NEURODEGENERATIVE DISEASE

ASO-mediated *Trem2* lowering reduces amyloid pathology in mice

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In the past 10 years, large scale genetic studies have linked *TREM2* variants to Alzheimer's disease (AD). The discovery of *TREM2* risk variants has prompted extensive research to elucidate the role of triggering receptor expressed on myeloid cells-2 (TREM2) in AD pathology; but to date, the mechanistic link between the phagocytic receptor TREM 2 expressed on microglia, microglial dysfunction and neurodegeneration remains elusive. The effects of TREM2 manipulation on amyloid β-protein deposition – one of the pathological hallmarks of AD – are inconsistent across animal studies and models, suggesting that TREM2 function in AD is determined by the pathogenic and temporal context.

In a new study published in *PNAS*, investigators from Washington University in St. Louis used antisense oligonucleotides (ASOs) to acutely reduce *Trem2* levels in the mouse brain at specific times during the progression of AD (at 4, 7 and 10 months of age). Plaque analysis in APP/PS1 mice at 11 months of age revealed that intracerebroventricular injection of *Trem*2 KD ASOs during late-stage disease (post-plaque) reduced amyloid pathology, while injection at pre-plaque and early-plaque stages did not affect plaque load.

"By investigating a short-term *Trem2*-lowering paradigm in adult amyloid-depositing mice, this study supports a time- and/or duration-dependent role for TREM2 in mediating microglial responses to plaque pathology," explain the investigators in their report.

Schoch and colleagues analyzed brain tissues of 10 month-old APP/PS1 mice one week after *Trem2* KD ASOs injection, which revealed a pattern of increased microglial activation with induction of microglial and inflammation gene expression. These results suggest that acute *Trem2* reduction spurs microglial activation, which promotes phagocytosis and clears amyloid plaques over time.

The investigators explain that their ASO strategy presents several advantages over other approaches to study the role of TREM2 in AD. "Temporary ASO-mediated *Trem2* reduction does not recapitulate models of TREM2 loss from birth, but it may avoid potential compensatory effects or other confounds associated with genetic knockout mouse models and may help evaluate the effects of varying TREM2 expression over time," they write.

Schoch and colleagues also explain that to recapitulate different pathological contexts, the effects of *Trem2* KD ASOs should be evaluated in other models given that APP/PS1 mice used in this study do not exhibit overt tau pathology or neurodegeneration, thereby limiting the understanding of the role of TREM2 in these aspects of human AD.

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