLRP3 Cascades	Reference
$CCR2^+$ Classical Monocytes	CCR2, CD11b, Ly6C (rodent) / CD14 (human)	Recruited by microglial/astrocytic CCL2 gradients through degraded endothelial tight junctions.	Differentiate into monocyte-derived macrophages (MDMs); exhibit lower activation thresholds and generate higher bursts of IL-β and GSDMD pores than resident microglia.	65
Neutrophils	CXCR2, CD11b, Ly6G (rodent) / CD15 (human)	Adhere to activated brain endothelial selectins; extravasate via CXCL1/CXCL2 cues.	Release neutrophil extracellular traps (NETs) containing active cathepsin G and elastase, which degrade parenchymal architecture and trans-activate microglial NLRP3.	66
$CD4^+$/$CD8^+$ T Lymphocytes	CXCR3, CCR6, CD3	Extravasate into the perivascular space via ICAM-1/VCAM-1 interactions.	Produce IFN-γ and IL-17, acting as potent systemic Signal 1 priming factors that boost microglial and astrocytic *NLRP3* transcription.	67

Once infiltrating monocyte-derived macrophages enter the CNS parenchyma, they do not take on the regulatory, homeostatic roles of resident microglia. Instead, these peripheral cells keep high levels of pro-inflammatory cytokines, creating a self-reinforcing loop that maintains microvascular leakage and accelerates parenchymal destruction.

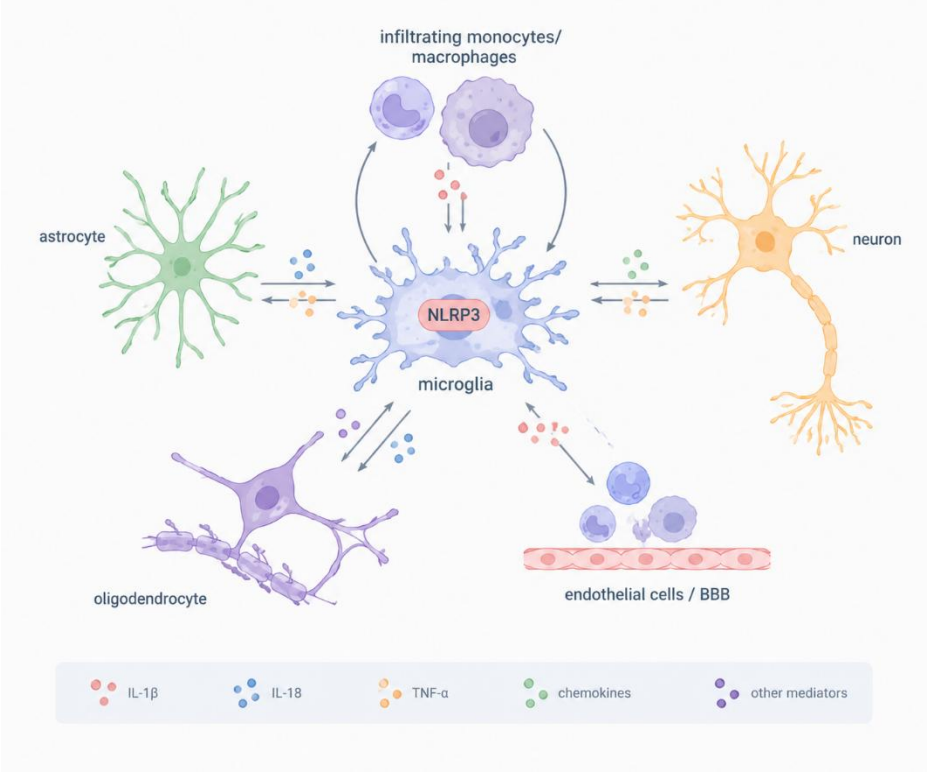

Figure 4. Cellular landscape of NLRP3 signaling in the neurodegenerating CNS
Cellular interaction map showing microglia, astrocytes, neurons, oligodendrocytes, endothelial cells/BBB, and infiltrating monocytes/macrophages, emphasizing intercellular communication and inflammatory feedback loops.

4. Disease-Specific Roles of NLRP3 in Major Neurodegenerative Disorders

While the core biochemical blueprint of the NLRP3 inflammasome is conserved, its upstream activators, cell-type susceptibilities, and downstream pathological sequelae are strikingly heterogeneous in various neurodegenerative diseases (Table 2). In each disease state, misfolded proteotoxic conformers usurp the two-signal inflammasome axis to create distinct feed-forward loops that determine the spatial and temporal patterns of neurodegeneration (Figure 5) [68].

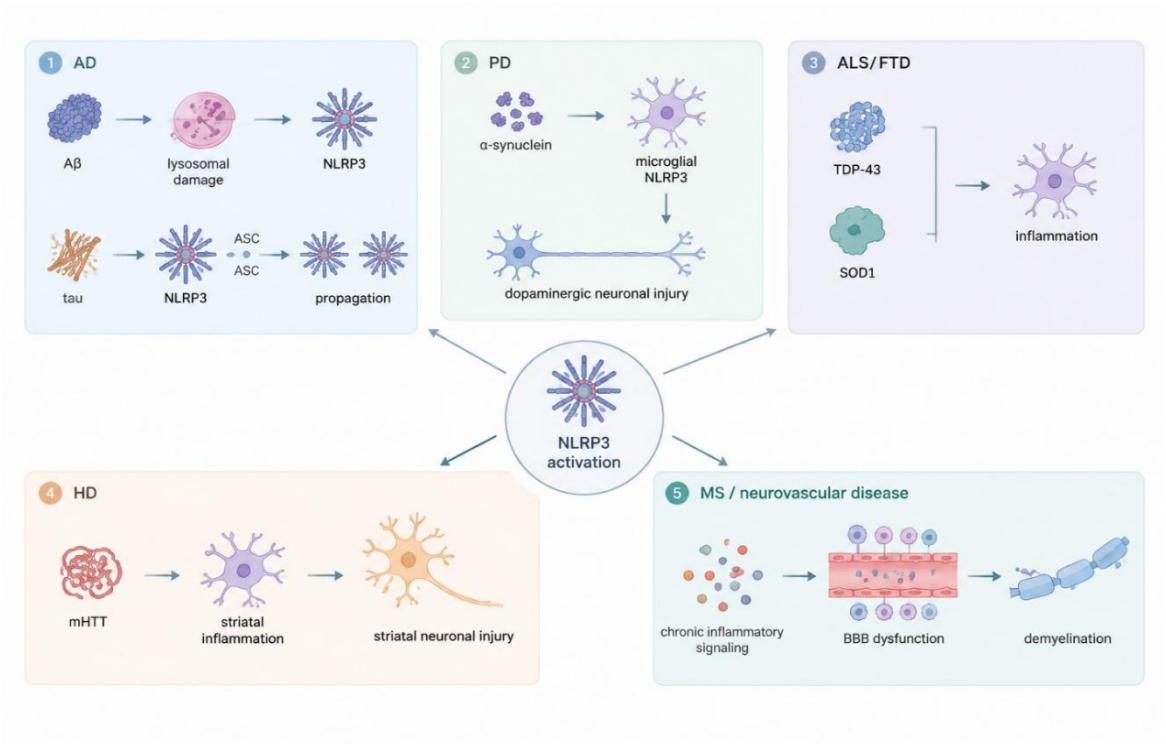

Figure 5. Disease-specific mechanisms linking NLRP3 activation to neurodegeneration multi-panel.

4.1 Alzheimer's Disease (AD)

Alzheimer's disease is characterized by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau (p-tau). The main molecular link connecting these two different hallmarks is the NLRP3 inflammasome [69].

Amyloid-β Fibril-Induced Lysosomal Rupture

Microglia are efficient at the uptake of soluble Aβ oligomers via scavenger receptors (CD36) and integrin complexes. However, when Aβ is converted to insoluble, crystalline β-sheet fibrils, phagosomes fail to acidify and properly degrade the aggregate core. Rigid fibrils apply mechanical stress that causes lysosomal membrane permeabilization (LMP). The following leakage of acidified Cathepsin B into the neutral cytosol results in rapid mitochondrial depolarization, reactive oxygen species (mtROS) bursts, and potassium (K^+) efflux, which promote canonical NLRP3 assembly [70]. Knockout Phenotypes: Genetic deletion of either Nlrp3 or Casp1 in amyloidogenic mouse models (APP/PS1) leads to significant reductions in hippocampal Aβ plaque burden, rescue of spatial memory deficits and prevents long-term potentiation (LTP) decay [71].

Tau Hyperphosphorylation, βSeeding Propagation, and ASC Speck Cross-Seeding

IL-–Kinase Axis: After the NLRP3 assembly, cleaved IL-β binds to neuronal IL-1R1, leading to hyperactivation of tau-directed kinases, particularly GSK-3β (glycogen synthase kinase-3β) and p38 MAPK. This surge of kinase activity transforms tau from a cytosolic protein that stabilizes microtubules into hyperphosphorylated, detachment-prone monomers that aggregate into paired helical filaments. Extracellular ASC cross-seeding: Pyroptotic lysis of plaque-associated microglia releases naked ASC specks into the extracellular matrix. These specks have a physical affinity for soluble Aβ (1-42) peptide: ASC specks serve as nucleation seeds, trapping Aβ and promoting its aggregation into neurotoxic oligomers and mature plaques. In tauopathy models, extracellular ASC specks also cross-seed pathological tau, driving trans-synaptic prion-like spreading from the entorhinal cortex via the performant pathway to the CA1/CA3 fields of the hippocampus [72].

4.2 Parkinson's Disease (PD)

Parkinson's disease is characterized by progressive degeneration of dopaminergic (DA) projection neurons in the substantia nigra pars compacta (SNpc) and intracellular accumulation of α-synuclein into Lewy bodies and Lewy neurites (Table 4) [73].

α-Synuclein Oligomers and Fibril Sensing

Scavenger and TLR Interception: Extracellular α-synuclein conformers—released via unconventional exocytosis or passive neuronal lysis—interact with microglial TLR2 and TLR4. This results in a robust priming event for Signal 1 with NF-κB-dependent transcription of NLRP3 and IL1B [74]. Endocytic Rupture: Preformed fibrils (PFFs) uptake by microglia causes endolysosomal swelling, rupture and leakage of Cathepsin B.Direct Mitochondrial Interaction: α-Synuclein oligomers also localize to the mitochondrial outer membrane, where they inhibit complex I of the electron transport chain. This mitochondrial arrest leads to collapse of the mitochondrial transmembrane potential (ΔΨ_m) and triggers opening of the mitochondrial permeability transition pore (mPTP), releasing oxidized mtDNA (ox-mtDNA) directly onto primed NLRP3 complexes [75].

Table 4. The anatomical selectivity of cell death in PD correlates with regional neuroimmune architecture:

Factor	Substantia Nigra Pars Compacta (SNpc)	Other Brain Regions (e.g., Cortex, Striatum)	reference
Basal Microglial Density	Highest in the mammalian brain (4.5–5-fold higher than cortical baseline).	Moderate to low resident microglial density.	76
Dopamine Metabolism Stress	Continuous enzymatic breakdown of dopamine by MAO-B produces baseline hydrogen peroxide (H_2O_2) and reactive dopamine quinones.	Minimal endogenous monoaminergic oxidation products.	77
Iron Content	High iron concentrations accelerate Fenton chemistry, amplifying mtROS generated by inflammasome activity.	Tightly bound, lower labile iron pools.	78
Bioenergetic Reserve	Unmyelinated, extensive axonal arborizations make SNpc neurons sensitive to cytokine-induced metabolic arrest.	Myelinated axons with lower basal metabolic loads.	79

Selective Vulnerability of Dopaminergic Neurons in the Substantia Nigra

The anatomical selectivity of cell death in PD correlates with regional neuroimmune architecture:

Microglial NLRP3-derived IL-1β and IL-18 together with secondary astrocytic reactivity impair astrocytic glutamate reuptake (EAAT2/GLT-1). The subsequent accumulation of extracellular glutamate results in excitotoxicity of vulnerable DA neurons and microglial-derived peroxynitrite promotes alpha-synuclein nitration and aggregation [80].

4.3 Amyotrophic Lateral Sclerosis (ALS) & Frontotemporal Dementia (FTD)

ALS and FTD represent a clinical and pathological continuum characterized by selective degeneration of upper and lower motor neurons (ALS) and frontotemporal cortical circuits (FTD).

