

MINI-SYMPOSIUM: Astroglia in Neurodegenerative Diseases

Diversity of astroglial responses across human neurodegenerative disorders and brain agingIsidro Ferrer ^{1,2,3,4}¹ Department of Pathology and Experimental Therapeutics, University of Barcelona, Barcelona, Spain.² Institute of Neuropathology, Pathologic Anatomy Service, Bellvitge University Hospital, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain.³ Institute of Neurosciences, University of Barcelona, Barcelona, Spain.⁴ Biomedical Network Research Center on Neurodegenerative Diseases (CIBERNED), Institute Carlos III, Madrid, Spain.**Keywords**

aging, astrocytes, astrocytic gliosis, astrocytopathy, astrogliopathy, neurodegenerative diseases with abnormal protein aggregates.

Corresponding author:

I. Ferrer, Department of Pathology and Experimental Therapeutics, University of Barcelona, campus Bellvitge, Feixa Llarga sn; 08907 Hospitalet de Llobregat, Spain (E-mail: 8082ifa@gmail.com)

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Abstract

Astrogliopathy refers to alterations of astrocytes occurring in diseases of the nervous system, and it implies the involvement of astrocytes as key elements in the pathogenesis and pathology of diseases and injuries of the central nervous system. Reactive astrocytosis refers to the response of astrocytes to different insults to the nervous system, whereas astrocytopathy indicates hypertrophy, atrophy/degeneration and loss of function and pathological remodeling occurring as a primary cause of a disease or as a factor contributing to the development and progression of a particular disease. Reactive astrocytosis secondary to neuron loss and astrocytopathy due to intrinsic alterations of astrocytes occur in neurodegenerative diseases, overlap each other, and, together with astrocyte senescence, contribute to disease-specific astrogliopathy in aging and neurodegenerative diseases with abnormal protein aggregates in old age. In addition to the well-known increase in glial fibrillary acidic protein and other proteins in reactive astrocytes, astrocytopathy is evidenced by deposition of abnormal proteins such as β -amyloid, hyper-phosphorylated tau, abnormal α -synuclein, mutated huntingtin, phosphorylated TDP-43 and mutated SOD1, and PrP^{Sc}, in Alzheimer's disease, tauopathies, Lewy body diseases, Huntington's disease, amyotrophic lateral sclerosis and Creutzfeldt-Jakob disease, respectively. Astrocytopathy in these diseases can also be manifested by impaired glutamate transport; abnormal metabolism and release of neurotransmitters; altered potassium, calcium and water channels resulting in abnormal ion and water homeostasis; abnormal glucose metabolism; abnormal lipid and, particularly, cholesterol metabolism; increased oxidative damage and altered oxidative stress responses; increased production of cytokines and mediators of the inflammatory response; altered expression of connexins with deterioration of cell-to-cell networks and transfer of gliotransmitters; and worsening function of the blood brain barrier, among others. Increased knowledge of these aspects will permit a better understanding of brain aging and neurodegenerative diseases in old age as complex disorders in which neurons are not the only players.

ASTROCYTES: GENERAL ASPECTS

Astrocytes are neural stellate cells with long processes which are in contact with neurons and synapses, myelin sheaths, oligodendrocytes, microglia and blood vessels (capillaries, arterioles and venules); subpial, subventricular and perivascular astrocytes separate neurons from the cerebrospinal fluid and blood (172, 408). Astrocytes are arranged in non-overlapping domains but form syncytial networks united by gap junctions (69, 164). Astrocytes are non-excitable cells but they respond to various stimuli, they are enriched in potassium, calcium and water channels and participate in synaptic transmission through the control of neurotransmitters and transporters (219).

The coverage domain of a single astrocyte is estimated between 20,000 and 140,000 synapses in the rodent hippocampus, but

between 250,000 and 2 million synapses in humans (69, 324, 325). Astrocytes in the white matter have more elongated processes; they are organized along nerve fibers and surround blood vessels by podocytes; it is not clear whether coverage domains of astrocytes in the grey matter have any counterpart in the white matter in connection with fiber tracts.

Glial fibrillary acidic protein (GFAP) is currently used as a marker of astrocytes, and GFAP immunostaining is particularly useful to label a subset of astrocytes under reactive conditions (Figure 1). However, not all astrocytes are GFAP-immunoreactive and not all cells which express GFAP are astrocytes (218, 323, 417). Neural stem cells of the subventricular zone are GFAP-immunoreactive but they are not considered astrocytes (323). It has been estimated that only about 15% of the total volume of

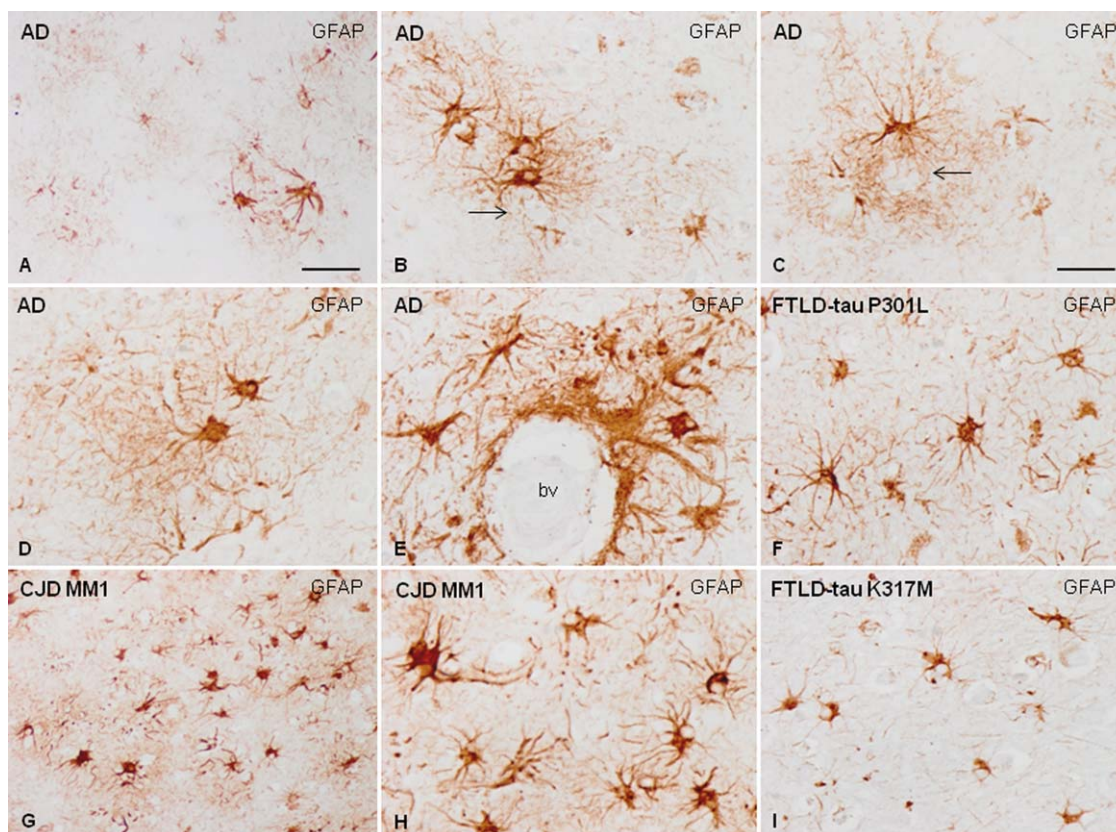


Figure 1. Reactive astrocytes as revealed with GFAP immunohistochemistry in AD (**A–E**), FTLD-tau P301L (**F**), CJD subtype MM1 (**G, H**) and FTLD-tau K317M. Reactive astrogliosis in AD tends to form clusters in the vicinity of β -amyloid core deposits (**A–C**, **B** and **C** arrows), but they are also occasionally distributed with no apparent association with senile plaques (**D**). Reactive astrogliosis is also frequent in contact with the blood vessels (**bv**, **E**). In contrast, reactive astrogliosis in CJD and FTLD is more diffuse and does not form clusters (**F–I**). Reactive astrocytes in CJD are usually large with robust

cellular processes strongly stained with GFAP antibodies (**G, H**). However, reactive astrocytes in FTLD-tau are usually smaller in size with short, fine cellular processes which are more striking in FTLD-tau K317M (**I**) than in FTLD-tau P301L (**F**). This panel illustrates the diversity of GFAP-reactive astrocytes in different neurodegenerative diseases, and highlights the atrophic morphology of astrocytes in FTLD-tau K317M. Paraffin sections slightly counterstained with hematoxylin; **B–F, H, I**, bar in **C** = 35 μ m; **A** and **G**, bar in **A** = 75 μ m.

astrocytes is revealed by GFAP immunohistochemistry in tissue sections of the rodent hippocampus (69). There are 10 isoforms/splice variants identified (217). The most abundant in the brain and spinal cord is GFAP- α (isoform 1); GFAP- δ (GFAP- ϵ ; isoform 2) is expressed by neurogenic astrocytes in the subventricular zone (207). GFAP- α , GFAP- ϵ and GFAP- κ are the most well characterized isoforms of GFAP in the central nervous system. Other isoforms are expressed in the peripheral nervous system and other organs. Four isoforms of GFAP, collectively named GFAP + 1, are expressed in a subset of astrocytes throughout the brain. One GFAP + 1 is found in a subset of astrocytes in senile plaques in Alzheimer's disease (208).

Vimentin, another intermediate filament of the cytoskeleton; the calcium-binding protein S100 β ; aquaporin 4 water channel (AQ4); aldehyde dehydrogenase family 1, member 1 (ALDH1L1); glutamate transporters solute carrier family 1, member 1 (GLAST/EAAT1); solute carrier family 1, member 2 (GLT-1/EAAT2); and bystin, connexin 43 and nestin are also molecular components of astrocytes (79) (Figure 2). YKL-40 (CHI3L1) has recently been identified as a biomarker of reactive astrocytes linked to

inflammation (44, 45, 263) (Figure 3). Other molecules are also expressed in astrocytes such as glutamine synthetase, N-myc-down-regulated gene 2 (NDRG2) and the receptor for hyaluronic acid CD44 (7, 129). Sox9, a transcription factor, has been recently reported to be selectively expressed in the nuclei of astrocytes (430)

TYPES OF ASTROGLIAL CELLS

Astrocytes, astroglial cells or astroglia were first categorized into protoplasmic and fibrous (15). However, the use of the Golgi method and other silver stains permitted the visualization and identification of a large variety of astrocytes (365). Subsequent studies classified the main types of astroglial cells in the central nervous system as protoplasmic astrocytes, fibrous astrocytes, radial glia, Bergmann glia, ependymal astrocytes, perivascular glia, marginal glia, tanyocytes and velate glia (108). Two additional types are specific to human and other primates: interlaminar astrocytes and varicose projection astrocytes (89, 90, 324, 325). Recent classifications

