

The NLRP3 inflammasome in Parkinson disease: Breaking a self-reinforcing neuroimmune circuit

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INTRODUCTION

Parkinson disease (PD) is defined by progressive loss of dopaminergic neurons in the substantia nigra and the accumulation of misfolded α -synuclein. Therapeutic development has traditionally focused on neuronal dysfunction and protein aggregation. However, neuroinflammation is increasingly viewed not simply as a consequence of degeneration, but as an active contributor to disease progression.

Among innate immune pathways implicated in PD, the NLR family pyrin domain-containing 3 (NLRP3) inflammasome has emerged as a potentially tractable therapeutic node. The complex consists of the NLRP3 sensor, the adaptor apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1. Its activation promotes caspase-1-dependent maturation of interleukin-1 β (IL-1 β) and IL-18, as well as gasdermin D-mediated pyroptosis. Experimental evidence suggests that NLRP3 activation links pathological α -synuclein to sustained microglial activation, inflammatory signalling and neuronal injury.

This relationship is relevant because α -synuclein pathology and inflammatory activity may amplify one another. NLRP3 may form part of a feed-forward circuit that sustains neuroinflammation and accelerates neurodegeneration. Interrupting this circuit may offer an opportunity for disease modification or, if applied early enough, disease interception—defined as blocking or delaying the conversion to clinical phenocopy during the prodromal phase, as distinguished from slowing progression in established disease.

Notably, the functions of NLRP3 in the central nervous system are highly cell-type-dependent: microglial NLRP3 primarily drives neuroinflammation, whereas neuronal NLRP3 serves as a parkin substrate and can drive dopaminergic neuron death independently of microglia. This review focuses on microglial NLRP3 as a more therapeutically accessible node.

A SELF-REINFORCING NLRP3- α -SYNUCLEIN CIRCUIT

Misfolded α -synuclein acts as an endogenous danger signal. α -synuclein preformed fibrils activate NLRP3-dependent inflammatory signaling in microglia, leading to caspase-1 activation and IL-1 β release.¹ Lysosomal injury, mitochondrial stress, reactive oxygen species and ionic imbalance are plausible upstream contributors, although their precise sequence remains incompletely resolved.

NLRP3 activation may in turn aggravate α -synuclein pathology. Active caspase-1 has been reported to cleave α -synuclein into aggregation-prone species. Pyroptotic cell death may release intracellular α -synuclein into the extracellular space, facilitating propagation within neural circuits. Inflammasome-associated cytokines could further impair proteostasis, mitochondrial function and synaptic integrity. Together, these processes establish a self-reinforcing circuit: pathological α -synuclein activates NLRP3, whereas NLRP3 activation promotes further α -synuclein aggregation, dissemination and neurotoxicity (Figure 1A).

This circuit differs from previous models in two aspects. First, it involves reciprocal causation and self-amplification: pathological α -synuclein activates NLRP3 and NLRP3-derived caspase-1 cleaves α -synuclein into aggregation-prone fragments while pyroptosis releases intracellular α -synuclein extracellularly—thus constituting a self-sustaining closed loop. Second, it supports a therapeutic logic of “upstream circuit interruption”: disrupting NLRP3 as the circuit hub simultaneously blocks both the inflammatory amplification and inflammation-driven dissemination of α -synuclein pathology, whereas targeting α -synuclein clearance or single cytokines alone may be insufficient if other nodes remain active. NLRP3 thus represents a critical gatekeeper that perpetuates neuroinflammation. Liu et al. describe this interaction as a core driver of PD progression.¹ Support comes from toxin-induced and α -synuclein-based models, although its relevance to human disease remains uncertain.

DIRECT INHIBITION AND NETWORK MODULATION

Selective NLRP3 inhibitors provide the most direct way to test this hypothesis (Figure 1B). MCC950, among the best-characterized compounds, has shown anti-inflammatory and neuroprotective effects in preclinical PD models, but its development was constrained by dose-dependent liver transaminase elevation in clinical trials. More recently, next-generation brain-penetrant inhibitors have emerged. MCC7840 (Inzomelid/Emlenoflast) has demonstrated favorable brain penetration and oral bioavailability in α -synuclein PFF mouse models, with efficacy even when administered after symptom onset, supported by PET-MRI biomarkers for non-invasive assessment of target engagement and treatment response in preclinical studies. Among these agents, OLT1177 (Dapansutril) is of particular translational interest for PD, having been evaluated clinically in non-neurological inflammatory disorders with an established safety profile. Its recent evaluation in α -synuclein-based PD models has yielded promising results.

In α -synuclein preformed-fibril propagation models and PLP- α -synuclein transgenic mice, chronic oral OLT1177 improved motor performance, reduced α -synuclein inclusions and gliosis, and attenuated nigral neurodegeneration.² Single-cell transcriptomic analyses further indicated partial reversal of disease-associated microglial signatures. Plasma IL-18 and neurofilament light chain were associated with pathological and functional outcomes, raising the possibility that they could serve as pharmacodynamic measures in early-stage trials.² Nonetheless, preclinical benefit does not establish disease modification in patients; central target engagement, durable efficacy and safety must be demonstrated in human studies.

