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NEURODEGENERATIVE DISEASE

Complement mediates pathological pruning

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Synapse loss is thought to be an important contributor to cognitive decline in Alzheimer disease (AD) and to begin long before the appearance of the amyloid plaques that characterize later stages of the disease. Stevens and colleagues now report findings that indicate that the classical complement cascade and microglia are involved in pre-plaque synapse elimination in mouse models of AD.

During development, components of the complement cascade, including C1q and C3, are expressed by neurons and mediate circuit refinement through synaptic engulfment by phagocytic microglia. To ascertain whether similar mechanisms are involved in AD, the authors examined synapse loss in two transgenic mouse models of AD (J20 and APP/PS1 mice). By 3 months of age — before plaque formation — the mice exhibited both synapse loss and increased levels of C1q immunoreactivity in the hippocampus. Furthermore, the colocalization of C1q with synaptic puncta was enhanced in J20 mice in comparison to controls.

Soluble oligomeric amyloid-β (oAβ) is proposed to contribute to synapse loss in AD. The authors found that systemic injection of J20 mice with an inhibitor of Aβ production decreased C1q deposition at synapses, whereas injection of oAβ into the lateral ventricles of wild-type mice increased both synapse loss and C1q deposition in the hippocampus. Thus, the deposition of C1q at synapses may be induced by oAβ and may mediate its synaptotoxic effects. Indeed, the authors showed that injection of oAβ in mice lacking C1q or in mice that received a simultaneous injection with an anti-C1q antibody did not result in synapse loss.

During development, C1q mediates its effects on synapse elimination by activating C3. The authors showed that oAβ injection in wild-type mice induced C3 deposition and localization at synapses, an effect that depended on the presence of C1q. Furthermore, when the authors crossed APP/PS1 mice with mice lacking C3 they observed reduced synapse loss in comparison to that in mice in which C3 was present. This suggests that C1q-mediated synapse loss in these models involves the classical complement cascade.

Activation of microglia by the complement cascade induces synaptic phagocytosis during development. To examine the role of microglia in synapse loss in AD, the authors measured synaptic engulfment in mice that express a fluorescent synaptic marker. Injection of oAβ increased synaptic internalization by microglia; however, this effect was eliminated in mice lacking the C3 receptor, CR3.

These findings indicate that activation of the complement cascade and the subsequent initiation of microglial synapse engulfment may contribute to the synaptotoxic effects of oAβ in early stages of AD. Whether similar mechanisms contribute to later stages of synapse loss or to synapse loss in other neurodegenerative diseases is unknown.

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