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Glial cell inclusions and the pathogenesis of neurodegenerative diseases

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Abstract

In this review, we discuss examples that show how glial-cell pathology is increasingly recognized in several neurodegenerative diseases. We also discuss the more provocative idea that some of the disorders that are currently considered to be neurodegenerative diseases might, in fact, be due to primary abnormalities in glia. Although the mechanism of glial pathology (i.e. modulating glutamate excitotoxicity) might be better established for amyotrophic lateral sclerosis (ALS), a role for neuronal–glial interactions in the pathogenesis of most neurodegenerative diseases is plausible. This burgeoning area of neuroscience will receive much attention in the future and it is expected that further understanding of basic neuronal–glial interactions will have a significant impact on the understanding of the fundamental nature of human neurodegenerative disorders.

Keywords

Protein aggregation; tau; α -synuclein; SOD₁

Adult onset neurodegenerative diseases represent a major health problem, especially with an aging population. They include disorders as diverse as Alzheimer's disease (AD), Parkinson's disease (PD), ALS, Huntington's disease (HD) and the spinocerebellar ataxias. Although the symptoms are divergent, there are two common observations from the pathology of these diseases that indicate some similarities. First, there is a progressive loss of neurons in specific regions of the CNS, which relate approximately to the symptoms that develop. For example, loss of dopaminergic neurons in the substantia nigra in PD is associated with the movement disorder seen in these patients. Secondly, there are protein aggregates, which are often ubiquitin immunoreactive, in either the cytoplasm or nuclei of the remaining neurons (reviewed by Ciechanover and Brundin, 2003). Many of these disorders also have familial forms in which genetic mutations promote the tendency of these proteins to aggregate (Taylor *et al.*, 2002).

What is perhaps less appreciated is the contribution of glial cells and their interactions with neurons to the neurodegenerative process. Reactive glial changes occur in most, if not all, neurodegenerative diseases. These changes include gliosis in astrocytes (Eng and Ghirnikar, 1994) and activation of microglia (Nelson *et al.*, 2002). There is substantial evidence that such reactive and inflammatory responses make significant contributions to neuronal damage in neurodegenerative diseases. There are excellent reviews of the role of glia in inflammatory responses in AD (McGeer and McGeer, 2002a; Monsonego and Weiner, 2003), PD (Hirsch

et al., 2003; Teismann *et al.*, 2003) and ALS (McGeer and McGeer, 2002b). Here, we discuss sporadic and familial neurodegenerative disorders with glial pathology that include inclusion bodies that are composed of protein aggregates analogous to those found in neurons (Chin and Goldman, 1996). First, we describe select examples of glial inclusions in neurodegeneration and highlight the similarities and differences between neuronal and glial inclusions. Some examples of these protein-containing inclusions are demonstrated in Fig. 1. We also discuss recent evidence that non-neuronal cells actively contribute to neuronal loss. This is best illustrated by elegant experiments using transgenic mice that express mutant Cu/Zn superoxide dismutase (SOD1), which is associated with familial ALS. These examples reinforce the idea that glia might not be simple bystanders in the neurodegenerative diseases, but are important contributors to disease pathogenesis.

Glial cell pathology and intracellular protein inclusions (Table 1)

Tauopathies with glial involvement

The microtubule-binding protein tau is recognized as the major protein component of neurofibrillary tangles (NFTs). NFTs are intraneuronal proteinaceous inclusions that, along with extracellular amyloid plaques, are a defining pathological hallmark of AD. Mutations in the *MAPT* gene, which is located on chromosome 17 and encodes the tau protein, are associated with a related disorder, frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). As its name implies, FTDP-17 has a range of clinical and pathological phenotypes, including cognitive and motor presentations.

