neuroglia

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Review

Astrogliopathy in Tauopathies

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Abstract: Astrocytes are involved in many diseases of the central nervous system, not only as reactive cells to neuronal damage but also as primary actors in the pathological process. Astrogliopathy is a term used to designate the involvement of astrocytes as key elements in the pathogenesis and pathology of diseases and injuries of the central nervous system. Astrocytopathy is utilized to name non-reactive astrogliosis covering hypertrophy, atrophy and astroglial degeneration with loss of function in astrocytes and pathological remodeling, as well as senescent changes. Astrogliopathy and astrocytopathy are hallmarks of tauopathies—neurodegenerative diseases with abnormal hyper-phosphorylated tau aggregates in neurons and glial cells. The involvement of astrocytes covers different disease-specific types such as tufted astrocytes, astrocytic plaques, thorn-shaped astrocytes, granular/fuzzy astrocytes, ramified astrocytes and astrocytes with globular inclusions, as well as others which are unnamed but not uncommon in familial frontotemporal degeneration linked to mutations in the tau gene. Knowledge of molecular differences among tau-containing astrocytes is only beginning, and their distinct functional implications remain rather poorly understood. However, tau-containing astrocytes in certain conditions have deleterious effects on neuronal function and nervous system integrity. Moreover, recent studies have shown that tau-containing astrocytes obtained from human brain tauopathies have a capacity for abnormal tau seeding and spreading in wild type mice. Inclusive conceptions include a complex scenario involving neurons, glial cells and local environmental factors that potentiate each other and promote disease progression in tauopathies.

Keywords: astrocytes; tau; seeding; spreading; tauopathies; progressive supranuclear palsy; corticobasal degeneration; Pick's disease; aging-related tau astrogliopathy; primary age-related tauopathy; frontotemporal degeneration-tau; astrocytopathy

1. Introduction

Tauopathies are adult-age clinically, biochemically and anatomically heterogeneous neurodegenerative diseases, defined by the depositing of excessively phosphorylated tau protein, which is abnormally folded and eventually forms aggregates in nerve cells. Tau deposits in nerve cells form neurofibrillary tangles (NFT, neurofibrillary degeneration) and pre-tangle deposits, aggregates in neuronal and glial cell processes form neuropil threads, inclusions in astrocytes give rise to different morphological types, and inclusions in oligodendrocytes mainly form coiled bodies and, rarely, globular inclusions. Certain regions of the brain, and certain cell populations, are vulnerable to the pathology of tau, although the mechanisms of regional vulnerability and selective cellular vulnerability in tauopathies are poorly understood. Tau proteins are encoded by the microtubule-associated protein tau gene *MAPT*, the transcription of which, by alternative splicing, produces six isoforms in the brain. Some

tauopathies are identified as 4R-tauopathies (4Rtau) and others as 3R-tauopathies (3Rtau) depending on the axon 10 splicing.

2. Human Tauopathies

The clinical and pathological phenotype of human tauopathies is, in part, determined by (a) the types of tau deposits (3Rtau or 4Rtau); (b) the specific regional and cellular vulnerability to each tauopathy; (c) the involvement of neurons and/or glial cells (astrocytes and oligodendrocytes); (d) the type of mutation in *MAPT* in familial tauopathy; and (e) the accompanying presence of extracellular amyloids, as in Alzheimer's disease (AD) (in which the tauopathy is associated with extracellular deposits of amyloid β (Aβ) giving rise to β-amyloid plaques), but also in British familial dementia (FBD) and Danish familial dementia (FDD) linked to distinct mutations in *BRI2* (or *ITMM2B)* and producing amyloids ABri and ADan, respectively. Certain families with Gerstmann–Straüssler–Scheinker syndrome (GSS) linked to mutations in *PRNP* (which encodes the prion protein) are associated with prionopathy and tauopathy.

The most frequent human sporadic tauopathy, in addition to sporadic AD, are primary age-related tauopathy (PART), a neuronal 4Rtau + 3Rtau similar to AD but without the Aβ component; aging-related tau astrogliopathy (ARTAG), a selective astrocyte 4Rtau; argyrophilic grain disease (AGD), a 4Rtau with predominant pre-tangles in neurons, protrusions in dendrites (grains) and inclusions in astrocytes and oligodendrocytes; Pick's disease (PiD), a 3Rtau with mainly neuronal involvement (Pick bodies) but also with tau deposits in astrocytes and oligodendrocytes; progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), both 4R-tauopathies with the involvement of neurons and oligodendrocytes, and with disease-specific tau deposits in astrocytes; and globular glial tauopathy (GGT), a 4Rtau with neuronal involvement and unique tau inclusions in astrocytes and globular tau deposits in oligodendrocytes [1–29].

The most common pure hereditary tauopathy is frontotemporal lobar degeneration linked to *MAPT* mutations (FTLD-tau). Clinically, FTLD-tau is manifested by frontal dementia (FTD) and parkinsonism; tau deposits are composed of 4Rtau, 3Rtau or 4Rtau + 3Rtau depending on the site of the mutation [30–34]. Globular glial tauopathy is mostly sporadic but certain tauopathies linked to *MAPT* mutations show variable amounts of globular inclusions in oligodendrocytes and bizarre astrocytic inclusions resembling sporadic GGT [35–38].

The most frequent combined tauopathy and amyloidopathy is familial AD linked to mutations in amyloid β precursor protein (APP)-related genes: *APP*, presenilin1 (*PSEN1*), or presenilin 2 (*PSEN2*). British familial dementia, FDD and GSS with tauopathy are extremely rare [21,39–41]. Other tauopathies can be reviewed elsewhere [25].

A combination of different tauopathies is not rare in old-age individuals [28,42,43]. The combination of AD, AGD and ARTAG is frequent in old-age individuals. The association of PSP or CBD and ARTAG and AGD is usual.

3. Non-Human Primate Tauopathies in Old Age

Tauopathy also occurs in aged non-human primates. Major research is focused on AD-related changes (Aβ deposits and tau deposits) in old-age animals. Interestingly, AD-like pathology is not rare in non-human primates, although there are marked species differences.

In cynomologous monkey (*Macaca fascicularis*), intraneuronal and oligodendroglial tau accumulation is found in the temporal cortex and hippocampus before the age of 20 years and before the presence of amyloid deposits; at advanced ages, NFTs and tau accumulate in dystrophic neurites [44]. An age-related increase of Aβ deposits in the form of plaques and around blood vessels is frequent, with gender differences, in the neocortex and hippocampus of western lowland gorilla (*Gorilla gorilla gorilla*), housed in American zoos and aquarium-accredited facilities. Neurons stained for the tau marker Alz50 are found in the neocortex and hippocampus of gorillas at all ages. Occasional Alz50-, MC1- and AT8-immunoreactive astrocyte and oligodendrocyte coiled bodies and neuritic

clusters are seen in the neocortex and hippocampus of the oldest gorillas [45]. Aged wild mountain gorillas (*Gorilla beringei beringei*) which spent their entire lives in their natural habitat also display an age-related increase in APP and/or Aβ-immunoreactive blood vessels and plaques, but very limited tau pathology, in the frontal cortex [46]. In contrast, old-age baboons (*Papio hamadryas*) show NFTs in the hippocampus and limbic system, and tau-positive inclusions in astrocytes located in subependymal, subpial and perivascular locations, as well as in oligodendrocytes [47]. The first description of AD-like neuropathology in an aged chimpanzee (*Pan troglodytes*) included tau deposits in neurons, neuropil threads and plaque-like clusters throughout the neocortex with moderate Aβ deposition in blood vessels and rarely in plaques [48]. Subsequent studies in a larger series of chimpanzees revealed Aβ plaques, Aβ-angiopathy, and neurons with pre-tangles, NFTs and neuritic clusters [49].

