Astrocytes in Neurodegenerative Disease

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Astrocytes contribute to the maintenance of the health and function of the central nervous system (CNS). Thus, it is not surprising that these multifunctional cells have been implicated in the onset and progression of several neurodegenerative diseases. The involvement of astrocytes in the neuropathology of these diseases is likely a consequence of both the loss of normal homeostatic functions and gain of toxic functions. Intracellular aggregates in astrocytes are a common feature of various neurodegenerative diseases, and these aggregates perturb normal astrocytic functions in ways that can be harmful to neuronal viability. Here, we review the role of astrocytes in neurodegenerative diseases, focusing on their dysfunction in Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS).

NEURONS AND ASTROCYTES IN CONTEXT

Astrocytes play a critical role in the viability and function of the central nervous system (CNS). As reviewed in other articles in this monograph series, astrocytes play integral roles in the formation, maintenance, and elimination of synapses in development and disease (reviewed in Chung and Barres 2012). The release of vasoactive substances, such as prostanoids from astrocytes, can couple cerebral blood flow to neuronal energy demand, and astrocytes supply neurons with vital metabolites, such as lactate in response to neuronal activity (reviewed in Allaman et al. 2011). Additional homeostatic functions of astrocytes include water, ion, and glutamate buffering, as well as tissue repair after insult or injury (reviewed in Stevens 2008; Belanger and Magistretti 2009; Perea et al. 2009; Sofroniew and Vinters 2010; Allaman et al. 2011; Sidoryk-Wegrzynowicz et al. 2011; Chung and Barres 2012). In light of the central role played by astrocytes in the function of the CNS, it is not surprising that they have also been implicated in the onset and progression of neurodegenerative diseases. The question of whether the involvement of astrocytes in these diseases is a consequence of the loss of their normally supportive roles (loss-of-function), or to a toxic gain-of-function, or both, is currently under active investigation. Here, we review the role of astrocytes in neurodegenerative diseases, focusing on their dysfunction in Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS).

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Role of Astrocytes in Neurological Disease—Loss of Normal Function or Gain of Toxic Function?

Astrocytes are required for neuronal survival (Wagner et al. 2006), and the loss of normal astrocyte function can be a primary contributor to neurodegeneration (Brenner et al. 2001; Li et al. 2005; Quinlan et al. 2007). For example, disorders, such as Alexander disease and hepatic encephalopathy (HE), are a consequence of astrocyte dysfunction. Alexander disease is a leukodystrophy, caused by autosomally dominant mutations in the gene fibrillary acidic protein (GFAP). The disease is characterized by intra-astrocytic protein aggregates, consisting of mutant GFAP, heat shock protein 27, and αβ-crystallin (Brenner et al. 2001; Li et al. 2005; Quinlan et al. 2007). These aggregates, called Rosenthal fibers, are thought to compromise normal astrocytic functions, leading to the abnormal myelination and neurodegeneration characteristic of this disease.

Hepatic encephalopathy, a neuropsychiatric syndrome that results from liver disease, is another example of how dysfunctional astrocytes can be a primary cause of neurological disease (reviewed in Felipo and Butterworth 2002; Haussinger and Schliess 2008; Butterworth 2010). Acute or chronic liver disease leads to the accumulation of high concentrations of ammonia in the brain; this ammonia is primarily detoxified by astrocytic glutamine synthase. This detoxification results in the intracellular accumulation of osmotically active glutamine; the accumulation of glutamine leads to astrocytic swelling and changes in expression of key astrocyte proteins, such as the glutamate transporter GLT-1, the aquaporin Aqp4, the glucose transporter GLUT1, and GFAP. The cytotoxic astrocytic swelling and alterations of key astrocytic proteins, in turn, can alter the normal astrocytic functions required to maintain CNS homeostasis.

Reactive Gliosis—Complex Interplay between Neurotoxic and Neuroprotective Processes

Reactive astrogliosis is the response of astrocytes to insult or injury in the CNS (reviewed in Sofroniew 2009; Sofroniew and Vinters 2010). Reactive gliosis is a graded response that encompasses a spectrum of changes that range from hypertrophy to proliferation and migration (discussed in Sofroniew 2009). The nature and extent of the astrocytic response is determined by the context in which it occurs and by the duration and nature of the instigating stimulus. For example, lipopolysaccharide (LPS), stroke, and neurodegenerative disease can induce very different kinds of reactive gliosis (Zamanian et al. 2012; Phatnani et al. 2013). Reactive astrocytes can release a wide variety of extracellular molecules, including inflammatory modulators, chemokines and cytokines, and various neurotrophic factors. These factors can be either neuroprotective (e.g., cytokines, such as interleukin-6 [IL-6] and transforming growth factor-β [TGF-β]) or neurotoxic (such as IL-1β and tumor necrosis factor-α [TNF-α]) (reviewed in Sofroniew 2009).

