

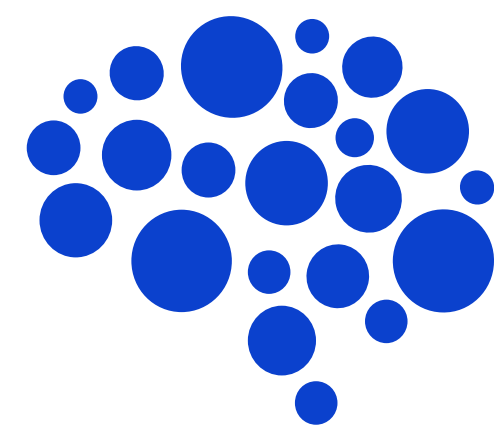
Investigating the role of the NLRP3 inflammasome in the pathogenesis of Alzheimer's disease



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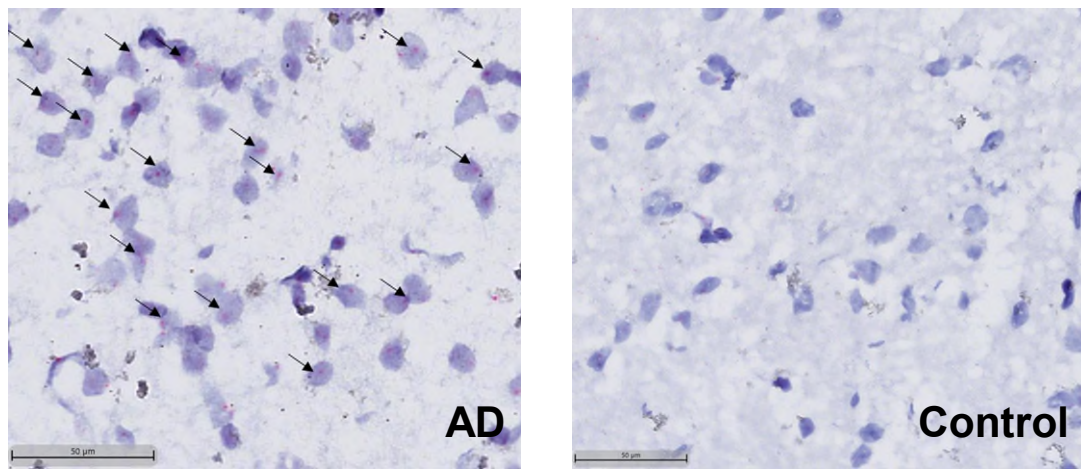
What does this mean for the Alzheimer's disease (AD) community?

- The NLRP3 inflammasome plays a key role in the pathogenesis of AD, amplifying damage-induced inflammatory signalling and linking amyloid and tau pathologies to the neurodegenerative cascade¹⁻³
- NLRP3 represents a promising therapeutic target that has the potential to modulate both amyloid and tau pathology and thereby prevent neurodegeneration in AD

Background

- The NLRP3 inflammasome is a multiprotein sensor of cellular stress and damage in myeloid cells, including microglia, that amplifies inflammatory signalling and drives chronic cellular degeneration¹⁻³
- Post-mortem studies show enhanced expression of NLRP3 in the brains of people with AD (**Figure 1**), suggesting that NLRP3 may play a role in AD pathogenesis^{4,5}

Figure 1. NLRP3 mRNA in the temporal cortex.⁴



- In this study, we used human *in vitro* cellular models to investigate the role of NLRP3 in AD pathogenesis

Methodology

Effect of amyloid-beta (Aβ) on NLRP3 activation *in vitro*

- Lipopolysaccharide (LPS)-primed THP1 cells were used to evaluate the effects of varying Aβ species (monomers, oligomers and fibrils) on NLRP3 activation and cell death
- Nigericin, an antibiotic known to induce NLRP3 activation,⁶ was used as a positive control in THP1 cells to evaluate the effects of Aβ species
- NLRP3 activation was assessed by measuring levels of interleukin (IL)-1β
- Cell death was assessed using propidium iodide (PI) staining

