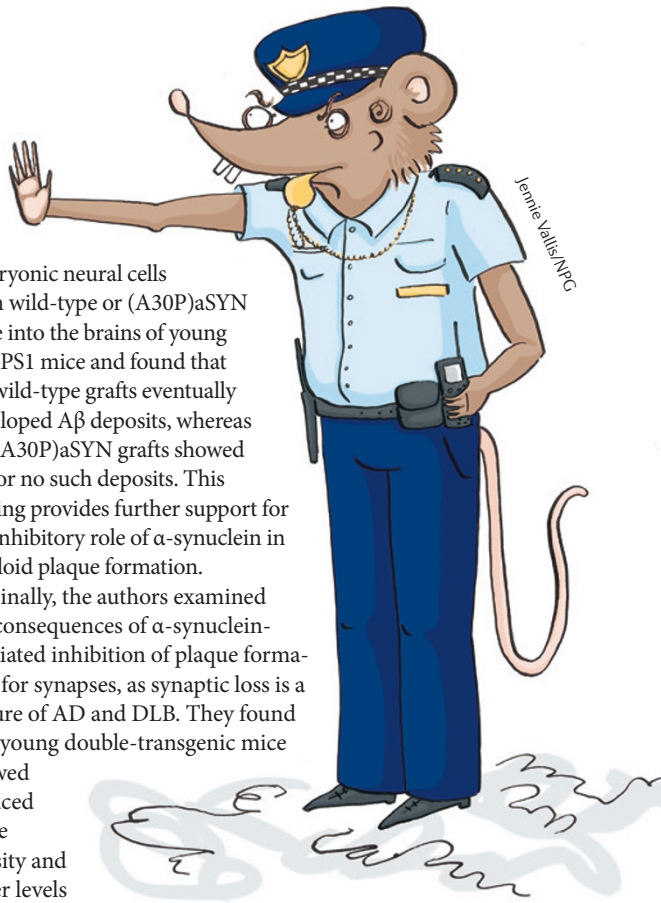
NEURODEGENERATIVE DISEASE

Impeding deposition



Lewy bodies and other types of α-synuclein-rich pathology are typically associated with Parkinson disease but can also be found in many cases of Alzheimer disease (AD). Several studies have indicated that α-synuclein and amyloid-β (Aβ) — the principal component of one of the hallmark pathologies of AD, namely amyloid plaques — interact, but it is unknown whether α-synuclein affects Aβ pathology *in vivo*. Now, Bachhuber *et al.* show in mice that α-synuclein inhibits amyloid plaque formation and, as a result, might exacerbate synaptic pathology.

Previous studies have found that fibrils of α-synuclein could induce the aggregation of tau, another protein implicated in several neurodegenerative diseases. Thus, the authors examined whether α-synuclein could similarly 'cross-seed' amyloid plaque formation. To do so, they used mice that expressed mutant forms of amyloid precursor protein (APP; from which Aβ is derived) and presenilin 1 (which is involved in APP processing) in neurons and eventually developed amyloid plaque pathology (APPPS1 mice), and mice that expressed a mutant form of α-synuclein and eventually developed Lewy body pathology ((A30P)aSYN mice).

The authors intracerebrally injected 6-week-old, pre-pathology APPPS1 mice with brain homogenate from wild-type mice, APPPS1 mice with amyloid plaques or (A30P)aSYN mice with α-synuclein pathology. They found that only the APPPS1 homogenate induced plaque formation in the hippocampus, indicating that α-synuclein does not initiate plaque formation.

To examine whether α-synuclein may have some other role in plaque development, the authors crossed the APPPS1 and (A30P)aSYN mice to generate 'double-transgenic' animals. These double-transgenic mice exhibited reduced hippocampal plaque load compared with APPPS1 mice at 4 months of age, although both groups had similar brain levels of APP and the two main forms of Aβ.

The findings described above suggest that α-synuclein might in fact impair plaque formation. In further support of this assertion, cerebral injection of brain homogenate from plaque-harbouring APPPS1 mice induced markedly less hippocampal plaque formation in the double-transgenic mice than in the APPPS1 mice. Moreover, in APPPS1 mice, injection of a mixture of brain homogenates from plaque-containing APPPS1 and (A30P)aSYN mice induced considerably less cross-seeding than did injection of APPPS1 brain homogenate. Finally, frontal cortex homogenates from patients with AD who had plaque pathology induced much more seeding in APPPS1 mice than did those from patients with dementia with Lewy bodies (DLB), which is usually associated with both Aβ and α-synuclein pathology.

The authors had previously shown that Aβ was able to infiltrate and form deposits in grafted wild-type cells in mice. Here, they introduced embryonic neural cells from wild-type or (A30P)aSYN mice into the brains of young APPPS1 mice and found that the wild-type grafts eventually developed Aβ deposits, whereas the (A30P)aSYN grafts showed few or no such deposits. This finding provides further support for the inhibitory role of α-synuclein in amyloid plaque formation.

Finally, the authors examined the consequences of α-synuclein-mediated inhibition of plaque formation for synapses, as synaptic loss is a feature of AD and DLB. They found that young double-transgenic mice showed reduced spine density and lower levels of synaptophysin (a marker of synapses) compared with young APPPS1 or (A30P)aSYN mice, suggesting that the presence of both α-synuclein and Aβ might exacerbate synaptic pathology.

Together, these findings show that α-synuclein can inhibit Aβ deposition and hence plaque formation. Whether this effect results from a direct interaction between these proteins remains unclear, and the consequences of their interaction require further investigation.

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ORIGINAL RESEARCH PAPER
Bachhuber, T. *et al.* Inhibition of amyloid-β plaque formation by α-synuclein. *Nat. Med.* **21**, 802–807 (2015)

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