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Invited review: Prion-like transmission and spreading of tau pathology

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Prion-like transmission and spreading of tau pathology

Filaments made of hyperphosphorylated tau protein are encountered in a number of neurodegenerative diseases referred to as 'tauopathies'. In the most prevalent tauopathy, Alzheimer's disease, tau pathology progresses in a stereotypical manner with the first lesions appearing in the locus coeruleus and the entorhinal cortex from where they appear to spread to the hippocampus and neocortex. Propagation of tau pathology is also characteristic of argyrophilic grain disease, where the tau lesions appear to spread throughout distinct regions of the limbic system. These findings strongly implicate neurone-to-neurone propagation of tau aggregates. Isoform composition and morphology of tau filaments can differ between tauopathies suggesting the existence of conformationally diverse tau strains. Altogether, this points to prion-like mechanisms in the pathogenesis of tauopathies.

Keywords: propagation, tauopathy, transmission

Tau protein and tauopathies

In the adult human brain, there are six isoforms of the microtubule-associated protein tau produced from a single gene (*MAPT*) located on chromosome 17q.31. They differ from each other by the presence or absence of a 29- or 58-amino acid N-terminal insert and a 31-amino acid repeat that is encoded by exon 10. The six isoforms can thus be divided into two groups of three isoforms each: those with three tandem repeats (3R) and those with four tandem repeats (4R) [1]. Natively unfolded, the microtubule-associated protein tau becomes hyperphosphorylated, insoluble and filamentous in a number of neurodegenerative diseases collectively referred to as tauopathies [2,3] (Table 1, and see also the review by Kovacs *et al*. in this issue). In Alzheimer's disease (AD) and tangle-only dementia (TD), 3R and 4R tau isoforms make up the neuronal inclusions [4,5], whereas in Pick's disease (PiD) tau isoforms with 3R predominate in the neuronal deposits [6]. The assembly of 4R tau into filaments, both in neuronal and glial cells, is a characteristic of progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and argyrophilic grain disease (AGD) [7–10]. Filaments from human tauopathy brains exhibit a range of morphologies [11], and specific conformers of aggregated tau give rise to distinct cellular tau pathologies. Thus, in AD and TD, tau inclusions occur in the form of neurofibrillary tangles (NFTs) and neuropil threads (NTs). NFTs are located in the somatodendritic compartment, whereas NTs are found in distal axons and dendrites. In AGD, abundant argyrophilic grains in neuronal processes, pretangle neurones, as well as glial tau inclusions in astrocytes and oligodendrocytes make up the hallmark lesions [12,13]. PSP brains are characterized by neuronal tau inclusions known as globose-type NFTs and NTs [14], as well as by glial changes in the form of tufted astrocytes and oligodendroglial coiled bodies [15,16]. CBD brains show intracytoplasmic pathological tau in NTs, pretangle neurones or small NFTs, as well as astrocytic plaques and

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Table 1. The spectrum of human tauopathies

Diseases with tau inclusions
Alzheimer's disease
Amyotrophic lateral sclerosis/parkinsonism-dementia complex
Argyrophilic grain disease
Chronic traumatic encephalopathy
Corticobasal degeneration
Diffuse neurofibrillary tangles with calcification
Down's syndrome
Familial British dementia
Familial Danish dementia
Frontal variant of Alzheimer's disease
Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by MAPT mutations
Gerstmann–Sträussler–Scheinker disease
Guadeloupean parkinsonism
Myotonic dystrophy
Neurodegeneration with brain iron accumulation
Niemann–Pick disease, type C
Non-Guamanian motor neurone disease with neurofibrillary tangles
Pick's disease
Postencephalitic parkinsonism
Prion protein cerebral amyloid angiopathy
Progressive subcortical gliosis
Progressive supranuclear palsy
SLC9A6-related mental retardation
Subacute sclerosing panencephalitis
Tangle-only dementia
White matter tauopathy with globular glial inclusions

coiled bodies [17–19], whereas Pick bodies are mainly present in nerve cells of patients with PiD [20]. Mutations in the tau gene lead to cases of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17*T*) associated with abundant tau positive-inclusions, demonstrating that dysfunction of tau protein *per se* is sufficient to cause neurodegeneration and dementia [21–23]. Neuropathologically, FTDP-17*T* presents with severe nerve cell loss, astrocytic gliosis and spongiosis, with filamentous tau inclusions in nerve cells or in both nerve cells and glial cells. Depending on the mutation, the cerebral inclusions are composed predominantly of 3R, 4R or a mixture of all six tau isoforms [24] (see also the review by Ghetti *et al.* in this issue).