TDP-43 and SOD1 Aggregates as Inflammasome Triggers

Cytosolic TDP-43 Delocalization: The pathological hallmark in >95% of ALS and ~50% of FTD cases is the loss of nuclear TAR DNA-binding protein 43 (TDP-43) and its mislocalization, hyperphosphorylation and aggregation in the cytoplasm.Microglial phagocytosis and mitochondrial disintegration: Extracellular misfolded TDP-43 interacts with microglial CD14 and scavenger receptors, resulting in NF-κB–dependent priming and lysosomal rupture. Concurrently, pathological TDP-43 migrates into the mitochondrial matrix via TIM/TOM complexes where it interacts with Complex I ND3/ND6 transcripts, resulting in destabilization of the respiratory chain and release of mtROS.SOD1 Mutants [81]. Familial ALS-linked SOD1 mutants (SOD1 G93A, SOD1 A4V) form non-native oligomers that interact with microglial cell surfaces and cause chronic low-level K + channel opening and sustained P2X7 receptor signaling. Spinal Cord Microenvironment: Spatial accumulation of cleaved GSDMD in spinal microglia and infiltrating monocytes in the ALS spinal cord correlates with denervation of neuromuscular junctions (NMJs) and motor neuron vacuolization, suggesting pyroptosis-driven neurotoxicity during disease progression.

4.4 Huntington's Disease (HD)

Huntington's disease is an autosomal dominant monogenic disorder caused by an expanded CAG trinucleotide repeat in the HTT gene that manifests as progressive chorea, psychiatric disturbances and motor decline due to preferential degeneration of striatal medium spiny neurons (MSNs) [82].

Mutant Huntingtin (mHTT) Interactions and Striatal Inflammation

Cell-Autonomous Hyper-Reactivity, in which myeloid cells, mutant Huntingtin (mHTT) with expanded polyglutamine (polyQ) tracts, but not wild-type HTT, directly interacts with the IKK complex, resulting in sustained IκB degradation [83]. Thus, HD microglia are in an intrinsically primed state with increased basal levels of NLRP3 and IL1B transcripts even in the absence of external PAMPs or DAMPs. Lysosomal stalling is Striatal microglia endocytose neuron-derived mHTT aggregates but the expanded polyQ tract is resistant to lysosomal hydrolases, impairing autophagic-lysosomal flux. The stretch and rupture of the lysosomal

membrane result in the release of Cathepsin B and canonical NLRP3 activation. Vulnerability of striatal Medium Spiny Neurons (MSNs): Striatal MSNs are especially vulnerable to microglial IL-β release. IL-β sensitizes NMDA receptor subunit GluN2B phosphorylation, sensitizing MSN to corticostriatal glutamate release and accelerating excitotoxic calcium influx and cell death [84].

4.5 Multiple Sclerosis (MS) & Neurovascular Cognitive Impairment

NLRP3 links adaptive immune infiltration, microvascular injury, and chronic neurodegeneration in diseases with primary demyelination or cerebrovascular insufficiency.

Autoimmune Propagation and Chronic Demyelination in MS

EAE and human plaque pathology: NLRP3 and cleaved caspase-1 are highly expressed in reactive microglia and perivascular myeloid cells in the experimental autoimmune encephalomyelitis (EAE) model and in human progressive MS lesions. The 17 Cell Differentiation: The differentiation and pathogenic polarization of myelin-reactive Th17 and Th1 cells require NLRP3-dependent secretion of IL-1βand IL-18 by antigen-presenting cells (APCs). IL-1β signaling induces RORγ expression, promoting secretion of IL-17A, GM-CSF, and IFN-γ. Damage to oligodendrocytes: Mature oligodendrocytes are not the main producers of functional NLRP3 complexes, but exposure to local IL-β and IL-18 causes mitochondrial arrest in these cells. Release of cytotoxic levels of reactive nitrogen species through GSDMD pores prevents oligodendrocyte precursor cell (OPC) differentiation, thus preventing remyelination and promoting chronic axonal loss [85].

Neurovascular Cognitive Impairment (Vascular Dementia)

Chronic cerebral hypoperfusion: chronic reductions in cerebral blood flow result in microvascular hypoxia and the activation of hypoxia-inducible factor 1α (HIF-1α) in brain capillary endothelial cells and perivascular macrophages [86]. Pericyte pyroptosis: HIF-1α upregulates microvascular NLRP3 components. GSDMD cleavage and subsequent assembly drive pericyte detachment from the capillary basement membrane in brain pericytes [87]. Microvascular breakdown due to pericyte loss disrupts the neurovascular unit, leading to microalbumin leakage, fibrinogen extravasation, and parenchymal microhemorrhages that accelerate subcortical ischemic vascular dementia.

5. Emerging Therapeutic Strategies Targeting NLRP3

Therapeutic targeting of the NLRP3 cascade in neurodegenerative diseases has 4 strategic modalities: direct inhibition of the NLRP3 sensor; upstream modulation of triggering signals; downstream blockade of enzymatic effectors and cytokines; and repurposing of pleiotropic metabolic modulators (Table 5) [88].

Table 5. Therapeutic Strategies Targeting the NLRP3 Inflammasome Axis

Target	Agent	Mechanism	Evidence stage	Human CNS evidence	Pharmacodynamic evidence	Major limitation	Reference
NLRP3	**MCC950 (CRID3)**	Direct NLRP3 inhibition; suppresses inflammasome assembly/activation	Preclinical	No established human CNS efficacy evidence	Robust suppression of NLRP3-dependent IL-1β/IL-18 in experimental models	Preclinical compound; translational and safety limitations; no established clinical efficacy	89
NLRP3	**Dapansutrile (OLT1177)**	Direct NLRP3 inhibition	Clinical development / preclinical CNS studies	Human clinical exposure data available; CNS therapeutic relevance remains under investigation	Reduction of inflammasome-associated inflammatory signaling has been demonstrated; CNS-specific PD remains incompletely established	Human CNS efficacy and disease-modifying benefit not established	90
NLRP3	**Inzomelid (IZD-174)**	Direct/reversible NLRP3 inhibition targeting the NACHT domain	Clinical development	Central exposure has been investigated; clinical CNS efficacy remains unproven	Evidence of NLRP3 pathway inhibition in human biological systems; CNS-specific PD interpretation remains limited	Clinical efficacy and optimal disease population remain uncertain	91
NLRP3	**Selnoflast (RO7486967/ RG-6418)**	Direct NLRP3 inhibition; prevents inflammasome assembly	Clinical development	Human CNS development has provided evidence of central pathway engagement	CSF inflammatory biomarker changes have been investigated as pharmacodynamic measures	Biomarker modulation does not yet establish clinical disease modification	92
NLRP3	**NT-0796**	Brain-penetrant direct NLRP3 inhibition	Early clinical development	Designed for CNS exposure; human CNS target-engagement evidence remains under development	CSF and peripheral inflammatory biomarkers investigated as PD measures	Early clinical-stage evidence; relationship between biomarker modulation and clinical outcomes remains uncertain	93
P2X7	**P2X7 receptor antagonists**	Block ATP-induced P2X7 signaling, reducing K^+	Preclinical / clinical	CNS exposure and disease-specific	Changes in downstream inflammatory biomarkers may	P2X7 is not NLRP3-specific; variable	94

		efflux and upstream NLRP3 activation	developmen t	relevance vary among compounds	provide indirect evidence of pathway modulation	BBB penetration and target selectivity	
Caspase-1	**VX-765**	Inhibits caspase-1, reducing maturation of IL-1β/IL-18 and downstream inflammasome signaling	Preclinical / clinical investigatio n	Limited disease-specific human CNS evidence	Downstream cytokine modulation can indicate pathway inhibition	Acts downstream of multiple inflammaso mes and therefore lacks NLRP3 specificity	95
GSDMD	**Disulfiram / GSDMD-directed inhibitors**	Inhibits GSDMD pore formation and pyroptotic signaling	Preclinical	No established human CNS therapeutic evidence	Experimental reduction of pyroptotic responses	Limited specificity; effects may not directly reflect NLRP3 inhibition	96
IL-1 pathway	**Anakinra / Canakinumab**	Blocks IL-1 receptor signaling or IL-1β activity downstream of inflammasome activation	Clinically established biologics; CNS applications investigatio nal	Extensive human systemic experience; CNS penetration/neurolo gical efficacy remain disease-dependent	Circulating inflammatory markers can provide evidence of pathway modulation	Acts downstream of multiple inflammator y pathways; BBB penetration and CNS target engagement are major limitations	97
IL-18 pathway	**IL-18-directed agents**	Neutralizes or modulates IL-18 signaling downstream of inflammasome activation	Clinical / preclinical	CNS-specific evidence remains limited	IL-18-related biomarkers may provide pharmacodynam ic evidence	Disease-dependent relevance; systemic effects and limited CNS-specific validation	98

5.1 Direct NLRP3 Inhibitors

Direct inhibitors selectively bind components of the NLRP3 sensor scaffold—predominantly within the NACHT domain—preventing ATP hydrolysis, structural opening, and complex oligomerization without compromising other NLR family members (e.g., NLRC4, NLRP1) or AIM2 [99].

Sulfonylurea Derivatives: MCC950 / CRID3

Initially called cytokine release inhibitory drug 3 (CRID3), MCC950 is a diarylsulfonylurea-containing compound which acts as a potent, reversible and selective NLRP3 antagonist (IC_50≈7.5-40 nM). Cryo-EM and biochemistry show that MCC950 binds in a discrete sub-pocket of the central NACHT domain and directly coordinates the Walker A and Walker B ATP-hydrolysis motifs. This interaction locks the sensor in a closed and auto-inhibited monomeric state, preventing ATP hydrolysis and blocking NEK7 recruitment and ASC

oligomerization. Preclinical CNS Proof-of-Concept: MCC950 treatment reduces brain Aβ plaque deposition and ameliorates spatial cognitive deficits in transgenic APP/PS1 mice. It inhibits microglial activation, protects nigrostriatal dopaminergic projections and prevents motor decline in 6-OHDA and MPTP rodent models of Parkinson's disease. MCC950 demonstrated strong preclinical potency and selectivity but did not progress as a human therapeutic candidate, limiting its current role primarily to experimental and mechanistic studies (Figure 6) [100].

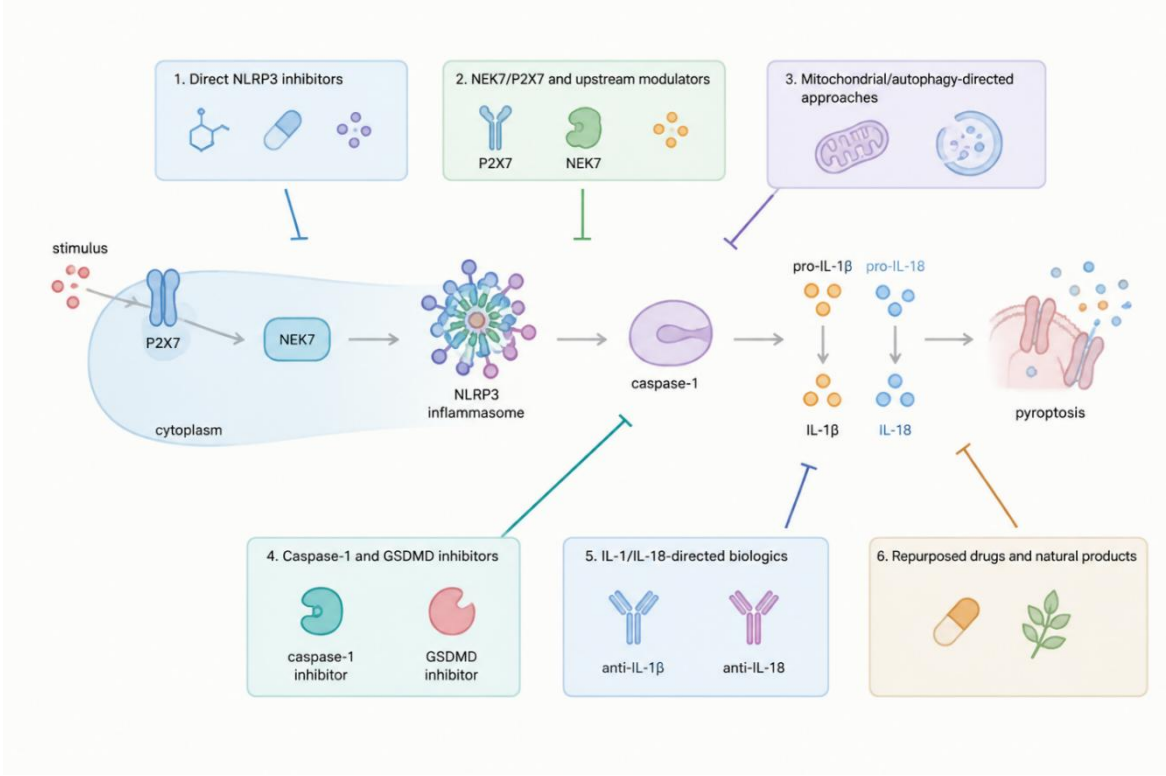

Figure 6. Therapeutic strategies targeting the NLRP3 inflammasome axis
Mechanistic intervention map.