Effect of the NLRP3 inflammasome on tau phosphorylation *in vitro*

- The effects of NLRP3 expression on tau phosphorylation were assessed in H4 cells using a tetracycline-controlled transcriptional activation (T-REx™) system, in which tau overexpression is induced by doxycycline

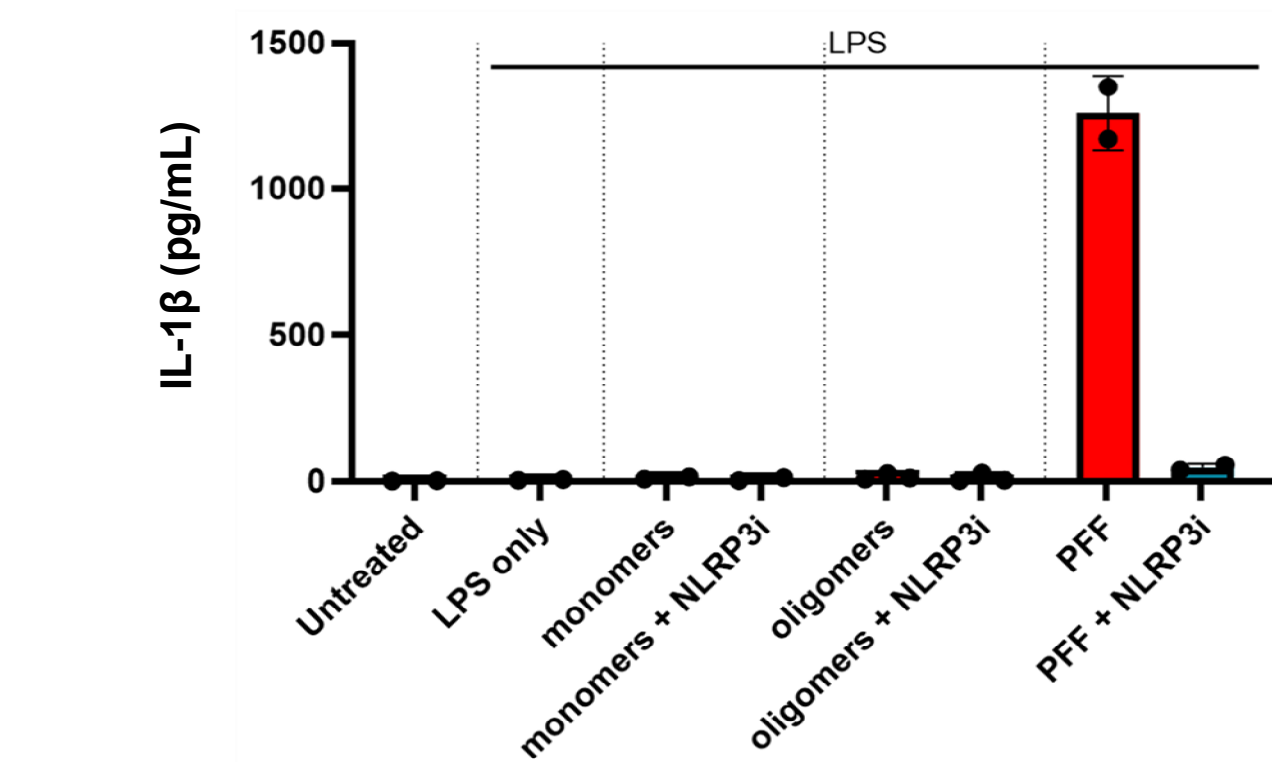
Results

Effect of Aβ on NLRP3 activation *in vitro*

- Of the Aβ species evaluated, only preformed fibrils (PFF) induced NLRP3 activation (**Figure 2**)

Results cont.