During the clinical course of AD and AGD, filamentous tau inclusions propagate throughout the brain following a stereotypical pattern, thereby providing the basis for disease staging. In AD, tau pathology is staged using a six-tiered system of criteria defined by Braak & Braak [25,26]. Braak stages I and II correspond to the appearance of NFTs in the transentorhinal and entorhinal cortex and are not associated with clinical dementia. More pronounced involvement of these two regions and formation of NFTs in the hippocampus, the fusiform gyrus and temporal cortex are characteristics of stages III–IV. The degree of neuronal damage at stages III–IV may determine the appearance of first clinical symptoms. Stages V and VI correspond to abundant spreading of NFTs to isocortical association areas. Patients with Braak stages V and VI are severely demented and meet the neuropathological criteria for the diagnosis of AD. The six-tiered Braak stages of AD are based on silver-stained, hyperphosphorylated tau aggregates. In a more recent study, Braak and Del Tredici reported silver-negative but AT8-positive neuronal tau inclusions (first in proximal axons, and thereafter extending to the entire somatodendritic compartment) in the locus coeruleus of the majority of children and young adults, in the absence of beta-amyloid (Aβ) deposits (stages a–c, 1a, 1b) [27]. Neurones of the locus coeruleus project to the transentorhinal cortex suggesting anterograde axonal transport of tau aggregates, followed by their neurone-to-neurone transmission.

In AGD, the earliest changes are restricted to the ambient gyrus (stage I according to the classification proposed by Saito *et al.* [28]), from where the pathological process extends to the anterior and posterior medial temporal lobe (stage II), followed by the septum, insular cortex and anterior cingulate gyrus (stage III). Stage III is characteristic of patients with a clinical diagnosis of dementia [28].

Experimental transmission of tauopathy

The propagation of tau pathology during the clinical course of tauopathies clearly points to the existence of mechanisms for the intercellular transfer of tau aggregates. Over the past years, these notions have been experimentally substantiated through the description of neurone-to-neurone propagation of tau aggregates, both *in vivo* and *in vitro*.

We were the first to demonstrate the experimental induction and propagation of tau pathology using mouse lines transgenic for single isoforms of human wild-type (line ALZ17) and mutant (line P301S) tau [29–31]. We injected brain homogenates from P301S mice with numerous AT100- and silver-positive filamentous tau inclusions (Figure 1A) into the hippocampus and overlying cerebral cortex of ALZ17 mice that never develop