The interplay between the neuroprotective and neurotoxic effects of reactive gliosis is exemplified by the process of glial scar formation. The glial scar serves to isolate the damaged area and prevents the spread of damage by restricting the infiltration of inflammatory cells. However, molecules secreted by reactive scar-forming astrocytes can also be refractory to neurite growth (reviewed in Sofroniew 2009). Dissecting various aspects of astrocyte responses to tissue injury has shed light on which signaling pathways are beneficial and which can be deleterious. For example, inflammatory signaling through STAT3 can be neuroprotective. Astrocyte-specific deletion of STAT3 impairs reactive gliosis, leads to increased inflammation and tissue damage, and compromises motor recovery after spinal cord injury (SCI) (Okada et al. 2006; Herrmann et al. 2008). On the other hand, inflammatory signaling in astrocytes can also be neurotoxic. Inhibition of astroglial NF-κB resulted in limiting tissue injury and impaired functional recovery after contusive SCI (Brambilla et al. 2005). This also increased neuronal sparing and sprouting of spinal tract axons (Brambilla et al. 2009a), increased neuronal survival in the retinal glial cell (RGC) layer after ischemia-reperfusion injury (Dvoriantchikova

et al. 2009), and reduced disease incidence and severity and promoted significant functional recovery in murine experimental autoimmune encephalomyelitis (EAE) (Brambilla et al. 2009b). Activation of NF-κB in astrocytes is also thought to contribute to pathogenesis in HD (Hsiao et al. 2013). However, blocking NF-κB activation in astrocytes in an ALS mouse model in vivo did not result in a change of disease progression (Crosio et al. 2011). The investigators of this paper concluded that "motor neuron death in ALS cannot be prevented by inhibition of a single inflammatory pathway because alternative pathways are activated in the presence of a persistent toxic stimulus."

ASTROCYTES IN ALZHEIMER'S DISEASE

AD is the most common cause of dementia (reviewed in Ballard et al. 2011). Histologically, it is characterized by extracellular amyloid plaques (deposits of amyloid-β or Aβ protein) and intracellular neurofibrillary tangles, the major constituent of which is tau, a microtubule-associated protein (reviewed in Ballard et al. 2011). Toxic concentrations of Aβ are thought to trigger changes in tau, which lead to the formation of neurofibrillary tangles, resulting in severe synaptic and neuronal loss (reviewed in Hardy and Selkoe 2002; Selkoe et al. 2004; Walsh and Selkoe 2004; Small and Duff 2008).

Reactive astrocytes are found at the site of Aβ deposits in postmortem human AD brains and in animal models of AD (Nagele et al. 2003; Olabarria et al. 2010; Simpson et al. 2010). In addition, it has been reported that astrocytes can internalize Aβ. For example, Aβ has been detected in astrocytes in human AD brains (Nagele et al. 2003). In addition, astrocytes can internalize Aβ in vitro and ex vivo. Astrocytes plated on Aβ-bearing brain sections from an AD mouse model associate with the Aβ deposits, which correlated with a decrease in Aβ levels (Wyss-Coray et al. 2003; Koistinaho et al. 2004). In addition, fluorescently labeled astrocytes transplanted into an AD mouse model migrate to and internalize deposited Aβ (Pihlaja et al. 2008), and wild-type (WT) astrocytes transplanted into AD mouse brains can clear Aβ plaques (Pihlaja et al. 2011). Consistent with these observations, Aβ-associated tissue damage correlates with both the amount of Aβ that accumulates in astrocytes as well as the extent of reactive gliosis (Nagele et al. 2003, 2004; Simpson et al. 2010).