The biochemistry of tau has been reviewed in detail elsewhere (Crowther and Goedert, 2000), but a few salient points are germane to this discussion. Six isoforms of tau are generated by alternative mRNA splicing and further micro-heterogeneity is produced by post-translational modifications. Tau is natively disordered in solution, but adopts a higher degree of secondary structure on binding to microtubules. Tau is prone to self-aggregation and aggregated forms of tau form filamentous assemblies that are characteristic of NFTs. The morphology of tau filaments varies depending upon the isoform composition of tau. Finally, tau is a phosphoprotein, and hyperphosphorylation is also associated with aggregation of the protein in NFTs (reviewed by Buee *et al.*, 2000). These properties are similar to another protein that is important in other neurodegenerative disorders, α -synuclein.

Although tau was once thought to be restricted to neurons (Binder *et al.*, 1985), more recent studies indicate that tau is also present in normal glial cells; however, only trace amounts of tau can be detected at basal levels in normal human, bovine and rodent astrocytes (Ksiezak-Reding *et al.*, 2003; Muller *et al.*, 1997; Zientek *et al.*, 1993). Tau is difficult to detect, even in cultured human fetal astrocytes exposed to activating conditions such as interleukin-1 β (Liu *et al.*, 1994) and phosphatase inhibitors, including okadaic acid (Ksiezak-Reding *et al.*, 2003). These results indicate that additional factors lead to the production and aggregation of tau protein within astrocytes in neurodegenerative diseases. Alternatively, adult astrocytes have properties that are distinct from fetal astrocytes, which are employed in most cell-culture studies.

Tau is easier to detect in oligodendrocytes, especially in brains that have been subjected to injury or stress, such as ischemia (Irving *et al.*, 1997). It is also readily detected in oligodendrocytes in culture (Ksiezak-Reding *et al.*, 2003; LoPresti *et al.*, 1995; Muller *et al.*, 1997), where it appears to be composed of restricted tau isoforms, similar to the isoform restriction that occurs in neurodegenerative diseases with glial tau inclusions. Specifically, alternative splicing of exon 3 of tau contributes to the heterogeneity in tau isoforms. The function of this domain is not known, but in neurodegenerative diseases that have abundant glial tau-positive inclusions, tau splice forms that lack exon 3 appear to accumulate, based upon

lack of immunostaining with exon 3-specific antibodies (Feany *et al.*, 1995; Nishimura *et al.*, 1997). The same is true of oligodendrocytes in culture (Ksiezak-Reding *et al.*, 2003; Richter-Landsberg, 2001).

As mentioned previously, the most widely recognized lesions composed of insoluble, fibrillar aggregates of tau are NFTs in AD, but there are many reports of tau-positive lesions in glia (both astrocytic and oligodendroglial lesions) in other degenerative disorders. The most common disorders with glial tau pathology include PSP, CBD, Pick's disease and argyrophilic grain disease (AGD) (Dickson, 2004). In each of these, tau-positive inclusions in oligodendrocytes, which are referred to as 'coiled bodies', vary in number and distribution between disorders (Fig. 1). Tau-positive astrocytic lesions also occur but are morphologically diverse. They also have more diagnostic significance than coiled bodies in oligodendrocytes. In particular, 'tufted astrocytes' of PSP and 'astrocytic plaques' of CBD are almost diagnostic of these disorders (Komori *et al.*, 1998). Less distinctive, tau-positive, glial lesions have been described in Pick's disease and AGD (Fig. 1).

Varying numbers of glial and neuronal tau-positive inclusions occur in morphologically diverse lesions in FTDP-17 (van Herpen *et al.*, 2003). To some extent, the type of glial lesion and their distribution in the brain vary with different *MAPT* gene mutations, which have different effects on expression and fibrillogenesis of the tau protein (Ghetti *et al.*, 2003). Lesions similar to those found in PSP, CBD and Pick's disease have all been reported in FTDP-17.