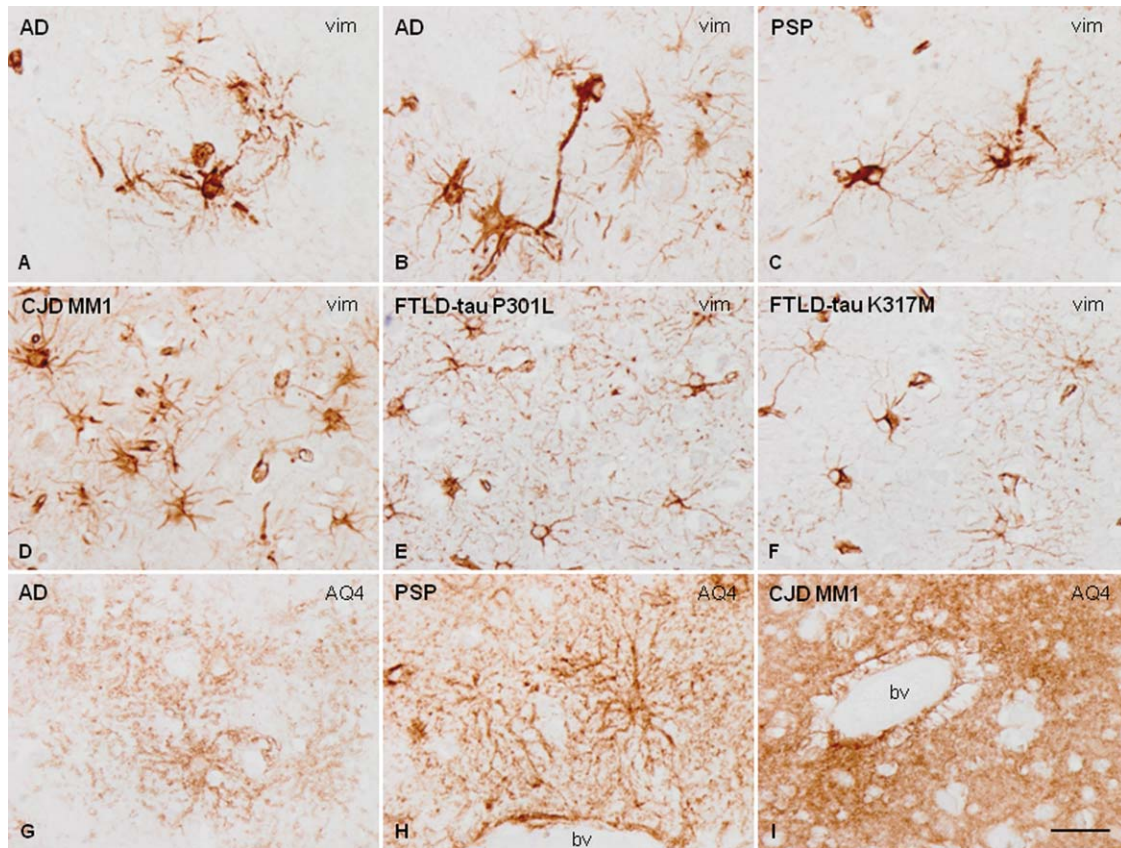


Figure 2. Vimentin (vim) immunohistochemistry shows that the morphology of cortical astrocytes varies in AD (**A**, **B**), PSP (**C**), CJD MM1 (**D**), FTLD-tau P301L (**E**) and FTLD-tau K317M (**F**). Astrocytes in FTLD, and particularly in FTLD-tau K317M, have small, fine branches and fewer astrocyte processes. Aquaporin 4 (AQ4) antibodies stain astrocytic processes in the neuropil and in the vicinity of blood vessels

(bv) in most neurodegenerative diseases with abnormal protein aggregates as in AD (**G**) and PSP (**H**). However, AQ4 immunoreactivity is stronger and more blurred in CJD, and vacuoles are formed at the periphery of blood vessels (bv, **I**). Paraffin sections, slightly counterstained with hematoxylin, bar = 35 μ m.

include 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 (454).

In addition to morphological features which distinguish different astrocytes, increasing knowledge of the organization and functional properties of astrocytes envisages a more complex scenario with additional types. Astrocytes are heterogeneous with respect to their coverage domains, ion channels, calcium responses, glutamate transporters and expression of neurotransmitter receptors (24, 69, 70, 108, 160, 164, 166, 182, 183, 194, 260, 275, 302, 303, 326, 331, 366, 396, 402). Moreover, astrocytes from primates have characteristics which differ from those in rodents (285, 323–325). Single cell gene expression profiling is useful tool to identify different types of astrocytes in the developing and adult brain, and following injuries such as focal cerebral ischemia (383). Although our understanding of the diversified types and functions of astrocytes is at its inception, available information points to the possibility of diversified astrocytic responses depending on the cell type and the

region in which a particular astrocyte is located, which in turn depends on its interaction with neurons, microglia and blood vessels. Gene expression studies of isolated neurons, astrocytes and oligodendrocytes help to improve understanding of cell diversity (72, 202, 261, 490, 491). However, identification of astrocyte subtypes and recognition of their gene expression profiles has not been achieved.

FUNCTIONS OF ASTROCYTES

Astrocytes are key and unique regulators of multiple brain functions. They are sensitive to different stimuli, responding through complex calcium signaling (403). Although not able to propagate action potentials along their processes as neurons do, astrocytes express potassium and sodium channels, and exhibit evoked inward currents (314). The following are the major physiological functions of astrocytes:

- Regulation of potassium, sodium and calcium homeostasis through specific channels and water by astrocyte-specific AQ4 water channels (199, 220, 311, 341).

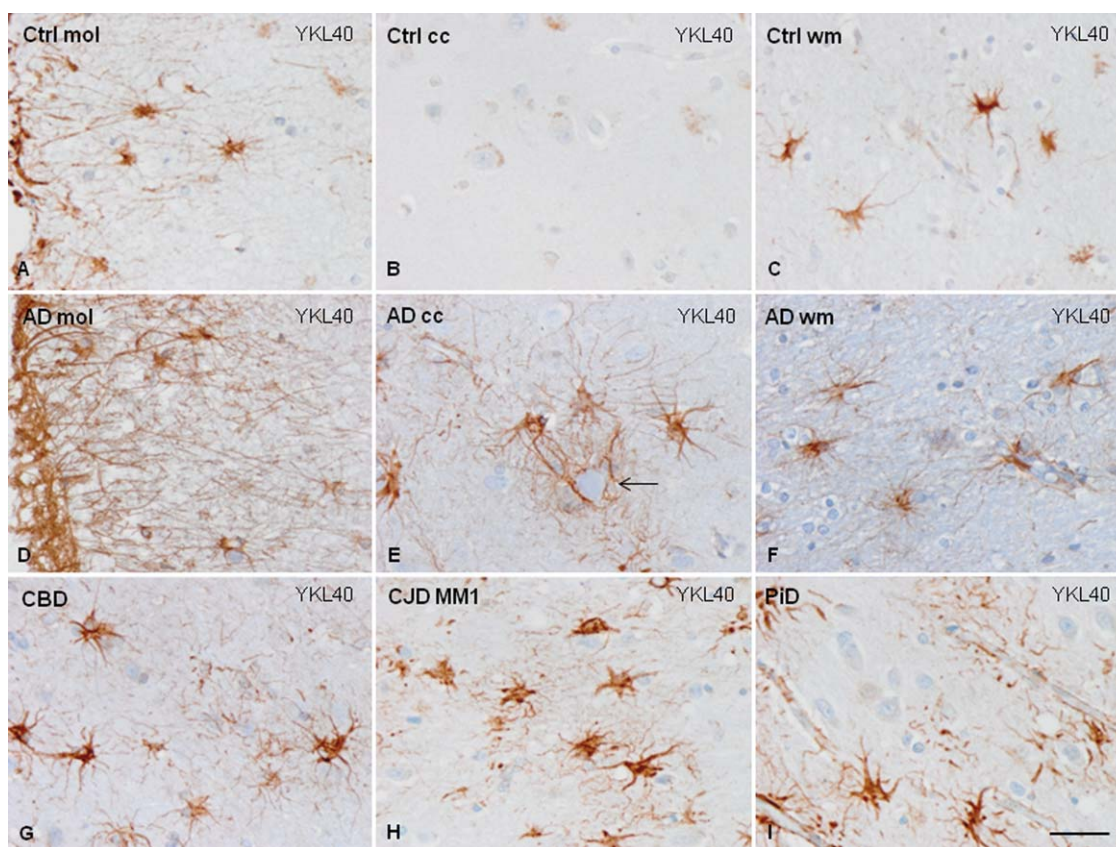


Figure 3. YKL40 immunoreactivity in astrocytes. YKL40 immunoreactivity in control brains is found in subpial astrocytes and in fibrous astrocytes in the white matter, but is almost absent in the cerebral cortex (**A–C**). However, strong YKL40 immunoreactivity is

found, in addition, in cortical astrocytes in AD, mainly surrounding amyloid cores (arrow, **D–F**), and in reactive astrocytes in the cerebral cortex in CBD (**G**) CJD MM1 (**H**) and PiD (**I**). Paraffin sections, slightly counterstained with hematoxylin, bar = 35 μ m.

- Cellular coupling through gap junctions mainly composed of connexins (314).
- Regulation of blood flow through the release of mediators such as arachidonic acid, prostaglandins and nitric oxide (152, 189).
- Participation in the functioning of the blood brain barrier (1, 26, 152, 223).
- Modulation of the synaptic transmission through the expression of glutamate, GABA and glycine transporters, thus facilitating turnover of neurotransmitters at the synapses (10, 314, 402).
- Release of neurotransmitters such as glutamate, GABA, D-serine, ATP and adenosine, thus functionally contributing to the tripartite synapse (17, 23, 162–164, 352).
- Catabolisation of glutamate by glutamine synthetase and adenosine by adenosine kinase (198, 494).
- Contribution to the formation, maintenance and pruning of synapses during development (29, 85, 423).
- Providing energy through the storage of glycogen, production of lactate and transfer to neighboring neurons and synapses (59, 60, 351, 427).
- Responsiveness to oxidative stress by producing glutathione, ascorbic acid and superoxide dismutases (SOD1, SOD2, SOD3) (106, 259, 411); up-regulation of heme-oxygenase 1 (387, 388).

ASTROGLIOPATHY

This term refers to alterations of astrocytes occurring in diseases of the nervous system, and it implies the involvement of astrocytes as key elements in the pathogenesis and pathology of diseases and injuries of the central nervous system (335, 349, 351, 452, 454, 455). Astrogliopathy covers the seminal concept of gliodegeneration (93) and stresses the cardinal role of astrocytic dysfunction in the pathogenesis of neurological diseases (395).

Astrogliopathy includes reactive gliosis and astrocytopathy. Reactive astroglia is a reaction secondary to trauma and ischemic injuries, external toxins, metabolic disorders and neuron damage in neurodegenerative diseases. The term astrocytopathy is here used to include non-reactive astroglia covering hypertrophy, atrophy and astroglial degeneration with loss of function manifested by variable and distinct molecular changes in astrocytes, and pathological remodeling (346). Senescent astrocytes can also be considered a particular form of astrocytopathy usually linked to old age. This classification is simplistic but it can be advantageous and instrumental to class molecular alterations in different settings and diseases.

Astrocytes can be the primary targets in rare genetic neurological diseases in which genetic alterations involve specific astrocytic genes. Astrocytes can also be vulnerable co-primary targets in

neurodegenerative diseases with abnormal protein aggregates such as Alzheimer's disease (AD), tauopathies, Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Creutzfeldt-Jakob disease (CJD).

Therefore, the term astrogliopathy points to a variety of alterations. Astrogliopathy following trauma and stroke is mainly manifested as reactive astrogliosis. Astrogliopathy in Alexander's disease is a typical genetic astrocytopathy. Astrogliopathies in neurodegenerative diseases are particularly complex as they occur in aged brains in which astrocytes may suffer from senescent changes, may have particular responses linked to reactive astrogliosis and, more importantly, may have disease-specific alterations with particular manifestations of astrocytopathy depending on the neurodegenerative disease. The boundaries between reactive astrogliosis and the various alterations covered by the term astrocytopathy in neurodegenerative diseases are often blurred as for example in AD.

The weight of astrocytes in neurodegenerative diseases is exemplified by the fact that the majority of de-regulated genes in mouse models of AD and ALS are expressed in astrocytes and microglia rather than in neurons, as revealed by the application of isolation techniques to analyze transcriptomes separately from neurons and glial cells (420).

Most neurodegenerative diseases have been considered cell autonomous meaning that damage of certain populations of neurons suffices to produce disease. However, convergence of damage of several cell types including astrocytes as well as damage to neurons may account for the selective vulnerability in many neurodegenerative diseases (193). The concept of non-cell autonomous toxicity, first exemplified in ALS, is crucial to understand the pathogenesis of most neurodegenerative diseases (193).

