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NEURODEGENERATION

Taming tangled tau

The protein tau forms abnormal filamentous aggregates called tangles in the brains of people with neurodegeneration. Structures of two such filaments offer pathways to a deeper understanding of Alzheimer's disease.

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In the early twentieth century, the German psychiatrist Alois Alzheimer reported the presence of 'tangled' intracellular structures in the brain of a person who'd had dementia. The tangles were later found to consist of abnormal aggregates, known as amyloid fibrils, of the protein tau[1]. Tau amyloid fibrils seem to be at the root of dozens of age-related types of dementia and movement disorders[2], most notably Alzheimer's disease. In a paper online in *Nature*, Fitzpatrick *et al.*[3] report a crucial step towards understanding tau amyloid fibrils, describing structures for the two types of fibril seen in Alzheimer's disease — paired helical and straight tau filaments.

Normal tau stabilizes molecular tracks called microtubules, along which cargo is transported in long neuronal projections in the brain. But when tau is overproduced or shed from microtubules, it stacks up, forming amyloid fibrils of various conformations that spread from cell to cell. Some evidence suggests that the various tau-related dementias may each result from fibrils of different conformations[4].

Fitzpatrick *et al.* extracted tau amyloid fibrils from the brain of a 74-year-old woman who had been diagnosed with Alzheimer's disease 10 years before her death. They visualized the fibrils using a technique called cryo-electron microscopy (cryo-EM)[5]. Of the protein's 441 amino-acid residues, the 73 residues that make up the stable core of tau amyloid fibrils are clearly visible in the cryo-EM maps, whereas most of the residues at the ends of the protein are too poorly ordered to be seen.

The authors found that a C-shaped curve, observed in a previous low-resolution study of fibrils[6], could be resolved as stacked copies of tau. Each copy formed the letter C; one half tracing a C-shaped curve, and the other half sharply reversing to trace another C inside the first ***[OK?]***. One C-shaped stack forms a protofilament, and two protofilaments wind around each other to form the amyloid fibril (Fig. 1). In the paired helical filaments, the protofilaments make contact symmetrically near the sharp turn, whereas in the straight filaments, the two protofilaments make contact asymmetrically nearer to the opposite tip of the C.

These molecular-level structures reveal some familiar and some unexpected features for an amyloid fibril. The curved stacks of tau in the protofilaments run parallel to each other, like threads in a sheet. The tau segment that makes up the outside C-curve packs tightly against the segment that makes up the inner curve, excluding water molecules to form a dry interface called a steric zipper[7]. Exclusion of water lends stability to the filaments, thereby impeding their clearance from the cell. This type of interface is characteristic of all amyloid fibrils studied at molecular resolution.

The sharp turn at the closed tip of the C-shape has an unexpectedly high level of structural complexity, more typical of structures that have evolved to provide some survival advantage. This motif, called a β-helix, requires a precise pattern of polar, apolar, and small and large amino-acid residues (Fig. 1). The complexity of its pattern suggests that it could be used to develop diagnostic markers to distinguish Alzheimer's disease from other tau-associated diseases.

Another surprising feature is the lack of repeated structural motifs. Tau has 4 imperfect repeats of a sequence around 31 amino-acids long[2]. Fitzpatrick *et al.* show that two of these, R3 and R4, are included in the core of the fibrils. However, structural similarity