Less frequently, tau-positive glial inclusions are detected in Guam Parkinson-dementia complex (Oyanagi *et al.*, 1997), post-encephalitic Parkinsonism and other neurodegenerative disorders that contain NFTs. Tau-positive astrocytic lesions are found in AD and in the aged human brain in the form of, so-called, 'thorn-shaped astrocytes' (Ikeda *et al.*, 1995), but these lesions, which are relatively restricted to the white matter of the medial temporal lobe and the periventricular and subpial regions in the basal forebrain, are not clinically significant and are of no diagnostic importance.

Glial cytoplasmic inclusions (GCI) have come to be recognized as the defining histopathologic hallmark of multiple system atrophy (MSA) (Lantos, 1998) (Fig. 1). These inclusions are found in oligodendroglia, rather than astrocytes, and differ from the inclusions noted previously in their inconsistent immunoreactivity with antibodies to tau epitopes (Cairns *et al.*, 1997), but constant immunoreactivity for ubiquitin and α -synuclein (see later). Finally, astrocytic, tau-positive inclusions have been noted in autosomal recessive juvenile-onset Parkinson's disease (ARJP) with a parkin gene mutation (van de Warrenburg *et al.*, 2001), although this has not been confirmed in larger autopsy studies of ARJP.

MSA: a sporadic α -synucleinopathy

MSA is a disorder with variable clinical presentations, including Parkinsonism, cerebellar ataxia and autonomic dysfunction (Wenning *et al.*, 1997). Unlike PD, MSA is not responsive to dopamine replacement therapy, which indicates that the Parkinsonism in MSA is due to more widespread degeneration that involves more than the dopaminergic neurons of the pars compacta of the substantia nigra. In fact, it is associated with significant pathology in the basal ganglia. However, the distribution of pathology in the brain is variable and reflects the predominant clinical phenotype, with the major clinical forms (MSA-P and MSA-C) associated with predominant pathology in the nigrostriatal system (MSA-P) and the olivopontocerebellar system (MSA-C).

The unifying histopathologic hallmark of MSA is the GCI, which is a round or crescent-shaped inclusion in the cytoplasm of oligodendroglia in white matter in affected brain regions (Papp *et al.*, 1989). GCIs were detected initially with silver stains (e.g. Gallyas stain) and ubiquitin

immunostaining; however, the most sensitive and specific method for detecting GCIs is immunostaining for α -synuclein (Arima *et al.*, 1998; Spillantini *et al.*, 1998; Wakabayashi *et al.*, 1998), which is a small soluble protein that is more abundant in neurons than glia (see later). The GCI is pathognomonic of MSA and a diagnosis of MSA is untenable in the absence of GCIs. It should be noted that many cases of MSA also have neuronal inclusions (both cytoplasmic and nuclear) composed of filamentous α -synuclein, but neuronal lesions are more limited in number and distribution than GCIs. MSA is associated with demyelination and GCIs in white matter tracts, as well as neuronal loss in the basal ganglia, substantia nigra, pontine nuclei, inferior olive and cerebellum. Given the presence of α -synuclein in GCIs it is reasonable to assume that α -synuclein and oligodendroglial dysfunction play central roles in the pathogenesis of MSA. However, it is still a mystery whether neuronal or glial deficits are primary to the disease process.

Several lines of evidence indicate that α -synuclein is a predominantly neuronal protein in the normal, adult CNS. Several immunostaining studies, including the early work of Maroteaux and others, have shown that α -synuclein localizes to the presynaptic terminals of neurons (Maroteaux *et al.*, 1988). The cognate mRNA is expressed in gray matter, but not in white matter, of normal, human brain (Solano *et al.*, 2000). Moreover, α -synuclein immunostaining in white matter tracts in human brain is generally attributed to neuronal α -synuclein protein (Irizarry *et al.*, 1996; Iwai *et al.*, 1995), although one report suggests weaker glial expression that is enhanced in proteinase K-treated sections (Mori *et al.*, 2002).