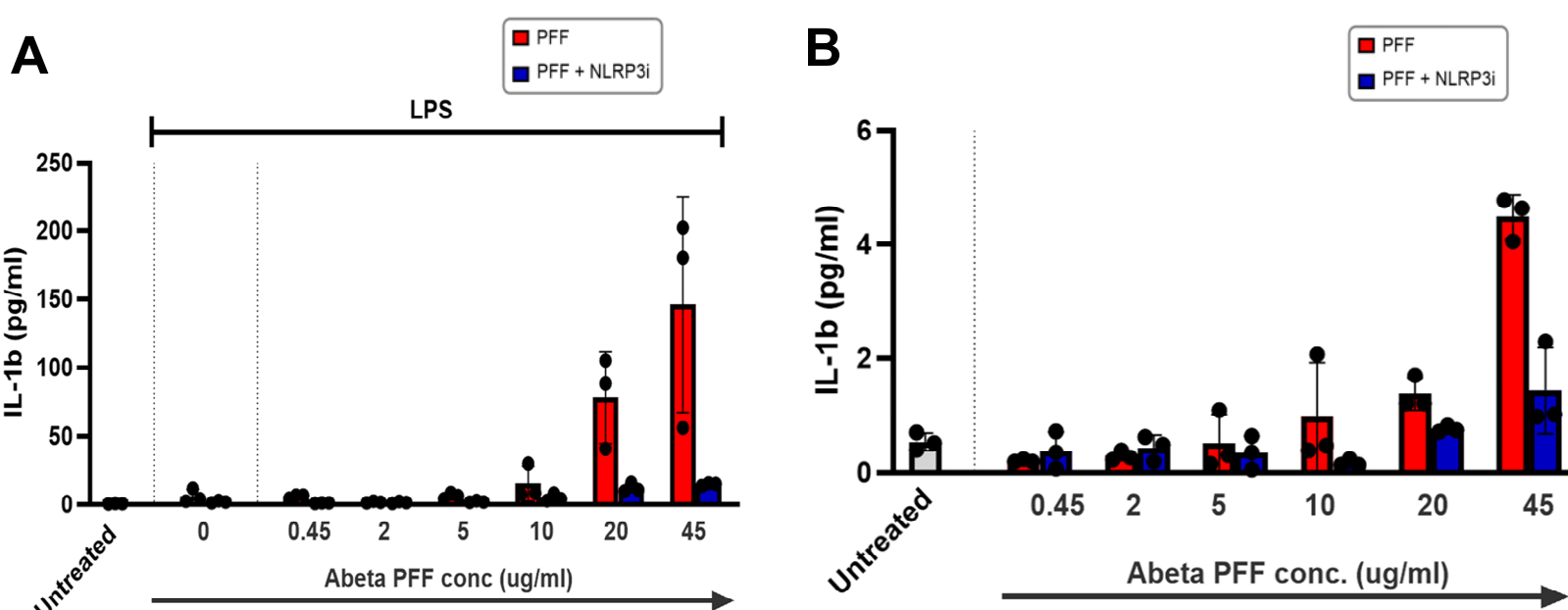
Figure 2. Effect of various Aβ species on NLRP3 activation.



NLRP3i, NLRP3 inhibitor.

