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ALZHEIMER DISEASE

Soluble TREM2 in CSF sheds light on microglial activation in AD

> CSF sTREM2 levels were abnormally increased about 7 years before the onset of dementia

Microglia-mediated neuroinflammation is strongly implicated in the pathogenesis of Alzheimer disease (AD), but its timing in relation to the amyloid cascade has been unclear. Using a soluble form of the microglial protein TREM2 (triggering receptor expressed on myeloid cells 2) as a cerebrospinal fluid (CSF) biomarker, researchers in Munich, Germany and St. Louis, USA have now provided evidence that microglial activation occurs after amyloid deposition but several years before the onset of cognitive impairment and dementia.

TREM2 is a transmembrane protein that is expressed by cells of the myeloid lineage, including the microglial cells of the brain. Proteolytic processing causes the ectodomain of this molecule to be shed into the CSF in the form of soluble TREM2 (sTREM2), the levels of which are thought to reflect the degree of microglial activation in the brain.

"We previously measured sTREM2 in the CSF in different clinical stages of sporadic AD, and we observed increased levels in the prodromal stage of AD," explains Michael Ewers, who led the new study in association with Christian Haass and Marc Suárez-Calvet. "These results raised the question of where in the pathological cascade of AD the abnormal change in TREM2 occurs."

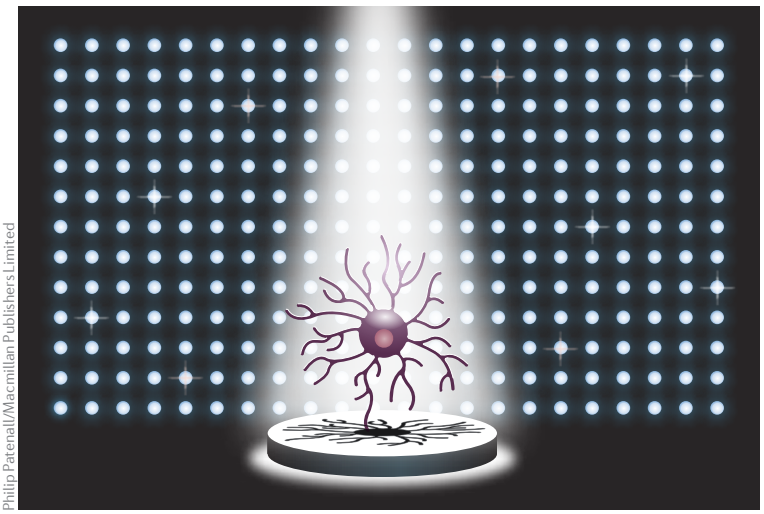
The study, which was reported in *Science Translational Medicine*, included 218 participants recruited from the Dominantly Inherited Alzheimer Network (DIAN) cohort: 127 presymptomatic individuals carrying AD-causing mutations, and 91 noncarrier siblings. As autosomal dominant AD has a predictable course, the researchers were able to calculate the expected time of symptom onset, which was then correlated with the CSF levels of sTREM2.

"We found that CSF sTREM2 levels were abnormally increased about 7 years before the onset of dementia symptoms but after changes in CSF amyloid-β (Aβ) peptide and tau," reports Haass. "These results suggest that amyloid deposition occurs first, and the neuroimmune response occurs subsequently within the pathological cascade of AD."

The increase in CSF sTREM2 levels was paralleled by raised CSF tau levels, indicating a possible link between sTREM2 and neuronal injury. The authors propose that the elevation in sTREM2 levels could actually represent a protective response — an assertion that is corroborated by a slight increase in CSF sTREM2 during normal ageing, and the discovery that loss-of-function mutations in the *TREM2* gene are prominent risk factors for AD. "In support of a protective action of TREM2, we have also recently shown that TREM2 promotes antibody-mediated clearance of amyloid plaques," points out Suárez-Calvet.

The authors acknowledge the limitations of the cross-sectional design of their study, and they now wish to explore whether CSF sTREM2 levels can be used to predict longitudinal clinical changes in AD, as well as to monitor the effects of anti-inflammatory drugs and anti-Aβ immunotherapies. "In addition, we are seeking mechanisms that might allow us to therapeutically modulate TREM2 activity," concludes Haass.

Heather Wood



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ORIGINAL ARTICLE Suárez-Calvet, M. *et al.* Early changes in CSF sTREM2 in dominantly inherited Alzheimer's disease occur after amyloid deposition and neuronal injury. *Sci. Transl. Med.* **8**, 369ra178 (2016)

FURTHER READING Suárez-Calvet, M. *et al.* sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. *EMBO Mol. Med.* **8**, 466–476 (2016) | Xiang, X. *et al.* TREM2 deficiency reduces the efficacy of immunotherapeutic amyloid clearance. *EMBO Mol. Med.* **8**, 992–1004 (2016)