Given that α -synuclein usually has limited expression in glial cells, how might it occur there in MSA? The most parsimonious explanation is that oligodendroglia express α -synuclein at low levels normally but that expression increases because of some abnormal stress in the disease. Transient expression of α -synuclein has been demonstrated in rat oligodendrocytes as they mature in culture (Richter-Landsberg *et al.*, 2000), and there is a report of the detection of low levels of α -synuclein in glia in vivo (Mori *et al.*, 2002). α -synuclein mRNA and protein is also found in astrogloma cells in vitro, where it can be upregulated by the inflammatory cytokine interleukin-1 β and serum deprivation (Tanji *et al.*, 2001). It is not known whether these stressors can increase α -synuclein expression in mature, non-transformed oligodendrocytes. More provocatively, one might hypothesize that apparent increased concentrations of protein are caused by post-translation stabilization or lack of turnover of α -synuclein in diseased glia. In support of this idea, tau can be induced to form inclusions in oligodendrocytes in culture, if the proteasome is inhibited and tau turnover is slowed (Goldbaum *et al.*, 2003).

An alternative, if less likely, possibility is that oligodendrocytes take up α -synuclein released from neurons. It has been shown that α -synuclein is present in cerebrospinal fluid (Borghi *et al.*, 2000) and plasma from human patients and in culture media from neuronal cell lines (El-Agnaf *et al.*, 2003). This demonstrates that some of the α -synuclein protein synthesized within cells is translocated to the extracellular space. However, these observations do not identify whether this is a regulated phenomenon or whether it results from membrane lysis in a small number of neurons. The observation that some α -synuclein might be glycosylated (Shimura *et al.*, 2001) indirectly supports the idea that secretion is active and regulated, as many proteins that undergo regulated secretion are glycosylated whilst passing through the ER and golgi. However, the molecular weight of α -synuclein from extracellular sources does not indicate any post-translational modification (Borghi *et al.*, 2000; El-Agnaf *et al.*, 2003). Once in the extracellular fluid, oligodendroglia would have to take up α -synuclein. Some cell lines can endocytose α -synuclein from media via a rab5-dependent pathway (Sung *et al.*, 2001). Whether mature oligodendrocytes in vivo have such capacity is unknown. Therefore, the hypothesis that α -synuclein is exported from neurons and acquired by glia is conjectural at present.

Some of these issues could be resolved by looking in detail at α -synuclein from GCIs. Recently, an ultrastructural study of GCIs revealed that full-length α -synuclein is present in GCIs (Gai *et al.*, 2003), which indicates that there is no requirement for protein truncation and post-translational modification before the protein accumulates in GCIs. Fibrils of α -synuclein in GCIs are in parallel bundles rather than the radiating pattern of α -synuclein fibrils in Lewy bodies, the predominant neuronal lesion found in PD and related disorders. This indicates that different fibrillization mechanisms might be involved in MSA compared to other α -synucleinopathies.

Hyperphosphorylation of α -synuclein has been suggested to be a key event in the formation of GCIs. Hyperactivity of casein kinases (Fujiwara *et al.*, 2002; Okochi *et al.*, 2000) and G-protein-coupled receptor kinases (GRKs) (Pronin *et al.*, 2000) has been implicated, because these enzymes have been shown to phosphorylate α -synuclein. Phosphorylation via GRKs interferes with the inhibitory effects of α -synuclein on phospholipase D2 (PLD2), which is important for phosphorylation of cytoskeletal proteins. Increased PLD2 activity can cause rearrangement of actin cytoskeleton (Pronin *et al.*, 2000). Interestingly, GCIs are immunoreactive for cyclin-dependent kinase (Nakamura *et al.*, 1998) and its activator, p39 (Honjyo *et al.*, 2001) indicating that upregulation of these proteins in oligodendroglia might be a mediating factor in increased cytoskeletal phosphorylation and subsequent GCI formation.