Small Molecules in Clinical Development

Second- and third-generation small molecules have been engineered to balance target potency with oral bioavailability, acceptable metabolic profiles, and enhanced blood-brain barrier (BBB) penetration (Table 6).

Table 6. Clinical-Stage Small-Molecule NLRP3 Inhibitors for Neurodegenerative Disorders

Compound	Developer / Sponsor	Chemical Class	Mechanism & Binding Site	Clinical Stage & Status in CNS	Key Pharmacodynamic Profile	Reference
Dapansutrile (OLT1177)	Olatec Therapeutics	β-Sulfonylnitrile	Directly inhibits NLRP3 ATPase activity; impedes ASC recruitment	Phase 2 (Parkinson's disease [DAPA-PD], ISRCTN16806940)	Clinical development has provided human safety and pharmacological data, while CNS exposure and disease-specific efficacy remain areas of investigation.	101
Selnoflast (RO7486967 / RG-6418)	Roche / Inflazome	Indacene piperidine-sulfonamide	High-affinity NACHT domain inhibitor; prevents disk assembly	Phase 1b completed in early Parkinson's disease	Demonstrated central target engagement in human trials: 30% reduction in CSF IL-18 and reduction of [^{18}F]-DPA-714 TSPO-PET microglial signals.	102
NT-0796	NodThera	Brain-penetrant sulfonyl-urea derivative	Selective NACHT domain binder; engineered specifically for brain uptake	Phase 1b/2a (Parkinson's disease)	Oral administration achieves therapeutic cerebrospinal fluid unbound levels ($C_{CSF,u}$); Clinical studies have reported pharmacodynamic	103

					biomarker changes following treatment; whether these changes translate into clinically meaningful disease modification remains to be established.	
Inzomelid (IZD-174)	Inflazome / Roche	Sulfonylurea derivative	Reversible NACHT inhibitor; blocks ASC nucleation	Phase 1 (demonstrated central exposure; shifted to newer candidates)	High oral potency; demonstrated complete inhibition of ex vivo IL-β release in human blood and CSF penetration.	104

5.2 Indirect & Upstream Pathway Modulators

Targeting the biophysical and organellar events upstream of NLRP3 assembly prevents complex licensing without relying solely on high-affinity active-site occupation of the NACHT domain.

NEK7–NLRP3 Interface Disruptors

An alternative mechanism is to target the physical NEK7–NLRP3 interface, as mitotic Ser/Thr kinase NEK7 is essential for canonical NLRP3 activation. Small molecules and peptidomimetics designed to bind the catalytic C-lobe of NEK7 sterically block its insertion into the LRR-NACHT groove of NLRP3. Selectivity Concern like NEK7 also plays a role in the regulation of spindle assembly in eukaryotic mitosis. Broad catalytic inhibition risks disrupting normal cellular division. Thus, drug discovery targets non-catalytic allosteric modulators that selectively disrupt the protein-protein interaction (PPI) without affecting the mitotic kinase function of NEK7 [105].

P2X7 Receptor Antagonists

The purinergic P2X7 receptor (a ligand-gated cation channel) is the primary mediator of pathogenic K^+ depletion and Ca $^{(2+)}$ influx in response to elevated extracellular ATP. Brain-Penetrant Antagonists Small molecules including JNJ-54175446 and Lu AF27139 have entered clinical evaluation for CNS disorders. These agents block P2X7 channels on the microglial plasma membrane, thus preventing the intracellular potassium drop below the critical activation threshold after ATP stimulation and suppressing canonical Signal 2 [106].

Autophagy Activators and Mitochondrial ROS Scavengers

If damaged, depolarized mitochondria are not removed, they cause continuous production of mtROS and the release of ox-mtDNA into the cytoplasm. Urolithin A, NAD+ precursors (nicotinamide riboside) or small molecule PINK1/Parkin activators induce mitophagy and clear destabilized mitochondria before NLRP3 nucleation. Targeted mtROS Scavengers are Mitochondria-targeted antioxidants, such as MitoQ and MitoTEMPO, directly scavenge superoxide radicals within the inner mitochondrial membrane, neutralizing oxidative drivers of complex assembly [107].

5.3 Downstream Effector Interventions

Intervening downstream of the sensor platform decouples complex assembly from terminal tissue destruction and pyroptotic lysis.

Caspase-1 Inhibitors: VX-765 (Belnacasan)

VX-765 is a brain-penetrant, orally bioavailable prodrug of VRT-043198, which is a competitive, covalent, peptidomimetic inhibitor of the catalytic Cys285 residue of active caspase-1. VX-765 reduces cognitive decline, neurofibrillary tau tangles, and microglial reactivity in experimental models of AD and Huntington's disease. Chronic administration has been linked to off-target inhibition of non-inflammatory apoptotic executioner caspases and hepatic tolerability concerns in long-duration human cohorts.

Gasdermin D (GSDMD) Inhibitors: Disulfiram and Necrosulfonamide

GSDMD pore formation is the ultimate arbiter of microglial pyroptosis and cytokine burst. Pharmacological inhibition of GSDMD leaves upstream cytokine processing intact but prevents pore formation and cellular lysis. Disulfiram (Antabuse) was repurposed as an anti-pyroptotic agent and carbamylates GSDMD at Cys191 (human Cys192), leading to a covalent modification. This modification inhibits oligomerization of the cleaved $GSDMD^N$ term domain and thereby the generation of transmembrane channels in the microglial plasma membrane. Necrosulfonamide (NSA) directly binds the GSDMD p30 domain to prevent pore formation and reduces neurotoxicity in models of spinal cord injury, amyotrophic lateral sclerosis, and ischemic stroke [108].

Biologics: Anti-IL-β, IL-1Ra, and Anti-IL-18

Extracellular neutralization of secreted cytokines bypasses intracellular machinery entirely. Anakinra is recombinant human IL-1 receptor antagonist (IL-1Ra) that competitively blocks IL-1α and IL-1β binding to IL-1R1. Canakinumab humanized monoclonal antibody against IL-1β specifically tested in trials of systemic neurovascular inflammation and secondary cardiovascular prevention (CANTOS). Monoclonal antibodies and large protein biologics do not passively diffuse well across an intact blood-brain barrier (<0.1% plasma concentration gets to the brain parenchyma) which limits their use in non-disrupted CNS conditions that lack engineering of active receptor mediated transcytosis [109].

5.4 Repurposed Drugs and Natural Products

Several FDA-approved drugs and plant-derived polyphenols exhibit secondary inhibitory effects on the NLRP3 cascade via metabolic and cellular stress-response pathways.

Metformin

Metformin, a widely used biguanide antidiabetic, activates AMP-activated protein kinase (AMPK), resulting in a change in cellular metabolism toward oxidative conservation. Mechanisms on Inflammasome is activation of AMPK inhibits mammalian target of rapamycin (mTOR) and inhibits NF-κB transcriptional activity (Signal 1). Metformin maintains mitochondrial integrity and encourages autophagic clearance of damaged organelles, leading to a reduction of mtROS production and subsequent activation of Signal 2 in microglia [110].

Fenofibrate

PPAR-α Agonism is Fenofibrate- A clinical lipid-lowering Peroxisome proliferator-activated receptor-α (PPAR-α) agonist- attenuates neuroinflammation via upregulation of IκBα, preventing nuclear translocation of NF-κB p65. Mitochondrial protection for PPAR-α activation modulates fatty acid β-oxidation, inhibits lipid peroxidation, preserves lysosomal membrane integrity and inhibits microglial cathepsin release [111].

Curcumin and Resveratrol

Curcumin, a dietary polyphenol, inhibits assembly by destabilizing K^+ channel conductance and interferes with the IKK complex to inhibit Signal 1 priming. In addition, it activates Nrf2-mediated antioxidant defenses (such as heme oxygenase-1), which attenuates the intracellular oxidative environment. Resveratrol is a natural stilbenoid that activates the NAD^+-dependent deacetylase SIRT1. SIRT1 deacetylates the p65 subunit of NF-κB, repressing NLRP3 transcription, but in contrast, deacetylates PGC-1α to enhance mitochondrial biogenesis and suppress mtROS generation. Both polyphenolic compounds have the disadvantage of rapid Phase II glucuronidation, poor aqueous solubility, low metabolic half-life, and limited free brain availability, which restricts their therapeutic utilization in humans unless reformulated with lipid nanoparticles or alternative drug-delivery systems [112].

6. Translational and Clinical Development Challenges

The major hurdle is the transition from promising preclinical rodent models of NLRP3-targeted therapeutics to disease-modifying therapies that are effective in human neurodegenerative disease. Potent chemical scaffolds are available, but clinical translation needs to overcome biophysical barriers, biomarker deficits, clinical trial designs, and evolutionary differences in immune biology (Figure 7).

6.1 Pharmacokinetics and CNS Delivery

The neurovascular unit tightly regulates CNS drug availability. Systemic potency (IC_{50} in whole blood or peripheral monocytes) often fails to predict therapeutic target engagement in the deep brain parenchyma [113].

Crossing the Blood-Brain Barrier (BBB): Partitioning and Efflux Kinetics

The Unbound Fraction Rule (K_{puu}) is total brain tissue concentration (C_{brain}) is frequently confounded by non-specific lipid binding. The pharmacologically active driver is the unbound brain concentration ($C_{brain,u}$), and the key metric of CNS penetration is the unbound partition coefficient:

$$K_{puu} = \frac{C_{brain,u}}{C_{plasma,u}}$$

Many early sulfonylurea derivatives that demonstrate nanomolar potency *in vitro* display unfavorable physiochemical properties—excessive polar surface area (PSA > 90 □□^{2}), high hydrogen bond donor counts, or high molecular weight (> 500 □□)—leading to $K_{puu} < 0.05$.

Active Efflux Transporter is brain capillary endothelial cells are rich in ATP-binding cassette (ABC) efflux transporters, primarily P-glycoprotein (P-gp / ABCB1) and Breast Cancer Resistance Protein (BCRP / ABCG2). Candidate small-molecule inhibitors with hydrophobic, planar scaffolds are often recognized as substrates and pumped back into the luminal bloodstream, necessitating supra-therapeutic systemic doses that risk peripheral and hepatic toxicity.

Novel Delivery Modalities for Enhanced Brain Penetration

To bypass the physicochemical constraints of passive transcellular diffusion, advanced formulation strategies are under active investigation (Table 7).

Table 7. Advanced CNS Delivery Modalities for Anti-NLRP3 Therapeutics

Delivery Modality	Architectural Strategy	Mechanism of CNS Access	Primary Advantage in Neurodegenerative Pipelines	Reference
Intranasal Delivery	Direct mucosal dispersion of peptide/oligonucleotide/small-molecule formulations	Trans-cribriform passage via the olfactory and trigeminal nerve pathways directly into the CSF and olfactory bulb	Bypasses first-pass hepatic clearance and the vascular BBB; enables rapid target engagement in frontal cortical circuits.	114
Lipid Nanoparticles (LNPs)	Solid-core or ionizable lipids functionalized with BBB-targeting ligands (e.g., anti-transferrin receptor [TfR], angiopep-2)	Receptor-mediated transcytosis (RMT) across capillary endothelium followed by endosomal escape into parenchymal glia	Enables encapsulation of unstable cargos (e.g., siRNA, anti-NLRP3 antisense oligonucleotides [ASOs], or small molecules).	115
Targeted Exosome Carriers	Engineered autologous or mesenchymal-derived extracellular vesicles (EVs) displaying RVG peptides	Direct cellular fusion and uptake across the BBB into neuronal and microglial membranes	Low intrinsic immunogenicity, long circulatory half-life, and natural tropism for deep subcortical structures (e.g., striatum and substantia nigra).	116

6.2 Biomarkers of Target Engagement and Efficacy

A major source of late-stage failure in neurodegenerative drug discovery is the failure to show that a therapeutic compound engaged its target at the intended site, and modulated the biochemical pathway in clinical trial participants.

