Role of Amyloid Responsome in Amyloid Aggregation

[1]Yona Levites, [1]Yong Ran, [1]Farhana Afroz, [1]Kyu Hwan Shim, [1]Xuefei Liu, [1]Mihir Beheray, [1]Cindy Hillah, [1]Danny Ryu, [2]Joshna Gadhavi, [3]Stefan Prokop, [2]Nicholas Seyfried, [1]Todd Golde

[1]Department of Pharmacology and Chemical Biology and [2]Department of Biochemistry, Center for Neurodegenerative Disease, Emory University School of Medicine, Atlanta, USA
[3] Department of Pathology, College of Medicine, University of Florida, Gainesville, FL, USA

Proteomic and biomarker research reveals that Alzheimer's disease (AD) involves complex brain changes across all cell types, culminating in organ failure. Cross-species comparisons of brain proteomes, including AD patients and Aβ-depositing mice, have identified a conserved Aβ amyloid responsome. A key network, M42, contains proteins that accumulate in plaques, cerebrovascular amyloid (CAA), and dystrophic neurites, marking them as potential therapeutic targets. According to the "amyloid scaffold" hypothesis, Aβ aggregation alone may not cause neurodegeneration unless accompanied by the buildup of amyloid-associated proteins (AAPs). Prior studies showed that overexpressing M42 proteins like midkine and pleiotrophin increases amyloid deposition. Building on this, we tested the effects of additional M42 proteins—Vtn, Sdc4, and Smoc1—by overexpressing them in CRND8 mouse brains via AAV delivery. Mice receiving these constructs showed robust gene expression and a striking reduction in amyloid deposition. The overexpressed proteins also influenced APP processing and Aβ aggregation in distinct ways, underscoring the complex role of M42 proteins in AD pathogenesis. This work highlights the intricate molecular landscape of AD, validates five key proteins involved in disease progression, and supports the hypothesis that Aβ acts as a scaffold for bioactive proteins that modulate degeneration. Continued multi-omics research and broader disease modeling are needed to further elucidate amyloid-driven mechanisms and uncover new therapeutic strategies.

Sponsored By: grant from NIH R01AG074569

Presenter Name and contact information:
Yona Levites, PhD, Associate Professor
Department of Pharmacology and Chemical Biology
Center for Neurodegenerative Disease
Emory College of Medicine
yona.levites@emory.edu