Candidates for Astrocyte-Mediated Toxicity in AD

Additional evidence supports the view that internalized Aβ compromises normal astrocyte functions. For example, calcium homeostasis was perturbed in reactive astrocytes proximal to Aβ plaques in mouse AD brains (Kuchibhotla et al. 2009). Based on changes in the pattern of immunoreactivity toward connexin 43 (Cx43, a hemichannel protein that is a constituent of astrocytic gap junctions), it is believed that connectivity between astrocytes is altered in AD (Nagy et al. 1996; Mei et al. 2010). An increase in Cx43 levels has been shown to lead to increased toxic glutamate and adenosine triphosphate (ATP) release in vitro (Orellana et al. 2011a,b). Although glutamate release may be of limited relevance in vivo (Barres 2008), ATP release can affect synaptic transmission in vivo (Pascual et al. 2005; Barres 2008). Interestingly, blocking hemichannels in vivo led to improved memory without affecting Aβ plaque deposition, and has also been shown to delay disease progression in ALS (Takeuchi et al. 2011). Perturbations in energy metabolism and oxidative stress in AD astrocytes have also been reported (Allaman et al. 2010).

These perturbations are thought to render AD astrocytes toxic to neurons. The pretreatment of astrocytes by Aβ leads to decreased neuronal viability in vitro, and coculture with astrocytes accelerates and exacerbates neuronal death caused by Aβ treatment (Abramov et al. 2003, 2004; Paradisi et al. 2004; Allaman et al. 2010; Garwood et al. 2011). It is important to note that direct contact between neurons and astrocytes is not required for this toxicity (Allaman et al. 2010). Various mechanisms have been proposed for Aβ-induced neurotoxicity of astrocytes, including activation of neutral sphingomyelinase (Jana and Pahan 2010), over-

expression of S100β (Mori et al. 2010), calcium dysregulation (Kuchibhotla et al. 2009), and metabolic dysfunction (Allaman et al. 2010).

ASTROCYTES IN HD

HD is a progressive and fatal neurodegenerative disorder that is caused by mutations in the huntingtin gene. Mutant huntingtin is the result of an expanded CAG repeat that causes an expanded polyglutamine tract at the amino terminus of the protein (reviewed in Walker 2007; Ross and Tabrizi 2011). This polyglutamine tract can vary in length and causes a toxic gain-of-function in huntingtin.

Analogous to the observations in AD, the presence of mutant huntingtin (htt) in astrocytes is detrimental to both astrocytic and, consequently, neuronal health. Mutant huntingtin-expressing astrocytes have been shown to be toxic to WT neurons, perhaps by increased excitoxicity, as htt-expressing astrocytes were unable protect neurons against glutamate-induced or *N*-methyl-D-aspartate (NMDA)-induced toxicity in vitro (Shin et al. 2005). Interestingly, striatal astrocytes from HD model mice may have a reduced capacity to buffer extracellular K^+, likely caused by reduced expression of Kir4.1 channels, which could contribute to perturbed glutamate homeostasis and resultant excitotoxic neurodegeneration (Khakh and Sofroniew 2014; Tong et al. 2014).

When huntingtin 160Q (160 glutamines) was expressed under the control of the GFAP promoter in astrocytes, albeit at lower levels than endogenous protein, an age-dependent neurological phenotype was observed (Bradford et al. 2009). These transgenic animals showed loss of body weight accompanied by deficits in motor function, and died shortly after symptom onset. Thus, although mutant huntingtin tends to be more abundant in neuronal rather than in glial cells, the presence of htt in astrocytes alone can be sufficient to cause neurological deficits; htt-induced changes in both neurons and astrocytes likely synergize to cause HD. Consistent with this hypothesis, when htt was expressed in both astrocytes and neurons, more severe neurological symptoms and earlier death were observed (Bradford et al. 2010) compared with the expression of htt in neurons alone.

The severity of htt-induced astrocyte dysfunction appears to be determined by the length of the polyglutamine (polyQ) tract. Although htt-160Q expression in astrocytes was sufficient to cause neurological symptoms in transgenic mice (Bradford et al. 2009), when htt-98Q was expressed in astrocytes, the animals displayed no obvious neurological phenotypes, although they did show an increased susceptibility to glutamate-induced seizure (Bradford et al. 2010). Of note, astrocytes generated from induced pluripotent stem (iPS) cells derived from HD patients not only recapitulated features of HD seen in patients (diseased astrocytes showed a large number of vacuoles that increased over time), but the severity of the phenotype was dependent on the number of CAG repeats (a larger number of repeats was associated with a larger number of vacuoles), similar to observations in mouse models of HD (Juopperi et al. 2012).