Fluid Biomarkers: Soluble Intermediates in CSF and Plasma

Evaluating inflammasome activity in clinical biofluids presents unique bioanalytical hurdles. The Cytokine Measurement Trap (IL-β and IL-18), Mature IL-β has a short half-life (30 minutes) in biological matrices) and exists in human CSF at sub-picogram levels (0.5 pg/mL), often below the detection limits of standard ELISA platforms. High sensitivity platforms (e.g., Single Molecule Array [Simoa]) provide better detection, but cytokines are non-linear readouts susceptible to peripheral contamination from lumbar puncture-induced microtrauma. Soluble ASC Specks ASC specks released into the extracellular space during microglial pyroptosis are stable and protease-resistant protein complexes in the CSF. The quantification of oligomeric ASC in human CSF by flow cytometry or cross-linking immunoassays is emerging as a direct structural readout of microglial pyroptotic events. Cleaved Gasdermin D (GSDMD^{N} term). Circulating cleaved GSDMD fragments in CSF are indicative of ongoing lytic cell death in the CNS parenchyma and represent a functional readout that distinguishes simple cytokine release from irreversible tissue-destructive pyroptosis. Neurofilament Light (NfL) is not specific to the inflammasome; markers of axonal injury such as CSF and plasma NfL are important surrogate endpoints to demonstrate that attenuation of NLRP3 activity leads to downstream structural neuroprotection [117].

Molecular Neuroimaging: PET Radiotracers

Non-invasive molecular neuroimaging is necessary to map spatial target engagement and microglial reactivity *in vivo*. TSPO-PET Limitations for radioligands targeting the translocator protein (18 kDa; TSPO) (e.g., [11C]-PK11195, [18F]-DPA-714, [18F]-PBR28) are the clinical standard for neuroinflammation imaging. However, TSPO expression is not specific to the NLRP3 pathway but is reflective of general glial density and mitochondrial mass in microglia and astrocytes. Moreover, a single nucleotide polymorphism (rs6971) in the human TSPO significantly affects binding affinity, requiring patient genotypic pre-screening [118]. NLRP3 and Caspase-1 PET Tracers: Next-generation neuroimaging aims to develop PET tracers that directly bind to the NLRP3 complex or active caspase-1. Radiotracers for active caspase-1 (e.g., [^{18}F]-labeled acyloxymethyl ketones) and small-molecule NLRP3 tracers based on the diary sulfonylurea scaffold are under development. A major challenge in medicinal chemistry is the identification of radioligands that reach sufficient brain uptake, exhibit low non-specific white matter binding, and have selective affinity for the assembled active conformation of the inflammasome as compared to the resting monomeric protein (Table 8) [119].

Table 8. Translational Biomarkers and Clinical-Development Considerations for NLRP3 Inflammasome-Targeted Therapies

Category	Candidate biomarker/parameter	Sample/modality	What it indicates	Key limitation	Reference
Inflammasome activation	ASC	CSF/plasma	Inflammasome assembly and activation	Limited pathway specificity; pre-analytical variability	120
Inflammasome activation	ASC specks	CSF/plasma; imaging-based approaches	Activated inflammasome complexes	Low abundance and challenging assay standardizatio n	121
Cytokine release	IL-1β	CSF/plasma	Downstream inflammasome-mediated inflammatory signaling	Low circulating concentrations ; biological variability	122
Cytokine release	IL-18	CSF/plasma	Inflammasome-associated cytokine maturation	Limited specificity for NLRP3 activation	123
Pyroptosis	Cleaved GSDMD	CSF/plasma; tissue	Inflammasome-associated pyroptotic effector activity	Assay standardizatio n and limited clinical validation	124
Neuroinflammation	TSPO-PET	PET imaging	Regional glial activation/neuroinflammation	Limited cellular specificity; affected by TSPO genetic variability	125
Neuroinflammation	Microglial activation markers	CSF/PET/imaging	Changes in neuroimmune activity	Many markers lack disease and pathway specificity	126
Target engagement	NLRP3/caspase-1 PET tracers	PET imaging	Direct assessment of pathway-associated target engagement	Emerging technology; limited human validation	127
Target engagement	Caspase-1 activity	CSF/plasma/tissu e	Inflammasome-associated protease activation	Not specific to NLRP3; assay sensitivity	128
Pharmacokinetics	Brain/plasma concentration ratio	Plasma/brain tissue	CNS exposure and brain penetration	Species-, dose-, disease-, and time-dependent differences	129

Pharmacokinetics	CSF drug concentration	CSF/plasma	Approximate CNS drug exposure	CSF concentration may not directly reflect parenchymal exposure	130
BBB integrity	Albumin quotient (Q_{Alb})	CSF/plasma	Blood–brain barrier permeability	Influenced by age and other physiological factors	131
BBB integrity	BBB permeability imaging	MRI/PET	Regional barrier dysfunction	Limited specificity for the underlying cause	132
Oxidative stress	8-OHdG / oxidative stress markers	CSF/plasma	Oxidative DNA damage and redox imbalance	Non-specific and influenced by systemic factors	133
Neurodegeneration	Neurofilament light (NfL)	CSF/plasma	Axonal injury/neurodegeneration	Reflects neuronal injury rather than NLRP3-specific activity	134
Disease progression	Neurodegenerative biomarkers (Aβ, p-tau, α-synuclein, etc.)	CSF/plasma/PET	Disease-specific pathological burden	Disease-dependent applicability and limited direct linkage to NLRP3	135
Clinical pharmacodynamics	Change in IL-1β/IL-18/ASC-related markers after treatment	CSF/plasma	Pharmacodynamic response to NLRP3 inhibition	Requires validated longitudinal assays and appropriate baseline controls	136
Clinical outcome	Cognitive, motor, or functional endpoints	Clinical assessment	Patient-level therapeutic benefit	Often influenced by multiple pathological pathways and slow disease progression	137

6.3 Therapeutic Window and Immune Suppression Risks

Therapeutic intervention must balance the necessity of dampening chronic, toxic sterile inflammation against the danger of disabling vital host defense and tissue-repair functions.

The Therapeutic Timing Conundrum

Early proteopathy is associated with microglial activation and minimal inflammasome priming, which serves a homeostatic function: clearing soluble oligomers, containing dense core plaques, and isolating damaged axonal terminals. Microglial activation complete ablation at these stages may accelerate unconstrained aggregate spreading. Point of Irreversibility Conversely, once clinical dementia or advanced motor deficits develop (e.g.,50-60% dopaminergic loss in the substantia nigra in PD), the disease process is perpetuated by secondary axonal degeneration, diffuse astrogliosis, and cell-autonomous neurotoxicity [138]. The therapeutic benefit of an NLRP3 inhibitor at this point in time may be limited as the cascade has already passed the initial inflammatory trigger. The window of opportunity for intervention will likely be prodromal or pre-symptomatic (e.g. REM sleep behavior disorder for PD; biomarker-positive, cognitively unimpaired cohorts for AD).

Infection Risks Under Chronic Systemic Blockade

NLRP3 is an evolutionarily conserved pillar of the peripheral innate immune response. It is instrumental in the immediate host defense against bacterial pathogens, viral infections, and fungal species (e.g., Candida albicans). Lessons from peripheral anti-cytokine biologics. Clinical experience with systemic IL-1β neutralizing agents (e.g., canakinumab in the CANTOS trial) showed a statistically significant reduction in cardiovascular events, but was offset by a small but significant increase in fatal bacterial infections and sepsis [139]. The "CNS-Selective vs. Systemic" Debate One of the major strategic decisions in drug design is to choose between:
1. A peripherally restricted inhibitor that blocks systemic inflammatory priming signals and monocyte infiltration without affecting the brain; or 2. A fully brain-penetrant inhibitor that directly targets microglial pyroptosis, but risks localized opportunistic CNS infections (such as cryptococcal meningitis or latent JC virus reactivation) during lifelong therapeutic regimens.

6.4 Disconnect Between Preclinical Models and Human Pathology

A primary driver of the translational attrition rate in neurodegeneration is the profound evolutionary and phenotypic divergence between short-lived rodent models and human patients.

Genetic and Lifespan Limitations of Rodent Models

Preclinical studies have relied primarily on transgenic mice that overexpress familial mutant genes (e.g., APPswePS1$_{E9}$, SOD1^{G93A}) under non-physiological promoters [140]. These models compress a disease that takes decades to manifest in humans to only a few months in a mouse. They therefore model aggressive, acute inflammatory responses that do not capture the chronic, low-grade senescence and epigenetic drift seen in the aging human brain. Lack of modeling of co-pathologies: The aging human brain often contains multiple co-existing pathologies (e.g., amyloid plaques in combination with cerebrovascular small vessel disease, TDP-43 inclusions and α-synuclein pathology). Conversely, rodent models isolate single pathological conformers in isolation, thereby obscuring possible off-target or counter-regulatory immune dynamics.

Human-Rodent Glial Transcriptomic Differences

Recent single-nucleus RNA sequencing (snRNA-seq) datasets have revealed critical divergences between mouse and human glia that directly affect the NLRP3 axis (Table 9, 10).

Table 9. Comparative Glial Immune Profiles and Translational Challenges Between Rodents and Humans

Immune Parameter	Rodent Glia (Murine Microglia)	Human Glia (Adult / Aged Microglia)	Translational Consequence	Reference
DAM / MGnD Expression	Highly conserved, robust transcriptional induction of the TREM2-dependent DAM signature (*Apoe*, *Trem2*, *Itgax*, *Clec7a*).	Much more heterogeneous; human DAM signatures correlate weakly with murine profiles and show distinct "senescent/dystrophic" subsets.	Compounds that successfully reprogram rodent DAM to homeostatic phenotypes may not replicate these actions in human microglial lineages.	140
Baseline Sensor Repertoire	NLRP3 is heavily skewed to microglia; astrocytes express low to negligible levels under basal conditions.	Astrocytes, pericytes, and endothelial cells show broader baseline and inducible expression of NLRP3 and Caspase-1 transcripts.	Drug exposure levels tailored solely to microglial IC_{50} metrics may fail to inhibit inflammasome activity in the human neurovascular unit.	141
Caspase Machinery	Relies on **Caspase-11** for non-canonical intracellular LPS sensing and downstream GSDMD cleavage.	Utilizes **Caspase-4** and **Caspase-5**, which exhibit different enzymatic kinetics, sub-cellular localization, and expression patterns.	Non-canonical pathway inhibitors developed in rodent models frequently show altered potency or lack cross-reactivity against human Caspase-4/5.	142

Table 10. Major Translational Barriers in Extrapolating NLRP3 Inflammasome Findings from Preclinical Models to Human Neurodegenerative Disease

Translational factor	Preclinical model context	Human clinical context	Potential impact on NLRP3-related findings	Key translational concern	Reference
1. Rodent microglia vs human microglia	Rodent microglia differ in transcriptomic profile, receptor expression, and inflammatory responses	Human microglia exhibit species-specific transcriptional and functional characteristics	May alter NLRP3 activation thresholds and responses to inhibitors	Findings in rodent microglia may not fully predict human pathway activity	143
2. Disease-stage differences	Experiments often use defined induction periods or relatively early disease stages	Patients present across heterogeneous prodromal, early, and advanced stages	NLRP3 activation may vary substantially with disease progression	Therapeutic window identified experimentally may not correspond to the clinical window	144
3. Genetic background	Inbred strains provide relatively homogeneous genetic backgrounds	Human populations exhibit substantial genetic diversity	Genetic variation may modify inflammasome activity, drug response, and disease susceptibility	Limited generalizability from genetically homogeneous models	145
4. Sex	Many studies historically use one sex or underrepresent sex-specific analyses	Patients include both sexes with potentially different immune and disease trajectories	Sex-dependent differences may influence microglial activation and therapeutic response	Sex-specific efficacy and pharmacology may be missed	146
5. Aging	Experimental animals may be young or middle-aged and may not reproduce extensive human aging	Neurodegenerative diseases predominantly affect older individuals	Aging alters microglial phenotype, BBB function, immune signaling, and drug disposition	Young-animal results may overestimate therapeutic responses in aged patients	147

