

HW6b - ABSTRACT

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Alzheimer's Disease (AD)
Soluble Toxic α -Sheet Oligomers Induce Microglial NLRP3 Inflammasome Activity in Alzheimer's Disease
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Abstract (< 250 words)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by fibrillar amyloid- β (A β) plaque accumulation. These A β fibrils are known to activate the NOD-like receptor and pyrin domain-containing 3 (NLRP3) inflammasome in microglia, inducing a neuroinflammatory immune response. However, A β fibrils themselves are not implicated in cognitive dysfunction. Instead, newly discovered toxic soluble, oligomeric A β are responsible. Shea, et al. characterized the A β oligomers using SH-SY5Y neuroblastoma cells. They then confirmed a method of inhibition using transgenic APPsw mice that highly express human A β , *C. elegans* strain CL4176, and a *C. elegans* model with GFP-labeled endosomes. They elucidated a unique secondary α -sheet structure that could be targeted specifically by *de novo* synthesized α -sheet peptides. These designed α -sheet peptides also inhibited cytotoxicity and aggregation *in vivo* and can be used in future diagnostic and therapeutic tools. Lučiūnaitė, et al. were interested in further determining molecular effects of the A β oligomers and protofibrils on microglia and investigated the NLRP3 inflammasome using a microglial cell culture created from neonatal C57BL/6 (WT) mice. They found an increase in 'ASC speck' formation, caspase-1 activation, and IL-1 β secretion in the cells treated with A β oligomers and protofibrils. This indicates toxic A β oligomers activated the NLRP3 inflammasome and may upregulate innate immune responses prior to the deposition of plaque, instigating further neuropathological activity. Together, these discoveries provide a starting point and method of tracking soluble, toxic A β oligomers to further elucidate the molecular mechanisms through which A β oligomers interact with the immune system in AD.

References

- (1) Shea D, et al. 2019. α -Sheet secondary structure in amyloid β -peptide drives aggregation and toxicity in Alzheimer's disease. PNAS [Internet]. 116 (18): 8895-8900. Available from: <https://doi.org/10.1073/pnas.1820585116>
- (2) Lučiūnaitė A, et al. 2019. Soluble A β oligomers and protofibrils induce NLRP3 inflammasome activation in microglia. J. Neurochem [Internet]. 00:e14945. Available from: <https://doi.org/10.1111/jnc.14945>.