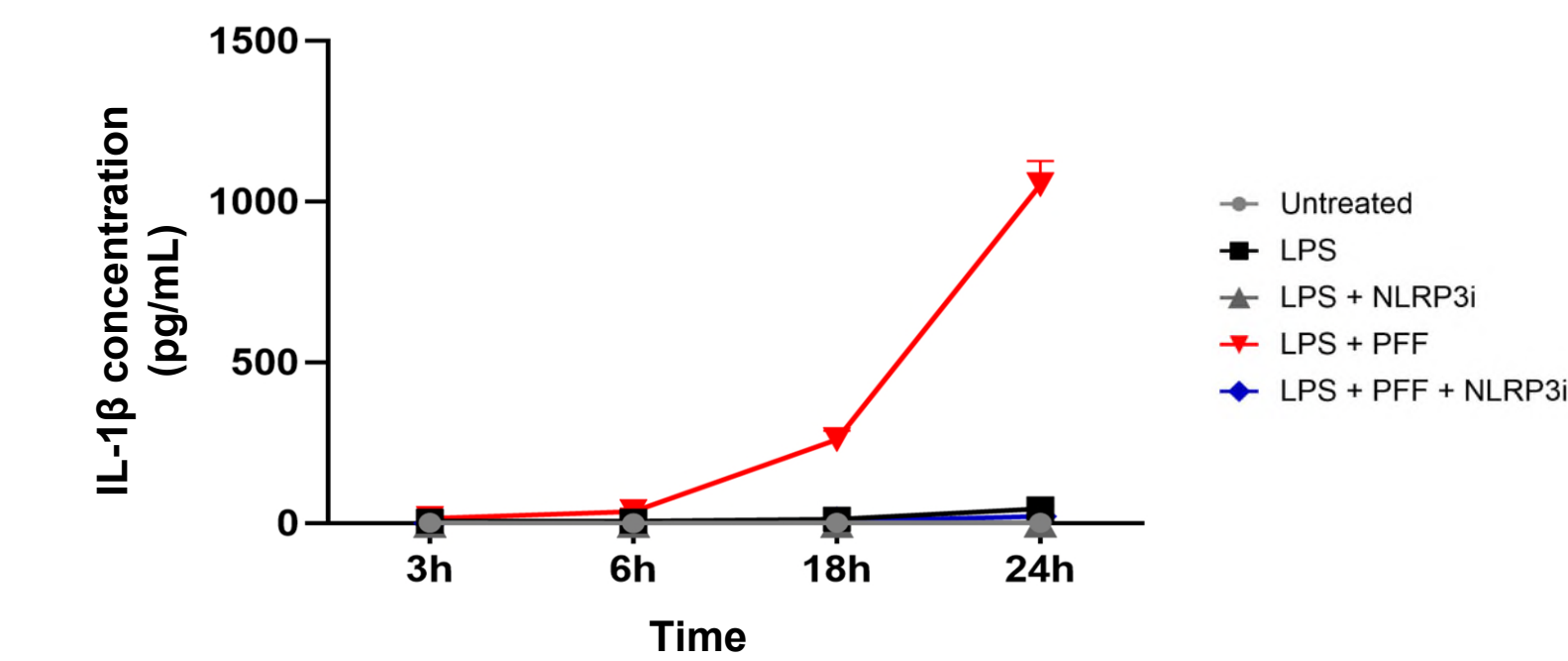
- Aβ-PFF-induced NLRP3 activation was dose dependent and occurred independently of LPS priming in THP1 cells (**Figure 3**)

Figure 3. Effect of PFF concentration on NLRP3 activation in THP1 cells A) with LPS priming and B) without LPS priming.



- IL-1β release was delayed following exposure to PFF, suggesting that the release is driven by cumulative cellular damage rather than rapid ion flux (**Figure 4**)

Figure 4. Release of IL-1β over time after PFF exposure.