SENESCENT ASTROCYTES

Astrocytes change with aging (371, 385). This is manifested by modifications in number, morphology of the cytoplasm and nucleus, accumulation of lipofuscin in the cytoplasm, hypertrophy of cytoplasmic filaments and increased expression of GFAP, S100 β and vimentin (38, 92, 128, 188, 237, 274, 316, 345, 360, 385, 426, 441, 468). It is commonly considered that aging is accompanied by increased numbers of GFAP-immunoreactive astrocytes. However, this is subject to species differences since no modifications in the number of astrocytes are observed with age in the occipital cortex of rhesus monkeys or in human neocortex (337, 353).

Senescence astrocytes exhibit increased oxidative damage and enhanced superoxide production (145) together with a senescence-associated secretory phenotype similar to that seen in other cellular types (74, 91, 135) manifested by increased production of pro-inflammatory cytokines (75, 240, 478). Isolated astrocytes from aged mice have increased inflammatory phenotype, increased zinc ion binding, decreased neuronal differentiation capacities and reduced hemoglobin synthesis when compared with astrocytes from young mice (334).

The senescence secretory phenotype can be triggered by different stimuli including oxidative stress, inflammation and inhibition of the ubiquitin-proteasome system (42). Increased inflammatory phenotype and decreased neuronal differentiation are also observed in human astrocytes subjected to oxidative stress-induced

senescence, although GFAP, and processing and presentation of antigens by major histocompatibility complex class II proteins, decrease in this cellular model (94). Reduction of GSH in glial cells induces neurotoxicity which may be relevant in aging and neurodegeneration (241).

Perivascular astrocyte senescence leads to altered blood brain barrier function in old age (1, 115, 298, 359). Aging in blood vessels is also accompanied by reduced expression of efflux transporters and increased expression of influx transporter receptor for advanced glycation end products which can participate in the abnormal transfer of β -amyloid, leading to its accumulation in blood vessels (406, 407). Astrocyte senescence has been implicated in the pathogenesis of neurodegenerative diseases (40, 83, 371, 372, 449).

REACTIVE ASTROGLIOSIS

The term reactive gliosis is used for the response of astrocytes, microglia and NG2-positive cells to different insults to the nervous system (67). Increased cytoplasmic size and robustness of branches (hypertrophy) accompanied or not by an increase in the number of astrocytes (hyperplasia) in response to external or intrinsic damage to the nervous system characterize reactive astrogliosis. Holzer and phosphotungstic acid hematoxylin stains, as well as several silver methods, were seminal used to identify astrogliosis. Increased expression of GFAP in astrocytes is considered a marker of reactive gliosis in histological sections (109, 481). However, GFAP immunohistochemistry does not permit the visualization of small astroglial processes as it is present only in the cytoplasm and proximal segments of radial branches; fine perisynaptic terminals and fine branches are not visualized by GFAP immunostaining. Moreover, subpopulations of reactive astrocytes have no substantial levels of GFAP.

The intensity of reactive astrogliosis is variable and categorized as mild, moderate or severe, the latter implying marked hypertrophy and frequent proliferation. Severe astrogliosis may eventually form a scar in which cellular processes of reactive astrocytes densely overlap and pack together, forming a compact barrier which separates the preserved neural tissue from the local severely damaged area. Reactive astrocytes in glial scars interact with pericytes, meningothelial cells and fibroblasts, and form dense fibrous collagen-rich barriers which are neuroprotective to potential external noxious agents (405). Reactive astrogliosis has been categorized into isomorphic/mild neuroprotective and anisomorphic/severe scar forming (350). This classification is also rather schematic as both forms may appear at different sites following a single injury, but again it is appropriate to separate polar forms of reactive astrogliosis.

Despite the apparent morphological similarities of reactive astrocytes, reactive astrogliosis is a very heterogeneous response that can be triggered by various stimuli, is mediated by different factors, has distinct functions, and leads to particular, even opposite, effects depending on diverse circumstances (67).

Reactive astrogliosis can be induced by molecules derived from external insults and from products of the metabolism of neurons, glial cells, pericytes, endothelial cells and other cell types. Mediators of the innate inflammatory response such as Toll receptors, neurotransmitters such as glutamate and noradrenaline,

purines, steroid hormones, transforming growth factor α , ciliary neurotrophic factor, IL-6 and other cytokines, oncostatin, leukemia inhibitory factor, serum proteins, nitric oxide, reactive oxygen species, ammonia, hypoxia and glucose deprivation, and peptides and proteins linked to particular neurodegenerative diseases such as β -amyloid, among many others, can trigger reactive astrogliosis (25, 140, 142, 181, 221, 246, 347, 350, 363, 415, 472). Transduction depends on several signaling pathways which regulate anti- and pro-inflammatory functions, expression of GFAP, vimentin and other cytoskeletal proteins, cell proliferation and chaperone function. Factors implicated in inter- and intracellular signaling pathways are signal transducer and activator of transcription 3 (STAT3), nuclear factor of kappa light polypeptide gene enhancer in B cells (NF- κ B), cyclooxygenase 2 (COX2), mitogen-activated protein kinases (MAPKs), nuclear factor erythroid 2 (Nrf2), suppressor of cytokine signaling 3 (SOCS3), cAMP, ATP, Olig2, endothelin 1, peroxisome proliferator activated receptor alpha (PPAR), epidermal growth factor (EGF) and fibroblast growth factor (FGF), *inter alia* (36, 37, 179, 185, 190, 210, 292, 313, 327, 328, 348–350, 401, 415, 417, 421, 440, 467). Small non-coding RNAs also participate in reactive astrogliosis (39, 187, 463). Resultant proteins are not uniformly expressed in the totality of reactive astrocytes but rather only in certain sub-populations even within the same setting (112, 113, 350, 383, 415–417, 467).

Some reactive astrocytes have the capacity to proliferate locally (28, 66, 415, 417) and some of them may transform into multipotential cells (65, 368, 413). Astroglia may induce neurogenesis from adult stem cells (418). Inflammation-induced NF- κ B activation promotes the conversion of astrocytes into neural progenitor cells (139). Proliferation results in an increase in the number of astrocytes which must not be mistaken for the mere enhancement of GFAP expression in already existent astrocytes. However, astrocyte proliferation in neurodegenerative diseases seems to be very limited (207, 209, 413, 426). Individual proteins and activation of certain pathways have distinct effects on particular settings (287). GFAP is a paradigm of potential dual opposite effects. Mice lacking GFAP are hypersensitive to traumatic cerebrospinal injury (312). Mice lacking GFAP and vimentin show reduced capacity for repair in the face of different noxious agents (248, 273, 346, 448, 469). Therefore, GFAP benefits the recovery of damaged nervous tissue. Yet excessive GFAP expression, as in scars, reduces the capacity for healing (271, 374). In this regard, astrocyte scar formation has been classically linked to reduced axonal regeneration (405). However, recent evidence indicates a more complex scenario in which early scar formation helps axon regeneration in the central nervous system (12).

The majority of signals and mediators have been identified in experimental models mimicking acute insults such as ischemia, excitotoxicity and spinal cord injury. Astroglial responses after ischemic stroke and focal traumatic lesions are classified into three phases: phase I, characterized by cell death and inflammation; phase II, recognized by cell proliferation and tissue replacement; and phase III, manifested by tissue remodeling (67).

However, it is worth stressing that comparative genomic analyses of reactive astrogliosis show marked stimulus-dependent differences in gene expression in the face of relatively simple injuries such as trauma, focal ischemia, acute inflammation and acute exposure to toxins (11, 348, 488).

Potential functional effects of reactive astrogliosis

Reactive astrogliosis is interpreted as a beneficial reaction geared to protecting the nervous system from harmful internal and external stimuli. However, certain continuing astrocytic responses, for example those producing chronic inflammation, may increase neuronal damage (350). This aspect is relevant in long-lasting neurodegenerative diseases in aging (461).

Reactive astrogliosis may protect neurons from excitotoxic damage, water and ionic imbalance, oxidative stress damage and infection (68, 82, 99, 114, 116, 179, 248, 295, 307, 362, 414, 415, 417, 431, 447, 451, 487).

However, reactive astrogliosis may also have adverse effects by increasing excitotoxic damage, increasing oxidative stress, facilitating the production of pro-inflammatory cytokines and chronic inflammation, and increasing the permeability of the blood brain barrier (18, 53, 55, 168, 431, 432, 487, 488). Thus, decline of particular functions in reactive astrocytes facilitates neuronal damage (328, 376, 412, 422, 446, 450, 452, 454, 455).

ASTROCYTOPATHY

Decrease in the number of astrocytes, atrophy/degeneration and loss of function may occur as a primary cause of a disease or as a factor contributing to the development and progression of a particular disease (350).

Primary genetic astrocytopathies

Alexander's disease caused by mutations in *GFAP* is characterized by abnormal astrocytes and production of Rosenthal fibers composed of aggregates of filaments and dense inclusions in the cytoplasm of astrocytes. This results in impaired maintenance of myelin and axons, and leukodystrophy in infantile cases (56, 289, 361). Similar alterations are found in GFAP transgenic mice (288, 289). Megalencephalic leukoencephalopathy with subcortical cysts is caused by mutations in *MLCI* gene the product of which is expressed in the distal processes of subpial, periventricular and perivascular astrocytes. The disease is manifested by myelin breakdown, vacuolization and formation of confluent cysts in the cerebral white matter (46, 179, 270, 390).

Secondary astrocytopathies to toxic and metabolic disturbances

Alzheimer II astrocytes, also known as naked reactive astrocytes, have a large, pale nucleus, often a prominent nucleolus and reduced GFAP immunoreactivity which is accompanied by increased numbers of mitochondria, enlargement of the endoplasmic reticulum and accumulation of glycogen. Alzheimer type II astrocytes are mainly observed in grey matter of the striatum, globus pallidus, substantia nigra and dentate nucleus following hyperammonemia linked to hepatoencephalopathy and related conditions as well as in experimental hyperammonemia (320, 321). Hyperammonemia in astrocytes alters potassium, sodium and calcium homeostasis, increases intracellular edema, interferes with glutamine synthetase and induces glutamate excitotoxicity (159, 200, 214, 250, 252, 297, 322).

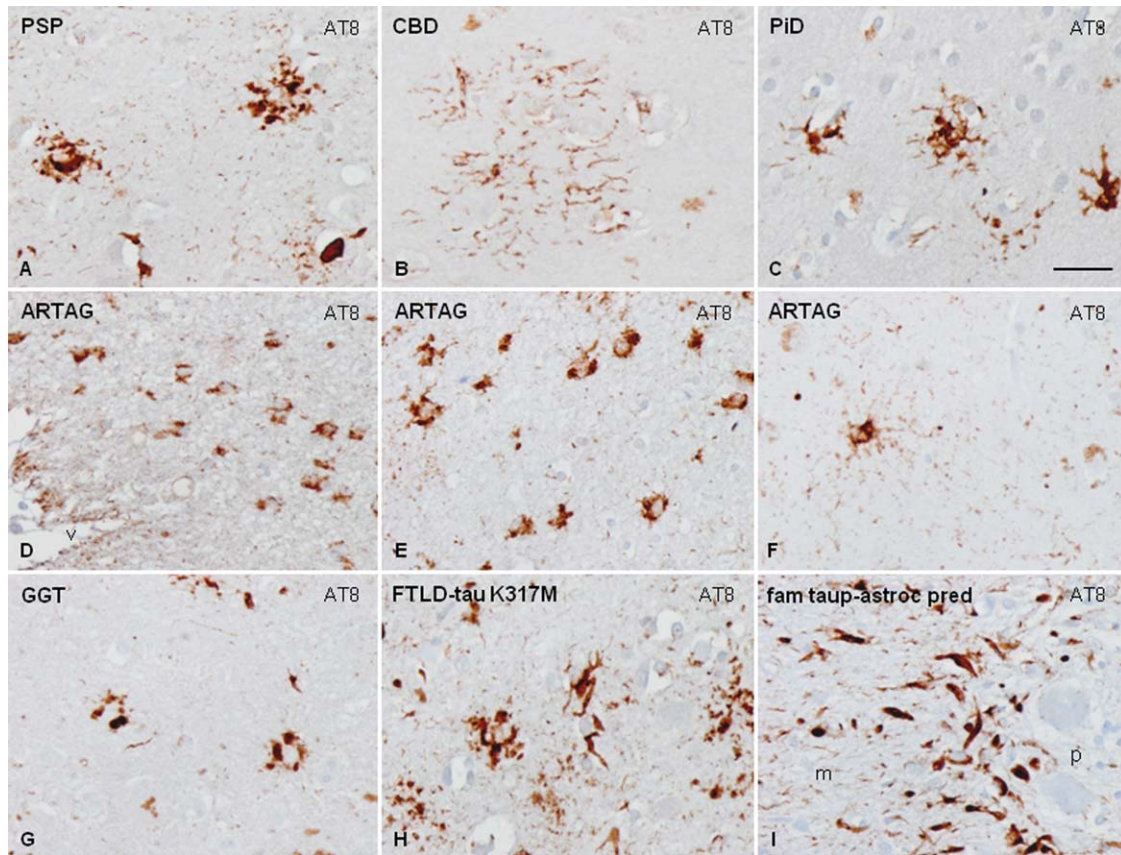


Figure 4. Morphology of astrocytes containing hyper-phosphorylated tau in several tauopathies, tufted astrocytes in PSP (**A**), astrocytic plaque in CBD (**B**), ramified astrocytes in PiD (**C**), periventricular thorn-like astrocytes (**D**) and clusters of thorn-like astrocytes in the temporal lobe (**E**) in ARTAG, astrocyte with thin diffuse granular hyper-phosphorylated tau in astrocytic processes in elderly (**F**), astrocytes

