TREM2-independent neuroprotection is mediated by monocyte-derived macrophages in a mouse model of Alzheimer’s disease

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Abstract

Background: The relative contributions of microglia and infiltrating monocyte-derived macrophages (MDMs) to containing Alzheimer’s disease (AD) are not fully understood. In the 5xFAD animal model of amyloidosis, disease-associated microglia (DAM) expressing the Triggering receptor expressed on myeloid cells 2 (TREM2), are found in close proximity to amyloid beta (Aβ) plaques. Deletion of TREM2 results in the absence of DAM and in an increased Aβ-plaque load. However, the necessity of TREM2 and DAM for resolving AD pathology is still debatable.

Method: Here, we activated systemic immunity by blocking the programmed cell death protein 1 / ligand (PD-1/PD-L1) pathway in TREM2−/− and TREM2+/+ 5xFAD mice, to decipher the roles of the different myeloid populations in mitigating AD pathology.

Result: We found that anti-PD-L1 treatment resulted in cognitive improvement in TREM2−/− and TREM2+/+ 5xFAD mice. In addition, in both TREM2−/− 5xFAD and TREM2+/+ 5xFAD, the treatment resulted in a reduction in water soluble-Aβ, while reduction of insoluble-Aβ was observed only in TREM2+/+ 5xFAD mice. Eliminating monocytes using anti-CCR2 antibody fully abrogated the observed effects of anti-PD-L1 treatment in TREM-/-5xFAD mice, and partially eliminated the effects in the TREM2+/+5xFAD. Single-cell RNA-seq of myeloid cells isolated from TREM2−/− 5xFAD brains revealed that MDMs express unique scavenger receptors, previously linked to soluble-Aβ removal, such as Macrophage scavenger receptor 1 (MSR1).

Conclusion: Overall, our findings highlight a novel TREM2-independent pathway by which cognitive improvement and removal of soluble-Aβ are achieved in an amyloidosis model. Thus, our results support the potential of MDM-harnessing immunotherapy in treating AD patients, irrespective of whether they carry a TREM2 mutation.