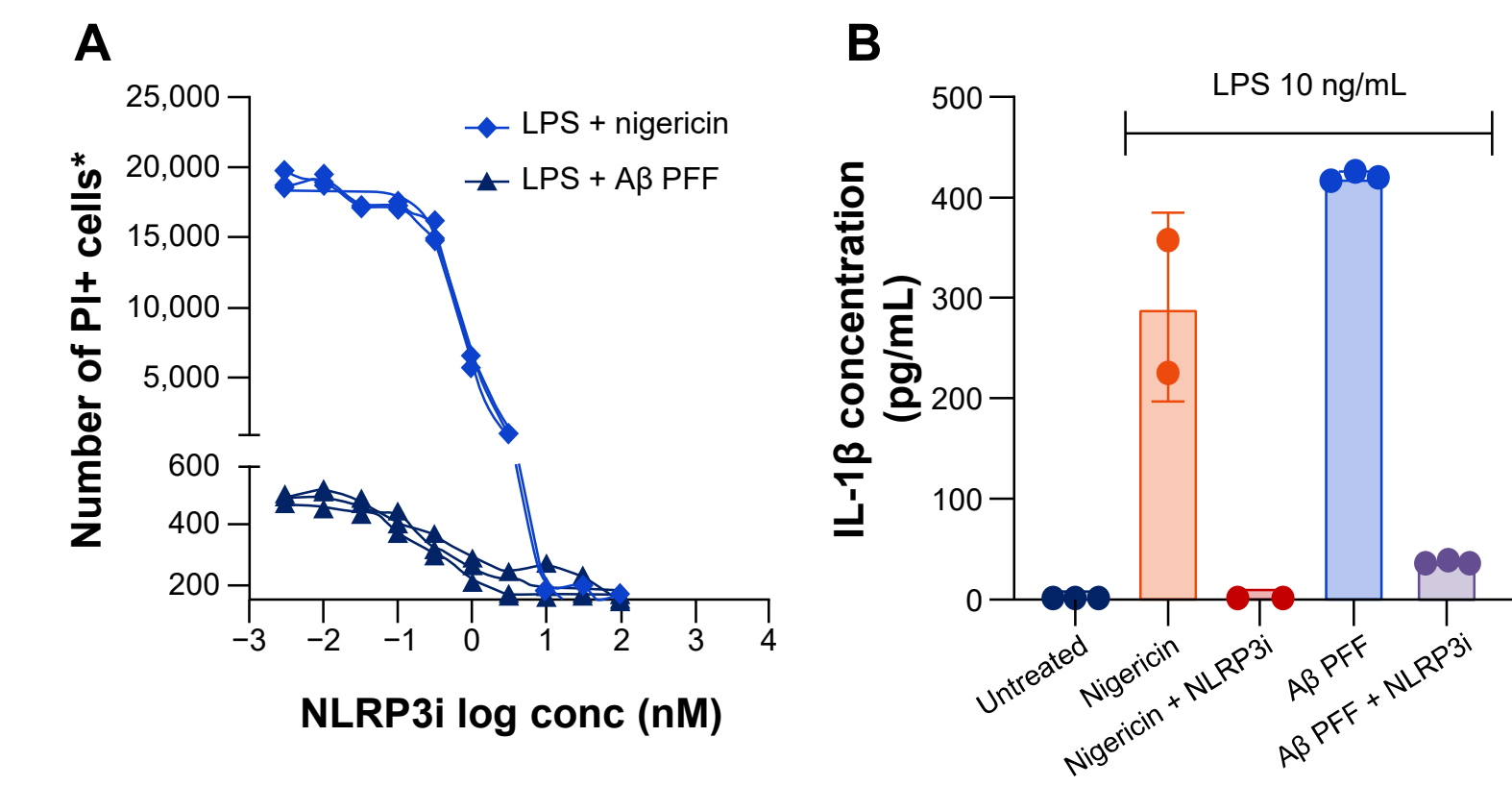
Conclusions

- NLRP3 is a mechanistic link between amyloid and tau pathologies driving neurodegeneration in AD:
 - Aβ fibrils activate NLRP3 in myeloid cells
 - Aβ fibrils-induced IL-1β and IL-18 release is blocked by NLRP3 inhibition
 - NLRP3-driven inflammatory signalling enhances tau phosphorylation
- Targeting the NLRP3 pathway offers a potential avenue to decouple Aβ accumulation from the subsequent neurodegenerative cascade

Results cont.

- Exposure to Aβ PFF induced similar levels of IL-1β release but lower levels of cell death than exposure to nigericin in THP1 cells (**Figure 5**)

Figure 5. Effect of 1-hour exposure to nigericin vs 24 hours of Aβ PFF on A) cell number and B) IL-1β concentration.



*Normalised to LPS alone.