Candidates for Astrocyte-Mediated Toxicity in HD

Several signs of astrocytic dysfunction have been observed in HD. The expression of polyQ-expanded htt by mouse striatal astrocytes was shown to impair glutamate transport (Faideau et al. 2010), and enhanced calcium-dependent glutamate release has also been shown from astrocytes of an alternative mouse model of HD (Lee et al. 2013b). The transport of other neurotransmitters may also be affected—the loss of astrocytic GABA release through GAT-3 has been implicated in reduced tonic inhibition in striatal output neurons from HD mice (Wojtowicz et al. 2013). Interestingly, there are indications that there may be enhanced coupling between astrocytes in HD, as increased connexin expression has been observed in human HD brains (assuming, of course, that these gap junctions are functional) (Vis et al. 1998).

As with other neurodegenerative diseases, astrocytic neuroinflammatory signaling pathways may also play a role in the pathogenesis of HD. As mentioned above, astrocyte-derived NF-

κB is thought to contribute to disease progression in a mouse model of HD (Hsiao et al. 2013). In addition, a positive role for cannabinoid signaling, known to modulate neuroinflammation (Saito et al. 2012), has also been proposed. In a rat model of HD generated by intrastriatal injection of mitochondrial complex II inhibitor malonate, only compounds able to activate cannabinoid receptor 2 (CB2) could protect striatal projection neurons from malonate-induced cell death (Sagredo et al. 2009). CB2 receptor-deficient mice were more sensitive to malonate than WT mice, and CB2 receptors, normally scarce in the striatum, were up-regulated after the lesion with malonate. CB2 receptors were up-regulated in reactive astrocytes and microglia, and CB2-receptor activation led to a reduction in levels of TNF-α (that had increased in response to the malonate lesion). Therefore, increased signaling through glial cannabinoid receptors was hypothesized to lead to reduction in levels of TNF-α and mitigate its proinflammatory effects (Sagredo et al. 2009). In addition, early defects in TGF-β1 production are thought to be associated with HD (Battaglia et al. 2011). Thus, the actions of proinflammatory mediators, such as NF-κB, TNF-α, and prostaglandins and cyclooxygenases (Tzeng et al. 2005), may be offset by the anti-inflammatory actions of cannabinoid signaling and cytokines, such as TGF-β.

Additional modes of astrocytic dysfunction in HD have also been proposed. For example, astrocytic mitochondrial dysfunction has been implicated in HD (Oliveira 2010; Schon and Przedborski 2011). In addition, HD astrocytes may be compromised in their ability to release trophic factors, as htt-expressing astrocytes express less brain-derived neurotrophic factor (BDNF) than WT astrocytes (Wang et al. 2012), and increasing BDNF production by astrocytes delays the onset of the motor phenotype in transgenic HD mice (Arregui et al. 2011). Mutant huntingtin has also been shown to hinder the suppression of production and secretion of the chemokine Ccl5/RANTES, which is another major trophic function of astrocytes (Chou et al. 2008). HD astrocytes may also have aberrant cholesterol production (reviewed in Valenza and Cattaneo 2011), as a cholesterol defect is marked across multiple rodent models of HD and is manifest in astrocytes (Valenza et al. 2010).

ASTROCYTES IN PD

PD is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the pars compacta of the substantia nigra (SN) and intraneuronal aggregates of α-synuclein (called Lewy bodies and Lewy neurites) in specific regions of the brain stem, spinal cord, and cortex (reviewed in Lees et al. 2009). In PD, loss of dopaminergic neurons in the SN is preclinical, accompanied by more widespread α-synuclein deposition (reviewed in Halliday and Stevens 2011). PD pathology is believed to have a focal initiation site before its propagation through the brain (Braak et al. 2003; Hawkes et al. 2007); at the earliest stages, α-Synuclein deposition occurs without neuronal loss or substantive clinical symptoms. Although the detailed molecular mechanisms are not known, mechanisms underlying disease initiation are thought to differ from those underlying disease progression (Nandhagopal et al. 2009).

Glial cells are thought to be involved in both pathological stages of PD—initiation before neuronal loss and subsequent progressive neurodegeneration (reviewed in Halliday and Stevens 2011). Nonfibrillized α-synuclein was found to accumulate in the cytoplasm of protoplasmic (but not fibrous) astrocytes early in disease (Song et al. 2009). α-Synuclein-containing astrocytes were found to be more broadly distributed than Lewy bodies, but were also found in regions without Lewy bodies (e.g., in striatum and dorsal thalamus, where there are likely to be dysfunctional neuron terminals) (Braak et al. 2007). This observation suggests that astrocytes take up altered α-synuclein that has escaped from axon terminals. Subsequent experiments confirmed that α-synuclein was transferred from neurons to astrocytes (Lee et al. 2010).