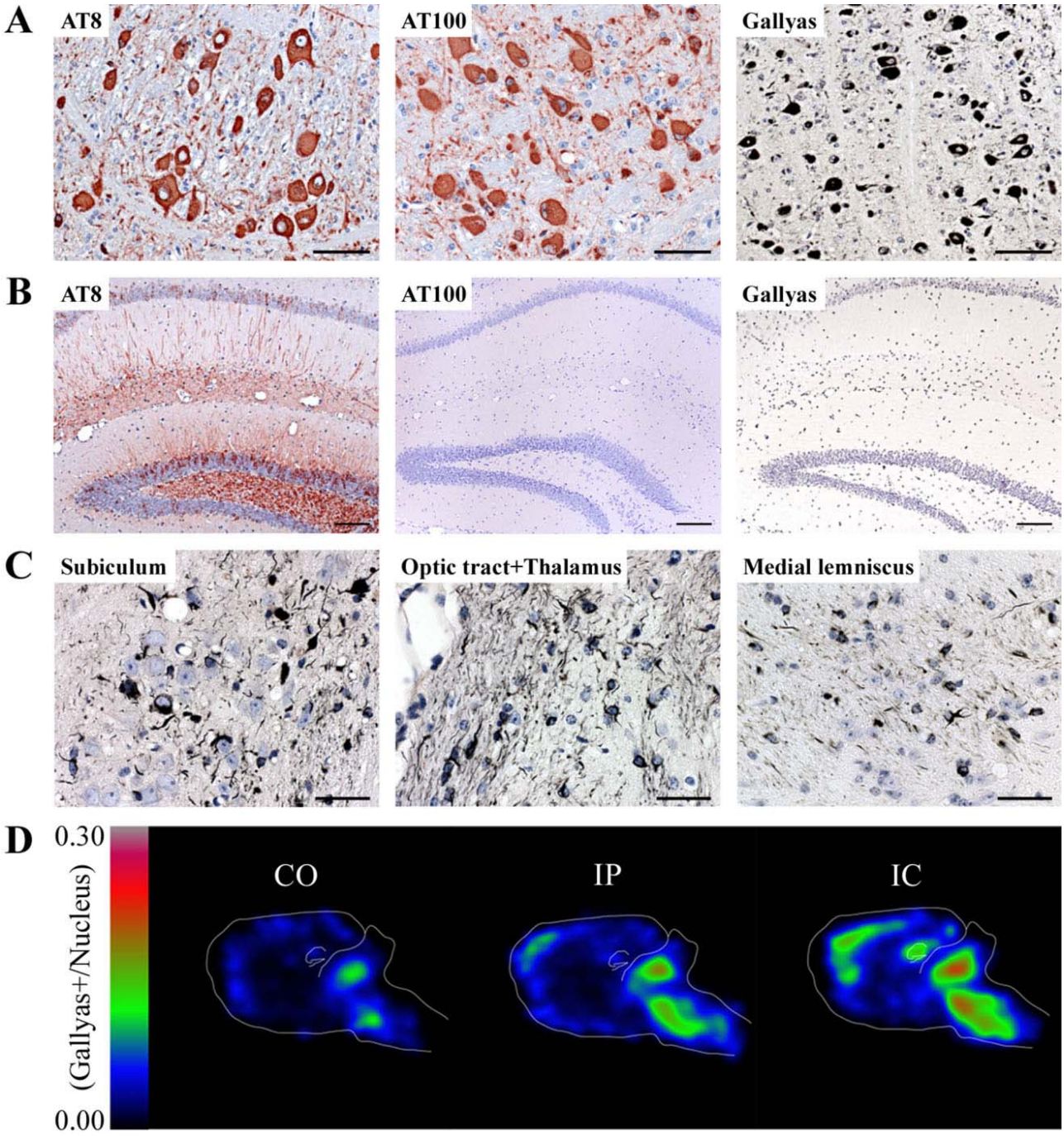

Figure 1. (**A**) P301S mice develop abundant hyperphosphorylated (AT8-immunoreactive) and filamentous tau inclusions (AT100-immunoreactive and Gallyas-Braak-positive) in various brain regions, as illustrated here in the brainstem. (**B**) ALZ17 animals exhibit hyperphosphorylated tau (as shown here for the hippocampus) that is immunoreactive for AT8, but AT100- and Gallyas-Braak-negative, indicative of the absence of tau filaments. (**C**) Spreading of filamentous tau pathology in ALZ17 mice injected with brainstem extract from mice transgenic for human P301S tau. Gallyas-Braak silver staining of brain regions (subiculum, optic tract and thalamus, medial lemniscus) at a distance from the injection sites 15 months post-injection. (**A–C**) Sections were counterstained with haematoxylin. Scale bars: **A** and **C**, 50 µm; **B**, 100 µm. (**D**) Twelve-month-old heterozygous P301S mice 9 months after intraperitoneal (IP) or intracerebral (IC) injection with brainstem extract from homozygous P301S mice. Gallyas-Braak silver-positive structures per cell nucleus (G/N ratios) in noninjected control mice (CO) and in IP or IC injected mice. Color maps representing average G/N ratios (CO, IP and IC) of five sagittal brain sections per group. IP-injected mice had statistically significant higher G/N ratios in the brainstem and neocortex than CO mice. The major difference between IP- and IC-injected animals was located in the hippocampus, one of the two intracerebral injection sites.