Inhibition of NLRP3

- In THP1 cells exposed to Aβ PFF, the addition of an NLRP3i reduced Aβ PFF-induced IL-1β and IL-18 release (**Figure 6**; **Table 1**)
- Similar potencies were observed across stimuli and outcome measures

Figure 6. Inhibition of NLRP3 activation with a NLRP3i in THP1 cells exposed to Aβ PFF.

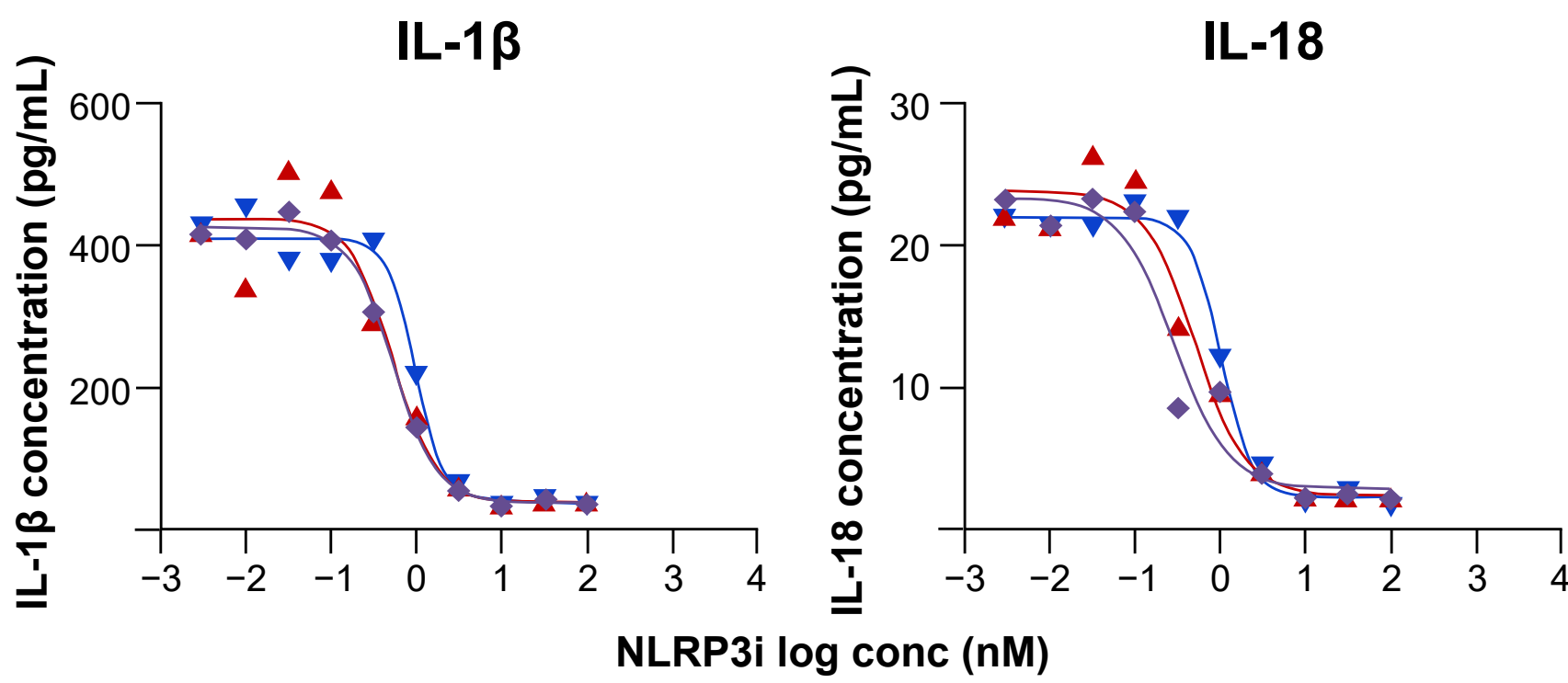


Table 1. Potency of NLRP3 inhibitor tool compound blocking nigericin or Aβ PFF-induced IL-1β and IL-18 release.