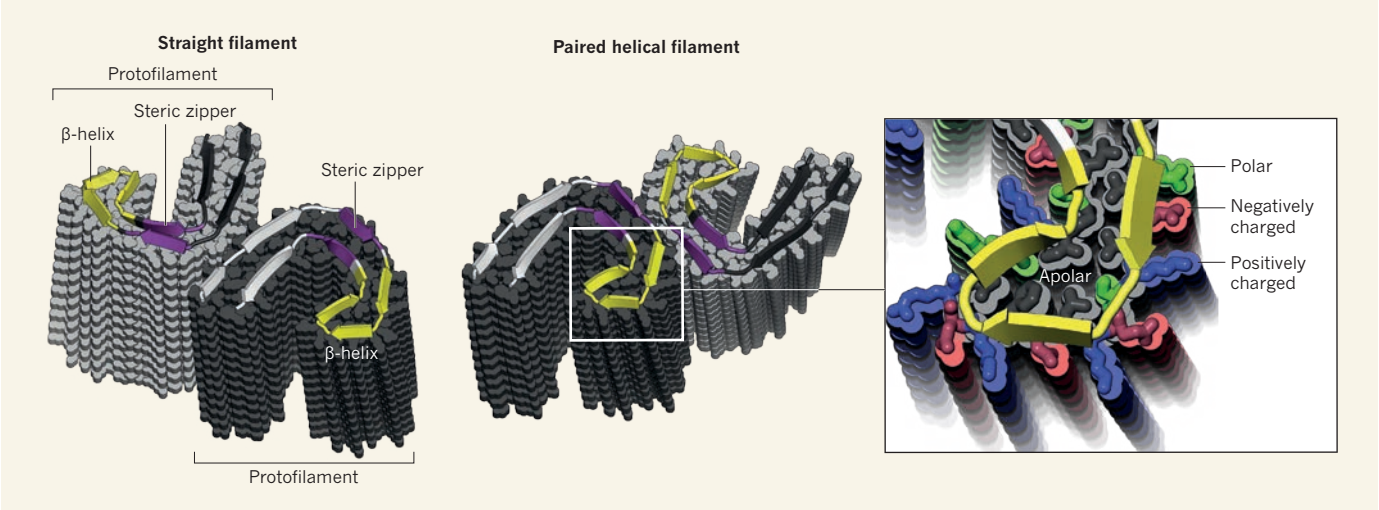

Figure 1 | Structures of tau protein filaments. Fitzpatrick *et al.*[3] imaged two types of abnormal tau aggregate — straight filaments and paired helical filaments — from the brain of a person who'd had Alzheimer's disease. In both cases, individual tau proteins form C shapes (the protein's main chain is indicated by a cartoon ribbon with arrows, side chains are shown in grey around the ribbon), which stack together to form protofilaments. Here, 14 protein layers are shown in each protofilament. The filaments are composed of two identical protofilaments, connected at different interfaces. Notable features of the protofilaments include a steric zipper (a common motif in aggregated proteins, which resists disassembly; purple) and a surprisingly complex structure called a β-helix (yellow). This structure (magnified in the inset) requires amino acids to occur in a precise pattern such that hydrophilic (charged and polar) amino-acid side chains face outward, and hydrophobic, apolar side chains face inward.

between R3 and R4 is limited to a short region spanning only eight residues. This disparity is a stark contrast to the common finding in structural biology that similar sequences adopt similar structures, and speaks to the challenge of predicting amyloid structure from sequence data alone.

These two tau filaments are the longest amyloid fibrils visualized at the molecular level so far. That the filaments come directly from a diseased brain confirms that the structure is relevant to Alzheimer's disease. Perhaps most importantly, the techniques used here could be applied to other disease-related amyloid fibrils, for which high-quality structures have proved equally elusive.

Fitzpatrick *et al*. collected some 2,000 images of fibrils at high magnification using cryo-EM. The images, which reveal tau molecules from many angles, were aligned computationally and averaged to reduce noise, permitting 3D reconstruction of the fibril structure. The authors minimized blurring due to small variations in fibril twists by cropping out all but the central, most coherent portion of the aligned images. Developing the software to accomplish these steps is a major achievement by one of the current study's authors[5].

The researchers chose cryo-EM, rather than another sophisticated technique for structure resolution called X-ray crystallography, to analyse tau amyloid fibrils because it is impossible to coax partially disordered fibrils into crystals. Although the lack of need for crystalline specimens is a huge advantage of cryo-EM, the structures determined do not fully resolve atoms, and additional information is often needed to nail down the structures. X-ray crystallography structures hold millions to billions of molecules in the same orientation, providing relatively noise-free information and permitting — in the best cases — resolution at truly atomic scales. An up-and-coming method, microelectron diffraction, shares features of both X-ray crystallography and cryo-EM, but so far has not determined amyloid structures as large as tau[8,9].

Fitzpatrick *et al*. acknowledge that their findings are the culmination of work that began with a conversation 34 years ago at the MRC Laboratory of Molecular Biology in Cambridge, UK, between chemist Aaron Klug and psychiatrist Martin Roth about the structural analysis of Alzheimer's filaments. Indeed, two of the authors started their work on tau in that research institute in the 1980s. The institute has funded the development of the cryo-EM methods for decades, enabling the authors to make a giant step and give us the first molecular-level structure of tau fibrils from the brain of a patient. An implicit lesson emerges from this groundbreaking study: long-term support is essential for influential science. ■

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