Cerebral Aβ deposition is found in aged cotton-top tamarins (*Saguinus oedipus*), lemurs (*Lemuroidae*), marmosets, cynomologous monkeys, rhesus monkeys (*Macaca mulatta*), vervets (*Chlorocebus pygerythrus*), squirrel monkeys (*Saimiri* sp.), baboons, orangutans (*Pongo* sp.), gorillas and chimpanzees [50]. The amyloid precursor protein and its shorter fragment, Aβ, are homologous in humans and non-human primates. However, *MAPT* sequence varies among primates, with differences being minimal between human and chimpanzees. This may account for differences between humans and non-human primates regarding tau pathology in old-age and related tauopathies [51]. Further studies are needed to elucidate possibly overlooked tau deposition in glial cells, and additional abnormal tau-containing deposits such as grains in aged non-human primates.

4. Main Types of Tau-Containing Astrocytes

Astrocytes containing hyper-phosphorylated tau have disease-specific traits in the majority of tauopathies: tufted astrocytes in PSP, astrocytic plaques in CBD, thorn-shaped astrocytes (TSAs) and granular/fuzzy astrocytes (GFAs) in ARTAG, ramified astrocytes in PiD and astrocytes with globular inclusions in GGT [4,17,18,20,24,25,52–66]. (Figures 1–3).

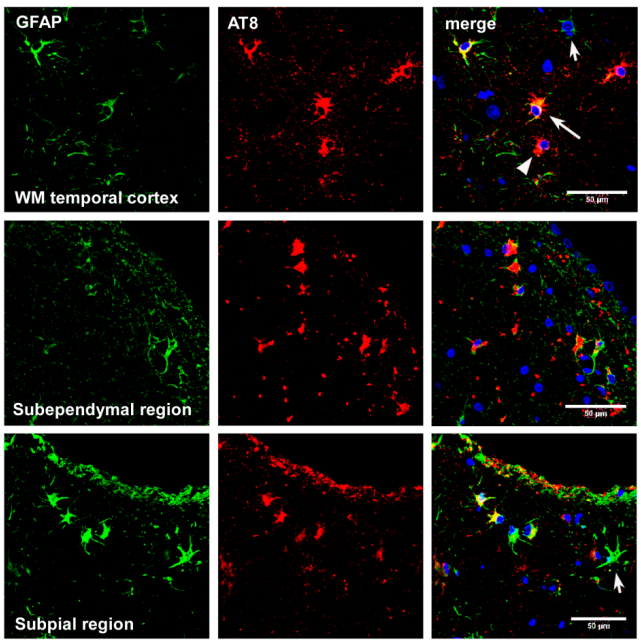


Figure 1. Double-labeling immunofluorescence to glial fibrillary acidic protein (GFAP) (green) and phospho-tau AT8 (red) showing the morphology of thorn-shaped astrocytes in the white matter of the temporal cortex, subependymal region and subpial region. Long arrow: cells with double staining; short arrow: cells only stained green; arrowhead: cells only stained red. Hyper-phosphorylated tau-containing astrocytes have reduced GFAP immunoreactivity. Paraffin sections; nuclei (blue) are stained with DRAQ5 (Biostatus, Leicestershire, UK); WM: withe matter; bar = 50 μm.

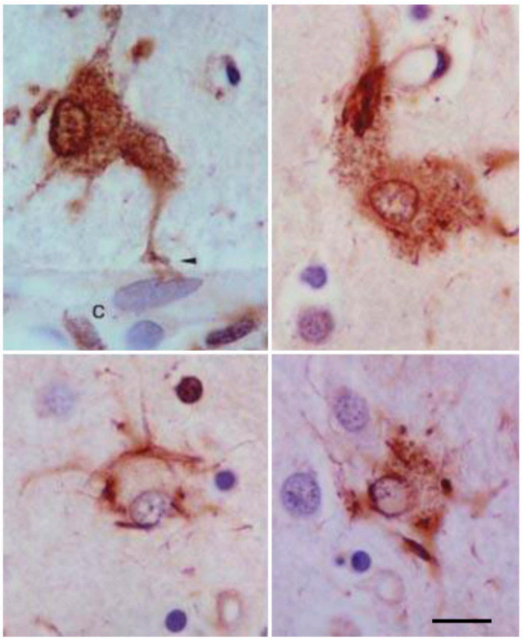


Figure 2. Tau-containing astrocytes in progressive supernuclear palsy (PSP). Typical tufted astrocytes are seen in the lower row. A perivascular astrocyte with a podocyte (arrowhead) in the vicinity of a capillary (C), and a reactive astrocyte also contain hyper-phosphorylated tau (upper row). Paraffin section, AT8 immunohistochemistry, slightly counterstained with hematoxylin, bar = 10 μm.

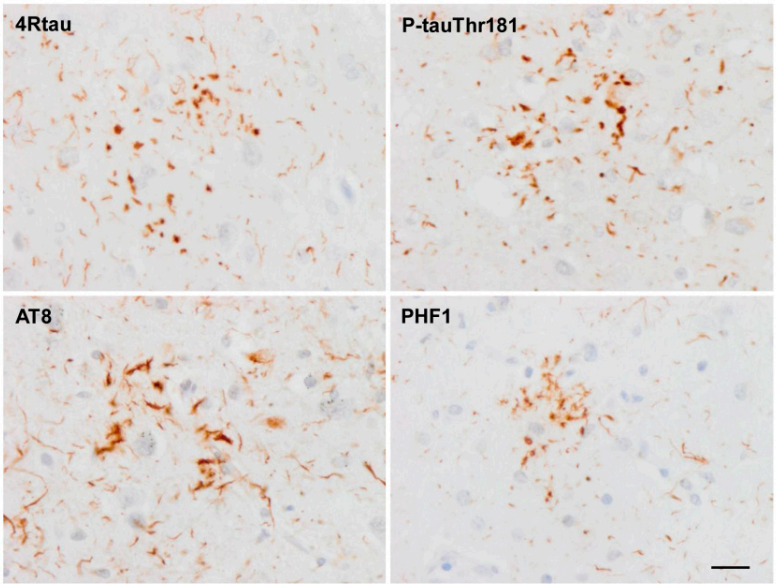


Figure 3. Astrocytic plaques in corticobasal degeneration (CBD), stained with 4Rtau, P-tauThr181, AT8 (P-tau Ser202-Thr205) and antibody PHF1 (P-tauSer396-Ser404). Paraffin sections slightly counterstained with hematoxilin, bar = 25 μm.

However, some tau-containing astrocytes are found in different tauopathies—for example, TSAs occur in aging, AGD, AD, PSP and CBD [14,19,67–72], and in traumatic chronic encephalopathy [73]. Granular/fuzzy astrocytes are seen in the elderly and ARTAG [26,70], but also in other tauopathies such as in PSP [37].

