What does TREM2 tell us about the role of microglia and inflammation in Alzheimer’s disease?

Monica J Carson, Yoshinori Otani, Deirdre S. Davis, Slawomir Sloniowski, Abdullah Madany, Alfredo Hernandez, Andrea Tenner, Devin Binder, Peter Hickmott, Iryna M Ethell.

University of California Riverside School of Medicine, Center for Glial-Neuronal Interactions

Abstract: Lack of a functional TREM2-DAP12 signaling pathway causes early onset cognitive dementia in humans evident by the third decade of life. More recently, a single heterozygous mutation in TREM2 was found to correlate with an ~3-fold increase in Alzheimer’s Disease. Although the clinical presentation initially suggested a neuronal defect, we find that within the CNS, TREM2 expression was detected only in microglia and that TREM2 was not detected in the CNS of PU.1 KO mice that lack microglia. TREM2 KO mice do not exhibit overt defects in development of brain structure. However, using immunohistochemistry and electrophysiology, we find that postnatal maturation of hippocampal vGlut1+ excitatory synapses is inhibited in TREM2 KO mice. Strikingly, the inhibition of the normal developmental increase in vGlut1+ synapses in unmanipulated TREM2 KO mice is similar to that observed in wild-type mice subjected to systemic inflammation during post-natal development. Using knock-out mice and co-culture studies, we report that homeostatic regulation of hippocampal excitatory synapses is dependent on TREM2 associated inhibition of neuroinflammation. Because TREM2 naturally decreases 30-fold as a function of normal development and aging, our studies suggest that age associated
decreases in TREM2 expression may contribute to age being the greatest risk factor for Alzheimer’s disease.

**Keywords:** microglia, TREM2, synapse, dementia and inflammation