Therapeutic potential of targeting FABP7 in a mouse model of Alzheimer's disease

Haylee L. Hamilton[1], Rachel S. Becker[1,2], Matteo T. Meyer[1], Sandhya Ramachandran[1,2], Caelan Wright[1,3], Marcelo R. Vargas[4], Mariana Pehar[1,5]

[1] Division of Geriatrics and Gerontology, Department of Medicine; [2] Neuroscience Training Program; [3] Cellular and Molecular Pathology Program; [4] Department of Neurology, University of Wisconsin Madison; and [5] Geriatric Research Education Clinical Center, William S. Middleton Memorial Veterans Hospital.

Multiple lines of evidence indicate that the activation of inflammatory processes has an early and important involvement in Alzheimer's disease (AD) pathology. However, clinical trials with anti-inflammatory agents have so far failed to show conclusive results. We previously showed that fatty acid-binding protein 7 (FABP7) upregulation induces a proinflammatory phenotype in primary mouse astrocytes and in iPSC-derived human astrocyte cultures. In addition, FABP7 is upregulated in the brain of AD patients and mouse models, most prominently in astrocytes surrounding amyloid plaques. Furthermore, we observed that astrocytes expressing higher levels of FABP7 display higher expression of inflammatory markers. Here, we evaluated the therapeutic potential of targeting FABP7 in APP/PS1 mice, a widely used AD mouse model. Using a viral vector approach to specifically knockdown FABP7 expression in astrocytes we observed that the downregulation of astrocytic FABP7 expression decreases astrocyte and microglia reactivity in the brain of APP/PS1 mice. This effect was particularly evident in the vicinity of amyloid plaques. Moreover, we observed a significant downregulation in the expression of inflammatory markers in astrocytes. Although we did not observe a significant effect on amyloid pathology (area occupied by amyloid plaques and size of the plaques), the downregulation of FABP7 in astrocytes attenuated the accumulation of phosphorylated-Tau in neurons and dystrophic neurites. Lastly, we observed beneficial effects of astrocytic FABP7 downregulation in the cognitive performance of APP/PS1. Collectively, our findings support the therapeutic potential of targeting astrocytic FABP7 to reduce the deleterious effects of chronic neuroinflammation observed in AD.

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Presenter Name and contact information:

Mariana Pehar, Ph.D.
Department of Medicine, Division of Geriatrics and Gerontology, University of Wisconsin-Madison; Geriatric Research Education and Clinical Center (GRECC), Madison VA Hospital, Madison WI 53792
Phone: (608) 265-8140
Email: mapehar@medicine.wisc.edu