consequence and an unrelated epiphenomenon for neurodegeneration; they have even been proposed to protect against neurodegeneration. The original interest in α-synuclein derives from its prominent presence in protein aggregates such as Lewy bodies in different neurodegenerative diseases. But Xu *et al*. argue that at least in dopaminergic neurons transfected with α-synuclein, the soluble form of α-synuclein is responsible for its cytotoxicity, as no insoluble α-synuclein can be detected in these cells. While the results do not rule out the possibility of cytotoxicity from the insoluble form of α-synuclein, they do support the notion that the soluble form is sufficient to induce cell death. In PD, however, Lewy bodies may also contribute to chronic neurodegeneration by sequestering 14-3-3, releasing proapoptotic molecules and thereby increasing cellular sensitivity to stress. Consistent with this possibility, 14-3-3 immunoreactivity has been detected in Lewy bodies in PD (ref. 12).

The 36–83-kD α-synuclein complex may exist both in dopamingeric neurons where α-synuclein is cytotoxic as well as in non-dopaminergic neurons where α-synuclein may be protective. Thus the 36–83-kD complex by itself may not explain the selective neurotoxicity. Although a general increase of total α-synuclein complex occurs in PD brain, there may be a preferential increase in a smaller α-synuclein-containing complex of 36–54-kD[3]. Furthermore, in dopaminergic cells transfected with α-synuclein but treated with an agent that inhibits dopamine synthesis and thus α-synuclein cytotoxicity, there is a selective reduction in this 36–54-kD complex. Perhaps dopamine promotes the preferential formation of this smaller α-synuclein complex, which is responsible for cytotoxicity. It will be very interesting to know the precise composition of this 36–54-kD complex—such as whether it contains 14-3-3. Another puzzle is the mechanism by which dopamine upregulates the 36–83-kD complex. In any case, Xu *et al*. provide a strong and testable hypothesis for further experiments by proposing that sequestration of 14-3-3 is key to neurodegeneration in PD.

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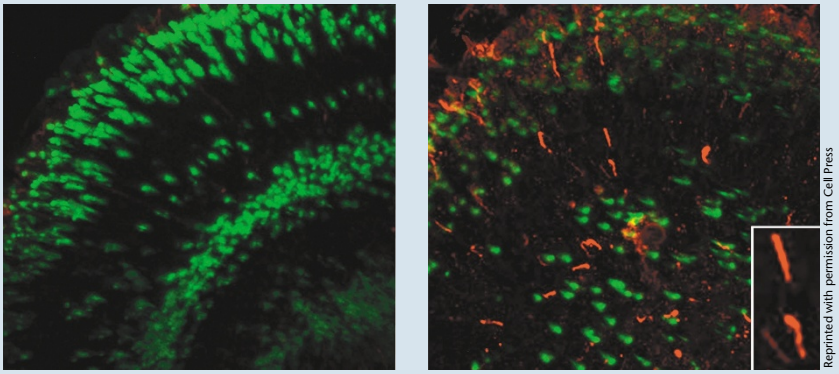
Flies tangle with tau



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In humans, neurofibrillary tangles in patients with Alzheimer disease (AD) and several other neurodegenerative disorders contain a hyperphosphorylated form of the microtubule-associated protein tau. Mutations in *TAU* have also been linked to a rare inherited form of frontotemporal dementia. Now it appears that flies coaxed to hyperphosphorylate tau may also have symptoms of neurodegeneration.

In the 16 May *Neuron*, Jackson *et al.* present results from flies engineered to overexpress tau. Tau overexpression set the stage for asking whether known modifiers of tau could lead to tangles. The researchers focused on glycogen synthase kinase-3β (GSK-3β), called shaggy in flies. This member of the Wnt signaling pathway phosphorylates tau *in vitro* and in mice, and interacts with other proteins implicated in AD, such as presenilin. The researchers found that overexpressing shaggy and human tau resulted in the hyperphosphorylation of tau, neurofibrillary tangles and cell death, all hallmarks of neurodegeneration.

On the right is a fly eye overexpressing shaggy and human tau, and on the left is an eye overexpressing only human tau. The eyes are stained for DNA (green) and with antibodies that recognize phosphorylated tau (red). In subsequent experiments using antibodies to cell components sensitive to cell death, the researchers found that the shaggy-overexpressing cells underwent apoptosis – that's consistent with the nuclear disorganization seen with DNA stains (right). Only in the presence of excess shaggy does tau form neurofibrillary tangles (on right and in inset) and initiate cell death.

The new data help clear up the question of whether hyperphosphorylation of tau is a cause, rather than a consequence, of tangle formation. In fact the researchers saw evidence of cell death before the formation of tangles, hinting that it may be tau itself and not tangle formation per se that leads to neurodegeneration. The fly model is particularly useful for genetic screens to look for additional modifiers of tau – and this study leads the way. The authors point out that in human disease, it may be defects in modifiers of tau, rather than tau itself, that initiate the neurodegenerative process.

CHARLOTTE SCHUBERT