TREM-2 induced microglial activation promotes the clearance of amyloid-beta in an AD mouse model

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Neuroinflammation is now recognized as a critical mediator of the neurodegenerative process of Alzheimer's disease and other chronic neurodegenerative conditions. Uncontrolled, chronic inflammatory processes of the central nervous system is likely to contribute to neurodegeneration, however, data also indicates that harnessing the ability of the immune system for clearance of pathological proteins such as amyloid deposits could be a target for therapeutic development. Indeed, anti-Aβ immunotherapy has leveraged such processes for amyloid clearance. Despite preclinical efficacy clinical trials of anti-Aβ immunotherapy, in clinical trials this approach seems to be most appropriate in early stage, preclinical prevention. We hypothesize that targeting neuroinflammation therapeutically may target multiple pathological processes that would provide clinical benefit later in the process.

Triggering receptor expressed on myeloid cells -2 (TREM2) is an innate immune receptor expressed on microglia which signals through DAP12 to trigger phagocytosis. TREM2 SNPs have been identified as significantly increasing risk of AD in GWAS studies. The hypothesis for this increased risk is that there is a loss of function, impairing the innate immune system to clear amyloid deposition efficiently. We hypothesized that activating TREM2 may engage the innate immune system. In the current study, we found that upregulation of TREM2 in vivo leads to the induction of pro-inflammatory mediators in microglia and to a significant reduction in amyloid deposition. Other outcome measures ongoing include further assessment of neuroinflammatory responses, cerebral amyloid angiopathy (CAA) and cerebrovascular events. These preliminary data suggest that TREM2 may be a promising target for treatment of Alzheimer's disease.