with globular inclusions in GGT (**G**), tufted-like polymorphous inclusions in astrocytes in FTLD-tau K317M (**H**) and Bergmann glia in familial behavioral variant FTLD with astrocyte-predominant tauopathy (**I**). Paraffin sections, processed for AT8 immunohistochemistry slightly counterstained with hematoxylin, bar = 35 μ m.

Secondary astrocytopathy with inhibition of glutamate transport occurs in thiamine deficiency and Wernicke-Korsakoff encephalopathy (173, 174), and after poisoning with heavy metals (451).

Astrocytopathy in neurodegenerative diseases in old age: Intracellular deposits of altered proteins

Combined neuronal damage and astrocytopathy is common in neurodegenerative diseases. The majority of neurodegenerative diseases with protein aggregates show accumulation of abnormal proteins in astrocytes and other glial cells (294).

Astrocytes containing hyper-phosphorylated tau are major elements of the pathology in most tauopathies (149, 191, 226). Principal phenotypes are tufted astrocytes in PSP, astrocytic plaques in CBD and ramified astrocytes in PiD (16, 104, 117, 171, 197, 305, 317, 318, 479) (Figure 4A–C). It has been suggested that tufted astrocytes and astrocytic plaques do not coexist in PSP and CBD (225). However, association of tufted-like astrocytes and astrocytic plaques is common in certain familial tauopathies linked to *MAPT* mutations (150).

Thorn-like astrocytes occur in old age individuals frequently in association with other tauopathies including argyrophilic grain disease and particularly in aging-related tau astrogliopathy (ARTAG) (126, 192, 228–230, 260, 267, 306, 319, 392, 438). Astrocytes with thin diffuse granular hyper-phosphorylated tau in astrocytic processes are seen in the elderly (228, 230) (Figure 4D–F). Astrocytes with globular inclusions occur in GGT (6, 41) (Figure 4G). All these inclusions are composed of 4R tau isoforms but certain astrocytes in PiD and PSP contain 3R tau isoforms (124).

Various types of astrocytic inclusions are generated in familial FTLD-tau, the morphology of which largely depends on the *MAPT* mutation (104, 149). Mutations in exons 1 and 10, and in introns following exons 9 and 10, are associated with neuronal and glial tau deposits (150). The varied morphology of intracytoplasmic tau-immunoreactive inclusions in FTLD-tau is represented by tufted-like astrocytes, astrocytic plaques, ramified astrocytes, thorn-like astrocytes and, rarely, astrocytes with globular inclusions (124, 150) (Figure 4H). Extensive astrocyte-predominant tauopathy involving brain astrocytes and Bergmann glia has been reported in a rare familial variant of FTLD-tau (Figure 4I). Familial PSP, CBD and GGT are suggested in some cases on the basis of the presence of “specific” astrocytic inclusions. However, it is premature to

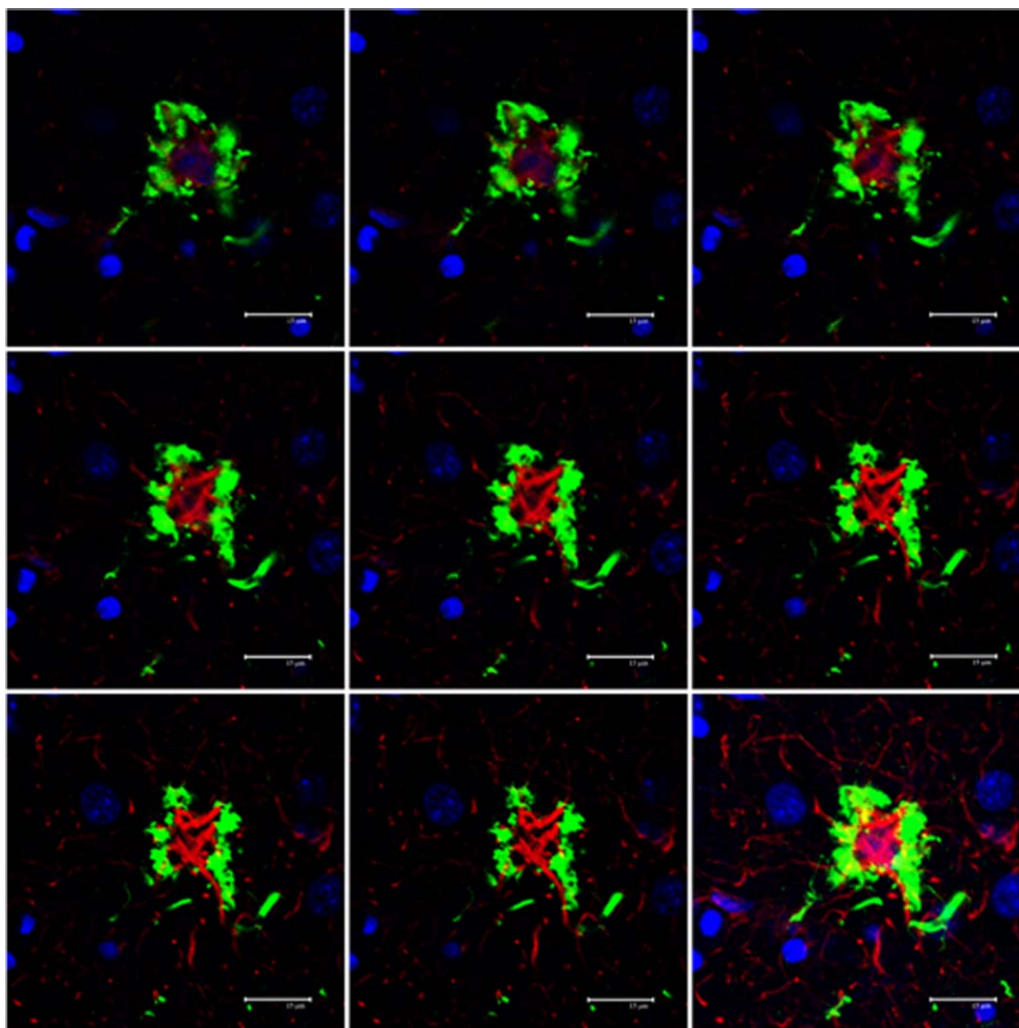


Figure 5. Serial reconstruction of a tufted astrocyte in PSP processed for double-labeling immunofluorescence and confocal microscopy using antibodies to P-tau (AT8, green) and GFAP (red). Note tufts of P-tau at the periphery of the cytoplasm and proximal part of astrocytic

branches, and redistribution of GFAP at the inner part of the cytoplasm with very poor GFAP immunostaining of astrocytic branches. Nuclei (blue) are stained with DRAQ5TM; bar = 15 μ m.

classify these disorders as genetic counterparts of common sporadic cases solely based on similar astrocytic pathology.

Tau phosphorylation, conformation and truncation in astrocytes have characteristics similar to their neuronal counterparts in tauopathies with equivalents to pre-tangles and tangle stages (124). Active Tau-kinases involved in tau phosphorylation are expressed in tau-containing astrocytes in tauopathies (22, 119–122, 125). 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 (191). Tau acetylation is rarer in astrocytes when compared to neurons in tauopathies (194).

The molecular bases of the different types of tau-bearing astrocytes in tauopathies are not known. Some differences are barely related to altered tau conformation and tau truncation (124). Redistribution of GFAP around the nucleus and surrounded by tufts of hyper-phosphorylated tau is characteristic of tufted astrocytes in PSP (Figure 5) and FTLN-tau/K317M (Figure 6). However, GFAP is disrupted by short segments or dots of hyper-phosphorylated tau

along the astrocytic processes in astrocytic plaques in CBD (Figure 7) and in astrocytes with proximal granular inclusions in FTLN-tau/P301L (124). Displacement of GFAP by hyper-phosphorylated tau is also observed in tau containing astrocytes in PiD (Figure 8). Although these differences may have functional implications, further study is needed to learn whether different types of astrocytes are selectively vulnerable to hyper-phosphorylated tau and whether different species of tau have different effects on certain subpopulations of astrocytes (124). This possibility is supported by experimental studies showing that the intracerebral brain homogenates enriched in tau fibrils from PSP, CBD and AGD injected into ALZ17 mice induce astrocytic pathology resembling the inclusions characteristic of these human tauopathies (86). Moreover, certain tau prion strains propagate in cells and define different tauopathies (386), and certain tau prion strains have the capacity to induce tauopathy in astrocytes (211).

The distribution of astrocytes with abnormal protein deposits does not match the distribution of reactive astrogliosis as first

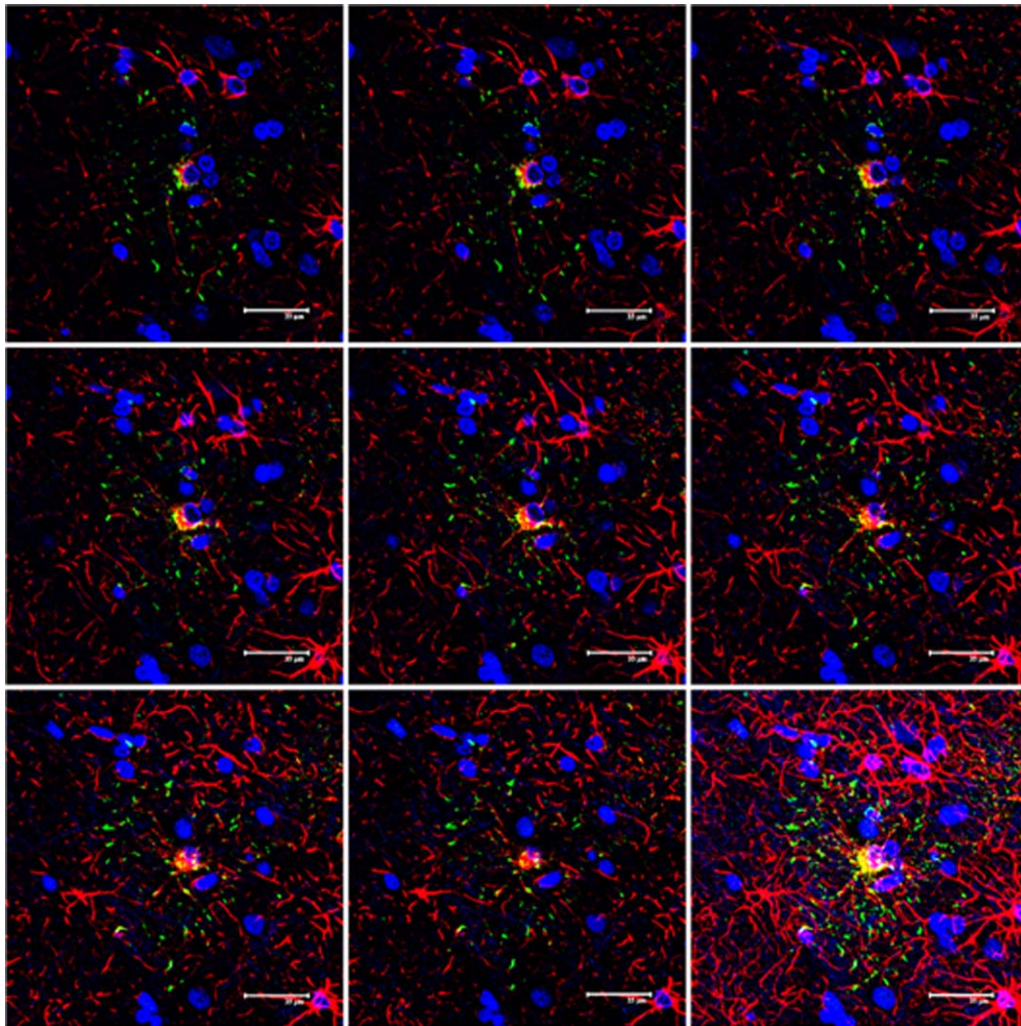


Figure 6. Serial reconstruction of an astrocytic plaque in CBD processed for double-labeling immunofluorescence and confocal microscopy using antibodies to P-tau (AT8, green) and GFAP (red). Note