filamentous tauopathy (Figure 1**B**). As a result, we observed the assembly of wild-type human tau of ALZ17 host mice into filaments in neurones (NFTs and NTs) and oligodendrocytes (coiled bodies) similar to the inclusions observed in human tauopathies. Strikingly, the induction of filamentous tauopathy was not restricted to the injection sites but progressed over time to both neighbouring and more distant synaptically connected brain regions, consistent with the intercellular transfer of tau aggregates (Figure 1**C**). This phenomenon was tau dependent as no such effect was observed when brain homogenates from P301S mice were immunodepleted for tau. Signs of frank neurodegeneration were not observed. These findings were confirmed and extended by additional work *in vivo*. One study reported the induction and propagation of tau pathology after the injection of tau oligomers from AD brain into wild-type mice [32]. Silver-positive staining was present in the brains of injected mice in the hippocampus but also in neighboring brain regions such as the cerebral cortex, the corpus callosum and the hypothalamus, confirming the propagation of the induced filamentous tauopathy. Two other research groups have confirmed this spreading phenomenon using mouse models expressing human mutant P301L tau restricted to the entorhinal cortex in order to investigate the propagation of tau pathology specifically along the entorhinal cortex/hippocampal pathway [33,34]. In these mice, an age-dependent accumulation of tau pathology was observed not only in transgene-expressing neurones of the entorhinal cortex, but several months after the occurrence of first tau inclusions in the entorhinal cortex, neurones in the hippocampal formation also developed filamentous tau pathology. Both studies seem to have ruled out the possibility that the tau pathology observed outside the entorhinal cortex may have resulted from leaky expression of the transgene, thus favoring a mechanism based on the neurone-to-neurone propagation of assembled tau.

In our study, we have shown that the induction and subsequent spreading of tau aggregates in ALZ17 mouse brains was almost exclusively related to the insoluble fraction of tau obtained from P301S brain homogenates [31]. This conclusion was supported by the demonstration that pure synthetic tau filaments assembled from human mutant recombinant protein promoted in a dose- and time-dependent manner NFT-like tau inclusions when injected into the brains of presymptomatic mice transgenic for human mutant P301S tau [35]. Again, the induced tau pathology propagated to brain regions synaptically connected to the injection sites: when synthetic tau fibrils were injected into the hippocampus, fibrillar tau was found in the entorhinal cortex and the contralateral (noninjected) hippocampus, whereas following injection into the striatum, filamentous tau appeared in the substantia nigra, the thalamus and the corpus callosum [35]. We obtained comparable results after the injection of tau filaments assembled from recombinant human P301S tau in the presence of heparin into the hippocampus and overlying cerebral cortex of 3-month-old homozygous mice transgenic for human mutant P301S tau. Abundant silver-positive tau inclusions had formed at the injection sites already 4 weeks after the injection [36]. Similar findings were obtained when young, presymptomatic P301S mice were injected with brain extracts from symptomatic P301S mice [37]. Induced neurofibrillary pathology was first detected 2 weeks after unilateral injection and increased in a stereotypic and time-dependent manner. Contralateral and caudo-rostral propagation of tau pathology was evident in nuclei with strong efferent and afferent synaptic connections to the injection sites revealing that anatomical spread was dependent on synaptic connectivity and not merely by proximity. Dujardin *et al.* have also demonstrated trans-synaptic spreading of tau via neuronal network by taking advantage of the lentivirus-mediated expression of the human tau protein [38]. Five months after injection, wild-type human tau protein was found in each area connected to the injection sites. In contrast, the lentiviral expression of P301L tau induced a rapid aggregation of tau. However, tau aggregates remained restricted to the site of injection suggesting that wild-type tau is more prone to propagation than mutant tau.

Recently, we have shown that the intraperitoneal injection of brain extracts from symptomatic mice transgenic for human mutant P301S tau into presymptomatic transgenic mice promoted the formation of tau inclusions in brain, albeit less efficiently than following intracerebral injection [39] (Figure 1**D**). The effects of other modes of peripheral injection and the underlying mechanisms remain to be identified.

Monomeric tau has also been detected in brain interstitial fluid and in cerebrospinal fluid, suggesting that it can be released from nerve cells in an activity-dependent manner, despite the lack of a signal sequence [40–42]. The secretion of tau appears to be a physiological and active process, independent of cell death. It is unclear,

