NEURODEGENERATIVE DISEASE

New ways of tackling A β toxicity

Amyloid- β (A β) peptides are thought to have a key role in the neurotoxicity and cognitive decline that occur in Alzheimer's disease (AD), but there have recently been several disappointments with late-stage clinical trials of agents that target A β . Two recent papers in *Nature Medicine* shed light on the mechanisms through which A β could contribute to the aetiology of AD and identify novel targets for drug development, as well as compounds that modulate these targets.

One of the ways in which A β is thought to contribute to the pathogenesis of AD is by disrupting

mitochondrial function. Shi Du Yan's group show that A β interacts with the mitochondrial permeability transition protein *cyclophilin D* (CYPD) in samples of AD brains and in cortical mitochondria of transgenic mice overexpressing a mutant form of human amyloid precursor protein (mAPP mice). This interaction was found to be responsible for increasing the production of reactive oxygen species (ROS) and reducing the mitochondria's membrane potential, thereby triggering the release of cytochrome c and neuronal apoptosis.

Neurons that lacked CYPD or that had been treated with the CYPD inhibitor cyclosporine A were resistant to A β -mediated mitochondrial swelling and the opening of the transition pore, as well as to A β -induced ROS generation and apoptosis. Importantly, the authors noted a significant amelioration of the detrimental effects of A β on spatial learning and memory in mice lacking CYPD and overexpressing mAPP compared with mAPP mice. These findings suggest that blocking CYPD could be a useful strategy for reducing A β -mediated mitochondrial dysfunction and cognitive decline in AD.

In the second study, Schilling *et al.* investigated the production of

pyroglutamate (pE)-modified A β peptides, which are thought to be particularly important in AD pathogenesis owing to their high propensity for aggregation. They found that pE-modified A β was formed by the enzyme glutaminyl cyclase, and that both glutaminyl cyclase and pE-modified A β are upregulated in samples of patients with AD compared with normal aging individuals.

Inhibition of glutaminyl cyclase using an orally administered agent, PBD150, resulted in a considerable reduction in the levels of pE-modified A β in two mouse models of AD and in a fly model overexpressing modified A β forms. Moreover, PBD150 decreased cortical plaque formation and gliosis and, in mice, improved context memory and spatial learning. These results emphasize the contribution of pE-A β to AD pathogenesis and suggest another new approach by which to tackle its deleterious effects.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPERS Du, H. *et al.* Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. *Nature Med.* **14**, 1097–1105 (2008) | Schilling, S. *et al.* Glutaminyl cyclase inhibition attenuates pyroglutamate A β and Alzheimer's disease-like pathology. *Nature Med.* **14**, 1106–1111 (2008)