the localization of P-tau in the distal regions of astrocytic branches and the irregular distribution of GFAP in the cytoplasm and astrocytic branches. Nuclei (blue) are stained with DRAQ5™; bar = 35 μm.

recognized in progressive supranuclear palsy (437) but later extended to the majority of tauopathies (Figure 9). Double-labeling immunofluorescence and confocal microscopy of astrocytic plaques, tufted astrocytes and astrocytes in the elderly reveal disruption of the astrocytic cytoskeleton manifested by reduction and reorganization of GFAP immunoreactivity (124) in subpopulations of astrocytes without the appearance of any reactive astrocytes.

Small heat shock proteins in glial cells are expressed in astrocytes with and without hyper-phosphorylated tau deposition in various tauopathies (266).

Loss of function in astrocytopathies of neurodegenerative diseases with abnormal protein aggregates

Impaired glutamate transport is postulated in several diseases as a consequence of decreased expression of glutamate transporters in astroglia. Reduced EAAT2/GLT-1 expression is found in ALS and related transgenic models (57, 132, 158, 184, 258, 276, 291, 340,

379–381), in certain tauopathies (96, 123), murine models of HD (34, 111, 254, 293), in some transgenic models of Alzheimer's disease (77, 283), and in A53T α -synuclein transgenic mice (156).

Release of other neurotransmitters by astrocytes is also selectively altered in certain neurodegenerative diseases. GABA release is increased in AD (201, 475) but reduced in the striatum in HD (473).

Altered astrocyte-dependent potassium homeostasis occurs in AD (333), HD (19, 439), PD (424, 466) and ALS (205).

Altered calcium signaling is found in models of AD (2, 3, 101, 153, 233, 358, 375, 432, 458), PD (48) and ALS (212, 281). Glucose metabolism is altered in AD and HD and in other neurodegenerative diseases. Whether these changes are partly due to altered glucose metabolism in astrocytes is controversial, depending on the disease and animal models used (36).

Cholesterol metabolism is impaired in several neurodegenerative diseases. Cholesterol is largely synthesized in astrocytes and is transported by ApoE 4 to neurons. ApoE 4 is a major risk factor for late onset AD and the substrates of this effect are related to decline

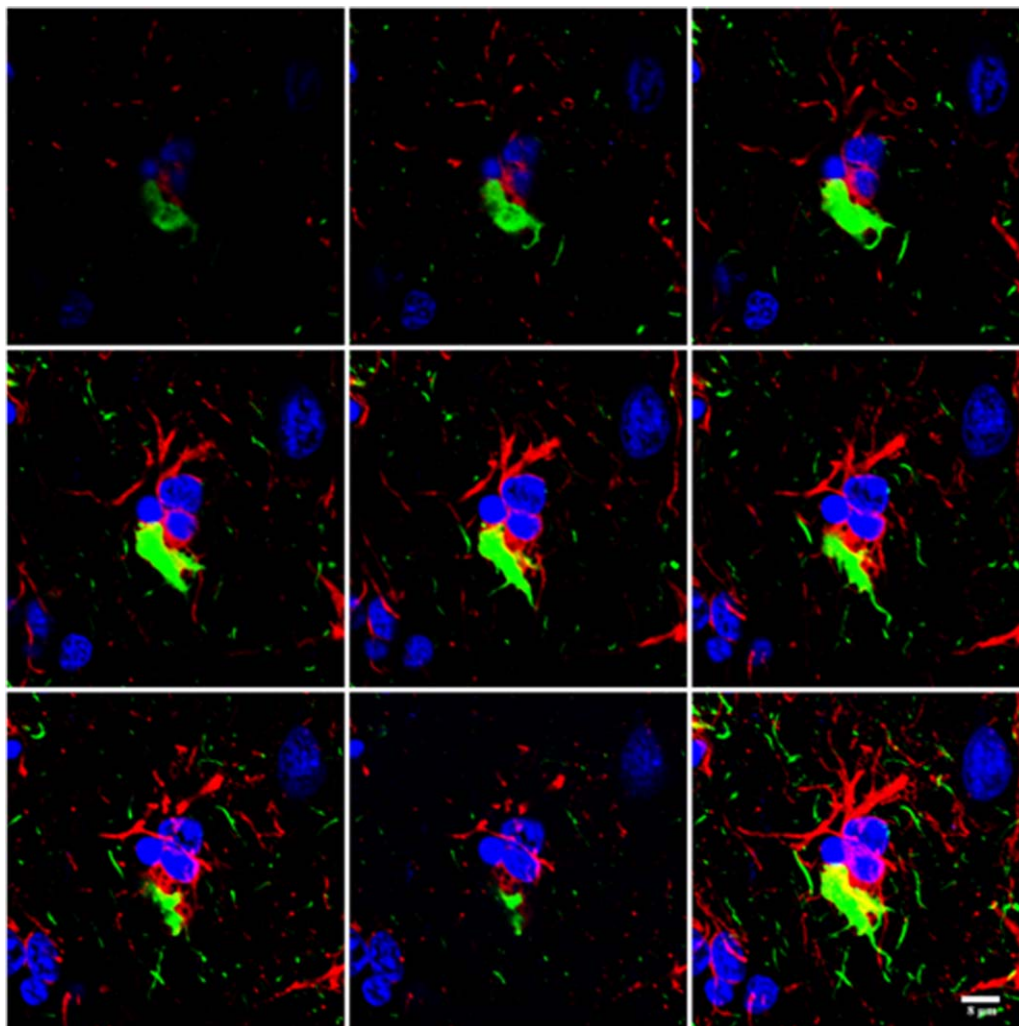


Figure 7. Double-labeling immunofluorescence and confocal microscopy using antibodies to P-tau (AT8, green) and GFAP (red) in FTLD-tau/K317M. Note the peripheral distribution of P-tau and the perinuclear localization of GFAP in tufted-like astrocytes. Nuclei (blue) are stained with DRAQ5TM; bar = 20 μ m.

cholesterol metabolism, abnormal APP processing and disrupted β -amyloid clearance (63). Cholesterol metabolism is altered in transgenic models of AD (333); cholesterol biosynthesis is also low in transgenic models of HD (399, 443–445).

Expression of astrocyte connexins is abnormal in several neurodegenerative diseases (95, 151, 286, 310, 459) thus sustaining possible modifications in gap junctions, and deteriorated function of cell-to-cell networks, ion homeostasis and transfer of gliotransmitters (47).

Worsening function of the blood brain barrier in several neurodegenerative diseases is thoroughly documented (493).

Oxidative stress and responses in astrocytes in neurodegenerative diseases with abnormal protein aggregates

Astrocytes in neurodegenerative diseases may be a source of reactive oxygen and reactive nitrogen species occurring in parallel with the generation of certain peptides and proteins such as β -amyloid, superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43)

and prion protein scrapie (PrP^{Sc}) (4, 9, 78, 133, 176, 373). Reactive astrocytes may also sustain oxidative stress responses, increasing glutathione, SOD2 and Nrf2 protein levels (3, 73, 81, 447).

Redox proteomic studies have identified several proteins which are oxidatively damaged in neurodegenerative diseases (71, 280, 428, 429 for review). Some of them are expressed mainly in neurons and their damage has been associated with loss of function. However, a large number of oxidized proteins are enriched in astrocytes. This is particularly important regarding proteins linked to glycolysis and energy metabolism, oxidative stress responses and cytoskeleton (280).

Although its significance is not known, GFAP is consistently oxidized in most neurodegenerative diseases assessed to date (279, 280, 304, 338). GLT-1 is oxidatively modified by 4-hydroxy-2-nonenal in AD (238).

DNA and mRNA are also oxidatively damaged in neurodegenerative diseases. However, the percentage of damage corresponding to astrocytes has not been determined in most of them. Astrocyte DNA oxidative damage has been reported in AD (409).

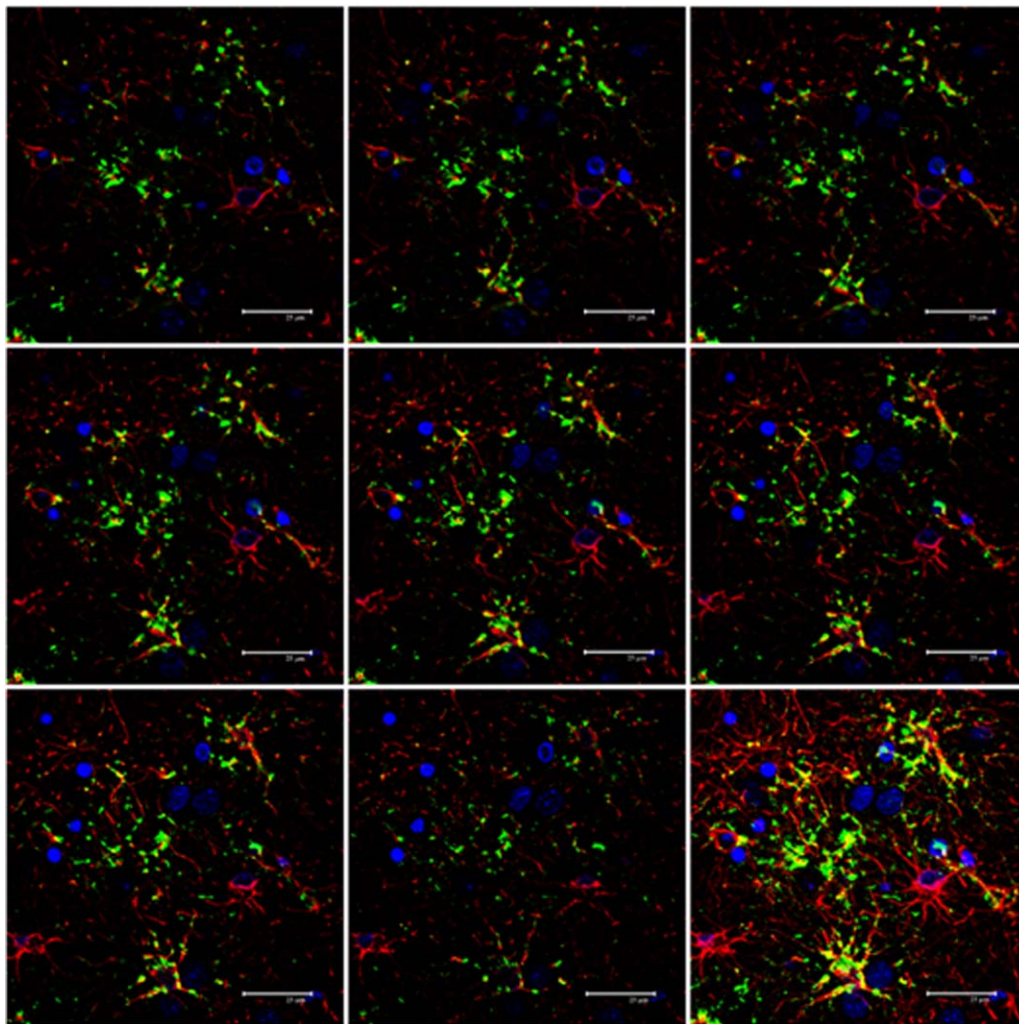


Figure 8. Serial reconstruction of a hyper-phosphorylated tau-containing astrocyte in PiD processed for double-labeling immunofluorescence and confocal microscopy using antibodies to P-tau (AT8, green)

and GFAP (red). Note the displacement of GFAP in the cytoplasm and the reduced number of GFAP-positive branches. Nuclei (blue) are stained with DRAQ5TM; bar = 8 μ m.

