ALZHEIMER DISEASE

Tau wanders around the brain

A study in mice has shown that mutant tau protein can cause wild-type tau to assemble into filaments, and that this pathology can then spread to adjacent brain regions. "This spreading process is very similar to what we observe during the natural progression of various tauopathies, including Alzheimer disease (AD)," comments senior author Markus Tolnay, of the University of Basel, Switzerland. Tolnay stresses, however, that "this does not mean, by a very long way, that AD is infectious and could be transmitted from human to human."

Neuronal tau inclusions are intimately associated with AD, as well as other neurodegenerative diseases such as Pick disease, progressive supranuclear palsy and corticobasal degeneration. Florence Clavaguera and colleagues prepared brain extracts from transgenic mice that expressed the Pro301Ser mutant form of human tau and showed obvious signs of neurodegeneration related to the build-up of tau filaments within neurons. Diluted brain extracts were injected into the hippocampus and overlying cerebral cortex of recipient ALZ17 mice, which express wild-type human tau. Analysis 6, 12 and 15 months later, using immunoelectron microscopy, Gallyas–Braak silver staining and immunoreactivity with the tau-filament-specific antibody AT100, showed that the recipient mice had developed intracellular assembled tau filaments (Figure 1). At the later time points, these filaments were present not only at the injection site but also in neighboring brain regions.

"This is a very important study—this process of 'inducible assembly' has also been shown for α-synuclein, amyloid-β and prion particles—we have suggested the term 'permissive templating' to describe it," comments John Hardy, of the Institute of Neurology, University College London, UK. Demonstrating that permissive templating occurs with tau should help us to understand how tau spreads between brain cells during the disease process. "So far, the research focus has been on what happens inside the cell as hyperphosphorylated tau detaches from microtubules and becomes misfolded and aggregated—we now have to look at how intracellular tau pathology passes from cell to cell," notes Michel Goedert, another senior author of the study, from the Medical Research Council Laboratory of Molecular Biology, Cambridge, UK. Hardy agrees that it is imperative to "understand the molecular species involved in the spread of tau pathology through the brain".

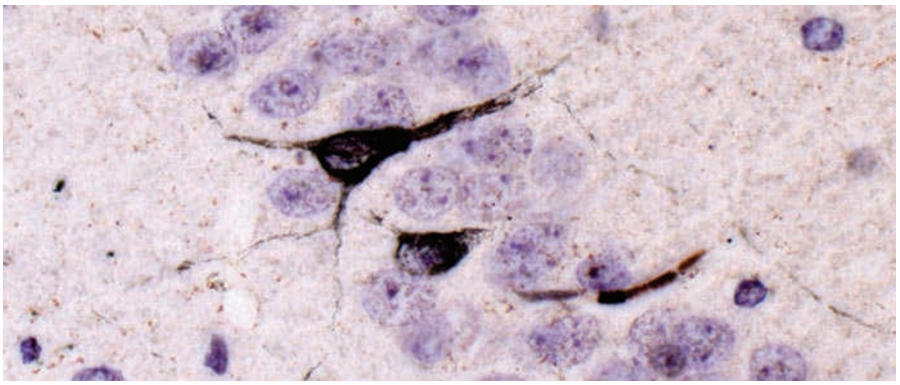

Figure 1 | Induced tau tangle in the brain of an ALZ17 mouse. The brain section was stained by the Gallyas–Braak method. The tangle closely resembles a neurofibrillary tangle, as seen in Alzheimer disease. Image provided by Prof. Markus Tolnay.

Goedert is convinced that studying the mechanisms by which tau becomes extracellular and is then taken up by other cells could reveal many new points for therapeutic intervention, including "clearance of extracellular tau, blocking release or uptake of pathological tau". John Trojanowski, of the Alzheimer Disease Core Centre, University of Pennsylvania School of Medicine, Philadelphia, PA, USA, stresses that the current study has important implications for how we think of disease pathogenesis for AD, other tauopathies and neurodegenerative brain amyloidoses. "It could also suggest new research pathways to answer some important questions—why, for example, tau filaments aggregate in neurons in tauopathies but not in surrounding glial cells or in the endothelial cells that line blood vessels that permeate the brain so profusely," Trojanowski explains.

Tolnay cautions that the current findings now need to be confirmed in other mouse models. "It will also be interesting to see if tau immunotherapy would work in our model," he suggests. Plans are being made to dissect which parts of the insoluble tau are responsible for the spread of tau-related pathology from one part of the brain to another. "We know that soluble tau has almost no effect, but we need to know which conformers are primarily responsible for spreading—*in vitro*-generated tau fibrils may be of help in this," explains Tolnay. Other intriguing questions include: do tau fibrils of other, non-mutant tauopathies, such as AD, Pick disease and progressive supranuclear palsy, also induce fibrillar tau pathology in recipient mice that express wild-type human tau protein? Also, do similarities exist between the prion strains and the tau isoforms that are important in transmission and spreading? "All the experiments we devise to answer these questions should still be aimed at finding new therapeutic options to stop the progress of tau pathology," concludes Tolnay.

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