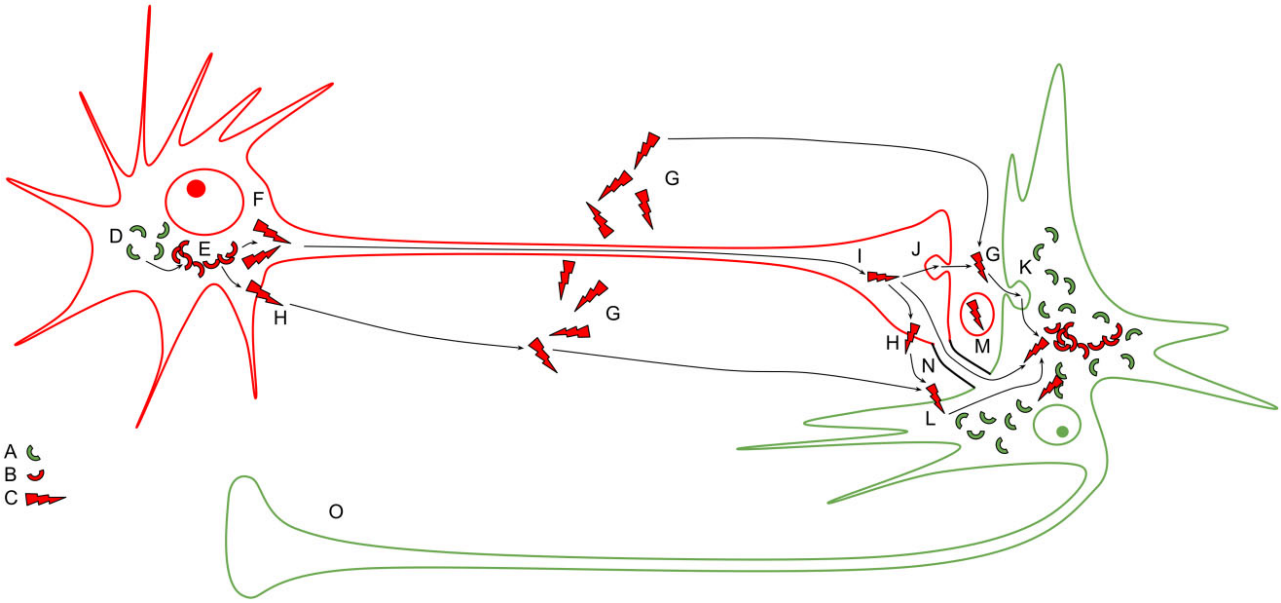

Figure 2. Potential routes of intercellular tauopathy spreading. Red: diseased 'donor' neurone; green: previously unaffected 'acceptor' neurone. (**A**) Soluble tau; (**B**) hyperphosphorylated tau, 'pre-tangle'; (**C**) aggregated tau in abnormal conformation. Soluble tau aggregates in neurones (**D–F**) and gets access to the extracellular space (**G**) either by traversing the cell membrane or due to cell death (**H**). Alternatively tau aggregates may first be transported anterogradely towards the synaptic terminal (**I**) where tau aggregates might be released by exocytosis (**J**) and subsequently are taken up by the unaffected cell by endocytosis (**K**) or membrane penetration (**L**). More direct transmission routes without membrane passage may involve exosomes (**M**), or direct cytoplasmic connections, e.g. tunneling nanotubes (**N**). It remains open whether the entry point into the acceptor cell is located at the somatodendritic region (as drawn here) or through axons (**O**) as well, potentially involving retrograde transport.

however, if tau is released in a free soluble form or if it is packaged into small membrane vesicles, such as exosomes. In a recent study, tau protein, under physiological conditions, was reported in the extracellular fluid in ectosomes rather than in exosomes [43]. Tau may also be transferred between cells through nanotubes (Figure 2). Concentrations of monomeric and aggregated tau have been reported to be in equilibrium in the extracellular space, but their relative concentrations were inversely related [40]. If the physiological role of monomeric tau is related to the pathological intercellular transfer of tau aggregates remains to be elucidated.

In vitro studies have also shown the induction and intercellular propagation of tau misfolding. When added to non-neuronal cells expressing soluble tau, filaments made of recombinant tau and tau filaments from AD brain are taken up by macropinocytosis and induce the aggregation of intracellular tau [44]. The aggregates co-localized with dextran, a marker of fluid phase endocytosis, but not with cholera toxin B, which marks lipid rafts, demonstrating the relevance of endocytic pathways rather than the simple penetration of the cell membrane. Aggregated intracellular tau, which misfolded after contact with extracellular tau filaments, was competent to seed further aggregation and could transfer between co-cultured cells. The seed-dependent polymerization of tau was also demonstrated when lipofection was used to introduce amyloid seeds into cultured cells [45]. In this model, 3R or 4R tau was transiently expressed in a neuroblastoma cell line. Filaments made of 3R tau seeded aggregation of tau in 3R tau-expressing cells but not in 4R ones. Conversely, 4R tau filaments induced aggregation of 4R tau, but not 3R tau, suggesting the specific assembly into amyloid fibers in the presence of seeds derived from tau protein with the same number of repeats. Separate *in vitro* work has demonstrated the templated transmission of the conformational properties of assembled recombinant tau. Filaments made of either wild-type or mutant tau adopted distinct conformations that were maintained via a templated conformational change [46]. It is well established that