Indirect modulation may offer complementary strategies. Microglia are a principal source of CNS NLRP3 activity, and their state is regulated by pharmacologically accessible receptors and stress-response pathways. Triggering receptor expressed on myeloid cells 2 (TREM2), a microglial receptor involved in phagocytosis and immune adaptation, is one such candidate. In an MPTP mouse model, TREM2 deficiency exacerbated dopaminergic neuronal loss and motor impairment, accompanied by increased NLRP3-associated signaling, cleaved caspase-1, IL-1 β and gasdermin D.³ Cell-based experiments implicated TLR4-MYD88-NF- κ B signaling. These findings suggest that TREM2 can restrain inflammasome-associated inflammatory and pyroptotic responses. Nevertheless, the net effect of TREM2 in PD is not uniform across disease stages: TREM2 promotes α -synuclein clearance in the early stage, whereas under chronic inflammatory conditions it may drive pro-inflammatory polarization of microglia, and its expression changes dynamically. Future TREM2-directed strategies should prioritize selective activation of its anti-inflammatory branches, as global enhancement or suppression may not achieve optimal outcomes.

DJ-1, encoded by *PARK7*, may represent another regulator of NLRP3 homeostasis. Best known for its roles in oxidative-stress responses and familial PD, DJ-1 was reported to bind NLRP3 and protect it from autophagy-lysosomal degradation in microglia.⁴ Accordingly, DJ-1 knock-down reduced NLRP3 abundance, caspase-1 maturation and IL-1 β secretion, without affecting NLRC4 or AIM2 inflammasomes, suggesting a context-dependent pro-inflammatory role for DJ-1. However, this role is not universal. DJ-1 functions are highly cell-type-dependent and stage-dependent: in neurons, DJ-1 exerts neuroprotective effects through ROS scavenging, Nrf2 activation and mitochondrial maintenance; loss-of-function mutations in *PARK7* cause early-onset PD, supporting its protective value in neurons. Within myeloid cells, DJ-1 may bidirectionally regulate NLRP3—suppressing NLRP3-activation under basal conditions, yet upon strong inflammatory stimulation, binding to NLRP3 shifts to protect it from degradation. Thus, simply inhibiting DJ-1 might attenuate inflammation in microglia but compromise neuronal antioxidant defenses. The optimal strategy may therefore be screening small molecules that specifically disrupt the DJ-1–NLRP3 binding interface, relieving NLRP3 stabilization without affecting DJ-1's

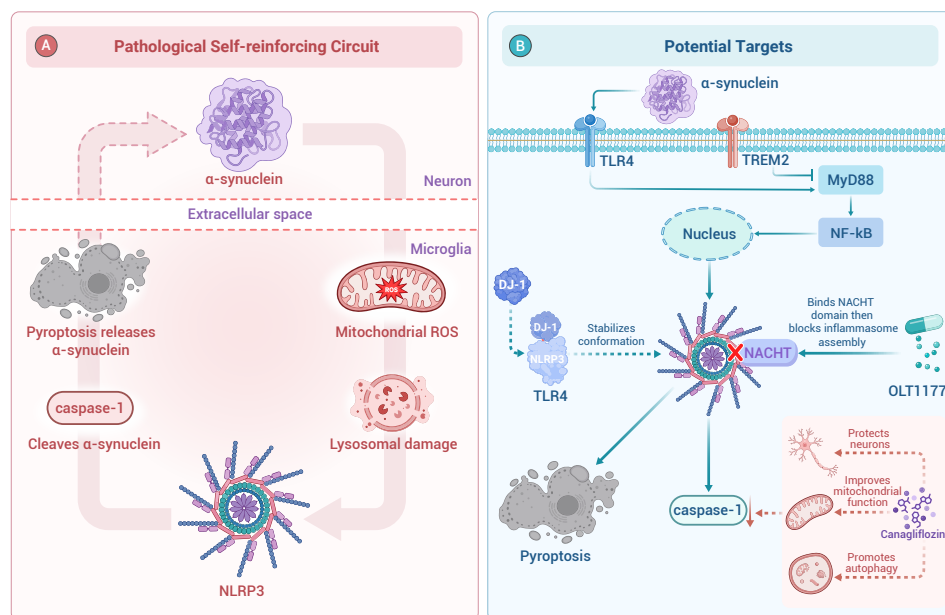


Figure 1. The NLRP3- α -synuclein self-reinforcing circuit in PD and its therapeutic modulation (A) Pathological Self-reinforcing Circuit. (B) Potential Targets.

suffice to interrupt establishment of the positive-feedback circuit, obviating lifelong maintenance dosing, whereas established PD requires more careful risk-benefit assessment.

(2) Cell-type-specific targeting. Microglial NLRP3 drives neuroinflammation, whereas neuronal NLRP3 can mediate cell death upon parkin dysfunction. Microglia-targeted delivery could relieve central inflammatory burden while preserving systemic immunity.