In light of the differences between α -synuclein in glial and neuronal inclusions, it is important to note that lesions can be found in both types of cells in some cases. In addition to MSA, α -synuclein-immunoreactive oligodendroglial inclusions are recognized increasingly in PD (Wakabayashi *et al.*, 2000). Likewise, α -synuclein-positive neuronal cytoplasmic inclusions can be present in MSA (Yokoyama *et al.*, 2001). These observations imply that there might be common mechanisms in neurons and glia that promote the formation of α -synuclein inclusions. One route to α -synuclein pathology in neurons and oligodendrocytes might be through a net increase in concentration of α -synuclein protein. The recent discovery that triplication of the α -synuclein gene results in a net doubling of the α -synuclein protein concentration in affected members of the 'Iowa kindred' provides direct support for this idea (Singleton *et al.*, 2003). Interestingly, in addition to Lewy body pathology, GCI-like pathology has been demonstrated in these cases (Gwinn-Hardy *et al.*, 2000) (Fig. 1). This provides further support for neuronal-glial interplay in the pathogenesis of MSA and also indicates that the mechanisms involved in the formation of neuronal and glial α -synuclein lesions might not be completely distinct.

Active contribution of glia to neurodegeneration

The presence of tau-positive and α -synuclein-positive glial inclusions indicates that astrocytes and oligodendrocytes play a role in the pathogenesis of neurodegenerative diseases. However, these observations do not easily answer a second, crucial question: Is this role primary or secondary? Clearly, reactive glial changes (e.g. microglia and astrocytes) are involved in all brain disorders in response to neuronal injury or loss, and they might play a more active or even a primary role in autoimmune and demyelinating diseases.

For reasons of brevity, the present discussion is limited to neurodegenerative diseases, where the contribution of glia to pathogenesis is less clearly defined. Although the role of glia in developmental and demyelinating disorders is not discussed, it is worth noting that mutations in the gene that encodes the astrocytic intermediate filament protein, glial fibrillary acidic protein (GFAP), cause Alexander's disease. This is an inherited leukodystrophy that is associated with marked loss of myelin and the presence of inclusion bodies, composed of the small heat-shock protein, α B-crystallin, in astrocytes (Messing and Brenner, 2003). This disorder provides insights into the roles of abnormalities in structural proteins of astrocytes on myelin integrity and of heat shock proteins on inclusion-body formation. Moreover, neuronal

loss in this disorder is either directly or indirectly attributable to mutations in a gene whose expression is restricted to astrocytes, which further emphasizes that, currently, we might underestimate the roles of glia in neurodegeneration.

Glial pathology in familial ALS

An example of the active role that glia can play in a neurodegenerative disease is given by familial ALS (FALS). Mutations in SOD1 are associated with autosomal dominant FALS, and a large number of mutations are scattered throughout this small but abundant cytoplasmic protein (see <http://alsod.org>). Since the initial discovery of mutations in this gene (Rosen *et al.*, 1993), several theories have been proposed for the dramatic loss of motor neurons in the cerebral cortex, brainstem and spinal cord (reviewed by Cleveland and Rothstein, 2001). The pathology of FALS is characterized by the presence of intraneuronal inclusion bodies, which are composed of SOD1 (Rowland and Shneider, 2001). This has led to the suggestion that protein aggregation might be a facet of this disease, as it is in several other degenerative disorders (Ciechanover and Brundin, 2003; Taylor *et al.*, 2002). The current predominant theory is that misfolding of mutant SOD1 contributes to neurotoxicity of motor neurons in FALS (Valentine and Hart, 2003). A recent example of this is the observation that an out of frame mutation (G127insTGGG) causes ALS with aggregate formation, even at low levels of expression of mutant SOD1 (Jonsson *et al.*, 2003). Hyaline inclusions, which are similar to Lewy bodies, have been described recently in astrocytes in some families with FALS (Kato *et al.*, 1997; Kato *et al.*, 2000) and in transgenic animals bearing FALS mutations (Bruijn *et al.*, 1997; Bruijn *et al.*, 1998). Inclusions have been noted in oligodendroglia in one transgenic model (Stieber *et al.*, 2000). Interestingly, inclusions can be present in both neurons and astrocytes in affected areas in humans (Jonsson *et al.*, 2003) and transgenic mice (Bruijn *et al.*, 1998), but whether this is causal or correlative cannot be distinguished. The time-course of formation of neuronal and glial inclusions has been reported in G93A-SOD1 transgenic mice (Stieber *et al.*, 2000).

