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NEURODEGENERATIVE DISEASE

Microglia in early disease stages

Increasing evidence suggests that early treatment is essential for efficacy of therapeutic intervention in neurodegenerative diseases such as Alzheimer disease (AD) and Parkinson disease (PD). Two new studies have highlighted a key role for microglia-mediated CNS inflammation in the initial stages of neurodegenerative pathology, suggesting promising therapeutic targets and strategies for early diagnosis.

In a paper published in *The Journal of Neuroscience*, Linda Van Eldik and colleagues investigated the therapeutic potential of a small-molecule investigational drug, MW-151, in an APP/PS1 knock-in mouse model of AD. MW-151 inhibits the production of proinflammatory cytokines by microglia in reponse to amyloid-β (Aβ) and, importantly, APP/PS1 mice show age-dependent increases in amyloid pathology and CNS inflammation.

"We tested two modes of drug administration—early, chronic treatment and late, acute treatment—to explore the therapeutic time window," says Van Eldik. In one group, mice received intraperitoneal injection of MW-151 three times per week for 5 months, beginning at 6 months, when cytokine levels in the brain were beginning to increase. "This time point would be equivalent to the stage in humans where memory changes are just beginning to occur," she explains. Mice in the other group received the drug at 11 months, when overproduction of cytokines was overt.

Compared with vehicle-treated APP/PS1 mice, early treatment with MW-151 attenuated microglial activation and reduced levels of the proinflammatory cytokine IL-1β. Early treatment also prevented loss of synaptic proteins such as postsynaptic density protein 95 and synaptophysin. Mice treated at the later time point showed some, but not all, of the beneficial effects observed in the early-treatment group. "This finding shows that the therapeutic time window is critically important in order to obtain optimal therapeutic responses," says Van Eldik.

Lastly, studies in brain slices showed that MW-151 treatment enhanced long-term potentiation in APP/PS1 mice, suggesting that the compound promotes synaptic plasticity and might, therefore, help to maintain memory function.

In another study, Daniela Perani and colleagues investigated microglial activation in patients in early stages of either PD or dementia with Lewy bodies (DLB), using PET imaging of the neuroinflammatory radiotracer ^{11}C-PK11195. The study involved six patients in each of the disease groups, all within 1 year of diagnosis, and 11 healthy controls.

"This PET imaging marker has been used to study microglial activation in other neurodegenerative diseases such as AD," says Perani, "but studies are lacking in PD, particularly in early-stage disease, and no previous reports exist for DLB."

The team showed that in early PD and early DLB, microglial activation in the putamen and substantia nigra was significantly increased compared with controls. Patients with DLB also showed increased ^{11}C-PK11195 binding in the caudate and several cortical areas. "Importantly, the patterns of microglial activation differed according to the distribution of neuropathological changes," says Perani.

Such disease-specific neuropathological signatures might assist in differential diagnosis of PD versus DLB, and could be used as a biomarker of early intervention strategies targeting neuroinflammation. Longitudinal studies are required to determine how changes in microglial activation correlate with clinical disease progression.

Together, these two studies highlight CNS inflammation and microglia as important biomarker and therapeutic targets in future efforts to intervene early in neurodegenerative disease.

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Original articles Bachstetter, A. D. *et al.* Early stage drug treatment that normalizes proinflammatory cytokine production attenuates synaptic dysfunction in a mouse model that exhibits age-dependent progression of Alzheimer's disease-related pathology. *J. Neurosci.* **32**, 10201–10210 (2012) | Iannaccone, S. *et al. In vivo* microglia activation in very early dementia with Lewy bodies, comparison with Parkinson's disease. *Parkinsonism Relat. Disord.* doi:10.1016/j.parkreldis.2012.07.002