Interestingly, tau-containing astrocytes are early lesions in PSP, CBD and FTLD-tau [28,74–76].

Various types of astrocytic inclusions are generated in familial FTLD-tau linked to mutations in exons 1 and 10 and in introns following exons 9 and 10, the morphology of which largely depends on the *MAPT* mutation. Intracytoplasmic tau-immunoreactive inclusions in FTLD-tau are represented by tufted-like astrocytes, astrocytic plaques, ramified astrocytes, TSAs, astrocytes with globular inclusions and other types with no specific names [17,33,34,36,37,66,77–86]. Tufted astrocytes and astrocytic plaques practically do not co-exist in PSP and CBD [57], but these lesions appear in combination in FTLD-tau [29] (Figure 4).

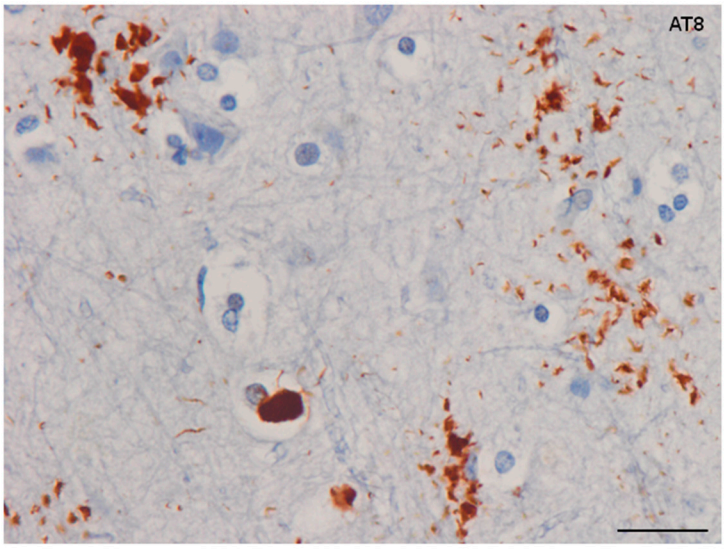


Figure 4. Frontotemporal lobar degeneration linked to *MAPT* mutations (FTLD-tau) K317M stained with antibody AT8 showing tufted-like astrocytes (reminiscent of tau-containing astrocytes in globular glial tauopathy (GGT)), astrocytic plaques and globular inclusion in an oligodendrocyte. Paraffin sections, slightly counterstained with hematoxylin, bar = 25 μm.

Extensive astrocyte-predominant tauopathy involving brain astrocytes and Bergmann glia has been reported in familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy; the morphology of abnormal astrocytes, including deposits in Bergmann glia, differs from all other tauopathies [87].

The localization of tau-containing astrocytes does not always match that of tau-containing neurons in tauopathies [14,19,28,76,88–92]. Curiously, tufted astrocytes and astrocytic plaques are often located near the blood vessels [93], and perivascular distribution is overwhelming in a rare familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy [87]. Regarding ARTAG, TSAs are found in regions proximal to the CSF and blood vessels [72].

Hyper-phosphorylated tau intracytoplasmic filamentous inclusions are common in transgenic mouse models of tauopathies both in animals over-expressing human tau and those bearing different tau mutations which are causative of human familial FTLD-tau. Tau pathology in glial cells has been generated in transgenic mice over-expressing human tau in neurons and glial cells. In these animals, a tau pathology resembling astrocytic plaques and coiled bodies in oligodendrocytes is found in old mice; these changes are associated with glial and axonal degeneration [94].

Transgenic mice bearing P301L tau develop cytoplasmic neuronal inclusions, and oligodendroglial and astrocytic filamentous inclusions composed of abnormal hyper-phosphorylated tau aggregates [95]. Similar neuronal and glial tau-immunoreactive inclusions occur in the P301S transgenic mouse (Figure 5).

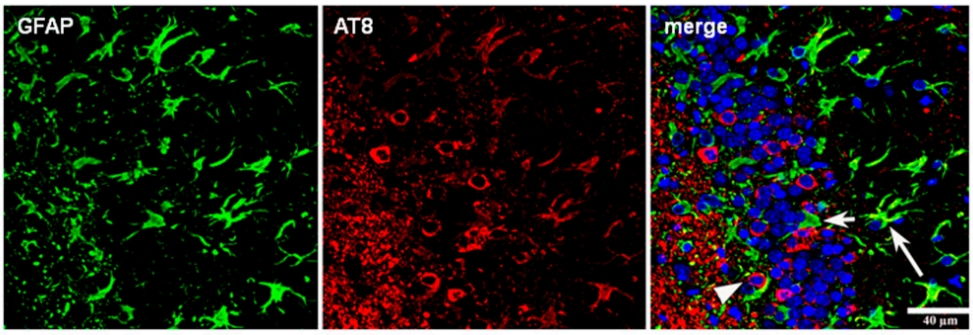


Figure 5. P301S transgenic mice aged 10 months. Double-labeling immunofluorescence to GFAP (green) and AT8 (red) showing cells with double staining (long arrow), cells only stained green (short arrow) and cells only stained red (arrowhead). Some astrocytes contain hyper-phosphorylated tau deposits. Paraffin sections; nuclei stained with DRAQ5 (Biostatus) (blue); bar = 40 µm.

5. Post-Translational Tau Modifications and Tau Kinases in Tau-Containing Astrocytes in Tauopathies

Tau in astrocytes is hyper-phosphorylated at different sites including Thr181, Ser199, Thr231, Ser262, Ser422, Ser202-Thr205 (antibody AT8), Ser396-Ser404 (antibody PHF1) and Thr212/Ser214 (tau-100), and it has an altered conformation as revealed with the antibodies Alz50 (amino acids 5–15) and MC-1 (amino acids 312–322) [37]. All these astrocytic inclusions in sporadic tauopathies are composed of 4Rtau isoforms, but certain astrocytes in PiD and PSP contain 3Rtau [37]. Astrocytic inclusions in FTLD-tau depend on the mutation, but they are largely composed of 4Rtau [33,37,66].

Astrocytes containing hyper-phosphorylated tau inclusions co-express phosphorylated tau kinases: mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), p-38 kinase, stress-activated kinase/c-Jun N-terminal kinase (SAPK/JNK) and glycogen synthase kinase-3 [14,82,96–100]. Co-expression in astrocytes suggests active phosphorylation of tau by specific kinases; such co-localization also occurs in neurons with pre-tangles and tangles in the same tauopathies.

The presence of truncated forms of tau in tau-containing astrocytes is not documented in detail. Most tau-containing astrocytes in tauopathies are not stained with the antibody tau-C3 which recognizes tau truncated at aspartic acid 421 [37]. Only small tau-C3 immunoreactive dots are occasionally seen in TSAs [71]. Exceptions are astrocytes with globular inclusions in GGT, astrocytes in certain FTLD-tau (as in the familial tauopathy linked to *MAPT* K317M), and astrocytes in familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy [37,87]. In such cases, tau-containing astrocytes are always ubiquitinated [37]. In contrast, tufted astrocytes, astrocytic plaques, TSAs and ramified astrocytes only very rarely contain ubiquitin-immunoreactive deposits [37] (Figure 6).

