Silencing astrocytic FABP7 mitigates neuroinflammation via down-regulation of NF-kB-mediated signaling.

Mariana Bresque[1], Daniel Esteve[1], Garret Balmer[1], Haylee L. Hamilton[2], Joshua S. Stephany[1] Mariana Pehar[2,3], Marcelo R. Vargas[1]

[1] Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA.

[2] Division of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin-Madison, Madison, WI, USA.

[3] Geriatric Research Education Clinical Center, Veterans Affairs Medical Center, Madison, WI, USA.

Fatty acid binding proteins (FABPs) are a family of small proteins involved in the subcellular trafficking of fatty acids (FAs). In the adult central nervous system, FABP7, a member of this family, is highly expressed in astrocytes and plays roles in lipid metabolism, gene expression regulation, and energy homeostasis. We previously identified the upregulation of FABP7 in reactive astrocytes in models of Alzheimer's disease and amyotrophic lateral sclerosis and demonstrated that FABP7 overexpression in astrocyte cultures elicits a pro-inflammatory phenotype that is toxic to co-cultured neurons. In this study, we investigated the role of FABP7 in regulating astrocyte-driven neuroinflammation. Using both primary murine and iPSC-derived human astrocyte cultures, we demonstrate that FABP7 knockdown significantly attenuates NF–κB activation and reduces astrocyte-mediated toxicity toward motor neurons following inflammatory stimulation. Extending these findings *in vivo*, astrocyte-specific FABP7 knockdown in a systemic LPS endotoxemia model attenuated cortical glial activation. Whole transcriptome RNA sequencing of the cortex revealed a distinct inflammatory profile characterized by reduced expression of astrocyte activation markers and diminished NF–κB–dependent transcription. Strikingly, this astrocytic modulation also corresponded with a shift toward a less reactive microglial phenotype. Collectively, our results suggest that FABP7 plays a key role in astrocyte-mediated neuroinflammation and highlight its potential as a therapeutic target for mitigating inflammatory responses in the central nervous system.

Sponsored By: NIH grants R01NS122973 and R01NS089640.

Presenter Name and contact information:
Mariana Bresque, Ph.D., Postdoc.
Department of Neurology
UW
Madison, Wisconsin, USA
Email: toledo@neurology.wisc.edu