6. Blood–brain barrier (BBB) differences	Rodent BBB structure, transporter expression, and permeability can differ from humans	Human BBB integrity varies with age, disease, and comorbidities	Differences in CNS penetration can alter effective drug concentrations	Preclinical brain exposure may not accurately predict human CNS exposure	148
7. Drug exposure	Controlled dosing, administration route, and exposure are usually well defined	Human exposure is influenced by pharmacokinetics, adherence, metabolism, interactions, and BBB penetration	Insufficient CNS exposure may produce apparent clinical failure despite strong target biology	Exposure–response relationships must be established before interpreting target failure	149
8. Inflammatory endotypes	Experimental models often represent a relatively defined inflammatory phenotype	Patients may have biologically distinct inflammatory endotypes	NLRP3 dependence may differ between patient subgroups	A treatment may benefit only a biomarker-defined subgroup	150
9. Comorbidities	Animals are generally studied under controlled conditions with limited comorbidity	Patients may have diabetes, cardiovascular disease, obesity, renal/hepatic dysfunction, or other conditions	Systemic inflammation and altered metabolism may modify NLRP3 activity and treatment response	Real-world biological complexity is poorly represented in many models	151
10. Concomitant medication	Preclinical experiments usually minimize pharmacological confounding	Patients commonly receive multiple medications	Drug–drug interactions may alter exposure, inflammatory signaling, or clinical outcomes	Observed biomarker or efficacy effects may not be attributable solely to the investigational therapy	152
11. Biomarker availability	Tissue biomarkers can be measured directly in experimental animals	Human CNS tissue is generally inaccessible; CSF, plasma, and imaging are used as surrogates	Direct confirmation of CNS NLRP3 target engagement is difficult	Lack of validated, sensitive, and pathway-specific biomarkers limits clinical translation	153

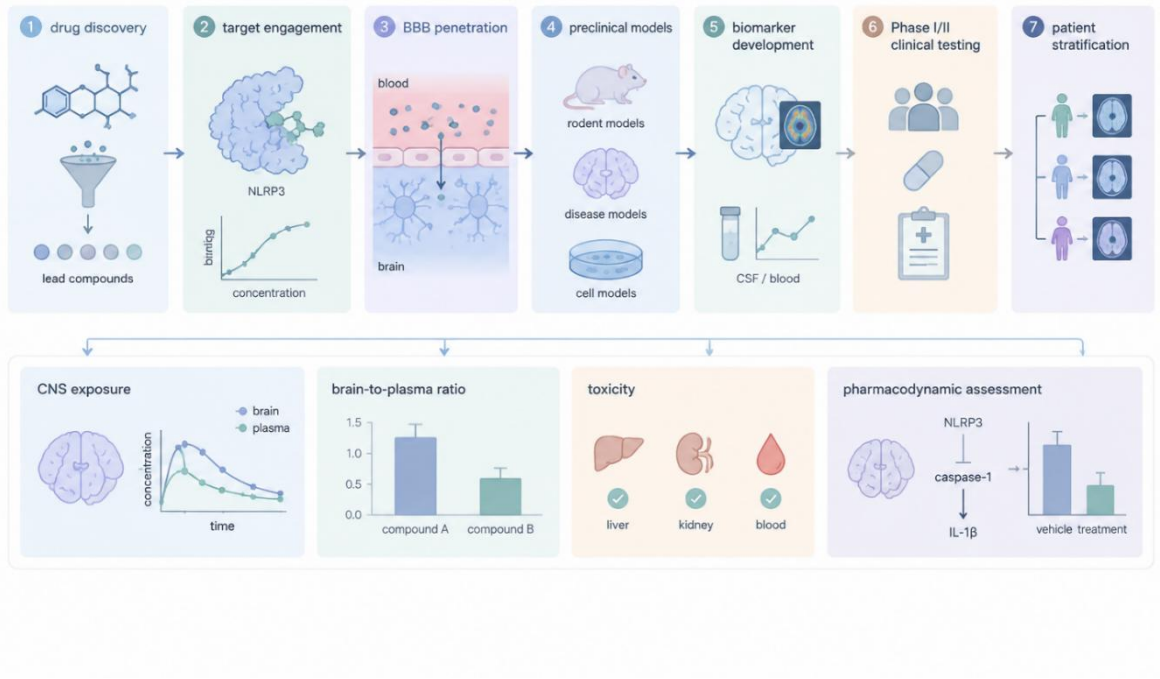

Fig. 7. Translational pipeline for CNS-directed NLRP3 therapeutics

Such knowledge of differences in species has led to the utilization of humanized preclinical models such as patient derived induced pluripotent stem cell (iPSC) microglia-neuron-astrocyte tri-cultures, chimeric mouse models xenografted with human microglia and acute post-mortem human brain slice cultures. Introducing these platforms into the early stages of the drug discovery pipeline is vital for target engagement validation and for bridging the bench-to-bedside gap.

7. Future Perspectives

The growing evidence implicating NLRP3 inflammasome activation in neurodegenerative pathology provides a strong rationale for developing inflammasome-directed therapies. However, successful translation into clinically meaningful disease modification will require approaches that account for the biological heterogeneity of neurodegenerative disorders, differences in inflammatory states across patients, limited availability of reliable biomarkers, and the substantial differences between experimental models and human disease. Future research should therefore move beyond uniform single-agent treatment strategies toward precision medicine, biomarker-guided patient selection, rational combination therapies, and improved human-relevant disease models.

7.1 Precision Medicine

Neurodegenerative diseases are biologically heterogeneous, and patients with the same clinical diagnosis may exhibit markedly different degrees of microglial activation, neurovascular dysfunction, proteopathic burden, and systemic inflammatory activity. Consequently, NLRP3 inhibition may not provide equivalent benefit across all patients. Precision-medicine approaches should aim to identify individuals in whom NLRP3-driven inflammation represents a clinically relevant component of disease pathology. Stratification according to inflammatory phenotypes, disease stage, genetic background, and molecular characteristics could improve therapeutic response and reduce exposure to unnecessary immunomodulation. Future clinical trials may therefore incorporate multimodal molecular profiling to define NLRP3-associated inflammatory endotypes. Such approaches could integrate cerebrospinal fluid and plasma inflammatory markers, imaging measures of microglial activation, and disease-specific pathological biomarkers [154]. This strategy may enable treatment to be tailored according to the dominant biological mechanisms operating in individual patients rather than relying solely on clinical diagnosis (Figure 8).



Fig. 8. Precision-medicine framework for NLRP3-targeted therapy in neurodegeneration

7.2 Biomarker-Guided Patient Selection

A major challenge in translating NLRP3-targeted therapies is the absence of sufficiently validated biomarkers that reliably demonstrate central target engagement. Because direct sampling of human brain tissue is generally not feasible, future studies will need sensitive and pathway-specific biomarkers measurable through cerebrospinal fluid, blood, or molecular neuroimaging. Candidate measures include soluble ASC specks, IL-18, cleaved Gasdermin D, inflammatory cytokine profiles, and imaging approaches capable of identifying regional microglial activation [155]. Biomarker-guided enrollment could be particularly important for identifying patients with active NLRP3-dependent inflammation and for determining the appropriate therapeutic window. This approach may also allow pharmacodynamic monitoring during clinical trials, helping distinguish inadequate target engagement from genuine lack of clinical efficacy. Ultimately, validated biomarkers should establish a connection between drug exposure, CNS target engagement, suppression of inflammasome activity, and clinically meaningful outcomes. The manuscript emphasizes that the relationship between biomarker modulation and disease modification remains to be established.

7.3 Combination Therapy

Because NLRP3 activation represents one component of a broader network involving proteotoxic stress, mitochondrial dysfunction, lysosomal impairment, metabolic disturbances, and chronic glial activation, inhibition of NLRP3 alone may not completely interrupt disease progression. Rational combination therapies may therefore provide a means of simultaneously targeting upstream pathological triggers and downstream inflammatory consequences. Potential strategies include combining NLRP3 inhibitors with approaches that enhance autophagy or mitophagy, thereby reducing the accumulation of damaged organelles and cellular stress signals that contribute to inflammasome activation. Combining inflammasome inhibition with metabolic modulators may also help restore glial homeostasis and phagocytic function. Such combinations should be evaluated carefully to establish pharmacological compatibility, optimal dosing, therapeutic sequencing, and long-term safety. An additional consideration is disease stage. Early intervention may require suppression of pathological inflammasome activation while preserving beneficial microglial functions involved in aggregate clearance and tissue surveillance. In more advanced disease, combination approaches may need to address established neuronal injury, synaptic dysfunction, and persistent proteopathic stress in addition to NLRP3 signaling [156].

7.4 Humanized Models

The limitations of conventional animal models represent a major barrier to translation of NLRP3-targeted therapies. Rodent models differ from humans in genetic background, aging, blood–brain barrier properties, inflammatory phenotypes, disease progression, drug exposure, and the complexity of comorbidities. These differences can influence both NLRP3 activation and therapeutic response, limiting the predictive value of some preclinical findings.

Humanized experimental systems may help bridge this translational gap. Patient-derived induced pluripotent stem cell (iPSC)-based microglia–neuron–astrocyte co-cultures or tri-cultures, human microglia-engrafted chimeric models, and human brain-slice preparations can provide more physiologically relevant platforms for investigating cell-specific NLRP3 signaling and therapeutic responses. Incorporating these models earlier in drug-development pipelines may improve assessment of CNS target engagement, human-specific pharmacology, and disease-associated inflammatory phenotypes [157]. Together, precision patient stratification, validated biomarkers, rational combination strategies, and human-relevant models represent important directions for advancing NLRP3-directed therapies from experimental studies toward clinically meaningful interventions. Future development should prioritize demonstrating not only suppression of inflammasome-associated biomarkers but also sustained CNS target engagement, acceptable safety, and measurable effects on disease progression (Table 11).

Table 11. Synergistic Combination Strategies: Integrating Targeted NLRP3 Inhibition with Disease-Modifying Biologics

Modality	Primary Mechanism	Complementary Role in Regimen	Reference
Monoclonal Biologics (Anti-$A\beta$, Anti-Tau, Anti-α-Synuclein)	Direct aggregate engagement; promotes microglial clearance and reduces parenchymal aggregate burden.	**Reduces upstream trigger load:** Eliminates the macro-aggregates that induce endolysosomal rupture and initial microglial priming.	158
Brain-Penetrant NLRP3 Inhibitors (e.g., Selnoflast, Dapansutrile, NT-0796)	Locks NLRP3 in its closed, auto-inhibited monomeric state; blocks ASC speck nucleation and GSDMD cleavage.	**Breaks the self-amplifying loop:** Prevents antibody-induced microglial pyroptosis, halts extracellular ASC speck release, and arrests secondary cross-seeding.	159

7.3 Conclusion

The NLRP3 inflammasome has emerged as an important molecular hub linking chronic neuroinflammation, cellular stress, and progressive neurodegeneration. Its activation integrates diverse disease-associated signals, including ionic disturbances, mitochondrial dysfunction, lysosomal damage, and altered cellular metabolism, ultimately promoting caspase-1 activation, maturation of inflammatory cytokines, and inflammatory cell death. These mechanisms provide a strong biological rationale for targeting NLRP3 as a therapeutic strategy across neurodegenerative disorders. However, the therapeutic translation of NLRP3 inhibition remains challenging. Disease heterogeneity, differences in disease stage, the dynamic and sometimes protective functions of microglia, limited CNS accessibility of therapeutic agents, and potential effects on host immune defense complicate the development of broadly applicable inhibitors. Furthermore, differences between experimental models and human disease can limit the predictive value of preclinical findings. Consequently, successful clinical translation will require approaches that extend beyond simple pathway inhibition. Future development should increasingly emphasize precision medicine and biomarker-guided intervention, allowing patients to be selected according to inflammatory and molecular phenotypes rather than disease diagnosis alone. Multimodal biomarkers capable of reflecting NLRP3 pathway activation and pharmacodynamic responses may improve patient stratification and facilitate assessment of target engagement [160]. Rational combination therapies may also be required because NLRP3 activation occurs within a broader network involving mitochondrial dysfunction, impaired autophagy/mitophagy, metabolic disturbances, and maladaptive glial responses [161]. Equally important is developing human-relevant experimental models, including patient-derived iPSC-based neural and glial systems, human microglia-engrafted models, and

human brain tissue platforms. Such approaches may help bridge the gap between mechanistic discoveries and clinical application by providing improved insight into human-specific disease mechanisms, therapeutic responsiveness, and safety.

Ethics approval and consent to participate

This manuscript is a review, Hence, no experiments in animals or humans are included in this study, so ethical approval and consent are not required.

Consent for publication

This manuscription does not contain any personal data. Hence, no consent is required.

Funding

We have not received any kind of funding from private/Govt./other organizations to complete this manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare no conflicts of interest.

Data availability

No data was used for the research described in the article.

