Nature Reviews Neurology | Published online 21 Jul 2017; doi:10.1038/nrneurol.2017.107

ALZHEIMER DISEASE

Tau pathology in atomic detail

> the structural knowledge could be used to aid rational design of therapeutics

The atomic structures of tau filaments that form in the human brain in sporadic Alzheimer disease (AD) have been revealed for the first time in *Nature*. The work will provide the basis for future investigation of tau filaments as therapeutic targets in tauopathies, and for studies of protein filaments that form *in vivo* in other diseases.

"Tauopathies are characterized by the presence of abundant filamentous tau deposits, and their formation is believed to cause disease," explains Michel Goedert, who led the study with Sjors Scheres at the Medical Research Council Laboratory of Molecular Biology, Cambridge, UK. "It is therefore important to know what a tau filament looks like at the atomic level." This knowledge is important for understanding how the filaments develop and, therefore, how their formation might be prevented.

Structures of other disease-associated filaments have been resolved, but only from filaments grown *in vitro*, leaving uncertainty about their similarity to structures that form *in vivo*. In their study, Goedert, Scheres and colleagues investigated tau filaments that had arisen in the brain of a patient with AD.

The researchers isolated paired helical filaments and straight filaments from post-mortem samples of the cerebral cortex of a woman who had died aged 74 years after 10 years with AD. They then used cryo-electron microscopy (cryo-EM) to visualize the structures of these filaments.

"Cryo-EM was ideal to work with the small amounts of unlabelled protein that one can purify from the human brain," says Scheres. "X-ray crystallography requires 3D crystals, which are very hard to obtain for these types of samples, and NMR requires isotope-labelled samples, precluding work with human tissue."

3D reconstructions of the two filament cores revealed that both are made up of two C-shaped protofilaments that each comprise eight β-sheets. Arrangements of the protofilaments differed: in paired helical filaments, the two protofilaments were packed symmetrically, whereas they were packed asymmetrically in straight filaments.

The authors say the structural knowledge could be used to aid rational design of therapeutics that block tau aggregation, and to develop specific tracers for imaging of AD-associated tau pathology. The technique that was used to image filaments from human brain tissue could also be applied to other diseases.

"Our work shows that cryo-EM can be used to obtain high-resolution structures of filaments from human brain. Besides tau, this may apply to amyloid-β, α-synuclein, prions and more," says Goedert. "It will be important to see how tau filaments from other human diseases differ from those of AD at the atomic level."

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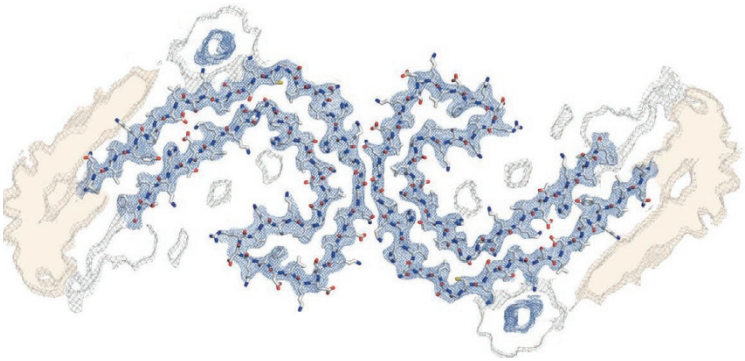

Cross section of the protofilament core structure in the paired helical tau filament from the brain of a patient with Alzheimer disease, identified with cryo-electron microscopy. Modified with permission from Nature Publishing Group © Fitzpatrick, A. W. *et al. Nature* http://dx.doi.org/10.1038/nature23002 (2017).

ORIGINAL ARTICLE Fitzpatrick, A. W. *et al.* Cryo-EM structures of tau filaments from Alzheimer's disease. *Nature* http://dx.doi.org/10.1038/nature23002 (2017)