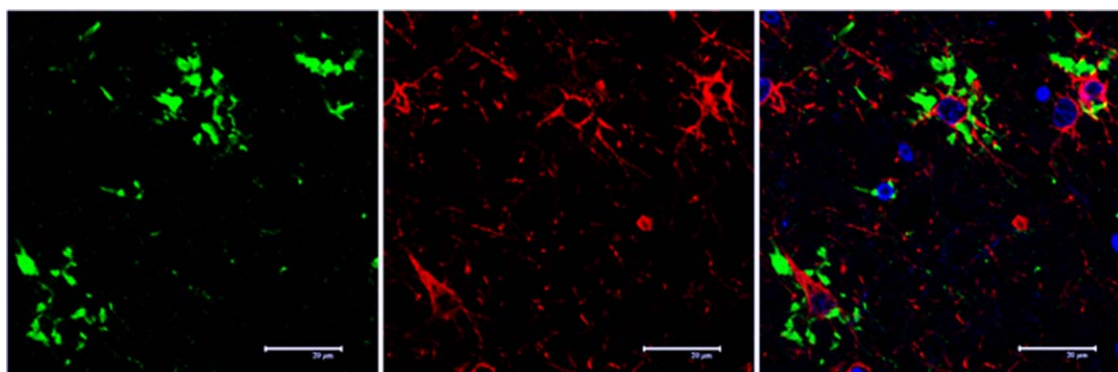


Figure 9. Serial reconstruction of thorn-like astrocytes in ARTAG processed for double-labeling immunofluorescence and confocal microscopy using antibodies to P-tau (AT8, green) and GFAP (red). Note the presence of P-tau in some astrocytes whereas P-tau is absent in other GFAP-positive astrocytes. Nuclei (blue) are stained with DRAQ5TM; bar = 25 μ m.

Astrocytes and inflammation in neurodegenerative diseases with abnormal protein aggregates

Aging is accompanied by low levels of activated innate inflammatory responses (265, 269, 272, 482). Microglia and astrocytes, together with neurons, participate in the process of activation of inflammatory responses in aging and in neurodegenerative diseases with abnormal protein aggregates (175, 355). Moreover, microglia has the capacity to transform a subset of reactive astrocytes through the combination of IL-1 α , TNF and C1q (253). These astrocytes lose the ability to promote neuronal survival, outgrowth, synaptogenesis and phagocytosis, and induce the death of neurons and oligodendrocytes (253). They are common in AD, PD, HD and ALS.

Inflammatory responses are disease-, region- and stage-dependent, thus largely differing in AD, tauopathies, CJD, PD, DLB and ALS (14, 143, 144, 262, 265, 268, 269). Several cytokines and mediators are expressed in reactive astrocytes in these diseases, although the precise localization of individual inflammatory mediators is largely unknown. No particular attention has been devoted so far to learning about specific inflammatory responses in the different types of abnormal astrocytes with abnormal hyperphosphorylated tau in tauopathies.

Regular use of non-steroidal anti-inflammatory therapy reduces the number of astrocytes (and active microglia) in AD (8).

ASTROGLIOPATHY IN ALZHEIMER'S DISEASE

Reactive astrogliosis

Astrocytes are key players in the cellular phase of AD involving β -amyloid turnover, calcium homeostasis, tripartite synaptic function, neuroinflammation and oxidative stress responses, among others (148, 382, 425).

Astrogliosis is a relatively early event in AD and related mouse models (32, 76, 177, 236, 328, 370, 454, 457, 484). Reactive astrocytes are mainly found around β -amyloid deposits in plaques and blood vessels in humans and AD models (308, 328, 370, 410, 450). Nevertheless, reactive astrocytes are also found in areas without plaques (31, 208, 410) (Figures 1A–E and 2A,B).

The majority of studies dealing with reactive astrogliosis in AD involve β -amyloid. Reactive astrocytes contain β -amyloid (137, 157, 309, 315) and N-terminal truncated β -amyloid (435). Reactive astrocytes cluster around β -amyloid plaques and perivascular β -amyloid deposits where they internalize and degrade β -amyloid fibrils (224, 476). Apolipoprotein E promotes aggregation and degradation of β -amyloid in astrocytes as this function is attenuated in ApoE KO mice (224). Low density lipoprotein receptor-related protein 1 (LRP1) is involved in the uptake of β -amyloid and it is also a receptor of ApoE (30, 217). All these observations point to that astrocytes are involved in plaque formation.

Astrocytes transplanted into the brain of a transgenic AD model migrate to the site of β -amyloid deposition, internalize β -amyloid and clear β -amyloid plaques (356, 357). The mechanisms used by reactive astrocytes to degrade β -amyloid are multiple and complementary, including activation of metalloproteinases (480, 485) and lysosomal degradation (30, 249, 477).

β -amyloid can also be generated in glial cells, as β -secretase (BACE) is expressed in astrocytes under appropriate conditions (177, 377, 378, 492).

The characteristics of reactive astrogliosis and the role played by reactive astrocytes depend on the region and local environment at a particular stage of the disease (32, 206, 222, 232, 236, 328, 450, 484). It has been suggested that astrocytes around plaques may be protective (284). The protective role of subpopulations of astrocytes is supported by the observation of increased plaque load and increased dystrophic neurites surrounding β -amyloid plaques in APP/PS1 GFAP^{-/-}Vim^{-/-} transgenic mice (232). Yet these observations were not validated in another study (206). Evidence of possible harmful effects of activated astrocytes on neurons come from *in vitro* studies showing that astrocytes in contact with β -amyloid increase neuronal vulnerability in several co-culture paradigms (2–4, 9, 147, 339). β -amyloid-induced glutamate release by astrocytes might be a contributory factor (433). De-regulation of specific metabotropic glutamate receptors in astroglia is also a putative harmful effect of β -amyloid (255). Acquisition of pro-inflammatory profile and activation of the β -amyloidogenic pathway further potentiates toxicity (493).

Astrocytes themselves show fragmentation of calpain-immunoreactive processes (146), and increased caspase 3 and CD95 immunoreactivity and increased apoptosis (230).

In addition to the relation with plaques, astrocytes also respond to neurofibrillary tangles; glial responses correlate positively with tangle burden and they increase linearly around existing plaques and in the vicinity of tangles (398).

Astrocytopathy

Astrocytes in AD-related transgenic mice show atrophy and reduced branching (33, 236, 484). Astrogliosis and astrocyte atrophy are region-dependent and occur in AD and transgenic models of AD (328, 372, 452). Reduced branching largely contributes to decreased astrocytic domain coverage in AD (350). In animal models, atrophy of astrocytes may precede reactive astrogliosis, thus suggesting that astrocytes are vulnerable at very early stages of the pathology (32, 236, 328, 452, 454).

Reduced glucose metabolism in AD can be sustained, at least in part, by decreased astrocyte metabolism linked to β -amyloid toxicity (9) but also to reduced metabolism of atrophic astrocytes.

Altered mRNA and/or protein expression of glutamate transporters and altered glutamate homeostasis have been reported in transgenic models of AD (77, 283). Expression levels of GLT-1 and glutamate homeostasis in prefrontal cortex are controversial in AD (235, 282). Another study shows inverse relation between GFAP (increase) and EAAT2 (reduction) expression with disease progression as defined by Braak stage of neurofibrillary tangle degeneration (410, 411).

Indirect data point to functional alterations of glutamate transporters in AD as a result of oxidative damage, splice variants and altered solubility of EAAT2 (107, 238, 394, 474). Glutamine synthase is reduced in reactive astrocytes in AD and related models (245, 329) thus resulting in decreased neuronal GABA-mediated inhibition (336).

Astrocytes bearing β -amyloid show abnormal calcium homeostasis (2–4, 153, 233, 234, 256, 375, 453). Connexin 43 expression is altered in AD and animal models (282, 306) which may

compromise the extent of coverage domain and synaptic function in neighboring neurons (234). β -amyloid peptides also induce mitochondrial dysfunction and oxidative stress in astrocytes (4).

Astrocytes surrounding plaques show increased expression of cytokines and mediators of the immune response in AD and related models (247, 299, 332, 333, 355). Transcriptional studies of isolated astrocytes from the cortex of aged controls and APP^{swe}/PS1^{dE9} transgenic mice show increased expression of inflammatory genes, and reduced expression of neuronal support genes and genes involved in neuronal communication (333). This phenomenon appears to be secondary to β -amyloid deposition, as the expression of neuroinflammatory markers increases in cultured astrocytes exposed to β -amyloid fibrils (244). Transcriptomics of laser-captured microdissection using GFAP as a marker revealed marked dysregulation of insulin, phosphatidylinositol 3-kinase (PI3K)/Akt, and mitogen-activated protein kinase (MAPK) signaling pathways at advanced Braak stages of the disease; minor and different alterations were found at earlier stages thus indicating different responses of astrocytes along with disease progression and impaired key signals in astrocytes in AD (411).

Disruption of the immune/inflammatory calcineurin/nuclear factor of activated T-cells, using a GFAP promoter, reduces glial activation and β -amyloid burden, and improves cognitive and synaptic function in APP/PS1 transgenic mice (138).

Abnormal astrocytes in AD may contribute to the alterations in the function of the blood brain barrier (35, 493), partly due to the reduction in GLUT-1 expression (471).

Finally, whether astrocytes contribute to the spreading of β -amyloid and hyperphosphorylated tau and facilitate disease progression in AD is a hot question (98).

ASTROGLIOPATHY IN TAUOPATHIES

Tauopathies are a heterogeneous group of diseases having in common the deposition of hyper-phosphorylated tau in neurons and glial cells with specific characteristics with reference to regional vulnerability, morphology of deposits in different cell types, and biochemical traits of abnormal tau (105, 226).

Reactive astrogliosis

Reactive astrogliosis is common in all tauopathies and its distribution correlates with the degree of regional vulnerability to neuronal degeneration and neuronal loss.

In PSP, reactive astrogliosis is marked in the subthalamic nucleus, substantia nigra and colliculus and, to a lesser extent in the globus pallidus; astrogliosis is mild or moderate in the striatum and cerebral cortex (Figure 2C). This correlates with the presence of neurofibrillary tangles and neuron loss rather than with the presence of tufted astrocytes (437).

In CBD, reactive astrogliosis is marked in the cerebral cortex mainly in the upper cortical layers, the immediate subcortical white matter and the substantia nigra. Reactive gliosis is mild or moderate in the striatum, pallidum and subthalamic nucleus. Fibrillary astrogliosis is found in the white matter. Double-labeling immunofluorescence and confocal microscopy show that only some astrocytes in the cerebral cortex contain hyper-phosphorylated tau-conforming astrocytic plaques, whereas others do not. Reactive astrocytes in

the white matter do not contain abnormal tau, excepting clusters of thorn-like astrocytes when present (104).