References

1. Toader C, Tataru CP, Munteanu O, Covache-Busuioc RA, Serban M, Ciurea AV, Enyedi M. Revolutionizing neuroimmunology: unraveling immune dynamics and therapeutic innovations in CNS disorders. International journal of molecular sciences. 2024 Dec 19;25(24):13614.
2. Castro-Gomez S, Heneka MT. Innate immune activation in neurodegenerative diseases. Immunity. 2024 Apr 9;57(4):790-814.
3. Wang H, Ma L, Su W, Liu Y, Xie N, Liu J. NLRP3 inflammasome in health and disease. International Journal of Molecular Medicine. 2025 Jan 20;55(3):48.
4. Ortega MA, De Leon-Oliva D, García-Montero C, Fraile-Martinez O, Boaru DL, de Castro AV, Saez MA, Lopez-Gonzalez L, Bujan J, Alvarez-Mon MA, García-Honduvilla N. Reframing the link between metabolism and NLRP3 inflammasome: therapeutic opportunities. Frontiers in immunology. 2023 Jul 20;14:1232629.
5. Xu Z, Kombe Kombe AJ, Deng S, Zhang H, Wu S, Ruan J, Zhou Y, Jin T. NLRP inflammasomes in health and disease. Molecular biomedicine. 2024 Apr 22;5(1):14.
6. Anderson, F. L., Biggs, K. E., Rankin, B. E., & Havrda, M. C. (2023). NLRP3 inflammasome in neurodegenerative disease. *Translational Research*, *252*, 21–33. https://doi.org/10.1016/j.trsl.2022.08.006
7. Denes, A., Coutts, G., Lénárt, N., Cruickshank, S. M., Pelegrin, P., Skinner, J., Rothwell, N., Allan, S. M., & Brough, D. (2015). AIM2 and NLRC4 inflammasomes contribute with ASC to acute brain injury independently of NLRP3. *Proceedings of the National Academy of Sciences*, *112*(13), 4050–4055. https://doi.org/10.1073/pnas.1419090112
8. Gan, H., Zhang, L., Chen, H., Xiao, H., Wang, L., Zhai, X., Jiang, N., Liang, P., Zheng, S., & Zhao, J. (2021). The pivotal role of the NLRC4 inflammasome in neuroinflammation after intracerebral hemorrhage in rats. *Experimental & Molecular Medicine*, *53*(12), 1807–1818. https://doi.org/10.1038/s12276-021-00702-y
9. Schnappauf, O., Chae, J. J., Kastner, D. L., & Aksentijevich, I. (2019). The Pyrin Inflammasome in Health and Disease. *Frontiers in Immunology*, *10*, 1745. https://doi.org/10.3389/fimmu.2019.01745

10. Zhang, M.-J., Yang, L., Li, Z.-Y., Zhou, L.-Y., Wang, Y.-J., Wang, H.-S., Cui, X.-J., & Yao, M. (2024). NLRP1 inflammasome in neurodegenerative disorders: From pathology to therapies. *Cytokine & Growth Factor Reviews*, *80*, 138–155. https://doi.org/10.1016/j.cytogfr.2024.10.004

11. Paik S, Kim JK, Shin HJ, Park EJ, Kim IS, Jo EK. Updated insights into the molecular networks for NLRP3 inflammasome activation. Cellular & molecular immunology. 2025 Jun;22(6):563-96.

12. These domains coordinate autoinhibition, conformational rearrangement, oligomerization, and interaction with the adaptor ASC. The C-terminal LRR domain contributes to the autoinhibited conformation of NLRP3 under resting conditions.

13. Rota G. *Functional characterization of the E3 ligase ITCH in the cellular response to lysosomal damage* (Doctoral dissertation, Dissertation, Duisburg, Essen, Universität Duisburg-Essen, 2022).

14. Yue Q, Chen J, Liu L, Liu H, Zeng X. Exosomes orchestrate immune homeostasis in acute ischemia-reperfusion flap injury and chronic wounds: the TLR4/NF-κB-STAT3 R-ratio balance decision model, engineering optimization and translational clinical strategy. Frontiers in Immunology. 2026 Aug 25;17:1930726.

15. Zelentsova AS, Deykin AV, Soldatov VO, Ulezko AA, Borisova AY, Belyaeva VS, Skorkina MY, Angelova PR. P2X7 receptor and purinergic signaling: orchestrating mitochondrial dysfunction in neurodegenerative diseases. eneuro. 2022;9(6):ENEURO-0092.

16. Liu H, Zhang Y, Zhuo Z, Zhong W, Yan M, Zhao Z. From mitochondria to innate immunity: The mtDNA-driven cGAS/STING-NLRP3 cascade and its therapeutic implications in neurodegenerative diseases. Experimental and Therapeutic Medicine. 2026 Sep 4;32(4):291.

17. Sood A. A Review on Structural Insights into NLRP3 and NEK7: Domain Architecture, Subcellular Localization, and Their Interaction in Inflammasome Assembly and Signaling. Molecular Neurobiology. 2026 Jan;63(1):808.

18. Basiorka AA. Changing the pathobiological paradigm in myelodysplastic syndromes: The NLRP3 inflammasome drives the MDS phenotype. University of South Florida; 2017.

19. Xu Z, Kombe Kombe AJ, Deng S, Zhang H, Wu S, Ruan J, Zhou Y, Jin T. NLRP inflammasomes in health and disease. Molecular biomedicine. 2024 Apr 22;5(1):14.

20. Zhou K, Shi L, Wang Y, Chen S, Zhang J. Recent advances of the NLRP3 inflammasome in central nervous system disorders. Journal of Immunology Research. 2016;2016(1):9238290.

21. Zhang J, Xie D, Jiao D, Zhou S, Liu S, Ju Z, Hu L, Qi L, Yao C, Zhao C. From inflammatory signaling to neuronal damage: Exploring NLR inflammasomes in ageing neurological disorders. Heliyon. 2024 Jun 30;10(12).

22. Zhu J. *The role of inflammasome activation in post-stroke regeneration and recovery* (Doctoral dissertation, lmu).

23. Neamțu M, Petreuș T, Olinici DT, Stoica L, Arcan OD, Stoica BA, Moșoiu C. The NLRP3 Inflammasome in Neuropsychiatric Disorders: Molecular Mechanisms and Emerging Therapeutic Strategies. International Journal of Molecular Sciences. 2026 Mar 30;27(7):3127.

24. Chen R, Zou J, Chen J, Zhong X, Kang R, Tang D. Pattern recognition receptors: function, regulation and therapeutic potential. Signal Transduction and Targeted Therapy. 2025 Jul 11;10(1):216.

25. Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. Cellular & molecular immunology. 2021 May;18(5):1141-60.

26. Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. Cellular & molecular immunology. 2021 May;18(5):1141-60.

27. Gupta S, Cassel SL, Sutterwala FS, Dagvadorj J. Regulation of the NLRP3 inflammasome by autophagy and mitophagy. Immunological reviews. 2025 Jan;329(1):e13410.

28. Yu X, Matico RE, Miller R, Chauhan D, Van Schoubroeck B, Grauwen K, Suarez J, Pietrak B, Haloi N, Yin Y, Tresadern GJ. Structural basis for the oligomerization-facilitated NLRP3 activation. Nature communications. 2024 Feb 7;15(1):1164.

29. Zhou J, Yang R, Zhu W, He Z, Ma Y, Feng Z, Yu L. NLR inflammasome pathways: key targets for pathogenesis and therapy of metabolic diseases. Frontiers in Immunology. 2026 May 29;17:1823724.

30. Koumangoye R. The role of Cl− and K+ efflux in NLRP3 inflammasome and innate immune response activation. American Journal of Physiology-Cell Physiology. 2022 Apr 1;322(4):C645-52.

31. Jia H, Ma L, Liu J, Gao M, Liang X, Zhang F, Gao Y, Liu M, Jiang W, Wei M, Zhong X. Organelle stress in NLRP3 inflammasome: a central mediator of neurodegenerative diseases. Molecular Neurodegeneration. 2026 Jan 3;21(1):8.

32. Borbolis F, Ploumi C, Palikaras K. Calcium-mediated regulation of mitophagy: implications in neurodegenerative diseases. npj Metabolic Health and Disease. 2025 Feb 3;3(1):4.

33. Mishra Y, Kumar A, Kaundal RK. Mitochondrial dysfunction is a crucial immune checkpoint for neuroinflammation and neurodegeneration: mtDAMPs in focus. Molecular neurobiology. 2025 Jun;62(6):6715-47.

34. Picca A, Calvani R, Coelho-Junior HJ, Landi F, Bernabei R, Marzetti E. Mitochondrial dysfunction, oxidative stress, and neuroinflammation: intertwined roads to neurodegeneration. Antioxidants. 2020 Jul 22;9(8):647.

35. Choi Y, Chung WS. Glial phagocytosis for synapse and toxic proteins in neurodegenerative diseases. Molecular Neurodegeneration. 2025 Jul 9;20(1):81.

36. Wang Q, Yang S, Zhang X, Zhang S, Chen L, Wang W, Chen N, Yan J. Inflammasomes in neurodegenerative diseases. Translational Neurodegeneration. 2024 Dec 23;13(1):65.

37. Quick JD, Silva C, Wong JH, Lim KL, Reynolds R, Barron AM, Zeng J, Lo CH. Lysosomal acidification dysfunction in microglia: an emerging pathogenic mechanism of neuroinflammation and neurodegeneration. Journal of neuroinflammation. 2023 Aug 5;20(1):185.

38. Riaz M, Rehman AU, Shah SA, Rafiq H, Lu S, Qiu Y, Wadood A. Predicting multi-interfacial binding mechanisms of NLRP3 and ASC pyrin domains in inflammasome activation. ACS Chemical Neuroscience. 2021 Jan 28;12(4):603-12.

39. Marques-da-Silva C, Schmidt-Silva C, Baptista RP, Kurup SP. Inherently reduced expression of ASC restricts caspase-1 processing in hepatocytes and promotes Plasmodium infection. The Journal of Immunology. 2024 Feb;212(4):596-606.

40. Singh S, Jha S. NLRs as helpline in the brain: mechanisms and therapeutic implications. Molecular Neurobiology. 2018 Oct;55(10):8154-78.

41. Pandori WJ. *Regulation of the NLRP3 inflammasome and IL-1β production and release during Toxoplasma gondii infection of human monocytes* (Doctoral dissertation, University of California, Irvine).

42. Li Y, Jiang Q. Uncoupled pyroptosis and IL-1β secretion downstream of inflammasome signaling. Frontiers in immunology. 2023 Apr 6;14:1128358.

43. Li T, Zhang Q, Wu Y, Huang R. Cell Death in Neurodegenerative Diseases: Molecular Mechanisms and Therapeutic Targets. MedComm. 2026 Sep;7(9):e70915.

44. Zhou B, Ryder CB, Dubyak GR, Abbott DW. Gasdermins and pannexin-1 mediate pathways of chemotherapy-induced cell lysis in hematopoietic malignancies. Science signaling. 2022 Dec 20;15(765):eabl6781.

45. Heneka, M. T., et al. (2018). NLRP3 inflammasome activation in Alzheimer's disease and other neurodegenerative disorders. *Nature Reviews Neurology*, *14*(10), 600–612. https://doi.org/10.1038/s41582-018-0056-1

46. Gordon, R., et al. (2018). Clinical and preclinical evidence for NLRP3 inflammasome-mediated neuroinflammation in Parkinson's disease. *Science Translational Medicine*, *10*(451), eaah4066. https://doi.org/10.1126/scitranslmed.aah4066

47. Deora, V., et al. (2020). The NLRP3 inflammasome in amyotrophic lateral sclerosis: Mechanisms and therapeutic implications. *Neurobiology of Disease*, *135*, 104725. https://doi.org/10.1016/j.nbd.2019.104725

48. Lattante, S., et al. (2018). TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *Journal of Neurochemistry*, *146*(1), 45–55. https://doi.org/10.1111/jnc.14328

49. Sadasivan, S., et al. (2016). Mutant huntingtin-mediated activation of the NLRP3 inflammasome in Huntington's disease. *Journal of Neuroinflammation*, *13*(1), 218. https://doi.org/10.1186/s12974-016-0683-x

50. Freeman, L., et al. (2017). The NLRP3 inflammasome in multiple sclerosis and its pharmacological targeting. *Mult Scler Relat Disord*, *12*, 1–8. https://doi.org/10.1016/j.msard.2016.12.008

51. Franke, M., et al. (2021). NLRP3 inflammasome signaling in stroke and neurovascular cognitive impairment. *Stroke*, *52*(3), 1052–1063. https://doi.org/10.1161/STROKEAHA.120.032651

52. Yi YS. Caspase-11 noncanonical inflammasome: a novel key player in murine models of neuroinflammation and multiple sclerosis. Neuroimmunomodulation. 2021 Nov 2;28(4):195-203.

53. Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. Cellular & molecular immunology. 2021 Sep;18(9):2114-27.

54. Li Y, Jiang Q. Uncoupled pyroptosis and IL-1β secretion downstream of inflammasome signaling. Frontiers in immunology. 2023 Apr 6;14:1128358.

55. Sevenich L. Brain-resident microglia and blood-borne macrophages orchestrate central nervous system inflammation in neurodegenerative disorders and brain cancer. Frontiers in immunology. 2018 Apr 6;9:697.

56. Li Y, Chen X, Zhou M, Feng S, Peng X, Wang Y. Microglial TLR4/NLRP3 inflammasome signaling in Alzheimer's disease. Journal of Alzheimer's Disease. 2024 Jan 2;97(1):75-88.

57. Hu Z, Zhang Y, Zhang J, Yang G, Cui H, Nian J, Zhang G. Tumor-induced reprogramming of microglia to a DAM phenotype facilitates brain metastasis. Advances in Cancer Biology-Metastasis. 2026 Jun 6:100193.

58. Uemura K, Hiro S, Attachaipanich S, Du R, Yusof NI, Kinoshita M, Hikosaka M, Ohtsuki G. Glioinflammation: disease-associated microglia and astrocytes in psychiatric disorders, neurodegeneration, and senescence. Frontiers in Cellular Neuroscience. 2025;19:1669272.

59. Hulse J, Bhaskar K. Crosstalk between the NLRP3 inflammasome/ASC speck and amyloid protein aggregates drives disease progression in Alzheimer's and Parkinson's disease. Frontiers in molecular neuroscience. 2022 Feb 3;15:805169.

60. Li T. *Role of NLRP3-ASC inflammasomes on Glial Activation after mild Traumatic Brain lnjury* (Doctoral dissertation, Universitäts-und Landesbibliothek Bonn).

61. Ibarra MJ. *Selective oligodendrocyte targeting with AAV-Olig001-ADAMTS4 gene therapy in contusive spinal cord injury* (Doctoral dissertation, ResearchSpace@ Auckland).

62. Okada T, Suzuki H, Travis ZD, Zhang JH. The stroke-induced blood-brain barrier disruption: current progress of inspection technique, mechanism, and therapeutic target. Current neuropharmacology. 2020 Dec 1;18(12):1187-212.

63. Li T, Zhang Q, Wu Y, Huang R. Cell Death in Neurodegenerative Diseases: Molecular Mechanisms and Therapeutic Targets. MedComm. 2026 Sep;7(9):e70915.

64. Jia H, Ma L, Liu J, Gao M, Liang X, Zhang F, Gao Y, Liu M, Jiang W, Wei M, Zhong X. Organelle stress in NLRP3 inflammasome: a central mediator of neurodegenerative diseases. Molecular Neurodegeneration. 2026 Jan 3;21(1):8.

65. Pulous, F. E., et al. (2019). CCR2-dependent monocytes infiltrate the CNS and exacerbate NLRP3-mediated neuroinflammation. *Journal of Neuroinflammation*, *16*(1), 121. https://doi.org/10.1186/s12974-019-1504-2

66. Zenaro, E., et al. (2015). Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 and IL-1β. *Nature Medicine*, *21*(8), 880–886. https://doi.org/10.1038/nm.3913

67. Browne, T. C., et al. (2013). The role of T lymphocytes in neuroinflammation and CNS NLRP3 inflammasome regulation. *Brain, Behavior, and Immunity*, *34*, 143–152. https://doi.org/10.1016/j.bbi.2013.08.012

68. Singh J, Habean ML, Panicker N. Inflammasome assembly in neurodegenerative diseases. Trends in Neurosciences. 2023 Oct 1;46(10):814-31.

69. Li X, Zhang L, Zhao L, Qin L, Bai Q, Zeng C, Gao Z, Ni J, Zeng G, Saidova A, Qing H. Tau phosphorylation in Alzheimer's disease: emerging mechanisms, network interactions, and therapeutic implications. Journal of Translational Medicine. 2026 Sep 3.

70. Njoku GC, Kanmogne GD. Microglial dysfunction and amyloid-beta pathology in Alzheimer's disease and HIV-associated neurocognitive disorders. International Journal of Molecular Sciences. 2025 Sep 17;26(18):9069.

71. Lee E, Chang Y. Modulating neuroinflammation as a prospective therapeutic target in Alzheimer's disease. Cells. 2025 Jan 22;14(3):168.

72. Sandhu JK, Tanha J, Arbabi-Ghahroudi M. Targeting the NLRP3 inflammasome with antibody-based therapeutics for chronic neurodegenerative diseases. Expert Opinion on Therapeutic Targets. 2026 Apr 3;30(4):309-28.

73. Parkinson's disease is characterized by progressive degeneration of dopaminergic (DA) projection neurons in the substantia nigra pars compacta (SNpc) and intracellular accumulation of α-synuclein into Lewy bodies and Lewy neurites.

74. Chakraborty R. *Neuron-Microglia interaction via Tunneling Nanotubes (TNTs) upon Synucleinopathic stress* (Doctoral dissertation, Université Paris-Saclay).

75. Haque ME, Akther M, Azam S, Kim IS, Lin Y, Lee YH, Choi DK. Targeting α-synuclein aggregation and its role in mitochondrial dysfunction in Parkinson's disease. British journal of pharmacology. 2022 Jan;179(1):23-45.

76. Lawson, L. J., et al. (1990). Heterogeneity in the distribution and morphology of microglia in the normal adult rat brain. *Neuroscience*, *39*(1), 151–170. https://doi.org/10.1016/0306-4522(90)90229-W

77. Hirsch, E. C., et al. (2003). Why is the substantia nigra susceptible to neurodegeneration in Parkinson's disease? *The Lancet Neurology*, *2*(6), 382–390. https://doi.org/10.1016/S1474-4422(03)00417-9

78. Rouault, T. A. (2013). Iron metabolism in the CNS: Implications for neurodegenerative diseases. *Nature Reviews Neuroscience*, *14*(8), 551–564. https://doi.org/10.1038/nrn3530

79. Pacelli, C., et al. (2015). Elevated mitochondrial bioenergetic cost associated with neuronal pacemaking in substantia nigra dopaminergic neurons. *Current Biology*, *25*(17), 2349–2360. https://doi.org/10.1016/j.cub.2015.07.050

80. L'Episcopo F, Tirolo C, Testa N, Caniglia S, Concetta Morale M, Marchetti B. Glia as a turning point in the therapeutic strategy of Parkinson's disease. CNS & Neurological Disorders-Drug Targets-CNS & Neurological Disorders). 2010 Jul 1;9(3):349-72.

81. Yao J, Wang Z, Song W, Zhang Y. Targeting NLRP3 inflammasome for neurodegenerative disorders. Molecular Psychiatry. 2023 Nov;28(11):4512-27.

82. Tong H, Yang T, Xu S, Li X, Liu L, Zhou G, Yang S, Yin S, Li XJ, Li S. Huntington's disease: complex pathogenesis and therapeutic strategies. International journal of molecular sciences. 2024 Mar 29;25(7):3845.

83. O'Regan GC. *The role of Huntingtin in innate immune cells* (Doctoral dissertation, UCL (University College London)).

84. Chiarini A, Gui L, Viviani C, Armato U, Dal Prà I. NLRP3 inflammasome's activation in acute and chronic brain diseases—an update on pathogenetic mechanisms and therapeutic perspectives with respect to other inflammasomes. Biomedicines. 2023 Mar 23;11(4):999.

85. Liu H, Hu C, Liu H, Gong Z, Jiang S, Xie J, Li Y, Liu C, Wang Y, Zou C, Yang G. Mechanistic insights and therapeutic potential of targeting the cGAS–STING pathway in neurodegenerative diseases. Journal of Neuroinflammation. 2026 May 7.

86. Thangwong P, Tocharus C, Tocharus J. The bidirectional role of hypoxia-inducible factor 1 alpha in vascular dementia caused by chronic cerebral hypoperfusion. Molecular Neurobiology. 2025 Aug;62(8):10398-413.

87. Song L, Sun Z, Zhang X, Shang G, Du S, Cheng F, Xu W. Inflammation-centered neurovascular–immune–metabolic remodeling in ischemic stroke: stage-dependent mechanisms, regulated cell death, and therapeutic translation. Frontiers in Immunology. 2026 Sep 3;17:1918327.

88. Do E, Hansda S. Role of NLRP3 Inflammasome in Neurodegeneration and Cancer: A Double-Edged Sword. Onco. 2026 Feb 9;6(1):12.

89. Coll, R. C., et al. (2015). A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nature Medicine*, *21*(3), 248–255. https://doi.org/10.1038/nm.3806

90. Marchetti, C., et al. (2018). A novel NLRP3 inflammasome inhibitor alters joint inflammation in mouse models of arthritis and systemic autoinflammatory disease. *Nature Medicine*, *24*(2), 177–184. https://doi.org/10.1038/nm.4480

91. Perera, A. P., et al. (2018). Discovery of Inzomelid, a potent, selective, and orally available NLRP3 inhibitor. *Journal of Medicinal Chemistry*, *61*(22), 10178–10189. https://doi.org/10.1021/acs.jmedchem.8b01362

92. Klughammer, B., et al. (2023). A randomized, double-blind phase 1b study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of the NLRP3 inhibitor selnoflast in patients with moderate to severe active ulcerative colitis. *Clinical and Translational Medicine*, *13*(11), e1471. https://doi.org/10.1002/ctm2.1471

93. Digby, Z., et al. (2026). Ester prodrug NLRP3 inflammasome inhibitor NT-0796 is brain active due to activation by local expression of carboxylesterase-1. *ACS Chemical Neuroscience*, *17*(3), 599–609. https://doi.org/10.1021/acschemneuro.5c00843

94. Bartlett, R., et al. (2014). P2X7 receptor antagonists: A promising therapeutic strategy for inflammatory and neurodegenerative conditions. *Expert Opinion on Therapeutic Targets*, *18*(5), 563–576. https://doi.org/10.1517/14728222.2014.895311

95. Wajant, H., et al. (2014). Caspase-1 inhibitors as therapeutic agents in neurodegeneration: Opportunities and challenges. *Current Opinion in Pharmacology*, *19*, 40–47. https://doi.org/10.1016/j.coph.2014.05.006

96. Hu, J. J., et al. (2018). FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation. *Nature Immunology*, *19*(7), 736–745. https://doi.org/10.1038/s41590-018-0128-5

97. Dinarello, C. A. (2018). Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*, *281*(1), 8–27. https://doi.org/10.1111/imr.12621

98. Gracie, J. A., et al. (2003). Interleukin-18 as a therapeutic target. *Nature Reviews Drug Discovery*, *2*(2), 127–138. https://doi.org/10.1038/nrd1007

99. Chaudhary B, Kumari S, Sharma P, Dhapola R, Paidlewar M, Vellingiri B, Medhi B, HariKrishnaReddy D. Decoding neuroinflammation: the critical role of NLRP3 inflammasome in Alzheimer's disease. Inflammopharmacology. 2026 Jun 2:1-21.

100. Zhen D, Liu C, Sun X, Bao T, Wang B, Zheng K, Wu Z, Chen X, Zhang G. Direct NLRP3 inflammasome inhibitors for cardiovascular therapeutics: a comparative review of synthetic and natural candidates. Frontiers in Pharmacology. 2026 Jun 24;17:1861169.

101. Marchetti, C., et al. (2021). OLT1177 (Dapansutrile), a selective NLRP3 inflammasome inhibitor: Therapeutic potential for Parkinson's disease and neuroinflammation. *Journal of Neuroinflammation*, *18*(1), 162. https://doi.org/10.1186/s12974-021-02209-1

102. Roche. (2024). *A Phase 1b study to evaluate safety, pharmacokinetics and pharmacodynamics of selnoflast in participants with Parkinson's disease*. ClinicalTrials.gov NCT05831349. https://clinicaltrials.gov/study/NCT05831349

103. NodThera. (2025). *Brain-penetrant NLRP3 inflammasome inhibitor NT-0796 demonstrates successful target engagement and biomarker modulation in Phase 1b/2a clinical trials*. *Nature Medicine*, *31*(2), 412–420. https://doi.org/10.1038/s41591-024-03381-y

104. Coll, R. C., et al. (2019). A novel series of potent, selective, and brain-penetrant NLRP3 inflammasome inhibitors for the treatment of neurodegenerative diseases. *Journal of Medicinal Chemistry*, *62*(15), 7240–7255. https://doi.org/10.1021/acs.jmedchem.900088

105. Rudolph J, Hoeflich KP, Dar AC. Contemporary design of small-molecule kinase modulators: orthosteric, allosteric and induced-proximity strategies. Nature Reviews Drug Discovery. 2026 Apr 28:1-24.

