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NEURODEGENERATIVE DISEASE

Loss of TDP-43 in microglia — friend or foe?

> abnormal phagocytic activity of these microglia resulted in significant synaptic loss

Removal of TDP-43 promotes the clearance of amyloid-β (Aβ) by boosting microglial phagocytosis, according to new research. However, this increased clearance comes at a cost, as it also results in a loss of synapses, which could play a part in neurodegeneration and cognitive decline.

Microglia are the resident innate immune cells of the CNS, and have key roles in immune defence, phagocytosis of cellular debris, and the removal of unwanted or damaged neurons and synapses. Studies have increasingly highlighted an important role for these cells in several neurodegenerative diseases, including Alzheimer disease (AD) and amyotrophic lateral sclerosis (ALS), particularly in the removal of protein aggregates that are present in these disorders.

In the new study, Lawrence Rajendran and colleagues investigated the genetic factors affecting the ability of microglia to engulf Aβ. The researchers selected 18 key genes involved in neurodegeneration, and individually silenced them in microglia cultured in Aβ-rich medium. The team found that depletion of TDP-43 — a protein that aggregates in many patients with ALS and frontotemporal dementia (FTD) — strongly increased the clearance of Aβ by microglia, indicating that this protein could have an important role in a range of neurodegenerative conditions.

To test the effect of TDP-43 loss in microglia *in vivo*, the team generated a conditional transgenic mouse model in which TDP-43 could be inducibly knocked out in microglia (TDP-43^{cKO}). When the researchers injected $A\beta_{42}$ oligomers into the cortex of wild-type and TDP-43^{cKO} mice, they found that depletion of TDP-43 was associated with an increased volume of microglia surrounding the injected Aβ, and that these cells engulfed a larger volume of Aβ than in wild-type mice. The team then crossed the TDP-43^{cKO} mice with mice that overexpressed human mutant amyloid precursor protein (APP^{arc}) and observed a significant reduction in Aβ levels in mice with TDP-43-depleted microglia compared with mice with the APP^{arc} mutation alone.

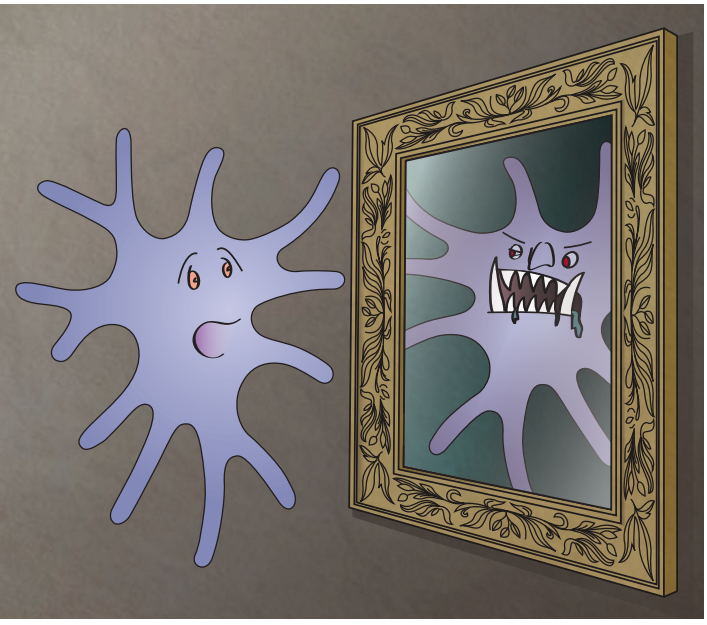
The researchers predicted that the increased clearance of toxic Aβ by microglia that lack TDP-43 would protect synapses, but they observed an unexpected effect on synaptic markers in these mice. "A major surprise came when we found that the abnormal phagocytic activity of these microglia resulted in significant synaptic loss," comments Rajendran. "Although removal of amyloid is desired, loss of synapses suggests that the neurodegeneration could occur because of this pathological microglial pruning."

Importantly, when the researchers examined synaptic markers in TDP-43^{cKO} mice that did not overexpress Aβ, they observed the same loss of synapses, indicating that the increased microglia-mediated pruning does not require Aβ. Depletion of TDP-43 in microglia might, therefore, underlie synaptic loss in other neurodegenerative disorders, such as ALS or FTD.

Finally, the team investigated how TDP-43 pathology affects microglial phagocytosis in patients with ALS. The group found that AD prevalence was considerably lower in patients with ALS aged >75 years than in the general population, consistent with a difference in the microglial clearance of Aβ. Furthermore, less Aβ was present in the post-mortem brains of patients who had ALS or FTD with TDP-43 pathology than in those of age-matched controls, and post-mortem brains of patients with ALS and TDP-43 pathology had increased levels of the microglial phagocytic marker CD68 compared with ALS patients without TDP-43 pathology.

The team plan to investigate how the loss of TDP-43 leads to aberrant phagocytosis in microglia, and what other implications this effect might have in neurodegerative disease. "One of the key aspects that intrigues me is that we also see the synapse loss in the absence of human Aβ, which has been thought to be a key player in synaptic dysfunction in AD," comments Rajendran, "We would like to investigate this potentially amyloid-independent synapse loss that occurs via microglia, and how it can contribute to neurodegeneration."

Charlotte Ridler



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