NEURODEGENERATIVE DISEASES

PAK up your troubles

PAKs (p21-activated kinases) are key regulators of the actin cytoskeleton that, in neurons, have a role in dendritic spine morphogenesis. In mice, mutation of *Pak3* causes X-linked, non-specific mental retardation, and perturbation of the PAK pathway leads to cognitive deficits and dendritic spine defects. Now, in *Nature Neuroscience*, Zhao *et al.* report a loss of PAK activity in the brains of patients with Alzheimer's disease (AD) and suggest that this might cause the dendritic spine and cognitive defects observed in AD.

PAK signalling inactivates cofilin, which destabilizes interactions between actin subunits, causing it to detach from actin. This enables another protein, drebrin, to bind and regulate actin in postsynaptic spines. In the absence of cofilin inactivation, pathological rods or inclusions form, features that are characteristic of AD. Zhao *et al.* show that soluble PAK levels are significantly reduced in the brains of patients with AD, and that phosphorylated PAK is redistributed to granular and tangle-like accumulations, suggesting a link between loss of PAK activity and cofilin aggregation, drebrin loss and synaptic defects observed in AD.

These same features were observed in an Alzheimer's model mouse engineered to produce high levels of amyloid-β (Aβ). Reducing the Aβ burden of these mice, by passive immunization with an anti-Aβ antibody, led to an increase in PAK and drebrin levels. Furthermore, the addition of Aβ oligomers to cultured primary hippocampal neurons induced rapid and persistant reductions in PAK and drebrin, which supports a role for Aβ in inducing PAK signalling defects. Expressing wild-type PAK1 in these neurons limited drebrin loss; conversely, pharmacological inhibition of PAK in adult mice recapitulated many of the features of AD.

These findings suggest that PAK and its downstream effectors represent potential therapeutic targets for AD.

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ORIGINAL RESEARCH PAPER Zhao, L. *et al.* Role of p21-activated kinase pathway defects in the cognitive deficits of Alzheimer disease. *Nature Neurosci.* **9**, 234–242 (2006)