In PiD, marked reactive astrogliosis involves the cerebral cortex of the frontal and temporal lobes, followed by the hippocampus. Moderate or severe reactive astrogliosis also occurs in the striatum and thalamus. Involvement of other regions parallels neuron loss. Reactive astrogliosis in PiD does not match with the presence of tau accumulation in a subpopulation of astrocytes, although many reactive astrocytes in the temporal cortex contain hyperphosphorylated tau ((305).

Astrogliosis and astrocyte degeneration occur in the cerebral cortex in frontotemporal lobar degeneration (58, 215). However, the extent and distribution of reactive astrogliosis varies depending on the *MAPT* mutation and the degree of neuronal damage. For example, reactive astrogliosis is moderate in most cases bearing the P301L mutation, whereas reactive astrogliosis is severe in FTLD-tau linked to K317M mutation (489). Interestingly, reactive astrocytes in FTLD-tau K317M, and to a lesser extent in some cases of FTLD-tau P301L, show atrophy and reduced numbers and predominance of thin astrocytic processes as revealed by GFAP and vimentin immunohistochemistry (Figures 1F,I and 2E,F).

In contrast to other tauopathies, the majority of astrocytes in FTLD-tau K317M contain hyper-phosphorylated tau as revealed by double-labeling immunofluorescence and confocal microscopy (Figure 6). Hyperphosphorylated tau and GFAP also occur in most astrocytes in the rare familial behavioral variant FTLD associated with astrocyte-predominant tauopathy (Figure 10).

Reactive astrogliosis also occurs in transgenic mouse models; the hippocampus is mainly affected in mice bearing the P301S mutation (265).

A characteristic response of reactive astrocytes in most tauopathies, including AD, is the expression of small heat shock proteins (HSP25/27 and α B-crystallin) which are rarely co-expressed in glial cells bearing hyper-phosphorylated tau (97, 266, 367, 393, 470). It is of note that tau in neurons induces HSP27 overexpression in astrocytes (127), and the production of small HSPs, together with peroxiredoxin, apolipoprotein E and latexin; in FTLD-tau astrocytes procure neuroprotection against tau toxicity (483).

Nevertheless, astrocytes in PiD and FTLD are vulnerable to degeneration and death; beaded processes and apoptosis as revealed by combined several markers are not uncommon (58, 278).

Astrocytopathy

In spite of the evident astrocytopathy, little is known about the functional effects of hyper-phosphorylated tau in tau-containing astrocytes in tauopathies (204). Overexpression of tau in cultured astrocytes leads to degenerative changes in the Golgi complex and cytoskeleton, and to cell death (486). Tau expression in astrocytes might putatively affect nuclear function and DNA transcription as postulated for tau-containing neurons in tauopathies and fly models (88, 136, 178, 213). FTD astrocytes derived from neural stem cells carrying the N279K *MAPT* mutation show increased vulnerability to oxidative stress and altered transcriptome profile. Moreover, co-cultures of mutant astrocytes with healthy neurons increase oxidative stress and produce marked modifications in the genomic expression of neurons (166).

It remains a challenge to learn the reasons for and the functional consequences of the various types, often disease-dependent, of

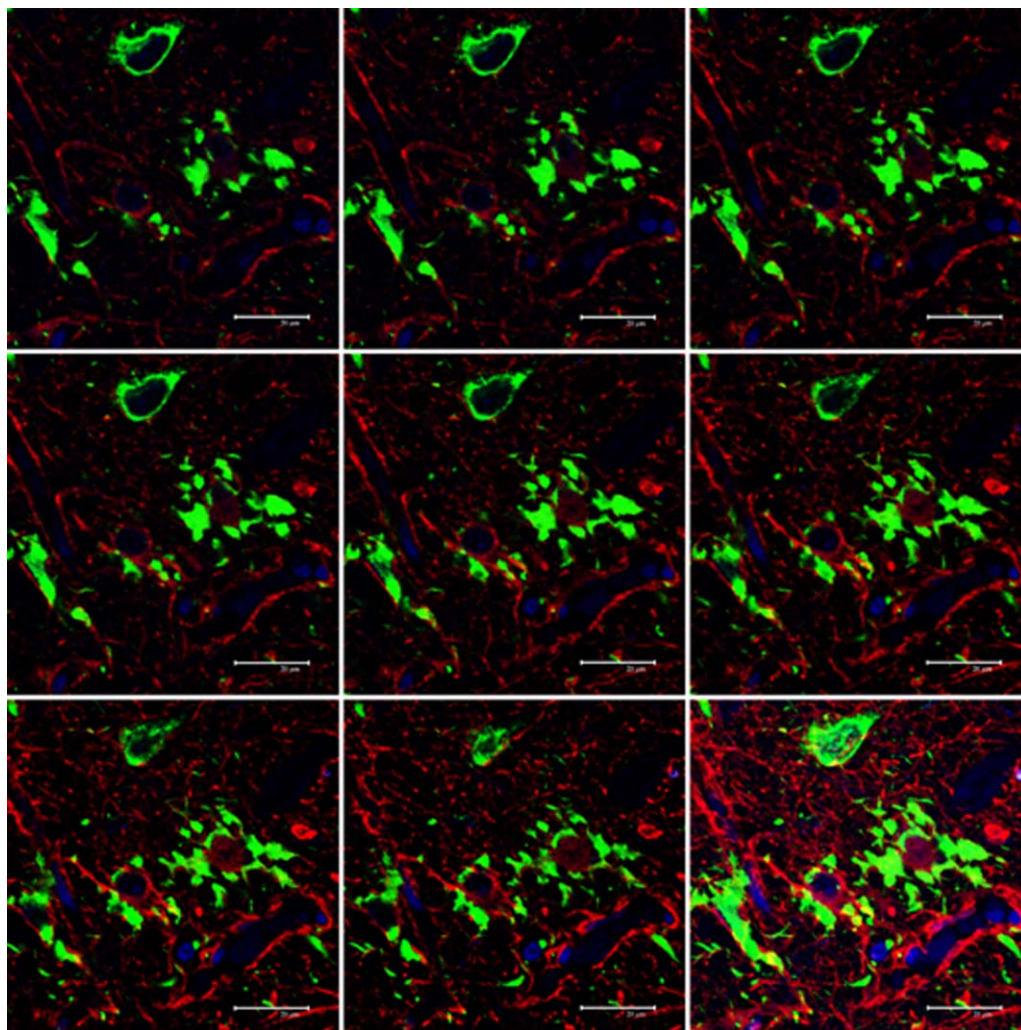


Figure 10. Serial reconstruction of hyper-phosphorylated tau-containing astrocytes in familial behavioral variant FTLD associated with astrocyte-predominant tauopathy, processed for double-labeling immunofluorescence and confocal microscopy using antibodies to P-tau

(AT8, green) and GFAP (red). Note the tufted-like cytoplasmic morphology and podocytes at the surface of a blood vessel. A tau-positive neuron is seen in the upper part of the figure. Nuclei (blue) are stained with DRAQ5™; bar = 20 μ m.

astrocytes accumulating hyper-phosphorylated tau species. Little is known about tufted astrocytes in PSP, astrocytic plaques in CBD and globose astrocytes in GGT except that they differ from reactive astrocytes by their different localization and GFAP distribution in the cytoskeleton.

Transgenic mice selectively expressing abnormal hyper-phosphorylated tau in astrocytes produce neurodegeneration which is accompanied by decreased expression of GLT-1 and GLAST in astrocytes (96, 130). GLT-1 expression is markedly reduced in most astrocytes bearing hyper-phosphorylated tau in a rare familial behavioral variant of frontotemporal dementia associated with astrocyte-predominant tauopathy not linked to mutations in *MAPT* (123).

Glutamate metabolism is also impaired in the hippocampus in transgenic mice bearing the P301L in *Mapt* (317).

Finally, an important aspect is the plausible role of astrocytes in seeding and progression of tauopathy. Tau obtained from several tauopathies inoculated into the mouse brain can spread to resident

astrocytes (43, 86). Certain tau prion strains have the capacity to induce tauopathy in astrocytes (211).

ASTROGLIOPATHY IN PARKINSON'S DISEASE

Reactive astrogliosis

Reactive astrogliosis is mild in the substantia nigra and other brain regions in PD even at advanced stages of the disease (131, 296). Different responses occur in experimental models of parkinsonism as marked reactive astrogliosis occurs in transgenic mice expressing A53T α -synuclein (156) and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism (169). Reactive astrocytes in an MPTP-induced model of parkinsonism in mice favor neuronal survival (169) modulated via β -catenin (243).

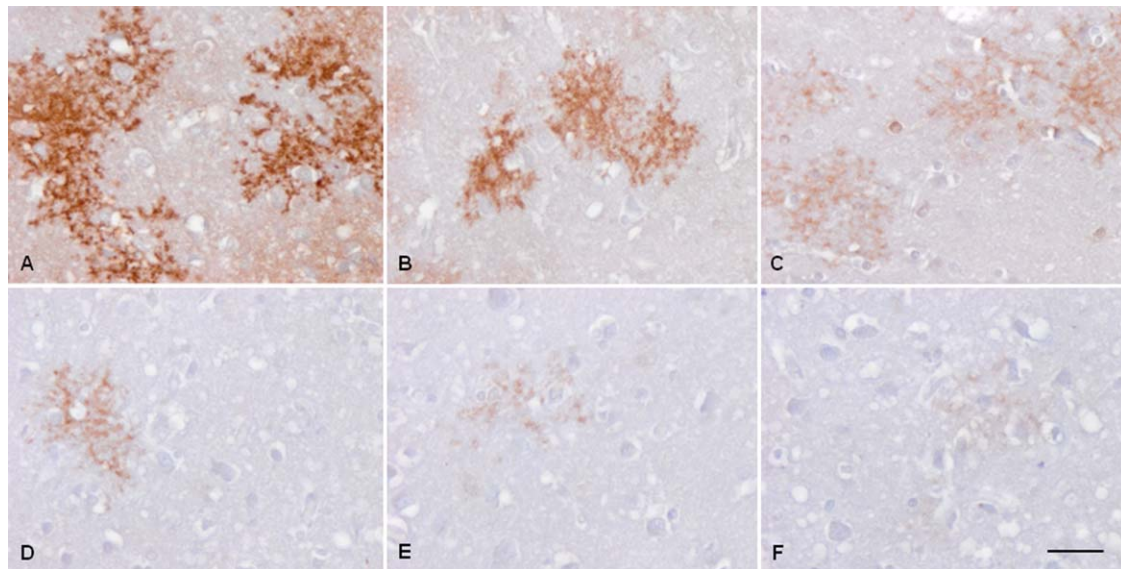


Figure 11. GLT-1 immunoreactivity in the cerebral cortex in control (**A**) and three CJD MM1 cases (**B–F**). Reduced immunoreactivity to almost absence is observed in parallel with spongiform change. Paraffin sections slightly counterstained with hematoxylin; bar = 40 μ m.

Astrocytopathy

Small amounts of α -synuclein composed of filaments of about 25–40 nm in diameter are found in protoplasmic astrocytes in PD, even in regions in which Lewy bodies and neurites are seldom observed, such as the striatum (49, 165, 419, 462). The use of the novel anti- α -synuclein 5G4 antibody, which strongly binds to the high molecular weight fraction of β -sheet rich oligomers, has shown α -synuclein immunoreactive thin threads associate with glial reaction and astrocytic α -synuclein as an important component of the pathology (227).

Astrocytes bearing abnormal α -synuclein generate abnormal mitochondria (52, 389), produce pro-inflammatory cytokines and other inflammatory mediators *in vitro* (240), which in turn can activate astrocytes and microglia (27). The number of inclusions correlates with the severity of nigral neuronal loss (462). Star-like astrocytes containing α -synuclein have also been reported in Lewy Body Disease; immunoreactivity of these inclusions is enhanced following formic acid pretreatment and using an antibody against the non-A β component portion of α -synuclein (434).

