

MR1/MAIT Cell Axis Impacts Innate Immunity and Synaptic Proteins in 5XFAD Mice

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Background:

Amyloid beta (A β)-induced synaptic dysfunction and inflammation are features of Alzheimer's disease (AD). One contributor to inflammation is mucosal-associated invariant T (MAIT) cells, an innate T cell that recognizes antigens presented by the MR1 molecule. Previously, we found increased MR1 expression in microglia near plaques and the loss of MR1/MAIT cell axis slowed the progression of A β pathology. This study aimed to determine contributions of the MR1/MAIT cell axis to immunity and synaptic proteins in the 5XFAD AD model mouse.

Methods:

We crossed 5XFAD mice with MR1-deficient mice (which lack MR1 and MAIT cells). At 2-, 4-, 6-, and 8-months of age, hippocampal and cortical brain tissue from wild-type, MR1KO, 5XFAD, and 5XFAD/MR1KO mice were analyzed by Western blot. Protein levels were analyzed with antibodies against GFAP (astrocytes), complement C3, and postsynaptic density protein (PSD)95. Additionally, Novel Object Recognition, Open Field, and Barnes Maze behavioral tests were performed in the 5XFAD mice to measure memory deficits.

Results:

Region-specific results were obtained for the hippocampus and cortex. The expression levels of PSD95 and C3 were significantly upregulated in the hippocampus of 5XFAD/MR1KO compared to 5XFAD mice at 6-8 months of age; in the cortex, GFAP levels were also significantly increased in 5XFAD/MR1KO mice. Finally, compared to wildtype C57BL/6 mice, 5XFAD mice showed memory deficits.

Conclusions and Potential Impact:

Approximately 6.7 million Americans are living with AD. This number is expected to double by 2050. Without any currently demonstrated therapy against AD, there is a need for therapeutic target(s) as part of novel treatment paradigms. Our results demonstrate an impact of the MR1/MAIT cell axis on postsynaptic proteins and consequent AD pathology. Thus, understanding the contribution of this axis could help reveal the role of innate immunity in AD and potentially serve as a future therapeutic target in AD patients.