ALZHEIMER DISEASE

Microglia, spreaders of Aβ seeds

Microglia could have an important role in the propagation of amyloid-β (Aβ) pathology, according to new research published in Nature Neuroscience. The findings add a new dimension to the involvement of microglia in Alzheimer disease (AD) and indicate a potential new therapeutic target.

Aβ pathology is known to propagate through the brain via a prion-like mechanism, whereby misfolded Aβ acts as ‘seeds’ to initiate further misfolding. The way in which Aβ seeds are transferred between cells, however, remains unclear. In their new study, Paolo d’Errico, Melanie Meyer-Luehmann and colleagues followed their suspicions about one possibility.

“Owing to the evident role of microglia in spreading pathological proteins such as tau, we decided to study whether this cell type can act as a cellular transporter for Aβ as well,” says Meyer-Luehmann.

Meyer-Luehmann herself first demonstrated that propagation of AD pathology could be studied with a grafting method in mice. In this procedure, healthy neurons from wild-type mice are grafted into the brains of AD model mice. Aβ pathology spreads to the grafted neurons, leading to their degeneration. The new study was based on the same approach.

In this work, the researchers grafted wild-type neurons into the brains of 5 × FAD mice, which develop Aβ pathology. The mice were further engineered to express green fluorescent protein in microglia. By 2 weeks after the transplantation procedure, microglia from the graft recipients had migrated into the grafts. The team then investigated whether these microglia could be taking Aβ with them.

They first exploited the fact that the phagocytic capability of microglia diminishes with age, and assessed whether the development of Aβ pathology in the graft differed between old and young mice. Aβ burden in the graft was much lower in older mice than in younger mice, indicating that microglia do transport Aβ and that this process becomes less efficient with age. Furthermore, in 5 × FAD mice with impairments in microglial function, Aβ deposition in the graft was less extensive than in mice with normal microglial function.

“Our study sheds new light on the involvement of microglia in the propagation of Aβ pathology from a diseased to a healthy region,” says d’Errico. “Microglia are known to have both beneficial and detrimental roles in AD, but the role of microglia in transporting Aβ from one region to another has never been described before.”

The researchers say their technique could be used to investigate other factors that influence Aβ propagation and to study other neurodegenerative diseases. However, their findings could also have more direct implications for patients: “We think our study could help to develop therapies that have microglia as a potential therapeutic target,” says d’Errico.