Experiments in vivo strongly support the idea that astrocytes play more than a correlative role in FALS. Expression of many variants of mutant human SOD1 in transgenic mice produces substantial loss of motor neurons in the spinal cord, clinically evident motor deficits and, eventually, death. One of the first examples was the generation of G93A mutant mice under control of the human SOD1 promoter (Gurney *et al.*, 1994). Although G93A-SOD1 is expressed in most cell types of the body, it produces selective loss of motor neurons. Subsequent experiments using restricted promoters have shown that expression in either neurons or glial cells alone is insufficient to trigger toxicity. Expressing G37R-SOD1 using the low molecular weight neurofilament protein promoter, which expresses in most neuronal types (Pramatarova *et al.*, 2001) does not cause disease, unlike previous reports using the same mutation (Wong *et al.*, 1995) but less restrictive promoters. Similarly, expression of G86R-SOD1 in astrocytes using the GFAP promoter does not result in loss of motor neurons (Gong *et al.*, 2000). Hence, expression of mutant SOD1 in non-neuronal cells is required, but not sufficient to induce motor neuron death.

The interpretation of some of these results might be clouded slightly by the use of different mouse strains in different experiments and the uncertainty of whether the absolute level of expression of the mutant proteins is equivalent with the different restrictive promoters. Some of these questions have been addressed more directly by Clement *et al.* in elegant experiments using chimeric mice (Clement *et al.*, 2003). By injecting wild-type embryonic stem (ES) cells into blastocysts from mice that express one of two mutant SOD1 genes, chimeric animals with different numbers of cells expressing mutant SOD1 were created. The animals with fewer cells that expressed mutant SOD1 survived longer than those in which more cells expressed the mutant SOD1 transgene. The same group repeated these experiments using another technique;

aggregation of morulae from wild-type and mutant mice. In this experiment, cellular identity (neurons versus glia) is beginning to be established in each of the morulae that are aggregated together, which leads to chimeras with different numbers of neuronal and non-neuronal cells that express mutant SOD1. Crucially, motor neurons expressing mutant SOD1 survived in some of these chimeric animals. If mutant-SOD1-mediated toxicity is purely a cell-autonomous event, then one would predict that all the neurons that express mutant SOD1 would be affected, but this was not the case. Furthermore, in some chimeras all the motor neurons were mutant, whereas non-neuronal cells were a mixture of mutant and wild type. In these animals, motor-neuron survival correlated with the proportion of non-neuronal cells that were wild type; thus expression of mutant SOD1 in non-neuronal cells provides a detrimental environment and promotes the damaging effects of mutant SOD1 in motor neurons.

What is the mechanism involved and what are the molecular targets of mutant SOD1 in non-neuronal cells? A large proportion of non-neuronal cells in the ventral horn of the spinal cord are astrocytes, which play key roles in maintaining a homeostatic environment. Shortly after the discovery of SOD1 mutations, Rothstein and colleagues reported a loss of glutamate transporter protein (either GLT1 or EAAT2) in glia from the spinal cord and cortex of patients with sporadic ALS (Rothstein *et al.*, 1995). This provides one of several lines of evidence that indicate a possible role of glutamate-mediated excitotoxicity in this disease (Shaw and Eggett, 2000). Subsequently, some studies show a loss of glutamate transport in astrocytes from transgenic animals expressing mutant SOD1 (Howland *et al.*, 2002). Mutant SOD1 reduces the activity of EAAT2 when co-expressed in oocytes (Trotti *et al.*, 1999), indicating a direct effect. Therefore, a reasonable target for mutant SOD1 in non-neuronal cells is astrocytic transport of glutamate from the synaptic cleft. It should be emphasized that the primary evidence for altered EAAT2 expression comes from sporadic, not FALS (Rothstein *et al.*, 1995). This might mean that failure of astrocyte-mediated glutamate transport is common to both forms of the disease and implies a central role of glial cells in neurodegeneration (Trotti *et al.*, 1998).

