

Panel 1: Microglial responses to pathological challenges

Microglia are highly dynamic and exist in various cellular states, ranging from a homeostatic surveillance state to a responsive state—referred to as disease-associated microglia (DAM).^{6,7} On various challenges, such as deposition of amyloid plaques, microglia turn on transcriptional processes, which allow them to migrate towards sites of injury, to secrete neurotrophic factors and cytokines, to induce phagocytosis, and to enhance energy and lipid metabolism.^{4,6-9} A combination of such defensive mechanisms allows microglia to digest the halo of amyloid plaques, which contains diffusible synaptotoxic A β oligomers¹⁰, and to compact the plaque core to prevent further release of such toxic peptides.^{4,11}

LOAD-associated heterozygous TREM2 risk variants prevent or reduce the protective functions of microglia. Distinct homozygous TREM2 loss-of-function mutations even completely abolish cell autonomous TREM2 signalling leading to neurodegeneration in Nasu Hakola disease¹². Another key function of microglia is to phagocytose neuronal synapses, a process required for proper brain wiring during development¹³. In various models of neurological diseases, including Alzheimer's disease, microglia-mediated synaptic engulfment is reactivated in a region-specific manner, contributing to pathological synaptic dysfunction and loss¹⁴⁻¹⁷. However, recent findings in development suggest that TREM2 is associated with engulfment of certain damage-associated synapses, raising the question of whether there is a protective role for TREM2-mediated synapse engulfment in Alzheimer's disease. Future experiments are needed to test this idea.^{18,19}

TREM2 is also implicated in surveying the neuronal microenvironment, which requires substantial energy expenditure, to which microglia display remarkable metabolic flexibility^{20,21}. Upon stress or pathological challenge, microglia turn on mTOR in a TREM2-dependent manner to meet increased demands for energy and protein synthesis⁹. Finally, TREM2 is essential for controlling lipid homeostasis in microglia^{4,22,23}.

Panel 2: Role of TREM2 in models of amyloid and tau pathology

Since the discovery of the Arg47His variant of TREM2 as a major risk factor for LOAD^{24,25}, extensive work has been done in mouse models of amyloid pathology, the findings of which collectively suggest a protective role of TREM2 in the microglial response to amyloid plaques⁴. In an attempt to model both amyloid and tau pathology (as seen in cases of Alzheimer's disease), tauopathy was induced by seeding exogenous insoluble tau aggregates isolated from the brains of people with Alzheimer's disease.²⁶ Strikingly, this experiment revealed that seeding and spreading of peri-plaque tau pathology was enhanced in the absence of Trem2 or in the presence of the human TREM2 Arg47His variant, suggesting that amyloid-mediated spreading of tau pathology is limited by Trem2. Similar conclusions were drawn in an independent study in which it was shown that the Trem2-dependent DAM phenotype is essential in delaying A β -induced propagation of tau pathology²⁷. Absence of Trem2 in an amyloid mouse model crossed to a tauopathy model also led to an exacerbation of tau pathology²⁸. Importantly, the absence of Trem2 had no effect on tau pathology when investigated in the pure tauopathy mouse model, indicating that Trem2-mediated microglial activation was essential for limiting amyloid-induced spread of tau pathology in the brain²⁸. However, studies on the role of TREM2 in pure tauopathy models have yielded inconsistent results, which may be due to the investigation of different tau models as well as different disease stages^{29,30}. Nevertheless, there is now strong evidence for protective functions of TREM2 for both amyloid pathology and amyloid-induced tau pathology, proposing TREM2 as a suitable target for a disease-modifying strategy.