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Talking up τ in Alzheimer's disease

Henry Nicholls, h.nicholls@elsevier.com

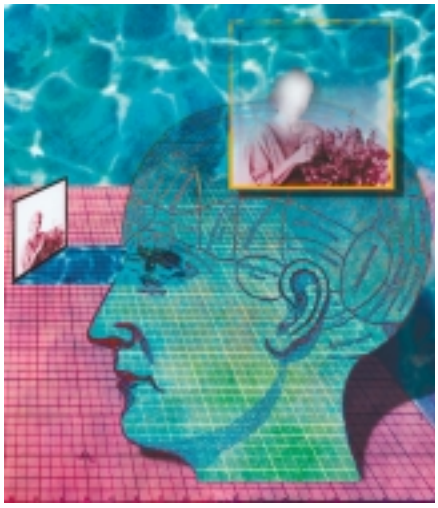
A β-amyloid vaccine is showing promise in preliminary studies of a primate model of Alzheimer's disease, say US scientists. But, say others homing in on the role of the τ protein in the disease, it would be more rational if therapies also targeted τ.

Neurodegenerative diseases are often characterized by an accumulation of proteins with abnormal conformation. In Alzheimer's disease, there are two main problem proteins – β amyloid and τ, although it is still controversial which of these is the primary cause of neuronal loss.

A β-amyloid vaccine

Sam Gandy, director of the Farber Institute for Neurosciences at Thomas Jefferson University in Philadelphia (http://www.jefferson.edu/fin/home/index.cfm), has just reported promising preliminary results of a β-amyloid vaccine in a monkey model of Alzheimer's. Animals treated with the vaccine showed no signs of brain inflammation six months later, Gandy and his colleagues report [1]. This replicates research on mouse models of Alzheimer's, which shows that vaccination with β-amyloid raises an immune response against the protein and clears plaques from the brain.

However, researchers from the Laboratory of Neurobiology at Rockefeller University in New York are



keen to stress that τ protein also has a role in the disease. 'It might be more rational to target both amyloid and τ pathologies in therapeutic approaches', write Bingwei Lu and his colleagues in *Cell* [2].

The microtubule-binding protein τ, normally a highly soluble protein abundant in axons, is clearly important in the onset of Alzheimer's, they say. When phosphorylated, τ becomes insoluble, and aggregates as neurofibrillary tangles (NFTs). It is these NFTs that often become surrounded by amyloid plaques.

PAR-1 generates toxic forms of τ

Lu and colleagues have identified a key enzyme involved in τ phosphorylation that could be an important new target for therapeutic intervention.

The enzyme, PAR-1, has a central role in conferring τ toxicity *in vivo*. 'Our study reveals PAR-1 function in triggering a temporally ordered phosphorylation process that is responsible for generating toxic forms of τ', note the Rockefeller researchers.

They engineered *Drosophila* with the human version of the τ protein, and found that PAR-1 phosphorylates τ directly at two residues. This event is a prerequisite for the action of downstream kinases, which phosphorylate several other sites, leading to the diseased state, they say.

Furthermore, mutation of the two residues that are phosphorylated by PAR-1, thereby preventing PAR-1 activity, caused a significant reduction in overall τ phosphorylation and toxicity, they report.

Studies in transgenic mice show that expression of mutant human τ alone can result in tangle pathology and neuronal loss without accompanying amyloid plaques, they argue. More attention needs to be paid to the role of τ in the pathology and treatment of this disease, they conclude.

References

1 Gandy, S. *et al.* (2003) Molecular and cellular basis for anti-amyloid therapy in Alzheimer disease. *Alzheimer's Dis. Assoc. Disord.* 17, 259–266

2 Nishimura, I. *et al.* (2004) PAR-1 kinase plays an initiator role in a temporally ordered phosphorylation process that confers tau toxicity in *Drosophila*. *Cell* 116, 671–682

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