Homeostatic microglia initially seed and activated microglia later reshape amyloid plaques in Alzheimer's Disease

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Background: Microglia are genetically implicated in Alzheimer's disease (AD), yet their precise role in amyloid plaque pathology remains unclear. While some studies suggest that microglia clear amyloid-β (Aβ). Others implicate them in promoting plaque formation and neurodegeneration. These conflicting results highlight that clarifying microglial functions across different stages of the disease is needed. In addition to microglia, the adaptive immune system has also been implicated in AD progression; however, its role in amyloid plaque formation remains controversial.

Objective: To clarify whether microglia play a beneficial or detrimental role in AD pathology, and to investigate the role of adaptive immunity in modulating amyloid plaques and microglia-plaque interactions.

Results: Using both pharmacological (PLX3397) and genetic ($Csf1r^{\Delta FIRE/\Delta FIRE}$) microglial depletion strategies in $App^{NL\text{-}G\text{-}F}$ mouse models, the study found that microglia are essential for the initial seeding of amyloid plaques. Early microglial depletion reduced insoluble Aβ and plaque numbers without affecting soluble Aβ levels, suggesting microglia initiate plaque formation rather than clear Aβ. In contrast, late-stage microglial depletion impaired plaque compaction and increased neuritic dystrophy, indicating a protective role for activated microglia. Transplantation of human microglia into microglia-deficient mice restored plaque seeding capacity, while human $TREM2^{R47H/R47H}$ microglia exacerbated plaque and neuritic pathology. Depletion of adaptive immune cells did not alter microglia-mediated effects, suggesting the adaptive immune system does not alter microglia-mediated modulation of amyloid plaques.

Conclusion: Microglia exhibit a dual role in AD pathogenesis—homeostatic microglia initiate amyloid plaque formation, while activated microglia later compact plaques to limit neuronal damage. Notably, transplantation of human microglia carrying the $TREM2^{R47H/R47H}$ risk variant exacerbated plaque pathology, further supporting the protective role of microglial activation during the progression of Alzheimer's disease.