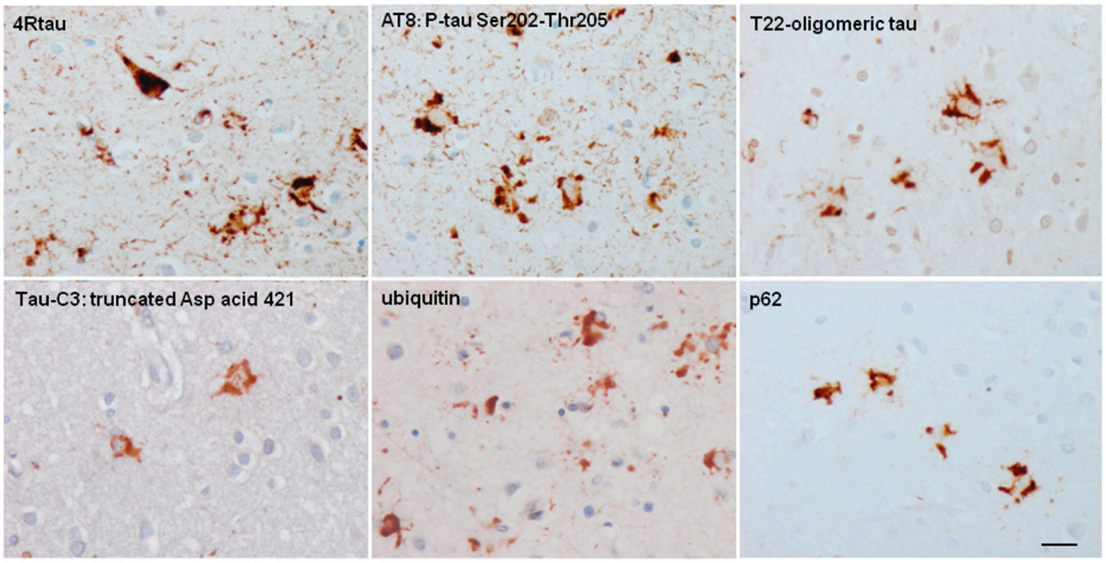
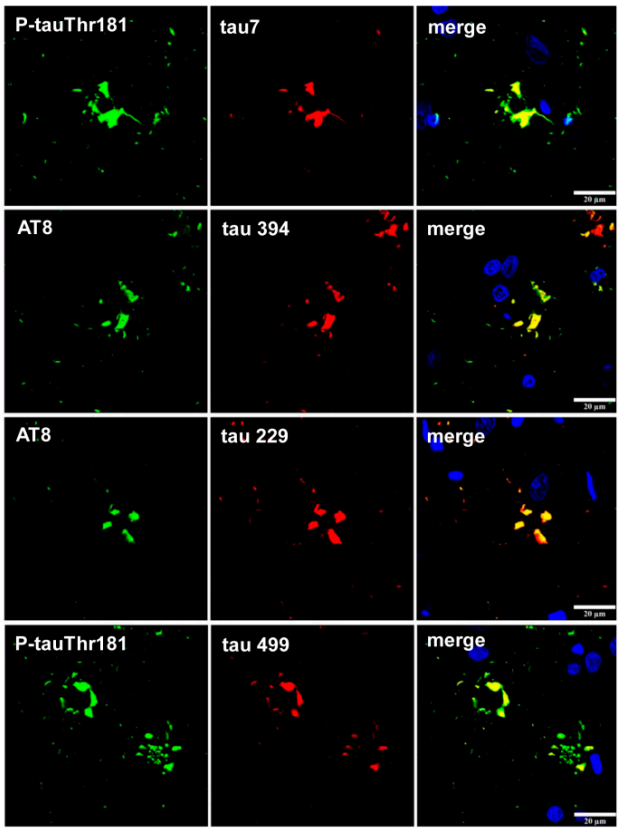


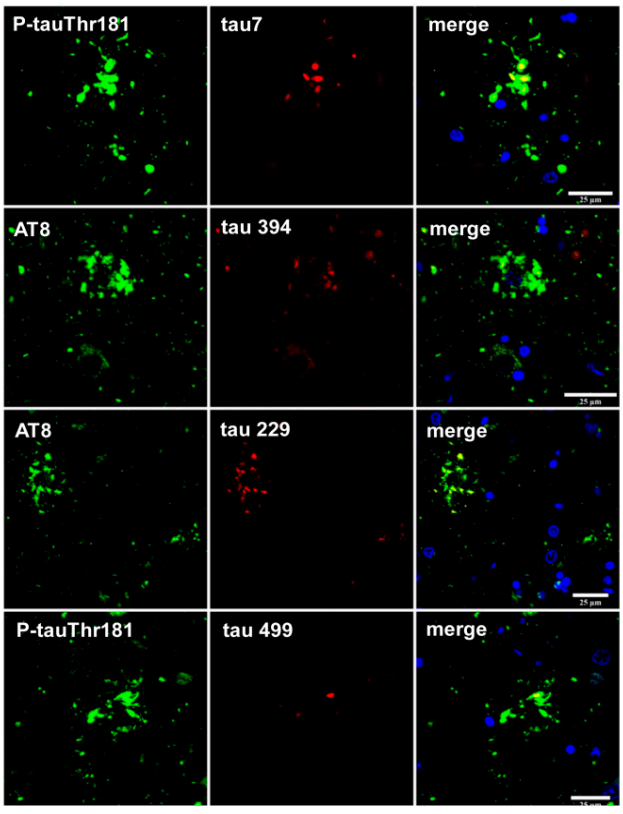
Figure 6. Globular glial tauopathy (GGT) showing abnormal tau-containing astrocytes with distinctive features stained with antibodies against 4Rtau, clone AT8 (directed against P-tau Ser202-Thr205), tau22 (anti-oligomeric tau), tau-C3 (against tau truncation at aspartic acid 421), ubiquitin and p62. One neuron is also observed in the section stained with anti-4Rtau. Paraffin sections slightly counterstained with hematoxylin, bar = 25 μm.

Tau phosphorylation, conformation and truncation in astrocytes have characteristics similar to their neuronal counterparts in tauopathies with equivalents to pre-tangles and tangle stages [37]. However, this must be interpreted with caution as knowledge is still limited. For example, a lack of epitopes derived from alternatively spliced exon 2 and 3 has been reported in glial tau when compared with neuronal tau in certain tauopathies [56,101]. Tau acetylation is rarer in astrocytes when compared to neurons in tauopathies [102]. Tau is acetylated in glial inclusions in FTLD-tau [102] but apparently not in AGD [103]. This is an important point, as tau acetylation inhibits tau function and promotes tau aggregation [104,105].

Finally, tau truncation may occur at different sites of tau; western blots of total brain homogenates show bands of low molecular weight in most tauopathies, but the method does not discriminate between neurons and glial cells. Immunohistochemistry utilizing tau antibodies directed against specific amino acids of tau (amino-terminal, carboxyl-terminal, middle segments) can be useful to uncover possible sites of tau truncation in astrocytes in tauopathies in addition to the characteristic truncation at aspartic acid 421 in astrocytes in minority tauopathies. Thorn-shaped astrocytes (TSAs) are stained with antibody 394 (amino acids 394–398, corresponding to the carboxyl-terminal); antibody 229 (against amino acids 229–233, middle region) and antibody 499 (directed against amino acids 14–26, amino-terminal) [106]. Tau-containing astrocytes in FTLD-tau 301T are stained with antibodies tau 7 (directed against amino acids 426–441), 394, 229 and 499 (Figure 7A). However, tufted astrocytes in PSP and astrocytic plaques in CBD are decorated with antibodies tau 7, 229 and 394 but barely or not at all with antibody 499, thus suggesting the reduction or absence of tau species containing the amino terminal of tau protein in tufted astrocytes and astrocytic plaques (Figure 7B,C).

