Neurodegeneration

Structural strains of tau protein classify diseases

Henning Stahlberg & Roland Riek

In diseases called tauopathies, misfolded tau proteins form aggregates called fibrils. Fibrils from nine different tauopathies show that tau misfolds in many ways, enabling the diseases to be classified according to fibril structure. **See p.359**

The protein tau contributes to the normal functioning of cells in the brain by adopting a specific structural conformation and stabilizing microtubules, which are protein filaments that act like railroads to enable various materials to be transported throughout the cell. However, in Alzheimer's disease and related diseases called tauopathies, misfolded tau molecules stack together in a manner similar to a one-dimensional crystal, and form needle-shaped fibrils around one micrometre long. Although all types of tau fibril are composed of tau molecules, these fibrils can occur in different 3D structural forms (strains), known as polymorphs. Shi *et al.*[1] report on page 359 the high-resolution structures of previously uncharacterized strains of tau fibril that were purified from the post-mortem brains of individuals with various neurodegenerative diseases, thereby establishing a disease classification based on tau fibril structure (Fig. 1).

Fibril strains were originally described for prion proteins[2], which act as infectious agents in prion diseases such as Creutzfeldt–Jakob disease by spreading between cells and seeding the formation of prion fibrils in infected cells. Like fibrils of prion protein, fibrils of misfolded tau grow by a mechanism in which individual tau molecules use the end of the fibril as a template to adopt the same protein conformation when attaching to the elongating fibril. Fibrils can also break apart to increase in number, and can somehow reach neighbouring brain cells, leading to the tau fibrils' spread. This eventually results in neurodegeneration and disease because the fibril entity, or a precursor of it, is thought to be toxic[3].

Genetic differences can be used to define different bacteria and viruses — for example, the various strains of the coronavirus SARS-CoV-2 in the COVID-19 pandemic. By contrast, strains of protein fibrils are defined by their distinctive 3D structures. Researchers from the same group as Shi *et al.* previously analysed several of these fibril strains for tau[4–8]. In these previous studies, tau fibrils were isolated from the brains of individuals with Alzheimer's disease, Pick's disease, chronic traumatic encephalopathy or corticobasal degeneration. The fibrils were analysed structurally using cryo-electron microscopy. Each of these four tauopathies was associated with tau fibrils that had different structures, and in individuals who had the same disease the same fibril polymorph was present.

Shi *et al.* now report the high-resolution structures of tau fibril strains purified from the brains of individuals who had been diagnosed with one of a further nine tauopathies. These included some tauopathies for which the causes are unknown, and others that result from specific mutations (for example, in the gene encoding tau).

In total, Shi *et al.* classified 14 conformations of tau in these fibrils. In some diseases, fibril polymorphs resembled those previously found in the brains of individuals with Alzheimer's disease or in people with chronic traumatic encephalopathy. In others, tau fibril polymorphs were found that had never been examined structurally before. In some diseases, a mixture of polymorphs was present. And, in most cases, individuals with the same disease showed the same tau strains, and the tau strains usually differed between diseases. This finding confirms a direct correlation between structural tau strains and specific tauopathies. Along with other work by Shi and members of this research group[9] that assessed posterior cortical atrophy, this establishes a classification of 14 neurodegenerative diseases (or 19 if disease subtypes are included) on the basis of the structures of their tau fibrils.

The structure–activity relationship is a well-known concept in protein science, and refers to the relationship between the structure of a protein and its function. Shi and colleagues' findings reveal a 'structure–disease relationship' between misfolded tau conformations and their association with different tauopathies — suggesting that medical approaches to diagnosing and treating the various tauopathies should take molecular structure into account.

It is possible that these fibrils represent the key to solving the mechanism of toxicity and the neurodegenerative processes that, in each of these diseases, affect respective brain regions in different ways and at different speeds. Where and how tauopathies initiate and progress, how cells are damaged and what role the fibrils have are key questions for individuals with tauopathies and the doctors treating them, as well as for pharmaceutical researchers.

