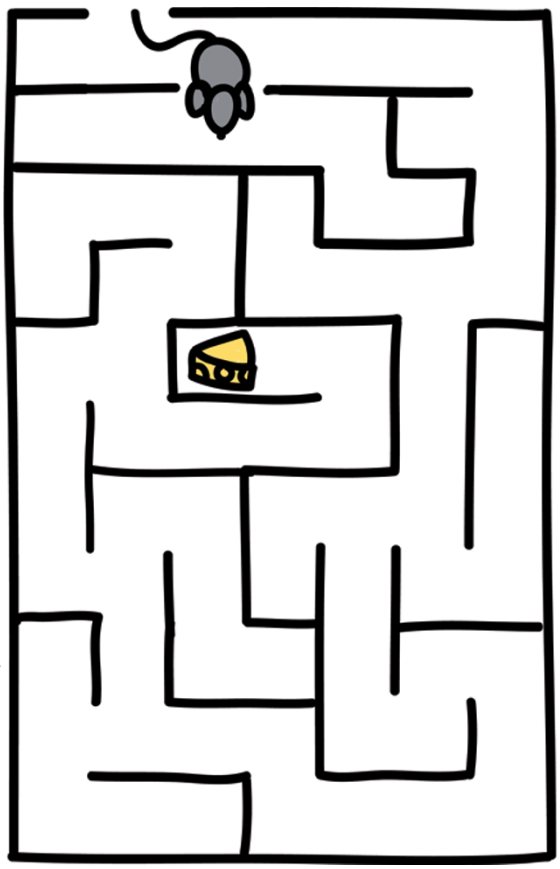
NEURODEGENERATIVE DISEASES

New kinase targets for Alzheimer's disease

Synaptic dysfunction due to the toxic effects of amyloid-β peptides is an early feature of Alzheimer's disease. Two recent studies show that inhibiting kinases involved in the regulation of amyloid precursor protein (APP) processing or protein synthesis by eukaryotic translation initiation factor 2α (eIF2α) attenuates disease progression in mice.

α-secretase-mediated cleavage of APP releases a soluble neuroprotective sAPPα fragment that hinders the formation of amyloid-β peptides. Reporting in *Nature Medicine*, Pietri *et al.* showed that the activity of tumour necrosis factor-converting enzyme (TACE), an enzyme that stimulates α-secretase, is reduced in patients with Alzheimer's disease and on the surface of neurons isolated from a mouse model of the disease. Furthermore, they found that 3-phosphoinositide-dependent protein kinase 1 (PDK1) activity is increased in both neurons affected by amyloid-β deposition and in the brains of patients. This triggers the internalization of TACE and impairs TACE-mediated α-secretase activity. When the authors inhibited PDK1 in three mouse models of Alzheimer's disease using the commercially available small-molecule inhibitor BX912 prior to the detection of plaque deposition, they found a decrease in the number of amyloid plaques and an increase in sAPPα levels compared with controls. Moreover, the treated mice showed improved performance in cognitive and memory tasks.



IllustrationCollection/Alamy

Interestingly, α-secretase also cleaves the cell surface prion protein PrP^{C}, preventing its conversion to pathogenic prions (PrP^{Sc}). Similar to the results in neurons from mice with Alzheimer's disease-like pathology, an upregulation of PDK1 activity and a concomitant reduction in TACE activity was observed in prion-infected neurons. When the authors inhibited PDK1 (with BX912 or small interfering RNA) in prion-infected mice before the onset of symptoms, they observed reduced impairments in motor function, an attenuation of neuronal loss in the cerebellum and reduced PrP^{Sc} deposition. These results suggest that inhibition of PDK1 could be a useful strategy to inhibit disease progression in both Alzheimer's disease and prion disease.

In a separate study, Ma *et al.* explored the mechanism underlying the increased phosphorylation of eIF2α, which has been observed in the brains of patients with Alzheimer's disease and in mouse models. eIF2α is a key regulator of mRNA translation and its activity is inhibited by phosphorylation. Alterations in eIF2α phosphorylation have been associated with memory impairments, so the authors examined whether Alzheimer's disease-associated impairments in synaptic plasticity and memory could be alleviated by lowering eIF2α phosphorylation. Genetically deleting either PERK or GCN2, two of the four kinases known to phosphorylate eIF2α, in a mouse model of Alzheimer's disease not only decreased the phosphorylation of eIF2α but also prevented the amyloid-β-induced impairments in synaptic plasticity and behavioural deficits that these mice inevitably develop. These findings could provide a basis for developing PERK and GCN2 inhibitors for Alzheimer's disease and potentially other diseases involving the disruption of translational homeostasis and memory dysfunction.

In both studies it will be interesting to determine whether inhibiting these kinases at later stages of the disease process could still be beneficial, given the challenges associated with early intervention in patients who develop Alzheimer's disease.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPERS Pietri, M. *et al.* PDK1 decreases TACE-mediated α-secretase activity and promotes disease progression in prion and Alzheimer's diseases. *Nature Med.* **19**, 1124–1131 (2013) | Ma, T. *et al.* Suppression of eIF2α kinases alleviates Alzheimer's disease-related plasticity and memory deficits. *Nature Neurosci.* **16**, 1299–1305 (2013)