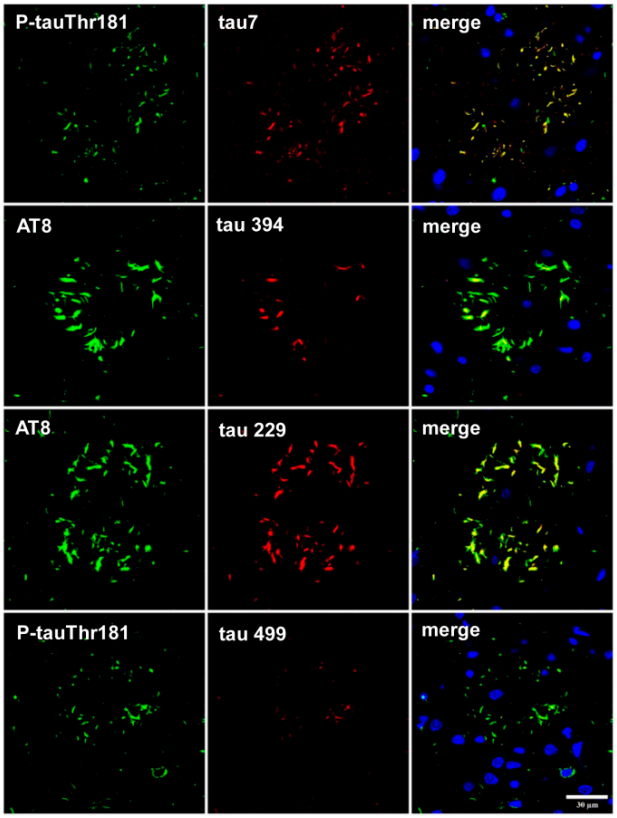


(**A**)



(**B**)

Figure 7. *Cont.*



(**C**)

Figure 7. Double-labeling immunofluorescence and confocal microscopy using antibodies tau 7 (directed against amino acids 426–441), 394 (amino acids 394–398, corresponding to the carboxyl terminal), 229 (against amino acids 229–233, middle region), and 499 (directed against amino acids 14–26, amino terminal) (green); and P-tauThr181 or AT8 (depending on the mouse or rabbit origin of the first anti-tau antibodies) (red) in FTLD-tau linked to 301T mutation (**A**); PSP (**B**) and CBD (**C**). Tau 7, 229 and 394 co-localize with phospho-tau deposits in astrocytes in FTLD-tau 301T, tufted astrocytes and astrocytic plaques; antibody 499 also co-localizes with phospho-tau in FTLD-tau 301T, but tufted astrocytes and astrocytic plaques almost lack 499 tau immunostaining, thus suggesting tau amino terminal truncation. Paraffin sections; nuclei (blue) are stained with DRAQ5 (Biostatus); A, bar= 20 μm; B, bar = 25 μm C; bar = 30 μm.

6. Cytoarchitectonic Changes Linked to Tau Deposits in Astrocytes

Not all astrocytes are immunoreactive to glial fibrillary acidic protein (GFAP) [107–110]. However, GFAP is currently used as a marker of astrocytes, mainly for reactive astrocytes.

Even considering these limitations, double-labeling immunofluorescence and confocal microscopy have been used to learn about cytoskeletal anomalies in astrocytes containing hyper-phosphorylated tau. Glial fibrillary acidic protein has been reported to be absent in tufted astrocytes in PSP [58,111]. However, small amounts of GFAP are commonly redistributed around the nucleus in tufted astrocytes in PSP and FTLD-tau. GFAP is disrupted by short segments or dots of hyper-phosphorylated tau throughout the astrocytic processes in astrocytic plaques in CBD, and in astrocytes with proximal granular inclusions in FTLD-tau/P301L. Glial fibrillary acidic protein immunoreactivity is also displaced by hyper-phosphorylated tau deposits in ramified astrocytes in PiD, TSAs in ARTAG, tau-containing astrocytes in GGT, and astrocytes in familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy [37,87,92] (Figure 8).

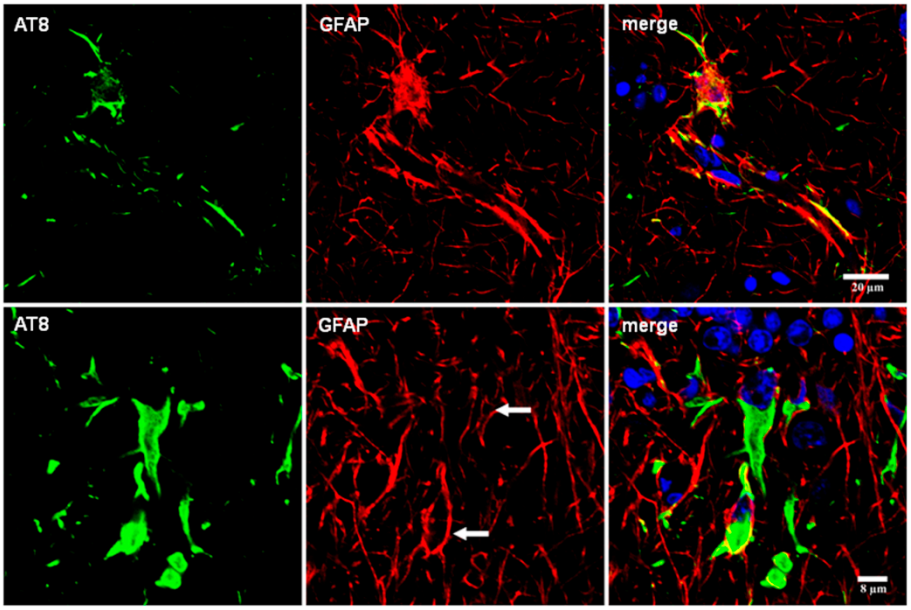


Figure 8. Double-labeling immunofluorescence and confocal microscopy to phospho-tau clone AT8 (green) and glial fibrillary acidic protein (red) in the cerebral cortex (upper row) and cerebellum (lower row) in familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy. Variable distortion of the glial cytoskeleton is found mainly in Bergmann glia. Nuclei are stained with DRAQ5 (Biostatus) (blue). Upper row, bar = 20 µm; lower row, bar = 8 µm.

7. Astrogliopathy

This term refers to alterations of astrocytes occurring in diseases of the nervous system, implying the involvement of astrocytes as key elements in the pathogenesis and pathology of diseases and in injuries of the central nervous system [112–122].

Reactive astrogliosis is a reaction secondary to neuronal damage in various injuries such as trauma and ischemia, external toxins, metabolic disorders and neurodegenerative diseases. The term astrocytopathy is used for non-reactive astrogliosis including hypertrophy, atrophy and astroglial degeneration with loss of function manifested by variable and distinct molecular changes in astrocytes, and pathological remodeling [112,117]. Senescent astrocytes are a particular form of astrocytophathy linked to old age which is manifested by modifications in the morphology of the nucleus and cytoplasm, cytoskeletal changes, oxidative damage, reduced energy production and secretory phenotype including production of inflammatory cytokines [92].