Whether aggregated SOD1 is important in mediating loss of EAAT2 function in FALS or whether the mutant proteins have a more direct action is unclear. However, it is interesting that blocking glutamate-mediated Ca^{2+} entry through a subclass of AMPA receptors decreases both protein aggregation and cell death of motor neurons in vitro (Roy *et al.*, 1998). Therefore, it is possible that stressors in the microenvironment surrounding motor neurons potentiate protein aggregation and cell death, and that damage to glia hampers their ability to prevent this stress-mediated effect. Whether similar mechanisms apply in other diseases is not yet clear, but the presence of inclusions in glial cells in several neurodegenerative conditions suggests that this is worth examining further.

Other models that include glial pathology

Are the observations of a contribution of glia to mutant SOD1 toxicity limited to ALS models, or are they more general phenomena in neurodegenerative diseases? Transgenic models expressing human tau sometimes have glial cell inclusions in addition to neuronal inclusions (Gotz *et al.*, 2001; Lin *et al.*, 2003) and, in one case, in the absence of obvious neuronal inclusions (Higuchi *et al.*, 2002). Most of these animals (including those with glial but not neuronal lesions) develop motor problems (Higuchi *et al.*, 2002). Thus, it is tempting to speculate that aggregation of tau in glial cells contributes to neuronal damage in a way that is similar to aggregation of SOD1 in glia. However, experiments to address whether expression of tau in glia alone, such as restricting to one cell type, is sufficient to trigger degeneration in surrounding neurons have not yet been performed.

The relatively restricted glial pathology in MSA might be indicative of similar glial-driven neuronal damage. This has been addressed, in part, using transgenic mice that overexpress α -

synuclein. Overexpression of α -synuclein from a neuronal promoter does not result in GCI-like pathology (reviewed by Hashimoto *et al.*, 2003). However, when α -synuclein is overexpressed exclusively in oligodendroglia via a proteolipid protein (PLP) promoter, GCI-like inclusions form in these cells (Kahle *et al.*, 2002). Although PLP- α -synuclein mice do not have a behavioral phenotype, the inclusions resemble human GCIs. Moreover, α -synuclein is hyperphosphorylated at residue S129 in this mouse model, a modification that is found in human α -synucleinopathies. The accumulation of phosphorylated α -synuclein might be an early event in the pathology of MSA because this post-translational modification is known to enhance α -synuclein fibrillization (Fujiwara *et al.*, 2002). As these PLP- α -synuclein mice demonstrate neither a behavioral phenotype nor argyrophilic inclusions, it is speculated that the α -synuclein-containing inclusions represent an early phase of GCI formation. Thus, ectopic expression of α -synuclein in oligodendroglia does not seem to be sufficient for the complete pathogenesis of MSA, but it might mimic early stages of cellular pathology. These experiments do not address directly the question of whether α -synuclein is expressed by oligodendrocytes in MSA or whether it is produced in neurons and exported to glia, as discussed previously.

Overall, these model systems only partly address whether glial pathology is a significant contributor to neuronal damage. However, it is tempting to speculate that glia make active contributions to neuronal cell death in diseases other than ALS, and experiments designed to address this hypothesis are eagerly awaited.

