Extracellular ASC Level as a Potential Biomarker for Alzheimer's Disease

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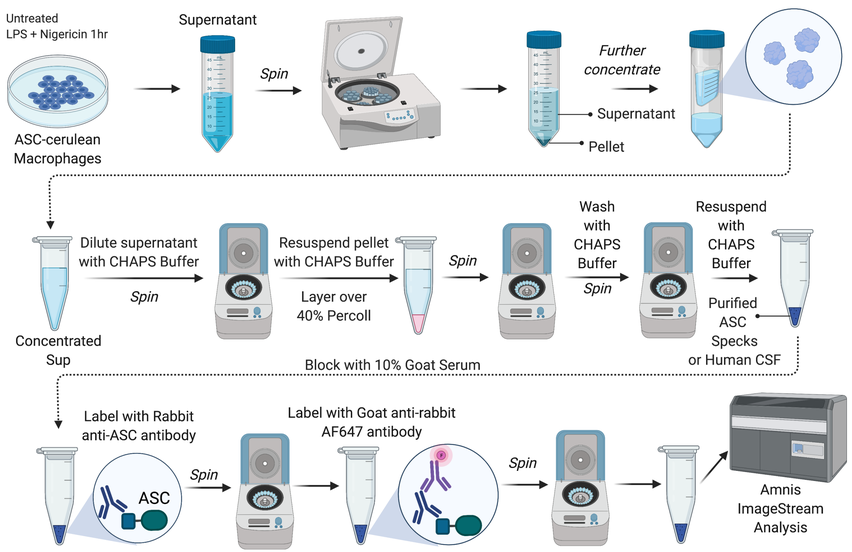
Background

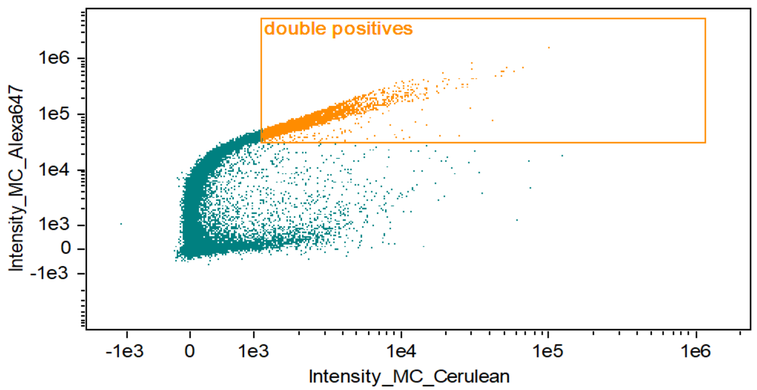
There is mounting evidence of a link between pathological tau (p-tau) and neuroinflammation in a group of neurodegenerative diseases named tauopathies including Alzheimer's Disease (AD). [1,2] In our previous studies, we found that p-tau can induce neuroinflammation through activating inflammasomes, a multi-protein complex that can recognize a variety of danger signals such as bacterial toxins like lipopolysaccharide (LPS), nigericin and endogenous danger signals such as extracellular ATP and p-tau. [3] We aim to obtain quantitative measurements of activated inflammasomes, specifically the levels of ASC (apoptosis-associated speck-like protein containing a CARD) specks, a key adaptor protein of inflammasomes, in the Cerebrospinal Fluid (CSF) samples of AD patients.

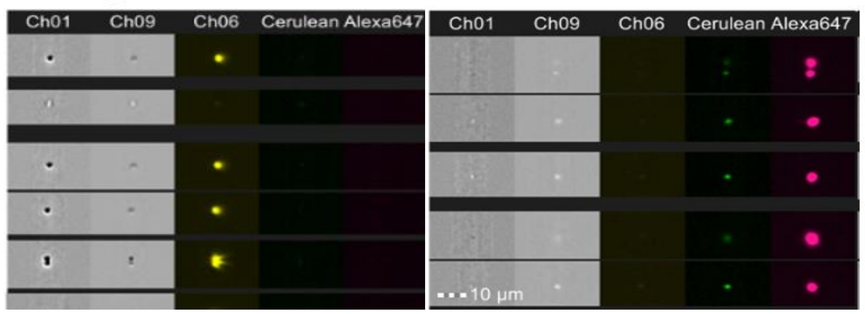
Methods



Results

ASC specks released by immortalized mouse macrophages that constitutively express ASC conjugated to the fluorescent protein cerulean

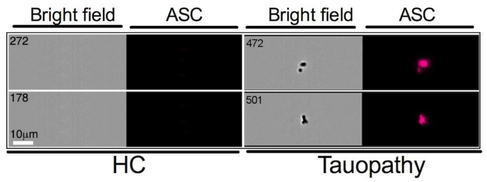


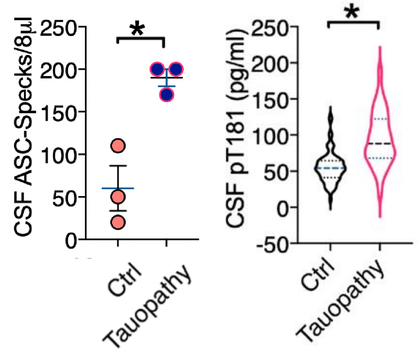


Untreated

Treated with LPS 3hr + Nigericin 1hr

ASC specks in CSF samples of healthy control and patients with tauopathies





Conclusions

Our results indicate Amnis can be used for detecting extracellular ASC specks. We also found there are more extracellular ASC specks in AD CSF samples compared to healthy controls. These results suggest that differential levels of ASC specks in extracellular environments including CSF may correlate with the disease severity and serve as a biomarker for AD and related dementia, which needs further investigation.

Future Directions

Experiments involving various negative controls will be performed to standardize accurate ASC level measurements. Correlation between ASC levels and disease progression will be further investigated.

References

1. Bhaskar K, Maphis N, Xu G, Varvel NH, Kokiko-Cochran ON, Ransohoff RM, Herrup K and Lamb BT (2014). Microglial-derived tumor necrosis factor alpha drives Alzheimer's disease-related neuronal cell cycle events. Neurobiology of Disease 62:273-85. (IF: 5.624) PMID: 24141019; PMCID: PMC3877710.
2. Maphis, N, Xu, G, Kokiko-Cochran, ON, Cardona A, Ransohoff RM, Lamb BT and Bhaskar K (2015). Reactive microglia drive tau pathology and contributes to the spreading of pathological tau in the brain. Brain Jun;138(Pt 6):1738-55. doi: 10.1093/brain/awv081. PMID: 25833819. PMCID: PMC4542622.
3. Jiang S, Maphis N, Binder J, et al. Proteopathic Tau Primes and Activates Interleukin-1ß(Il-1ß) via MyD88- and NLRP3-ASC-Inflammasome Dependent Pathways. SSRN Electron J. Published online May 8, 2019. doi:10.2139/ssrn.3379896

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