tau filament formation occurs through a nucleation-dependent polymerization mechanism *in vitro* [47]. In cells, the induction of insoluble tau aggregates also requires seeding [48]. When filaments generated from either Myc-tagged full-length human tau or truncated tau filaments were transduced into cells transfected with the longest wild-type human tau isoform, intracellular tau aggregates of various morphologies formed. Blocking endocytosis by incubation at 4°C reduced the percentage of aggregate-containing cells, whereas favouring adsorptive endocytosis at 37°C increased the number of tau aggregate-bearing cells, indicating that the spontaneous entry of tau filaments occurs through endocytosis. The internalization of aggregated tau also depends on the presence of sulphated glycosaminoglycans [49]. Tau aggregates are released into the extracellular space, but the underlying mechanisms remain to be identified. The uptake of different forms of tau has been investigated in several studies. In cultured nerve cells, only short tau fibrils and smaller aggregates, but not long fibrils, were internalized [50]. Moreover, in a separate study, paired helical filaments from AD brain were also internalized [51]. At present, however, the molecular identities of the tau species that propagate between nerve cells are not known.

Tau strains

We have recently shown that neuronal and glial tau filaments formed following the intracerebral injection of brain homogenates from humans with pathologically confirmed tauopathies into the hippocampus and the neocortex of ALZ17 mice [52]. Inclusions formed following the injection of brain homogenates from all cases of AD, TD, PiD, AGD, PSP, and CBD. However, specific lesions reminiscent of human cases were observed after injection of AGD, PSP and CBD. The ALZ17 line expresses a single isoform of wild-type 4R human tau. With the exception of PiD, where the tau inclusions consist predominantly of 3R tau, the inclusions of the other tauopathies are made of 4R tau (AGD, PSP and CBD) or of a mixture of 3R- and 4R-tau (AD and TD). Thus, the intracerebral injection of PSP brain homogenates into ALZ17 mice resulted in the formation of silver-positive astrocytic aggregates that resembled tufted astrocytes (the hallmark lesions of PSP) [15,16], the injection of CBD homogenates gave rise to the formation of silver-positive structures reminiscent of the astrocytic plaques found in CBD [17,18] and the injection of AGD homogenates resulted in the formation of silver-negative astrocytic tau pathology as observed in human AGD [12,13]. In addition, filamentous tau pathology propagated over time to neighbouring or brain regions synaptically connected to the injection sites for all tauopathies, with the exception of PiD, where induced tau filaments remained confined the injection areas. Similar inclusions also formed after intracerebral injection of brain homogenates from human tauopathies into nontransgenic mice (Figure 3**A**). Moreover, serial propagation of induced filamentous tau pathology was observed when brain homogenates from ALZ17 mice that had received a bilateral injection of brain extract from human P301S tau transgenic mice 18 months earlier were injected into 3-month-old ALZ17 mice. Twelve months after the injection, Gallyas-Braak silver staining and AT100 immunostaining revealed the presence of neuronal and oligodendroglial tau inclusions at the injection sites (Figure 3**B**, left panel). A second set of homogenates was prepared from the brains of nontransgenic mice that had been injected bilaterally with TD or AGD brain homogenates 18 months earlier. Twelve months after the intracerebral injection into ALZ17 mice, many NTs and tau aggregates in nerve cell bodies were present at the injection sites (Figure 3**B**, middle and right panels). All these findings strongly suggest that different tau strains exist that are capable of inducing distinct tauopathies. Our findings were confirmed and extended by a recent study showing that conformationally distinct tau strains made of 4R tau repeats (clones 9 and 10) formed in HEK293 cells [53]. Clone 9 was very efficient at seeding and produced small intranuclear aggregates, whereas clone 10 led to larger juxtanuclear inclusions. Protein transfer of these clones into naïve cells reproduced the original strains, and their inoculation into the hippocampus of young mice transgenic for human mutant P301S tau mice induced the unique pathologies that were stable through serial injection. When HEK293 cells expressing 4R tau were seeded with tau aggregates taken from the hippocampi of the third round of injected mice, inclusions formed that were similar to those present in the initial HEK293 cells.

