

Fascin expression protects against neurodegeneration in 5xFAD mice via modulation of neuroinflammation

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Alzheimer's disease, an insidious dementia, is characterized by pathological deposits of amyloid plaques, neurofibrillary tangles, and subsequent neuronal degeneration and cognitive loss. Mitochondrial dysfunction and neuroinflammation play an early and major role in the development and progression of Alzheimer's disease. Fascin, an actin-bundling protein, important for cancer metastasis via improving mitochondrial function and mitochondrial DNA (mtDNA) homeostasis, was notably reduced in the brain from patients with AD. Our prior studies demonstrated Fascin deficiency caused mitochondrial dysfunction and cognitive deficits, suggesting that the loss of Fascin may promote mitochondrial dysfunction and AD pathogenesis. In this study, we investigated whether overexpression of Fascin in the vulnerable forebrain neurons of 5XFAD mouse model can rescue cognitive function, alter pathological hallmarks such as amyloid pathology, mitochondria, and neuroinflammation, and finally provide molecular mechanisms behind its role. Our results show that Fascin overexpression rescued deficits in LTP and spatial memory, improved amyloid pathology and astrocytic activation, potentially through a mechanistical decrease in NFkB signaling via modulation of mtDNA homeostasis.

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