8. Reactive Astrogliosis

Reactive astrogliosis is common to all tauopathies and its distribution correlates with the degree of regional vulnerability to neuronal degeneration and neuronal loss [17,123,124]. However, tau-containing astrocytes do not match reactive astrocytes and they represent different although occasionally co-existent lesions [17,18,92,124].

Reactive astrogliosis also occurs in transgenic mouse models; the hippocampus is mainly affected in mice bearing the P301S mutation [125].

The expression of small heat shock proteins (HSP25/27 and αB-crystallin) is a characteristic response of reactive astrocytes in most tauopathies. However, HSPs are rarely co-expressed in astrocytes containing hyper-phosphorylated tau [126–129] (Figure 9). This suggests that generalized stress, rather than the restricted response in glial cells with abnormal protein aggregates, induces HSP expression [129]. Alternatively, it may be postulated that stress responses are directed to correcting

protein misfolding, and that they succeed to a certain extent, in that aggregates are not formed in many glial cells [92].

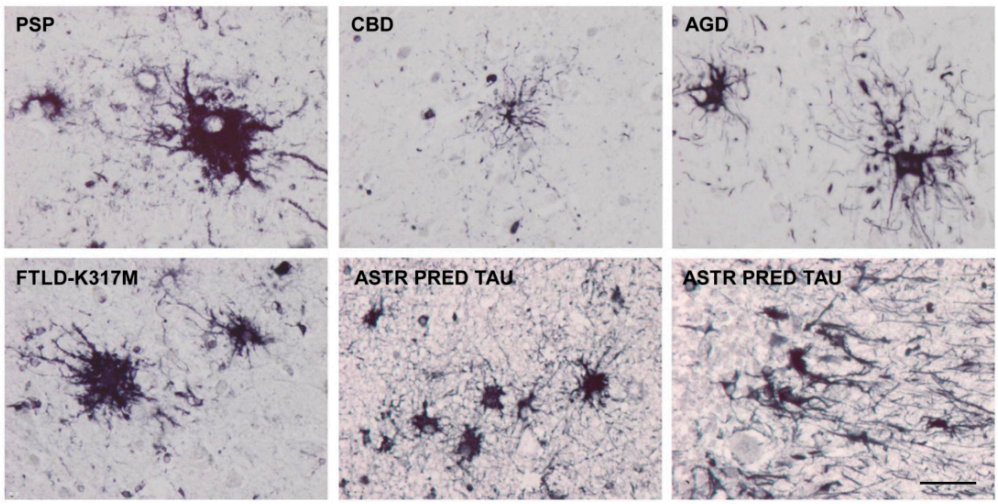


Figure 9. αB-crystallin-immunoreactive astrocytes in PSP, CBD, argyrophilic gain disease (AGD), FTLD-tau K317M and familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy. Paraffin sections visualized with diaminobenzidine, NH_4NiSO_4 and H_2O_2 without hematoxylin counterstaining; bar = 50 μm.

Additionally, it has been reported that intraneuronal accumulation of misfolded tau protein induces over-expression of Hsp27 in activated astrocytes [130].

9. Astrocytopathy

In spite of the evident astrocytopathy characterized by disease-dependent stereotyped tau deposits, little is known about the functional effects of hyper-phosphorylated tau in tau-containing astrocytes in tauopathies [131]. This is due to several factors: the diversity of astrocytes, diversity of functions and gene expression profiles under various conditions and regions, as well as the lack of studies considering these variables in tauopathies.

Astrocytes are not homogeneous cells. They can be classified into protoplasmic astrocytes of the grey matter, interlaminar astrocytes of the cerebral cortex, subpial astrocytes of the cerebral cortex, fibrous astrocytes of the white matter, perivascular astrocytes, Bergmann glia, stem astrocytes of subventricular zones, radial glia of the developing brain, tanycytes of the hypothalamus, pituicytes and Müller glia of the retina [116]. Moreover, they are heterogeneous with respect to their coverage domains, ion channels, calcium responses, glutamate transporters and expression of neurotransmitter receptors [92,132].

Gene expression studies of neurons and glial cells have contributed to our understanding of the variety of gene expression profiles that advance distinct functions in different cell types [133–140]. Microarray analyses of isolated astrocytes have identified particular transcription profiles in AD and related animal models [141,142].

Unfortunately, this approach has not been utilized in human tauopathies, and we are still in the dark concerning gene expression differences among TSAs, tufted astrocytes, astrocytic plaques and astrocytes with globular inclusions, to name just some examples.

Moreover, we do not know about similarities and differences among tau-containing astrocytes in the same disease but located in different regions; for example, subependymal, subpial, clusters in the frontal and temporal white matter, basal forebrain and perivascular TSAs in ARTAG.

These aspects are important in the present context as we do not know whether different tau inclusions affect different astrocyte types with particular vulnerability to tau species, or even if different tau species modify the morphology and function of the same type of astrocyte.

The over-expression of tau in cultured astrocytes produces degeneration of the cytoskeleton and Golgi complex, eventually leading to cell death [143]. Altered nuclear function and DNA transcription has also been posited for tau-containing neurons in tauopathies and fly models [144–147].

The expression of solute carrier family 1 member 2 (SLC1A2 or GLT-1) is markedly reduced in most astrocytes bearing hyper-phosphorylated tau in familial behavioral variant frontotemporal dementia associated with astrocyte-predominant tauopathy [87]. Decreased expression of GLT-1 and solute carrier family 1 member 3 (SLC1A3 or GLAST) also occurs in transgenic mice selectively expressing hyper-phosphorylated tau in astrocytes [148,149].

Whether tau-containing astrocytes have deleterious effects on neurons is an important question, as decreased GLT-1 expression alters glutamate metabolism and enhances excitoxicity. Hyper-phosphorylated tau deposits also have effects on the redistribution of organelles and reactive responses, but their functional effects are not known (Figure 10).

