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NEURODEGENERATIVE DISORDERS

A PIR-fect storm

Although amyloid-β seems to have a central role in Alzheimer's disease pathology, its precise role remains a subject of intense scrutiny. Shatz and colleagues now show that the murine immunoglobulin-like receptor PIRB (paired immunoglobulin-like receptor B; also known as LILRB3) and its human homologue LILRB2 (leukocyte immunoglobulin-like receptor B2) are high-affinity receptors for amyloid-β oligomers and that PIRB–amyloid-β interactions regulate synaptic plasticity.

Amyloid-β oligomers impair synaptic plasticity *in vitro* and *in vivo*, and several receptors for amyloid-β may mediate this effect. The authors assessed whether PIRB might be one such receptor, because they had previously shown that mice lacking PIRB have enhanced ocular dominance plasticity, whereas this form of plasticity is reduced in the transgenic APP/PS1 mouse model of Alzheimer's disease.

The authors first showed that human amyloid-β oligomers, but not monomers, could bind to both PIRB-expressing cells and LILRB2-expressing cells with a high (nanomolar) affinity, and that this binding required the two most amino-terminal immunoglobulin domains of the receptors.

Shatz and colleagues next assessed whether PIRB and LILRB2 mediate the effects of amyloid-β oligomers on hippocampal synaptic plasticity and memory. Although amyloid-β oligomers reduced long-term potentation in hippocampal slices from wild-type mice, it had no effect in slices from mice lacking PIRB. Similarly, performance on a hippocampus-dependent memory task was impaired in APP/PS1 mice but was normal in APP/PS1 mice that lacked PIRB.

The reduced ocular dominance plasticity previously observed in APP/PS1 mice during the critical period of visual cortex development is associated with increased long-term depression at layer 4–layer 2/3 synapses in the visual cortex. The authors demonstrated that these changes did not occur in the visual cortex of APP/PS1 mice lacking PIRB.

These functional studies suggested that PIRB mediates the negative effects of amyloid-β on hippocampal function and early cortical plasticity in the APP/PS1 model of Alzheimer's disease. So, what signalling mechanisms might be activated by PIRB–amyloid-β binding? A proteomic screen revealed that cofilin and the serine/threonine-protein phosphatases PP2A and PP2B/calcineurin (which can dephosphorylate and thereby activate cofilin) might be involved. Indeed, PIRB–cofilin, PIRB–PP2A and PIRB–PP2B interactions were increased and levels of phosophorylated cofilin were reduced in forebrains of APP/PS1 mice but not in control mice. APP/PS1 mice lacking PIRB did not show this reduction in phosphorylation. In agreement with this finding, addition of amyloid-β oligomers increased cofilin activity in cultured cortical neurons but not in neurons lacking PIRB. Importantly, the authors detected LILRB2 in human brain samples and found reduced cofilin phosphorylation in post-mortem brains of patients with Alzheimer's disease compared with control brains.

Together, these results support a model in which amyloid-β oligomer binding to PIRB (and, in humans, to LILRB2) promotes activation of cofilin by PP2A and PP2B/calcineurin. Cofilin activation is known to result in actin filament disassembly and spine loss, and this may underlie the changes in synaptic plasticity and impairment in hippocampal function seen in humans with Alzheimer's disease and in the APP/PS1 mouse model of the disorder.

This interesting study shows that 'immune receptors' may have a role in Alzheimer's disease and points to LILRB2 as a potential therapeutic target for this disorder.

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ORIGINAL RESEARCH PAPER Kim, T. *et al.* Human LilrB2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science* **341**, 1399–1404 (2013)

> "PIRB mediates the negative effects of amyloid-β on hippocampal function and early cortical plasticity in the APP/PS1 model of Alzheimer's disease"