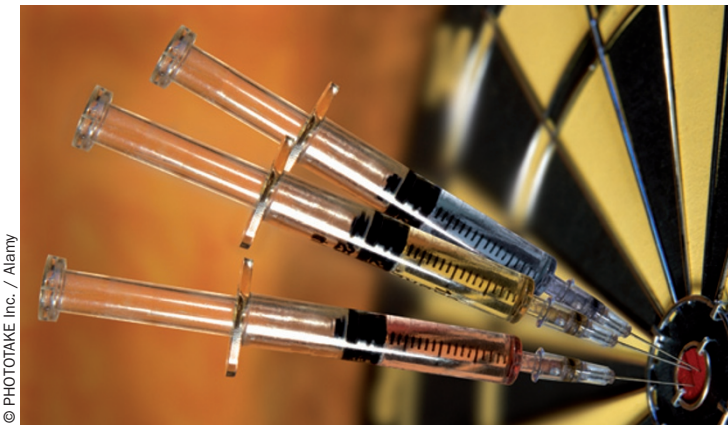
Nature Reviews Neurology **9**, 543 (2013); published online 10 September 2013; doi:10.1038/nrneurol.2013.193

NEURODEGENERATIVE DISEASE

PDK1—a common therapeutic target for AD and prion disease?



© PHOTOTAKE Inc. / Alamy

Researchers in France have identified a possible role for 3-phosphoinositide-dependent protein kinase 1 (PDK1) in progression of prion disease and Alzheimer disease (AD), indicating that this enzyme could be targeted therapeutically in both of these conditions. Inhibition of PDK1 leads to an increase in α-secretase activity at the neuronal surface, causing cellular prion protein (PrP^{C}) and amyloid precursor protein (APP) to be cleaved into nonpathogenic forms.

"Our research arises from a stem cell background to tackle basic and clinical challenges relating to neurodegeneration," explains lead investigator, Benoit Schneider. "We exploit a neuroectodermal stem cell—the 1C11 cell line—which can give rise to serotonergic or noradrenergic neurons, and is our main cell paradigm for prion studies."

Schneider and his colleagues discovered that infection of 1C11 cells with the pathogenic prion PrP^{Sc} triggered overactivation of PDK1, which resulted in phosphorylation and internalization of the α-secretase TACE. Cleavage of PrP^{C} by TACE produces a truncated form of the prion protein that cannot undergo conversion to PrP^{Sc}, so PDK1-induced loss of TACE activity at the neuronal surface tips the balance in favour of PrP^{Sc} replication and aggregation.

Another function of the TACE α-secretase is to cleave APP into a neuroprotective secreted form, which is known as sAPPα. Schneider's team found that neurons from APP-transgenic mice with amyloid-β (Aβ) pathology exhibited increased PDK1 activity and consequent TACE internalization, which prevented sAPPα generation and promoted further production of Aβ.

The researchers found that PDK1 inhibition—via the PDK1 inhibitor BX912 or a small interfering RNA that targeted the *Pdk1* gene transcript—relocated TACE to the neuronal surface. "Inhibiting PDK1 activity in prion-infected mice prolonged survival, counteracted motor deficits and decreased PrP^{Sc} levels," reports Schneider. "In three distinct APP-transgenic mouse models of AD pathology, quenching PDK1 activity rescued TACE-mediated neuroprotective cleavage of APP, decreased Aβ production and deposition, and counteracted memory and cognitive deficits associated with AD pathogenesis."

Schneider and colleagues found evidence of increased PDK1 activity in postmortem brain tissue samples from patients with AD, underlining the clinical relevance of the new findings. "Our work identifies PDK1 as a promising therapeutic target for both prion disease and AD," Schneider concludes. He points out, however, that BX912 displays neurotoxicity, so his team is currently testing other commercially available PDK1 inhibitors, as well as planning the development of new drugs directed against PDK1.

Heather Wood

Original article Pietri, M. *et al.* PDK1 decreases TACE-mediated α-secretase activity and promotes disease progression in prion and Alzheimer's diseases. *Nat. Med.* doi:10.1038/nm.3302