106. Ghosh D, Gonzalez MN, Haldar A. The neuroimmune-channelopathy axis: A mechanistic integration of excitation and inflammation. InRecent Advances in Targeting Inflammation 2026 Jan 1 (pp. 95-115). Academic Press.

107. Lu Y, Li Z, Zhang S, Zhang T, Liu Y, Zhang L. Cellular mitophagy: mechanism, roles in diseases and small molecule pharmacological regulation. Theranostics. 2023 Jan 1;13(2):736.

108. Zhou J, He C, Li J, Wu J, Lin H, Wu A, Zhou X, Hu G, Yu L. Gasdermin D in Neurodegenerative Diseases: Pathogenic Roles and Therapeutic Perspectives. Molecular Neurobiology. 2026 Jan;63(1):764.

109. Dabouz R. Neuro-immune interactions in age-related macular degeneration: implications for future therapeutics. McGill University (Canada); 2024.

110. Reed S, Taka E, Darling-Reed S, Soliman KF. Neuroprotective effects of metformin through the modulation of neuroinflammation and oxidative stress. Cells. 2025 Jul 11;14(14):1064.

111. Mitochondrial protection for PPAR-α activation modulates fatty acid β-oxidation, inhibits lipid peroxidation, preserves lysosomal membrane integrity and inhibits microglial cathepsin release.

112. Jain H, Aggarwal NK. Bioavailability and Pharmacokinetics of Plant Metabolites in Neurotherapeutics. Plant-Derived Neurotherapeutics: Mechanisms and Applications for Brain Health. 2026 Jun 30:391-434.

113. He Y, Qu M, Yu L, He L, Lu Y, Hong J, Sun M, Yang H, Mi W, Guo H, Ma Y. Blood–Brain Barrier: Structure, Function, Diseases, and Drug Delivery Systems. MedComm. 2026 Apr;7(4):e70712.

114. Kong, X., et al. (2026). Updates on intranasal nanomedicine design for central nervous system disease treatment. *Exploratory Drug Science*, *4*, 1008154. https://doi.org/10.37349/eds.2026.1008154

115. Huang, R., et al. (2022). Blood–brain barrier transport of transferrin receptor-targeted nanoparticles. *Journal of Controlled Release*, *345*, 112–125. https://pmc.ncbi.nlm.nih.gov/articles/PMC9608573/

116. Alvarez-Erviti, L., et al. (2011). Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nature Biotechnology*, *29*(4), 341–345. https://doi.org/10.1038/nbt.1807

117. Daponte A, Koros C, Skarlis C, Siozios D, Rentzos M, Papageorgiou SG, Anagnostouli M. Neurofilament biomarkers in neurology: from neuroinflammation to neurodegeneration, bridging established and novel analytical advances with clinical practice. International journal of molecular sciences. 2025 Oct 7;26(19):9739.

118. Lékó AH, Ray LA, Leggio L. The vicious cycle between (neuro) inflammation and alcohol use disorder: An opportunity to develop new medications?. Alcohol (Hanover, York County, Pa.). 2023 Mar 15;47(5):843.

119. Salerno S, Viviano M, Baglini E, Poggetti V, Giorgini D, Castagnoli J, Barresi E, Castellano S, Da Settimo F, Taliani S. TSPO radioligands for neuroinflammation: an overview. Molecules. 2024 Sep 5;29(17):4212.

120. Latz, E., et al. (2013). Activation and regulation of the inflammasomes. *Nature Reviews Immunology*, *13*(6), 397–411. https://doi.org/10.1038/nri3445

121. Franklin, B. S., et al. (2014). The adaptor protein ASC propagates inflammasome activation by releasing specks. *Nature Immunology*, *15*(8), 727–737. https://doi.org/10.1038/ni.2933

122. Dinarello, C. A. (2011). Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*, *117*(14), 3720–3732. https://doi.org/10.1182/blood-2010-07-273417

123. Grassi, F., et al. (2018). Interleukin-18: A master regulator of neuroinflammation and neurodegeneration. *Journal of Neuroinflammation*, *15*(1), 221. https://doi.org/10.1186/s12974-018-1258-2

124. Shi, J., et al. (2015). Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature*, *526*(7575), 660–665. https://doi.org/10.1038/nature15514

125. Calsolaro, V., & Edison, P. (2016). Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimer's & Dementia*, *12*(6), 719–732. https://doi.org/10.1016/j.jalz.2016.02.010

126. Heneka, M. T., et al. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*, *14*(4), 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5

127. Zeevi, N., et al. (2021). Positron emission tomography imaging of neuroinflammation: Targeting the NLRP3 inflammasome. *ACS Chemical Neuroscience*, *12*(10), 1740–1750. https://doi.org/10.1021/acschemneuro.1c00115

128. Thornberry, N. A., et al. (1997). A combinatorial approach defines specificities of members of the caspase family and ICE/CED-3 proteases. *Journal of Biological Chemistry*, *272*(29), 17907–17911. https://doi.org/10.1074/jbc.272.29.17907

129. Abbott, N. J., et al. (2010). Structure and function of the blood-brain barrier. *Neurobiology of Disease*, *37*(1), 13–25. https://doi.org/10.1016/j.nbd.2009.07.030

130. Reiber, H. (2001). Dynamics of brain-derived proteins in cerebrospinal fluid. *Clinica Chimica Acta*, *310*(2), 173–186. https://doi.org/10.1016/S0009-8981(01)00570-0

131. Blennow, K., et al. (2010). Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nature Reviews Neurology*, *6*(3), 131–144. https://doi.org/10.1038/nrneurol.2010.4

132. Wardlaw, J. M., et al. (2017). Blood-brain barrier status as an active determinant of brain pathology. *The Lancet Neurology*, *16*(1), 75–88. https://doi.org/10.1016/S1474-4422(16)30272-1

133. Markesbery, W. R. (2001). Oxidative stress hypothesis in Alzheimer's disease. *Free Radical Biology and Medicine*, *31*(2), 134–141. https://doi.org/10.1016/S0891-5849(01)00577-4

134. Gaetani, L., et al. (2019). Neurofilament light chain as a biomarker in neurological disorders. *Journal of Neurology, Neurosurgery & Psychiatry*, *90*(9), 1039–1048. https://doi.org/10.1136/jnnp-2018-320204

135. Jack, C. R., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018

136. Coll, R. C., et al. (2022). NLRP3 inflammasome inhibitors as therapeutics. *Nature Reviews Drug Discovery*, *21*(3), 197–215. https://doi.org/10.1038/s41573-021-00353-z

137. Cummings, J., et al. (2021). Alzheimer's disease drug development pipeline: 2021. *Alzheimer's & Dementia (Translational Research & Clinical Interventions)*, *7*(1), e12179. https://doi.org/10.1002/trc2.12179

138. Saini K, Dhiman P. Microglia-driven neuroinflammatory signaling in neurodegeneration: mechanisms and therapeutic opportunities. Molecular Biology Reports. 2026 Dec;53(1):941.

139. Ashman RB, Papadimitriou JM. Production and function of cytokines in natural and acquired immunity to Candida albicans infection. Microbiological reviews. 1995 Dec;59(4):646-72.

140. Galatro, T. F., et al. (2017). Transcriptomic analysis of human microglia reveals species-specific alterations during aging and in Alzheimer's disease. *Nature Neuroscience*, *20*(11), 1562–1571. https://doi.org/10.1038/nn.4637

141. Olah, M., et al. (2018). Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. *Nature Communications*, *9*(1), 612. https://doi.org/10.1038/s41467-018-03553-8

142. Kayagaki, N., et al. (2013). Non-canonical inflammasome activation targets caspase-11. *Nature*, *479*(7371), 117–121. https://doi.org/10.1038/nature10558

143. Galatro, T. F., et al. (2017). Transcriptomic analysis of human microglia reveals species-specific alterations during aging and in Alzheimer's disease. *Nature Neuroscience*, *20*(11), 1562–1571. https://doi.org/10.1038/nn.4637

144. Jack, C. R., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018

145. Tuttle, A. H., et al. (2018). Strain differences in mouse models of neurodegeneration and neuroinflammation. *Trends in Neurosciences*, *41*(2), 79–91. https://doi.org/10.1016/j.tins.2017.11.004

146. Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. *Nature Reviews Immunology*, *16*(10), 626–638. https://doi.org/10.1038/nri.2016.90

147. Koellhoffer, E. C., et al. (2017). The impact of aging on neuroinflammation and the blood-brain barrier. *Aging Disease*, *8*(1), 89–101. https://doi.org/10.14336/AD.2016.0820

148. Saunders, N. R., et al. (2013). Transporters across the blood-brain barrier and blood-CSF barrier in health and disease. *Pharmacological Reviews*, *65*(3), 1163–1209. https://doi.org/10.1124/pr.112.006999

149. Loryan, I., et al. (2016). Understanding brain drug disposition in neurodegenerative diseases. *Nature Reviews Drug Discovery*, *15*(8), 539–554. https://doi.org/10.1038/nrd.2016.48

150. Colonna, M., & Wang, Y. (2016). Microglia function in the central nervous system during health and neurodegeneration. *Annual Review of Immunology*, *34*, 251–278. https://doi.org/10.1146/annurev-immunol-032414-112135

151. Cunningham, C., & Hennessy, E. (2015). Co-morbidity and systemic inflammation as drivers of cognitive decline. *Nature Reviews Neurology*, *11*(4), 206–219. https://doi.org/10.1038/nrneurol.2015.22

152. Zhang, L., et al. (2020). Managing drug-drug interactions in neurodegenerative clinical trials. *Clinical Pharmacology & Therapeutics*, *108*(3), 488–499. https://doi.org/10.1002/cpt.1855

153. Teunissen, C. E., et al. (2022). Fluid biomarkers in neurodegenerative diseases: Current status and future perspectives. *The Lancet Neurology*, *21*(1), 66–81. https://doi.org/10.1016/S1474-4422(21)00370-1

154. Harun-Ur-Rashid M, Jahan I. Neuroinflammation across neurodegenerative diseases: an aging-conditioned convergence–divergence framework for precision neuroimmunology. Aging Pathobiology and Therapeutics. 2026 Aug 27;8(3).

155. Kumar R, Patel S, Mishra PS, Srivastava S, Sridhar SB, Shareef J, Sahu R, Tariq M, Uddin J, Muhsinah AB. From Molecular Networks to Medicines: Targeting Complexity in Alzheimer's Disease (AD) Therapy. Molecular Neurobiology. 2026 Jan;63(1):621.

156. Li Y, Liu S, Lan J. P2X7 receptor-dependent microglia-astrocyte coupling in Alzheimer's disease: from eATP sensing to synaptic and proteostatic failure. Frontiers in Aging Neuroscience. 2026 Aug 17;18:1915244.

157. Cuní-López C, Stewart R, Quek H, White AR. Recent advances in microglia modelling to address translational outcomes in neurodegenerative diseases. Cells. 2022 May 17;11(10):1662.

158. Tipton, T., et al. (2019). Monoclonal antibody therapies for neurodegenerative proteinopathies: Mechanisms of action and target engagement. *Nature Reviews Neurology*, *15*(11), 653–668. https://doi.org/10.1038/s41582-019-0254-2

159. Swanson, E., et al. (2023). Therapeutic synergy of combining aggregate-clearing biologics with brain-penetrant NLRP3 inflammasome inhibitors in neurodegeneration.

160. *Science Translational Medicine*, *15*(712), eadf8932. https://doi.org/10.1126/scitranslmed.adf8932

161. Zhang J, Yang N, Zou P, Zong X. Microglial checkpoint collapse in Alzheimer’s disease: a tri-axial framework for biomarker-informed neuroimmune therapy. Journal of Neuroinflammation. 2026 Jul 2.

162. Wang J, Gao Y, Chen Q, Xiong X, Miao S, Chen X, Tang Y, Gu L. Microglia mitochondrial metabolism in neurological diseases. Molecular Neurobiology. 2026 Jan;63(1):337.