Discussion

The findings summarized here favour the intercellular propagation of tau aggregates and support the existence

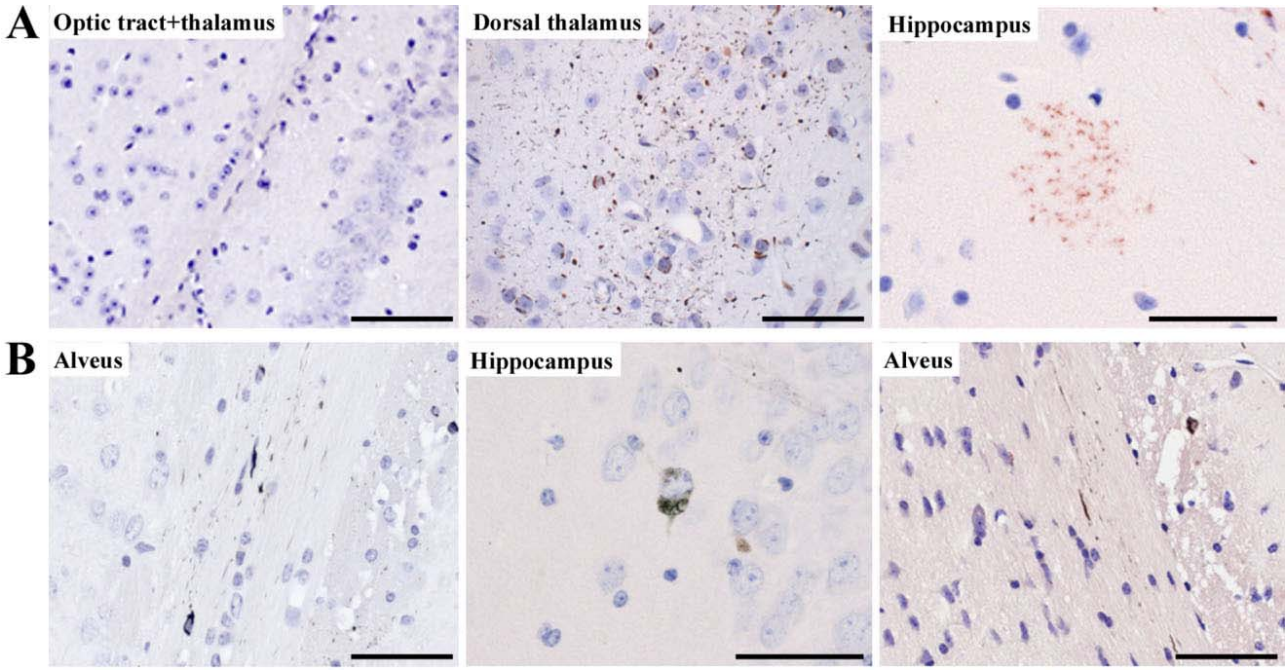

Figure 3. (**A**) Induction of tau inclusions in nontransgenic C57Bl/6 mice 12 months after the intracerebral injection of brain homogenates from sporadic human tauopathies. Gallyas-Braak silver impregnation failed to detect tau filaments in noninjected mice (left) but revealed the presence of neuropil threads and coiled bodies in the dorsal thalamus following the injection of AD homogenate (middle). AT100 immunostaining of the hippocampal region showed the presence of a tufted-like astrocyte following the injection of AGD brain extract (right). (**B**) Induction of tau inclusions into ALZ17 mice following the intracerebral injection of induced mouse brain homogenates, as detected by Gallyas-Braak silver impregnation. Neuropil threads and coiled bodies in the alveus of an ALZ17 mouse 12 months after the injection of brain homogenate from an ALZ17 mouse that had 18 months previously been injected with brainstem extract from a mouse transgenic for human mutant P301S tau (left). ALZ17 mouse 12 months after the injection of brain homogenate from a C57Bl/6 mouse that had 18 months previously been injected with TD (middle) or AGD (right) brain homogenate showing neurofibrillary tangle formation in the hippocampus (middle) and neuropil threads in the alveus (right). (**A**,**B**) Sections were counterstained with haematoxylin. Scale bars, 50 μm.