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Fig. 1. Glial lesions in neurodegenerative disorders, demonstrated by immunostaining for either tau or α -synuclein
 (A–F) Staining for tau, (G–J) staining for α -synuclein. (A) In cortico-basal degeneration (CBD), an astrocytic plaque appears as a cluster of short cell-processes around a central unstained astrocyte (arrow). (B) Tufted astrocytes in the motor cortex and basal ganglia are typical of progressive supranuclear palsy (PSP). (C) Tau-positive astrocytes (arrow) are common in the limbic lobe in argyrophilic grain disease (AGD). (D) Thorn-shaped astrocytes are restricted largely to subpial and perivascular regions in the temporal lobe in aging and Alzheimer's disease. (E) Oligodendroglial coiled bodies (arrow) are common to several of these disorders (e.g. PSP, CBD, AGD and Parkinsonism linked to chromosome 17). (F) Glial-cell pathology is not a prominent feature of typical Pick's disease, but astrocytic and oligodendroglial lesions (arrow) are detected sometimes, especially in white matter. (G) α -

synuclein-positive glial-cell inclusions (GCIs; arrow) are pathognomic of multiple system atrophy (MSA). (H) Neuronal Lewy body-like inclusions (arrow) are also detected often in MSA in the pontine nuclei. Note the presence of neuritic processes, which are similar to those in Lewy body disease. (I) Like MSA, some cases of Lewy body disease, such as those with triplication of the α -synuclein gene locus (Singleton *et al.*, 2003), have GCI-like inclusions (arrow) in affected regions of the basal ganglia and brainstem. (J) The defining lesion of Lewy body disease is the intraneuronal Lewy body [three Lewy bodies in a single neuron (arrow) from the same brain with α -synuclein triplication]. All images are $\times 400$.

Table 1
Glial-cell pathology in inherited and sporadic neurodegenerative diseases

Disease ^a	Areas of pathology	Genes and proteins	Glial-cell pathology	Refs
FTDP-17	Cerebral cortex, hippocampus, basal ganglia, thalamus, brainstem and cerebellum	<i>MAPT</i> gene, tau protein	Tau inclusions in astrocytes and oligodendrocytes	van Herpen <i>et al.</i> , 2003
PSP, CBD and AGD	Motor (PSP), limbic (AGD) and association (CBD) cortices, basal ganglia, thalamus, brainstem and cerebellum	Sporadic, tau protein	Tau inclusions in astrocytes (tufted astrocytes and astrocytic plaques) and oligodendrocytes (coiled bodies)	Chin and Goldman, 1996; Komori, 1999; Dickson, 2004
AD and Aging	Subpial and subependymal regions	Sporadic, tau protein	Tau-positive astrocytes (thorn-shaped astrocytes)	Ikeda <i>et al.</i> , 1995; Chin and Goldman, 1996
Familial PD/DLBD	Limbic lobe, basal ganglia and brainstem	<i>SNCA</i> gene, α -synuclein protein	α -synuclein positive inclusions in oligodendrocytes	Gwinn-Hardy <i>et al.</i> , 2000
Sporadic PD/DLBD MSA	Limbic lobe, basal ganglia and brainstem Basal ganglia, brainstem and cerebellum	Sporadic, α -synuclein protein Sporadic, α -synuclein protein	α -synuclein inclusions in oligodendrocytes α -synuclein inclusions in oligodendrocytes (GCIs)	Wakabayashi <i>et al.</i> , 2000 Reviewed by Dickson <i>et al.</i> , 1999
ALS	Motor cortex and spinal cord	<i>SOD1</i> gene, SOD1 protein	SOD1 aggregates in astrocytes	Kato <i>et al.</i> , 1997; Jonsson <i>et al.</i> , 2003

^a Abbreviations: AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; CBD, cortico-basal degeneration; FTDP-17, Parkinsonism linked to chromosome 17; MSA, multiple system atrophy; PD/DLBD, Parkinson's disease/diffuse Lewy body disease; PSP, SOD1, Cu/Zn superoxide dismutase.