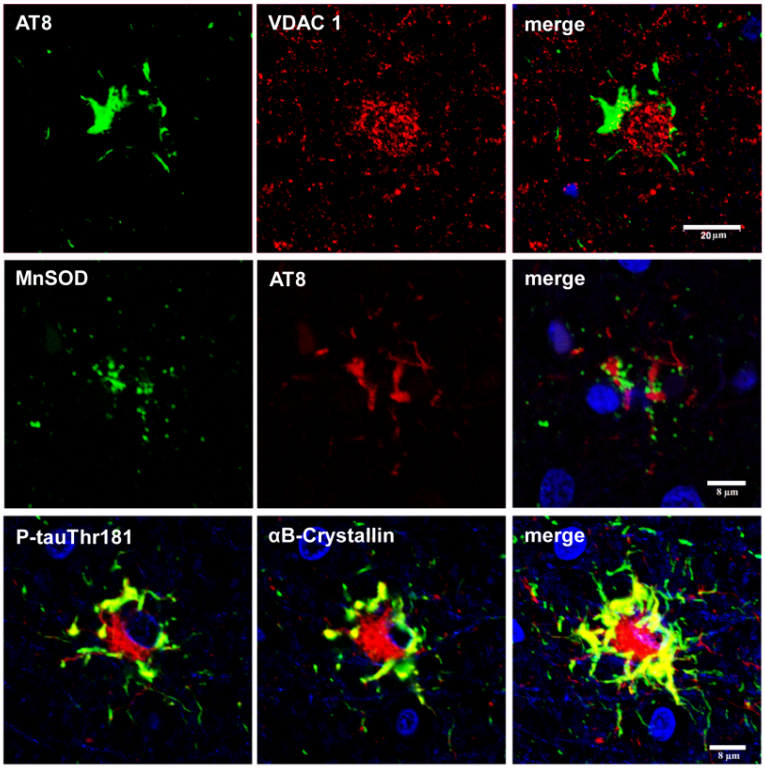


Figure 10. Double-labeling immunofluorescence and confocal microscopy of tufted astrocytes in PSP to AT8 and voltage-dependent anion-selective channel 1: VDAC1 (upper row), AT8 and superoxide dismutase 2: MnSOD, SOD2 (middle row), and serial sections of P-tauThr181 and αB-crystallin (lower row). VDAC1 is concentrated at the center of the cell due to the displacement of peripheral tau whereas SOD2 immunoreactivity is intermingled with phospho-tau deposits. αB-crystallin is found around the nucleus and surrounded by hyper-phosphorylated tufts. Paraffin sections; nuclei (blue) are stained with DRAQ5 (Biostatus); upper row, bar =20 µm; middle and lower row, bar =8µm.

Moreover, extracellular tau oligomers rapidly accumulate in astrocytes and reduce the release of gliotransmitters, thus impairing neuronal function [150].

Furthermore, FTLD-N279K *MAPT* astrocytes derived from neural stem cells increase oxidative stress and produce marked modifications in the genomic expression of co-cultured healthy

neurons [151]. Finally, P301S-derived astrocytes significantly decrease pre-synaptic and post-synaptic protein expression in cortical neuron cultures, whereas normal astrocytes enhance these markers, thereby suggesting that mutant astrocytes have reduced neuroprotective capacities [152].

10. Disease Progression: Seeding and Spreading; Role of Astrocytes

Tauopathies are progressive biological processes with a preclinical phase, prodromal phases and phases with clinical manifestations. The stages of NFT progression (stages I–VI of Braak) in AD are well known [153,154]. The stages of NFT pathology in PART are the same as those proposed for AD; whether PART is part of AD is a matter of discussion [155,156]. The majority of cases formerly classified as early stages of sporadic AD lack Aβ plaques [157,158] and are now considered PART, whereas the majority of cases with advanced Braak NFT stages are considered AD because of the presence of abundant Aβ deposits. Whatever the name, early stages of NFT are very common in old people as they occur in about 85% of individuals aged 65 years [157,159].

Different stages have also been proposed to categorize disease progression in AGD [14,160]. In contrast, only short series of incidental and early stages of PSP and CBD are available [74–76,161,162] to permit a validation of the several proposed sequences of events in disease progression.

The progression of AD and tauopathies is thought to occur by trans-cellular and trans-regional propagation of the abnormal protein in a similar way to what happens in prion diseases [163]. The exact mechanism of transmission is not known. Release and trans-synaptic transmission of tau [164,165], tau uptake via exosomes [166–168] or nanotubules [169] and free uptake of fibrillar proteins [170,171] have all been suggested as putative mechanisms using cultured neurons. Although astrocyte-to-neuron intercellular transfer mediated by cell-to-cell contact has been postulated for prions [172], no information is available concerning astrocyte-to-neuron transfer in tauopathies.

Transgenic mice with human tau over-expression or with tau mutations have been used to facilitate the mechanism of seeding and progression. Seeding and spreading of abnormal tau occurs after inoculation of brain homogenates from AD and other tauopathies into the brain of transgenic mice over-expressing human tau or mutated tau [163,173–175]. The type of deposits in the inoculated animals seems to be disease-dependent in the few tauopathies so far studied, which suggests the occurrence of different species or strains of tau depending on the disease [176–178]. However, these models have a natural substrate of abnormal tau production that makes it difficult to separate the propagation itself from what is induced.

Seeding of human tau from homogenates of AD and tauopathies with neuronal and glial components is also observed after inoculation into the brain of wild-type mice [178,179].

Additionally, the inoculation effect of recombinant tau is different from the effects using human brain homogenates enriched with tau fibrils from brains with tauopathy [178]. This suggests that different species ('strains') of tau have different properties and produce different effects. Another difference between the inoculation of recombinant tau fibrils and inoculation of tau from human brain homogenates is the accompanying inoculation, in the latter, of a number of associated proteins and enzymes which represents a probably disease-specific environment with unexplored properties.

All these experiments have been performed using brain samples of tauopathies with tau pathology only in neurons or with tau pathology in neurons and in glial cells. Abnormal tau in these paradigms can spread to resident neurons, astrocytes and oligodendroglia [176–178]. In other words, certain tau prion strains have the capacity to induce tauopathy not only in neurons but also in glial cells [180] (Figure 11).