IC ₅₀ (nM) in THP1 cells	IL-1β	IL-18	Cell death*
Aβ PFF	0.55	0.66	0.27
Nigericin	0.73	1.03	0.71

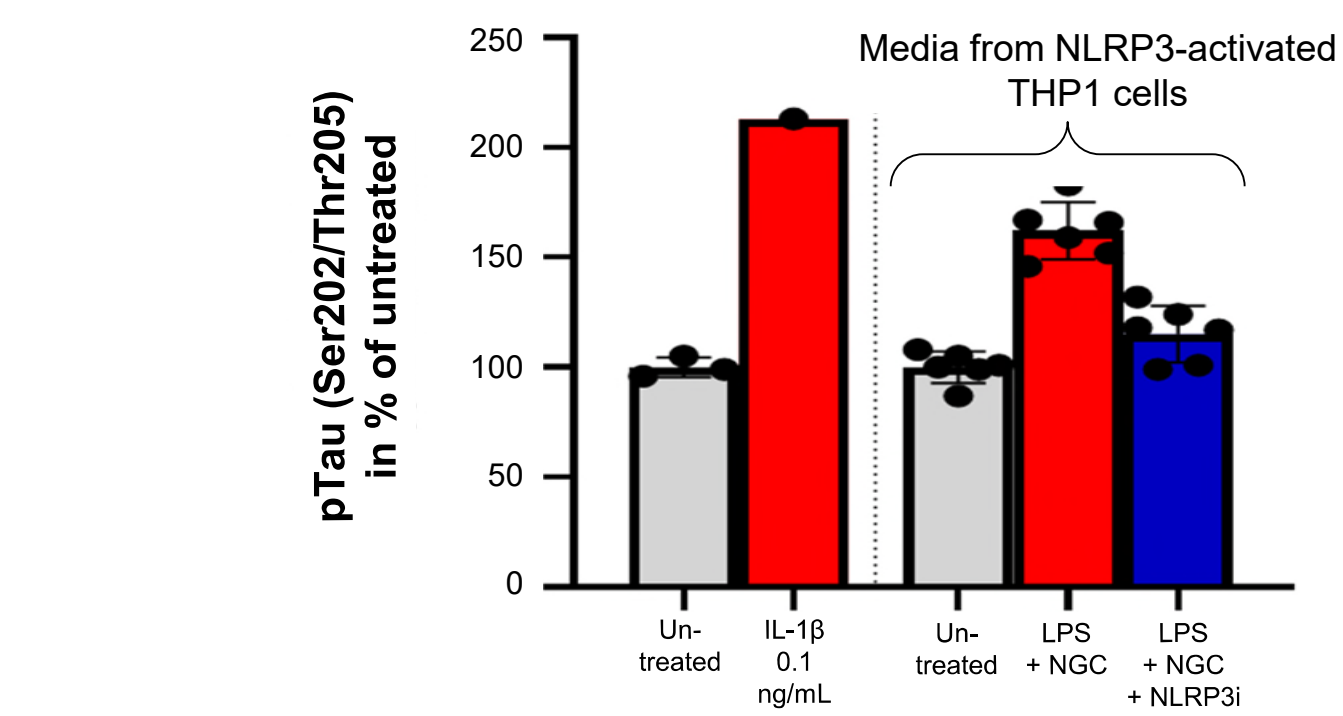
*Cell death was assessed using PI staining.

Results cont.

Effect of NLRP3 on tau phosphorylation *in vitro*

- In H4 cells, exposure to IL-1β or conditioned media from NLRP3-activated THP1 cells resulted in increased tau phosphorylation at 48 hours post-exposure (**Figure 7**)

Figure 7. Tau phosphorylation at 48 hours post-exposure to IL-1β or media from NLRP3-activated THP1 cells.