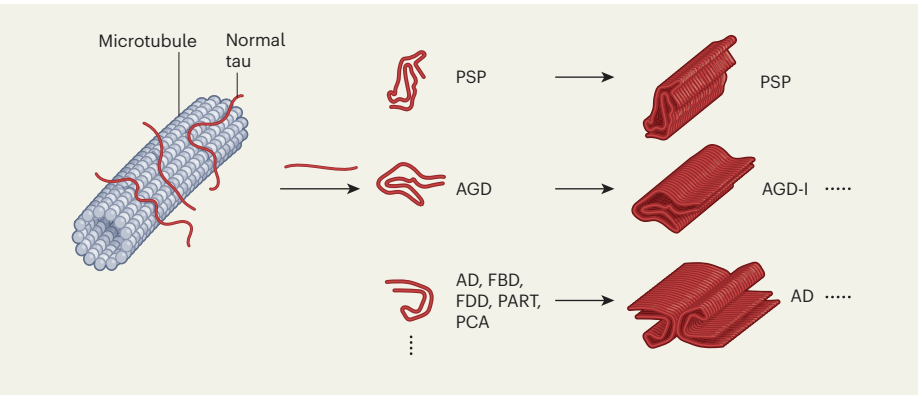

Figure 1 | Tau protein misfolds differently in the various tauopathies. The protein tau stabilizes protein filaments called microtubules that enable transport of vesicles and organelles in cells. In neurodegenerative diseases termed tauopathies, tau in brain cells misfolds and stacks together to form fibrils. Shi *et al.*[1] examined the structure of tau fibrils in post-mortem brain samples from people with nine different tauopathies, including progressive supranuclear palsy (PSP), a subtype of argyrophilic grain disease (AGD) termed AGD-I, familial British dementia (FBD), familial Danish dementia (FDD) and primary age-related tauopathy (PART). Individuals with the same disorder usually showed the same structural forms of tau fibril. Combined with previous work[4–9] showing the structures of misfolded tau in other tauopathies, including Alzheimer's disease (AD) and posterior cortical atrophy (PCA), these results enable classification of tauopathies on the basis of the tau fibril structure; three such structures are shown schematically here. In some diseases, tau fibrils consist of one protofilament; in others (such as Alzheimer's disease), they contain two interacting protofilaments. Dots indicate examples that are not shown.

Are fibrils a consequence of the disease, merely correlated with it, or a cause? In the context of this question, Shi and colleagues' finding that the fibril type differs between diseases, but is largely reproducible in people with the same disease, is an intriguing result. It is difficult to imagine a scenario in which the 19 different neurodegenerative tauopathy diseases analysed so far lead to the misfolding of tau into reproducible fibrils in a total of 17 different ways (in the structural data from this new work and the previous studies). As such, it would seem highly unlikely that the variation in fibril type is a secondary consequence — that is, an indirect effect of events that occur downstream of the main disease-causing mechanisms.

Another possible interpretation of Shi and colleagues' findings is that healthy tau can form many different strains of fibril under normal conditions, but that specific tauopathies favour the formation and propagation of some of the fibril polymorphs in certain cell types. This type of adaptation was previously documented for prion diseases. In the presence of the drug swainsonine, a population of drug-resistant prion fibrils emerged, whereas after the drug was removed the swainsonine-sensitive prion fibrils reappeared[10]. These findings indicate that, in the case of the prion protein, the infectious material is composed of a pool of several fibril polymorphisms[10].

A third possible interpretation of Shi and co-workers' findings is that a certain fibril type causes intracellular damage in a particular way — for example, by exposing a certain fibril surface that is toxic for a certain function of a specific cell type. Indeed, each of the fibril polymorphs determined in Shi and colleagues' work has different exposed surfaces and varying flexibilities or stabilities. Therefore, it seems probable that the fibril types specific to each disease have a causative connection with the mechanism by which damage occurs in the cell[11]. Whatever the underlying reasons for the observed fibril patterns turn out to be, Shi and colleagues' findings are a milestone in our understanding of the broader family of amyloid diseases, which involve the build-up of proteins, and of tauopathies specifically.

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Ageing

How overnight fasting could extend lifespan

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A feeding schedule of prolonged overnight fasting periods extends healthy lifespan in fruit flies by promoting night-time autophagy, a process in which material in cells is degraded and recycled. **See p.353**

Timing is said to be the secret to comedy and to success in life, but it could also be one of the secrets to a longer, healthier life. The quest to extend healthy lifespan has been made seemingly attainable in humans through manipulations of calorie intake, such as caloric restriction[1,2]. However, restricting calories for more than a short time is difficult because the intense hunger is hard to withstand for most. Manipulations that focus not on the number of ingested calories, but on the timing of ingestion, such as time-restricted feeding (TRF) might be much more sustainable. Ulgherait *et al.*[3] show on page 353 that, in the fruit fly *Drosophila melanogaster*, a TRF schedule that includes prolonged periods of overnight fasting extends healthy lifespan. It does so by promoting an intracellular degradation and recycling process called autophagy, specifically at night[4,5].

"This intermittent time-restricted feeding schedule increased lifespan by 18% in females and 13% in males."

Studies of intermittent fasting — a type of TRF schedule that cycles between periods of fasting and eating — in various species have consistently reported improvements in many health indices, even without reductions in calorie intake. The benefits of intermittent fasting in humans include abdominal fat loss and improvements in glucose metabolism, blood pressure, heart-rate variability and physical endurance[6–8]. Moreover, several of the main positive effects of caloric restriction on metabolism, organ function and disease resistance that have been seen in humans are recapitulated with intermittent fasting, and can be dissociated from those of weight loss and total caloric intake[1,6].

TRF and other types of intermittent-fasting schedule are lifestyle interventions that can be applicable worldwide and thus benefit people in a truly egalitarian way. But how TRF schedules promote health and extend lifespan must first be understood. Intermittent fasting induces a change from metabolism of sugar and carbohydrates to metabolism of fatty acids and other nutrients — a process called metabolic shifting. The health contributions of this process must be distinguished from those of caloric restriction and weight loss, which could result from fasting, if we are to grasp more fully the responses to each of these dietary manipulations.

Ulgherait and colleagues modified a standard TRF schedule that alternated 12-hour fasts with 12-hour feeding periods to a regime in which 20-hour fasting periods that included the night (when fruit flies, like humans, are least active) were alternated with feeding periods of 28 hours (Fig. 1a). This intermittent time-restricted feeding (iTRF) schedule increased lifespan by 18% in females and 13% in males, compared with flies that had unrestricted access to food.

An extended lifespan is undesirable when health is not preserved — as in the Greek myth of Tithonus, who became immortal but was destined to age forever because he lacked eternal youth. However, the authors showed that iTRF not only improved lifespan, but also protected against declines in muscular, neuronal and intestinal function with age.