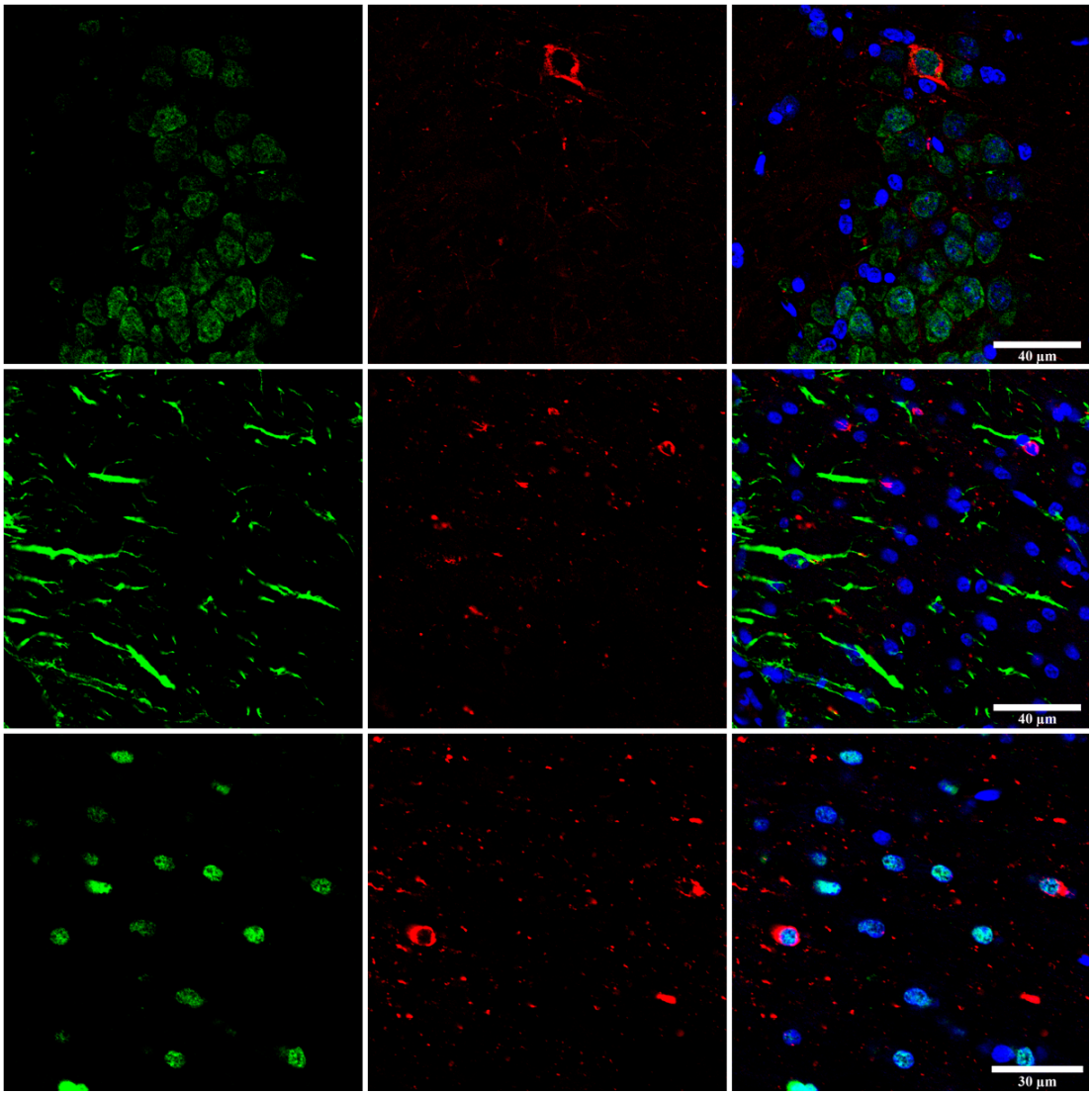


Figure 11. Wild-type (WT) mice inoculated with primary age-related tauopathy (PART) in the hippocampus at the age of 7 months and killed at the age of 10 months. Double-labeling immunofluorescence to neuronal nuclear protein (NeuN), GFAP and Olig-2 (green) and P-tauThr181 or clone AT8 (red). Subpopulations of neurons, astrocytes and oligodendrocytes contain hyper-phosphorylated tau (arrows). Paraffin sections, nuclei stained with DRAQ5 (Biostatus) (blue), bar, upper and middle row, bar = 30 µm; lower row, bar = 40 µm.

Whether astrocytic tau alone is able to induce tauopathy has recently been assessed. Tau-enriched fractions of brain homogenates from pure ARTAG (with no associated tauopathy) inoculated into the hippocampus (dentate gyrus and *cornu ammonis* (CA1) of wild-type mice generate intracytoplasmic hyper-phosphorylated tau inclusions in astrocytes, oligodendrocytes and neurons near the site of injection, and in nerve fiber tracts in the fimbria and *corpus callosum* [106] (Figure 12). These observations indicate that astrocytes containing hyper-phosphorylated tau have the capability of seeding tau to neurons and glial cells, thus highlighting the putatively cardinal role of astrocytopathy in the pathogenesis of tauopathies [106]. Moreover, inoculation of ARTAG, containing 4Rtau astrocytes, produces 3Rtau seeding in neurons and glial cells in addition to 4Rtau deposition [106]. This also points to the likely involvement of astrocytes in the development of tau-containing neuronal processes in the aged brain [181].

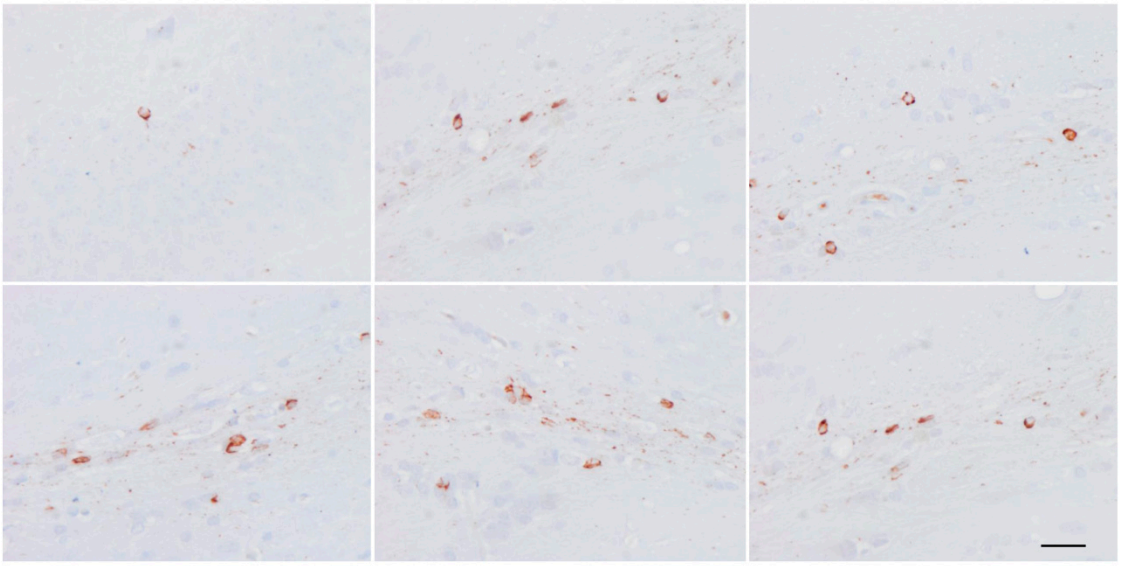


Figure 12. Wild-type mice inoculated with aging-related tau astrogliopathy (ARTAG) in the hippocampus at the age of 12 months and killed at the age of 19 months. The upper row corresponds to one mouse in which a hyper-phosphorylated tau-containing neuron is seen in CA1 region of the hippocampus (left) and several glial cells and fibers in the *corpus callosum* radiation of the ipsilateral side (middle) and contralateral side of injection (right). The lower row corresponds to another mouse showing hyper-phosphorylated tau fibers and glial cells in the *corpus callosum* radiation of the ipsilateral side (left), middle region of the *corpus callosum* (middle) and contralateral radiation of the *corpus callosum* (right). Paraffin sections immunostained with the AT8 antibody and slightly counterstained with hematoxylin, bar = 25 μm.

The fact that a neuronal tauopathy such as PART (only containing NFTs and threads) or pure forms of ARTAG (only containing TSAs) can produce seeding in neurons, astrocytes and oligodendrocytes in WT mice is an unexpected observation. This may be in part because different murine tau isoforms can be distinguished by the carboxyl terminal domains, and murine tau differs from human tau in a number of ways, including the absence of residues which are involved in tubulin binding [182].

Finally, environmental factors may influence tau pathology and seeding in astrocytes (and other cell types). Phosphoproteomics using bi-dimensional gel electrophoresis and mass spectrometry have shown a large number of phosphorylated proteins in addition to tau and related molecules in AD [183–185]. Other studies have identified GFAP phosphorylation in AD and in many other tauopathies [186,187]. More precise methods in several regions and different stages of disease have demonstrated the occurrence of very large numbers of phosphorylated proteins including kinases and synaptic proteins in areas with no relationship to β-amyloid deposits and NFTs [188]. Similar studies have recognized a number of phosphorylated proteins including phospho-kinases, neurofilaments, and synaptic and other neuronal proteins, in addition to phospho-GFAP and phosphorylated aquaporine-4 in the white matter in pure cases of ARTAG [106]. Although similar studies are not available in other tauopathies, these observations suggest that tau pathology in astrocytes should be interpreted not as an isolated process but in the context of a very particular environment which is hospitable to tau phosphorylation.

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