(3) Biomarker-guided dosing. Pharmacodynamic biomarkers such as IL-18 and NfL could facilitate individualized minimum effective dosing.

In summary, NLRP3 inhibition requires refined adjustment based on disease stage, cell type and biomarkers. Clinical development might begin with short-term prodromal intervention and biomarker-guided dose escalation,

protective functions.

Repurposed metabolic therapies may provide a less selective route to NLRP3 modulation. In a rotenone-induced rat model, the sodium-glucose cotransporter 2 inhibitor canagliflozin improved motor behavior and reduced levodopa-induced dyskinesia.⁵ These effects were accompanied by reduced nigral NLRP3 and caspase-1 expression, alongside changes in pathways related to autophagy, mitochondrial function, oxidative stress and dopaminergic neuronal maintenance. Such pleiotropy may be advantageous in a multifactorial disorder, but complicates attribution of benefit specifically to inflammasome inhibition.

FROM DISEASE MODIFICATION TO INTERCEPTION

The relevance of NLRP3 may extend beyond established PD. α -Synuclein pathology and inflammatory abnormalities can precede motor diagnosis by years. If NLRP3-dependent inflammation contributes to the early amplification of α -synuclein pathology, intervention during the prodromal phase may offer a more favorable therapeutic window than treatment after substantial nigrostriatal degeneration.

Realising this possibility will require biologically precise identification of individuals with prodromal α -synucleinopathy. α -Synuclein seed amplification assays, inflammatory mediators such as IL-18 and markers of neuronal injury such as neurofilament light chain may aid risk stratification and pharmacodynamic monitoring. No marker is likely to be sufficient alone; a multi-modal framework integrating clinical phenotype, α -synuclein status and measures of inflammatory activity will probably be necessary.

Trials in prodromal disease will also need feasible and biologically meaningful endpoints. Clinical phenoconversion remains essential, but requires long follow-up. Biomarker-guided enrichment, sensitive intermediate outcomes and adaptive trial designs could accelerate the evaluation of NLRP3-directed interventions.

CONCLUSIONS

The NLRP3 inflammasome occupies a potentially central position at the intersection of α -synuclein pathology, microglial activation and neuronal injury in PD. Its reciprocal relationship with pathological α -synuclein explains how inflammation becomes self-sustaining and contributes to progressive neurodegeneration. Direct NLRP3 inhibition and targeting regulators such as TREM2 and DJ-1 provide complementary avenues. Major challenges remain: establishing relevance in human PD, selecting appropriate populations, demonstrating central target engagement and ensuring long-term safety.

As NLRP3 is essential to antimicrobial host defense, sustained systemic inhibition warrants particular caution. Balancing therapeutic benefit against the risk of systemic immunosuppression is a central translational challenge. Future strategies should consider:

(1) Timing. Short-term pulse administration in the prodromal phase may

rather than long-term fixed-dose trials in the general PD population.

NLRP3 targeting nevertheless exemplifies a broader shift from a predominantly neuron-centered view towards recognizing neuroimmune dysfunction as integral to PD biology. The key question is not simply whether inflammation accompanies PD, but whether disruption of specific neuroimmune circuits early enough can alter its trajectory.

REFERENCES

- Liu, K., He, Z., Zhang, L. et al. (2026). The NLRP3- α -Synuclein Circuit: A Core Driver and Therapeutic Target in Parkinson's Disease. *J. Inflamm. Res.* **19**:1–17. DOI:10.2147/JIR.S597280
- Luque, M., Matic, M., Heras-Garvin, A. et al. (2026). Clinically advanced NLRP3 inhibitor modulates microglial transcriptome and alleviates α -synuclein-induced progression of parkinsonism. *J. Neuroinflammation* **23**:76. DOI:10.1186/s12974-026-03716-3
- Huang, P., Zhang, Z., Zhang, P. et al. (2024). TREM2 Deficiency Aggravates NLRP3 Inflammasome Activation and Pyroptosis in MPTP-Induced Parkinson's Disease Mice and LPS-Induced BV2 Cells. *Mol. Neurobiol.* **61**:2590–2605. DOI:10.1007/s12035-023-03713-0
- Miao, Q., Wang, T., Wang, H. et al. (2025). Loss of DJ-1 alleviates microglia-mediated neuroinflammation in Parkinson's disease via autophagy-lysosomal degradation of NLRP3. *Front. Immunol.* **16**. DOI:10.3389/fimmu.2025.1656729.
- Abdelaziz, A. M., Rasheed, N. O. A., Zaki, H. F. et al. (2025). Canagliflozin attenuates neurodegeneration and ameliorates dyskinesia through targeting the NLRP3/Nurr1/GSK-3 β /SIRT3 pathway and autophagy modulation in rotenone-lesioned rats. *Int. Immunopharmacol.* **146**:113839. DOI:10.1016/j.intimp.2024.113839

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AUTHOR CONTRIBUTIONS

C.Y.A. drafted the manuscript. Y.Y.L. and J.L. reviewed and edited the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.