of distinct tau strains that might explain the heterogeneity of human tauopathies. Besides aggregated tau, the same also appears to be true of aggregated Aβ and alpha-synuclein. Inclusions of tau, Aβ and α-synuclein account for the vast majority of cases of late-onset neurodegenerative disease [54,55]. Unlike inclusions made of tau and α-synuclein, Aβ deposits form in the extracellular space. The intracerebral injection into predepositing Aβ transgenic mice of Aβ-rich extracts prepared from human, mice or synthetic fibrils leads to the premature and abundant deposition of Aβ. Such induction depends on both the nature of the inoculated filaments and the injected animal suggesting the existence of polymorphic strains of Aβ [56–58]. Two recent studies support the existence of distinct strains of aggregated Aβ that could explain the clinical and pathological disparity observed in AD patients [59,60]. The prion-like transmission and propagation of proteopathy is also observed for α-synuclein. Like tau, α-synuclein is an intracellular protein, and they both exhibit parallel characteristics. In human subjects with incidental Lewy body disease, the first α-synuclein lesions appear in the dorsal motor nucleus of the glossopharyngeal and vagal nerves, the olfactory bulb and the anterior olfactory nucleus. They ascend from brainstem to midbrain and neocortex [61]. Similar to the tau transmission and propagation experiments described above, induction of synucleinopathy follows the intracerebral inoculation of pathogenic extracts into transgenic mice [62]. Moreover, α-synuclein fibrils exhibit distinct conformations, specific seeding properties and transmission of phenotypic features resembling prion strains [63–65]. Recent studies have shown that the intraperitoneal administration of Aβ and tau seeds promotes inclusion formation in respective transgenic mouse brains [39,66,67]. Similarly, the intramuscular injection of synthetic α-synuclein aggregates induced

cerebral synucleinopathy accompanied by strong motor impairments in transgenic mice [68]. Moreover, a recent study in rats has shown that α-synuclein from a Parkinson's disease patient brain lysate (containing different forms of α-synuclein – monomeric, oligomeric and fibrillar) or recombinant α-synuclein is taken up and transported retrogradely over a long distance via the vagal nerves from the gut to the brain, after being injected into the wall of the gastrointestinal tract [69].

There is now substantial *in vivo* evidence for intracerebral cell-to-cell transmission for both tau and α-synuclein aggregates; however, it is essential to know if this is also related to neurodegeneration. Several studies have shown that intracerebral injection of α-synuclein fibrils (synthetic fibrils or fibrils taken from brain samples of patients with Parkinson's disease, dementia with Lewy bodies or multiple system atrophy) into transgenic or wild-type mice resulted in neurodegeneration [70–72].

With the exception of a study demonstrating the loss of CA1 neurones after the intracerebral injection of large amounts of synthetic tau fibrils into young P301L transgenic mice [73], nerve cell loss has not been observed following the injection of tau fibrils. This suggests that the molecular tau species responsible for spreading and neurodegeneration may be different. It remains to be seen if the same applies to α-synuclein.

Other organisms, such as *Caenorhabditis elegans*, *Drosophila*, zebra fish and essentially any animal with a nervous system, can alternatively be employed to reproduce both morphological and functional features of tauopathies. Generally, nonmammalian models are more suitable for genetic and component screening than mice and will certainly be helpful in first-line identification of molecular players, modifiers and interactors of tau pathology. Such model systems have successfully been employed to identify tauopathy modifier genes [74–77] as well as nongenetic factors [78,79]. Most of these nonmammalian models, however, represent genetic tauopathies without the possibility to study intercellular spreading of disease. Even though not aimed at tau, a prion-domain containing fluorescent transgene in *C. elegans* requires vesicular transport for cell-to-cell spreading [80]. Thus, recapitulating intercellular tauopathy spreading in nonmammalian animals, in analogy to mouse models, is likely to pin down the molecular players required for tauopathy progression and, at the same time, will prospectively be of use for large-scale component screening. As they provide an entire nervous system, they overcome the common obstacles associated with any cell culture technology.

Altogether, better knowledge of the mechanisms that cause – tau strain specific – onset and subsequent propagation via cell-to-cell transmission in the various tauopathies will pave the way for future diagnostic (that is imaging using tau tracers [81–83]) and therapeutic options (see review on drug development for tauopathies by Grueninger in this issue).

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