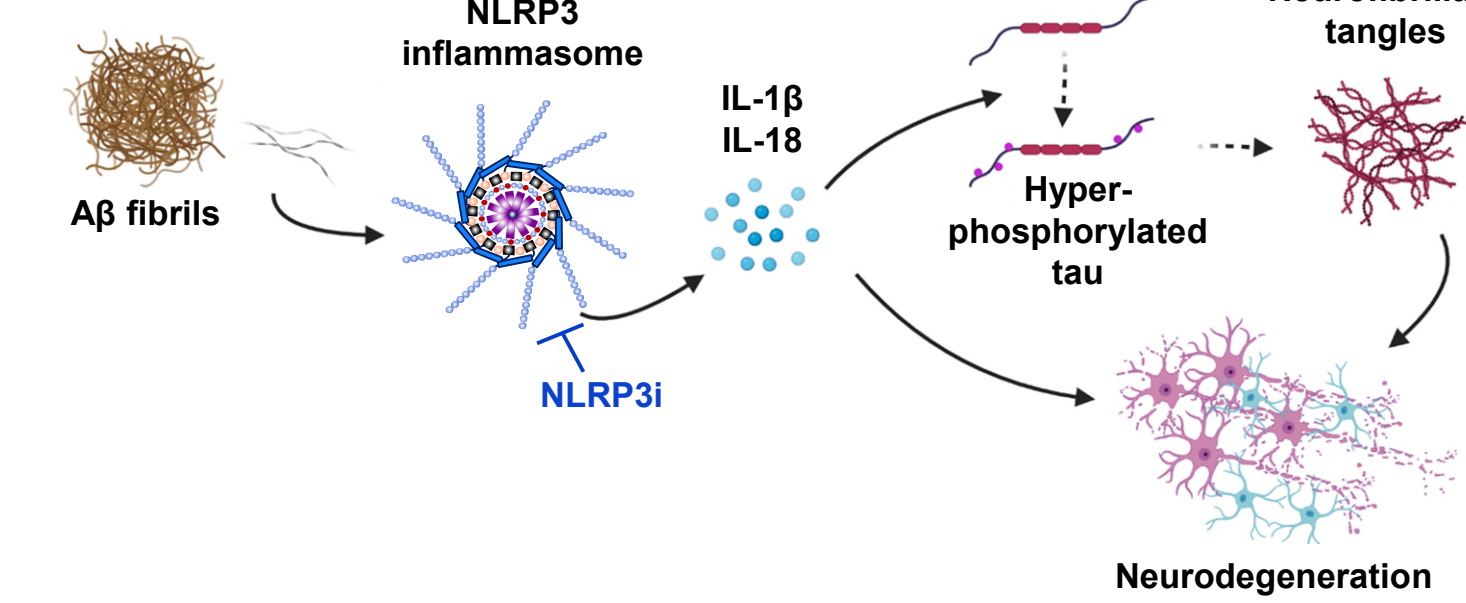


NGC, nigericin.

Discussion

- These results suggest that NLRP3 acts as a mechanistic link between amyloid and tau pathologies, driving neurodegeneration in AD (**Figure 8**)

Figure 8. NLRP3 as a link between amyloid and tau pathologies in AD.



- Our results add to existing evidence to demonstrate that:
 - Aβ fibrils activate NLRP3 in myeloid cells, leading to the release of IL-1β and IL-18^{7,8}
 - The effects of Aβ fibrils are fully blocked by NLRP3 inhibition^{7,8}
 - NLRP3-driven inflammatory signalling enhances tau phosphorylation, suggesting NLRP3 can act as central link between amyloid and tau pathologies⁹
- Exploration is ongoing in human triculture and organoid systems to assess the effects of NLRP3 activation on tau phosphorylation and neurofilament light chain release

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Disclosures

- GP, EM, EP, BZ, VM, SK, SA, LT, LK, NMM and GAK are employees of and own stock options in F. Hoffmann-La Roche Ltd

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