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Enrichment-dependent deficits in Hippocampal Neurogenesis mediated by familial Alzheimer's disease-linked PS1 variants are rescued by microglial depletion

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Presenilin 1 (PS1) plays a critical role in neurogenesis. We have demonstrated that ubiquitous expression of familial, early-onset Alzheimer's disease (AD)-linked PS1 (FAD-PS1) mutants impairs environmental enrichment (EE)-induced proliferation and neurogenesis of adult hippocampal progenitor cells (AHNPCs) in a non-cell autonomous manner. These impairments are, at least in part, due to alterations in the levels of specific chemokines and growth factors secreted from microglia expressing FAD-PS1 variants. Mice expressing PrP promoter-driven human wild-type PS1, M146L and □E9 were fed with PLX5562 for 7 days, then subject to Standard Housing or EE conditions for 1 month. PLX5622 is a CSF1 receptor antagonist, used to deplete microglia in adult brain. Animals were injected with a single bolus of BrdU, and sacrificed after 24 hours or 2 weeks. Baseline anxiety behavior was tested using Marble Burying and Dark/light test. Brain immunostaining was used to assess proliferation, neurogenic cell density, differentiation and survival of hippocampal progenitors. It was compared with mice expressing human WT PS1, mice expressing FAD-PS1 linked mutations exhibit lower rates of proliferation, neural stem cells and GFAP+ cells in the hippocampus following EE. These deficits were correlated with higher rates of baseline anxiety behaviors. PLX5622-mediated depletion of microglia in mice expressing FAD-PS1 linked variants rescued the deficits in AHNPC proliferation and differentiation and aberrant baseline anxiety. PLX5622-mediated depletion of microglia in mice expressing FAD-PS1 linked variants rescues deficits in AHNPC proliferation and baseline anxiety of those mice. These findings reinforce the important role of microglia in the regulation of neurogenesis in FAD-PS1 models.

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