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Neutrophils induce Alzheimer's-like disease via LFA-1-integrin and neutrophil extracellular traps

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Introduction: Inflammation has been correlated to Alzheimer's disease (AD) and a better understanding of inflammation mechanisms may potentially help to develop new approaches to treat this disorder.

Methods: Confocal microscopy studies were performed to evaluate inflammation mechanisms. Intra-vital microscopy studies using two-photon microscopy were performed to visualize and analyze the movement of neutrophils inside brain vessels and in the parenchyma. *In vitro* rapid adhesion assays were performed on integrin ligands whereas and integrin affinity was measured using Image Stream technology. Neuropathological studies, fear conditioning and Y maze tests were performed to analyze the effect of inflammation mechanism inhibition on disease.

Results: It was detected expression of vascular adhesion molecules and increased accumulation of neutrophils in 5XFAD and 3xTg-AD transgenic mice with cognitive impairment during early stage of AD-like disease. Using two-photon laser-scanning microscopy we observed that neutrophils crawl in blood vessels and transmigrate in high numbers in areas with amyloid plaques in both AD-like models. Interestingly, neutrophils released neutrophil extracellular traps (NETs) suggesting that NETosis may represent a potential neutrophil-dependent disease mechanism in AD. Amyloid beta peptide 1-42 induced high affinity state of LFA-1 integrin and LFA-1-dependent adhesion of neutrophils. Moreover, two-photon microscopy experiments showed that LFA-1 integrin blockade prevented neutrophil extravasation, and inhibited intra-parenchymal motility. Notably, neutrophil depletion or blockade of neutrophil trafficking by an anti-LFA-1 integrin antibody inhibited microglial activation, amyloid beta deposition and phosphorylated tauformation and rescued cognitive deficits in 5XFAD and 3xTg mice, suggesting that neutrophils play a key role in AD-like disease. Importantly, restoration of cognitive function in mice with temporary inhibition of neutrophil function during early disease was maintained also at later time points in aged animals. To understand the relevance of our data in humans, it was analyzed human cortical brain samples from subjects with AD. Obtained results showed that neutrophils adhered and spread inside brain venules or migrated into the parenchyma in high numbers and release NETs in AD brains compared to control subjects.

Conclusion: Obtained results demonstrate that neutrophils induce cognitive impairment in AD-like disease and suggest that inhibition of neutrophil trafficking may represent a new therapeutic strategy in AD.

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