Astrocytes expressing mutant A53T α -synuclein in transgenic mice have reduced expression of GLT-1 and GLAST, abnormal redistribution of GLT-1 in blood vessels, and altered expression of AQ4 in the soma and proximal astrocyte processes (156). All these changes may increase excitotoxic neuronal damage and impair regulation of the blood brain barrier in mutant mice. On the other hand, astrocytes may have neuroprotective functions, as Nrf2 overexpression in astrocytes increases neuron survival in the same transgenic model of α -synucleinopathy (141). Nrf2 expression in astrocytes also confers neuroprotection in the MPTP model of parkinsonism (81). Whether these mechanisms apply to PD is not known. Together, these observations suggest that astrocytes participate in the pathogenesis of PD linked to α -synuclein accumulation (61, 80).

The specific roles of astrocytes linked to other proteins whose mutations are causative of PD are poorly understood. Astrocytes

lacking DJ-1 have reduced capacities to protect neurons from mitochondrial and oxidative stress insults (300, 301). Nurr1/coREST in cultured astrocytes and microglia protects dopaminergic neurons from inflammation-induced cell death following lipopolysaccharide injection in mice (384). Although Nurr1 is an important regulatory factor in the generation of dopaminergic neurons, it is still too early to implicate alterations of this pathway in the pathogenesis of PD.

Parkin is induced in cultured astrocytes following unfolded protein stress, thus facilitating ubiquitination of substrates to be degraded by the ubiquitin-proteasome system (UPS) (239). This observation favors a potential role of astrocytes over neurons in the removal of parkin substrates via the UPS. This observation has been used to suggest that the expression of parkin mutations in astrocytes might reduce the UPS function in PD cases bearing parkin mutations (239).

Regarding capacities of neurons and astrocytes linked to seeding, α -synuclein can be transferred from neurons to astrocytes (240). Whether abnormal α -synuclein in astrocytes can be transferred to neurons is a matter of study.

ASTROGLIOPATHY IN HUNTINGTON'S DISEASE

Reactive astrogliosis

Marked reactive astrogliosis is found mainly in the striatum but also in the frontal cortex and other brain regions in HD; its intensity increases with disease severity (111, 460). Reactive astrogliosis is remarkably less marked in several transgenic mouse models of HD (37, 154, 155, 257, 439).

Astrocytopathy

Reduction of GLT-1 mRNA accompanied by decreased glutamate uptake has been reported in the striatum and cerebral cortex in two

transgenic mouse models of HD (34, 111, 254, 293). Studies in humans have shown reduced EAAT2 mRNA and protein expression in the striatum (21, 111). Glutamate transport is also reduced in prefrontal cortex in HD (170).

Glutamine synthase is reduced in animal models of HD thus decreasing glutamine levels and the putative production of GABA (254). Reduced astrocytic GABA increases cellular damage in the striatum in a mouse model of HD (473).

Abnormal huntingtin accumulates in the nuclei of astrocytes in rodent models and in HD, lending support to the hypothesis that astrocytes actively participate in the pathogenesis of the disease (51, 111, 404). Toxic capacities of astrocytes depend on the size of polyglutamine repeats (50, 51). This is further supported by the fact that astrocytes generated from induced pluripotent stem cells from HD patients show degenerating characteristics which are dependent on the number of CAG repeats (203).

Increased calcium-dependent release of glutamate by astrocytes (242) and deficient Kir4.1 potassium ion channel in astrocytes observed in different HD mouse models (216, 439) may contribute to neuronal damage in HD as well.

Astrocytes participate in the inflammatory response in HD through NF- κ B (185). Moreover, the astrocytic response reduces the survival of pericytes through an I κ B kinase-dependent pathway thus impairing vascular reactivity in HD (186).

Astrocytopathy in HD is also manifested by decreased production of brain derived neurotrophic factor (BDNF) and transforming growth factor- β (TGF- β) (20, 465). Other alterations of HD astrocytes compromise mitochondrial function (330, 391), cholesterol metabolism (399, 443–445) and connexin expression (459).

ASTROGLIOPATHY IN AMYOTROPHIC LATERAL SCLEROSIS

Reactive astrogliosis

Marked reactive astrocytosis is observed in the pyramidal tracts and anterior spinal roots of the spinal cord and affected nerves of the brain stem in parallel with severity and long-term involvement of the damaged tracts in ALS. Reactive GFAP astrocytes are present in the anterior horn of the spinal cord and motor nuclei of the brain stem, and less markedly in primary motor cortex. Astrocytic gliosis in the posterior columns and spinocerebellar tracts in certain sporadic and familial cases depends on the myelin and axonal damage of these tracts.

A small percentage of familial ALS cases are linked to mutations in *SOD1*. Astrocytosis is also observed in *SOD1* transgenic mouse models (62). Marked neuronal alterations accompanied by mild astrogliosis are found in the anterior thalamus of *SOD1* (G93A) ALS mice (100). Astroglial alterations precede clinical symptoms in ALS models (62, 184).

Astrocytopathy

A major alteration in ALS is reduced expression of glutamate transporters in astrocytes and the production of truncated EAAT2/GLT-1 protein with altered subcellular localization and impaired function resulting from aberrant *EAAT2* mRNA processing including intron-retention and exon-skipping (57, 132, 258, 276, 290, 379, 381). Loss of EAAT2/GLT-1 may increase excitotoxic motor neuron

damage and is considered a primary factor in the pathogenesis of ALS. However, truncated EAAT2/GLT-1 forms can be found in normal individuals, and their role in the pathogenesis of ALS is uncertain. Loss of EAAT2 is also observed in *SOD1* transgenic mice bearing the G85R mutation (184). The implication of glutamate transporters in ALS is further supported by analyzing the consequences of their manipulation in animal models. Over-expression of EAAT2 in astrocytes increases neuron survival in *SOD1* transgenic mice (158), whereas loss of the glutamate transporter modifies disease progression in ALS mice (340).

Another important point is the damaging effects of astrocytes on motor neurons in familial ALS cases bearing *SOD1* mutations. Mutant *SOD1* expression in neurons is not sufficient to cause cell death, and wild-type non-neuronal cells increase motor neuron survival in ALS mice, thus suggesting that astrocytes are crucial players in familial ALS due to mutations in *SOD1* (5, 87, 264). The key role of astrocytes is further supported by observations in primary co-cultures of mutant *SOD1* astrocytes with motor neurons in which mutant astrocytes decrease motor neuron survival when compared with co-cultures using wild astrocytes (102, 308). Therefore, mutant *SOD1* in astrocytes is crucial in the homeostasis of motor neurons in *SOD1* transgenic mice. Proteinaceous aggregates are found in spinal cord astrocytes in *SOD1* transgenic mice (342). Whether abnormal *SOD1* species are present in sporadic ALS is under study.

Mutant mouse astrocytes and human astrocyte-like cells obtained from sporadic and familial ALS cases are toxic for neurons (102, 103, 161, 277, 290, 308).

Astrocytes from ALS patients carrying mutations in *TARDBP* show intracytoplasmic TDP-43 inclusions and reduced cell survival, but they are not toxic for control and *TARDBP* mutant neurons (397).

Other proposed astrocyte-linked mechanisms leading to motor neuron demise in ALS are activation of the Fas cell surface death receptor (FAS), nitric oxide pathways and nerve grNGF/p75 signaling in astrocytes (118, 343, 364), disruption of the astrocytic tumor necrosis factor receptor superfamily 1-glia derived neurotrophic factor (TNFR1-GDNF) axis (54), and impairment of lactate transport (118), among other elements (78, 281, 344, 376). As in other situations, reactive astrocytes in ALS activate STAT3 pathway (400, 401). Astrocytes in ALS may also present altered respiratory function and impaired anti-oxidant responses (78, 277, 447). No less important is the participation of astrocytes in the inflammatory response (5, 14, 102, 354). The convergence of damaged neurons and accompanying alterations of non-neuronal partners in ALS supports the idea of non-cell autonomous toxicity in the pathogenesis of this disease and many other neurodegenerative disorders (193).

A final point is the putative involvement of astrocytes in mutant *SOD1* seeding and cell-to-cell progression; increased chromogranin-mediated secretion of mutant *SOD1* in ALS might facilitate both mechanisms (110, 442).

ASTROGLIOPATHY IN CREUTZFELDT-JAKOB DISEASE

Reactive astrogliosis

Marked astrogliosis is a characteristic feature in CJD which parallels spongiform change, microgliosis and neuron loss (64, 251).

Reactive gliosis may replace neurons in cerebral cortex in long-lasting diseases with massive neuron loss. Reactive astrocytes are often large and show strong GFAP (Figure 1G,H), vimentin (Figure 2D) and YKL40 (Figure 3H) immunoreactivity. CJD is characterized by a severe inflammatory response, with up-regulation of pro- and anti-inflammatory cytokines, receptors, chemokines and other mediators of the inflammatory response; astrocytes express several intermediates including IL-6 (262).

Reactive astrocytes in CJD, as in other prion diseases, contain α B-crystallin (464).

What triggers reactive astrogliosis in CJD is not fully understood, but the PrP 106–126 peptide obtained from the amyloidogenic region of the prion protein induces proliferation of cortical astrocytes (436).

Reactive astrocytes in CJD are enriched in aquaporin 1 and AQ4 (196, 369). Immunohistochemistry to AQ4 decorates the astrocytic processes at stages with moderate lesions; however, AQ4 immunoreactivity is blurred in areas with extensive spongiform change (Figure 2I).

Oxidation, glycoxylation, lipoxidation and nitration are found in CJD (133). Astrocytes are targets of oxidative damage, as 4-hydroxynonenal adducts accumulate in astrocytes in CJD and murine scrapie (13). Oxidative stress responses are also marked in reactive astrocytes in CJD as illustrated by increased SOD2 expression (133).

Astrocytopathy

GLT-1 immunoreactivity decreases in parallel with spongiform change in the cerebral cortex in CJD (Figure 11).

Clusterin, a heterodimeric glycoprotein, is up-regulated in CJD and expressed in astrocytes in association with punctate-type PrP^{Sc} and in PrP^{Sc} plaques. Clusterin in CJD has abnormal solubility and forms co-aggregates with PrP^{Sc}, thereby probably contributing to PrP^{Sc} pathogenesis (134).

Current immunohistochemical methods discriminate different patterns of PrP^{Sc} deposition in CJD—principally synaptic-like, perineuronal, plaque-like, kuru-plaque-like and globoid, depending on the PRP type and codon129 genotype. However, more precise methods show the presence of disease-associated prion protein linked to synapses, neuronal bodies, dendrites, axons, astrocytes and microglia (231). Moreover, *in vitro* studies show that human astrocytes have the capacity to take up and degrade normal and protease-resistant prion protein (84). These data suggest that astrocytes can contribute to the turnover of normal and abnormal prion protein. In this line, recent studies have shown that astrocytes form intercellular connections and nanotubes which drive the transfer of PrP^{Sc} from astrocytes to neurons, thereby contributing to prion disease progression (456).

CONCLUDING REMARKS

Astroglipathy is a key element in the pathogenesis and pathology of several neurological diseases including degenerative diseases of the central nervous system. Astroglipathy includes reactive astrogliosis and astrocytopathy (covering hypertrophy, atrophy/degeneration and loss of function and pathological remodeling) which overlap each other, and, together with astrocyte senescence, contribute to disease-specific astroglipathy in aging and

neurodegenerative diseases with abnormal protein aggregates in old age. In addition to deposition of abnormal proteins in astrocytes, impaired glutamate transport; abnormal metabolism and release of neurotransmitters; abnormal ion and water homeostasis; abnormal glucose and cholesterol metabolism; increased oxidative damage accompanied by altered oxidative stress responses; increased production of cytokines and mediators of the inflammatory response; altered expression of connexins with deterioration of cell-to-cell networks and transfer of gliotransmitters; and worsening function of the blood brain barrier, among others, actively participate in neuron and glial cell degeneration. Finally, although preliminary, recent observations suggest a role of astrocytes in the seeding and transfer of abnormal proteins, and in the progression of neurodegenerative diseases.

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