**Regulation of cell distancing in peri-plaque glial nets by Plexin-B1 affects glial activation and amyloid compaction in Alzheimer’s disease**

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**Presenter:** Wei-Hsiang Hsu **Date/Time:** 2024-12-19, 16:10-17:00

**Commentator:** Chun-Hsien Chu, PhD **Location:** Room 601, Med College Building

**Background** Alzheimer’s disease is the most common neurodegenerative disease, in which our brain is burdened with amyloid plaques and neurofibrillary tangles. It takes years to develop, first with mild cognitive disorder (MCI), yet after which it accelerates to full disease. Therapeutic targets include the production and processing of the amyloid precursor (APP), the amyloid fibrils as they aggregate, and the neuroglia which we may augment to defy the pathology. Nevertheless, those glia’s interactions are convoluted.

Genetic network studies utilizing genomic and transcriptomic data have identified for late-onset Alzheimer’s disease a central gene Plexin-B1 in astrocytes. Thanks to the MSBB and the ROS-MAP cohorts, this plexin was found among the top induced genes even in the early stages. Plexin-B1 is an axon guidance receptor on astrocytes, guiding development and regeneration by their semaphorin ligands on neurons. Its intracellular Ras-GAP (GTPase-activating) domain signals through Ras and Rap small GTPases to control cytoskeletal dynamics and cell adhesion.

**Objective** To explore Plexin-B1’s function in CNS pathology.

**Results** *APP/PS1* base model was chosen, whose human familial AD variants of both genes start amyloid deposition at 6 weeks of age. ***Plxnb1*** KO model was done through lacZ-IRES-PLAP insertion in its locus, such that its promoter activity can be seen with X-gal. By way of RNAscope ISH and IF staining, it was found that in the KO mice, peri-plaque glial nets were much more compact, with closer astrocyte spacing, fewer surrounding layers, and more astrocytic processes extending toward and into the cores.

Then, single-cell transcriptomics found overall augmented cell-cell communications in both ways between astrocytes and microglia, as well as downregulated genes associated with tissue inflammation and damage in both glia, in *Plxnb1* KO mice. By culturing *Plxnb1*-/- cells, astrocytes in the KO group were found to aggregate more readily in the hanging drop aggregation assay and not to shape microglial patterning in a co-culture experiment. Finally, induced astrocytes from human iPS cells with *PLXNB1* KO using CRISPR-Cas9 were used to mirror this result in a co-culture with WT human microglia.

**Conclusion** A proper glial response to amyloid deposition is that which compacts the amyloid. From a biochemical principle we know that more surface area allows Aβ fibrils to involve more proteins in incorrect folding. It’s exciting to know one such gene that does regulate the response and that poses a therapeutic potential.