Candidates for Astrocyte-Mediated Toxicity in PD

Consistent with the theme that intracellular aggregates cause astrocyte dysfunction, the pres-

ence of intra-astrocytic α-synuclein was shown to adversely affect astrocyte function in PD. Astrocytes with accumulated α-synuclein have been shown to produce proinflammatory cytokines and chemokines (Lee et al. 2010) and neuroinflammatory mediators, such as IFN-γ and TNF-α, have been shown to synergistically activate astrocytes and microglia in animal models of PD (Barcia et al. 2011). In addition, when A53T α-synuclein was expressed in mouse astrocytes, it led to non-cell-autonomous killing of neurons that resulted in a rapidly progressive paralysis (Gu et al. 2010). Presymptomatic and symptomatic accumulation of α-synuclein aggregates in astrocytes disrupted astrocytic glutamate transporters as well as the ability of astrocytes to regulate the blood–brain barrier (Gu et al. 2010). In addition, changes in astrocytes owing to α-synuclein aggregates led directly to microglial activation in the midbrain, brainstem, and spinal cord, where a significant loss of dopaminergic and motor neurons was observed (Gu et al. 2010). Suppression of this microglial activation extended survival, suggesting that astrocyte-mediated microglial activation can directly contribute to neurodegeneration (Gu et al. 2010).

An additional contributory factor to astrocyte dysfunction in PD is likely to be the dysregulation of astrocyte-specific functions of recessive PD genes, such as *DJ-1* and *parkin*. Moreover, the disruption of these astrocyte-specific processes highlights the multiple ways in which astrocytes can function to maintain neuronal health in the face of injury or disease. For example, *DJ-1* mutations or deletions that cause a rare form of autosomal recessive parkinsonism (Bonifati et al. 2003) have been shown to protect neurons via an astrocyte-mediated mechanism (Mullett and Hinkle 2009). In an astrocyte–neuron coculture system, down-regulation of *DJ-1* compromised the ability of astrocytes to protect neurons against stress inducers. This neuroprotection was selective for drugs that inhibit mitochondrial complex I, as neuronal death could not be rescued by the addition of antioxidants. Also, neuroprotection in this system was not caused by the release of glutathione or the up-regulation of astrocytic heme oxygenase. Thus, the role of *DJ-1* in astrocyte-mediated neuroprotection is specific to a mechanism involving mitochondrial complex I and is independent of the oxidative stress response. Consistent with these results, *DJ-1* is not required for the activation of the Nrf2-ARE pathway (Gan et al. 2010). The Nrf2-ARE pathway has been shown to confer protection against oxidative stress in many models of neurodegenerative disease (reviewed in Johnson et al. 2008). Astrocyte-specific overexpression of Nrf2 delayed disease onset and extended survival in a mouse model in which human mutant α-synuclein (A53T) was expressed in neurons (Gan et al. 2012). Activation of endogenous intracellular levels of Nrf2 in the striatum was also neuroprotective in an MPTP-based mouse model of PD (Williamson et al. 2012). These experiments highlight at least two independent ways in which astrocytes contribute to the maintenance of neuronal health in PD (one dependent on *DJ-1* and the other via the oxidative stress response).

Another PD-associated gene, *parkin*, which is thought to function in the ubiquitin proteasome system, may play an astrocyte-specific role in PD. The *parkin* mutations cause autosomal recessive parkinsonism (Kitada et al. 1998). By virtue of its ubiquitin ligase activity, *parkin* is thought to confer protection against stress-induced cell death caused by the unfolded protein response (UPR) (Imai et al. 2000, 2001; Shimura et al. 2000; Zhang et al. 2000). Parkin levels were differentially affected in astrocytes and neurons under conditions of UPR-induced stress—*parkin* was up-regulated and redistributed in stressed astrocytes but not neurons, suggesting that *parkin* may have a specialized, astrocyte-specific role under conditions of UPR-induced cellular stress (Ledesma et al. 2002). On the basis of these observations, the investigators hypothesized that mutations in *parkin* lead to astrocytic dysfunction (by compromising the ability of astrocytes to cope with UPR-induced stress), and that this dysfunction in astrocytes contributes to neuronal death. Indeed, reactive astrocytes and the UPR have been shown to contribute to neuronal survival in a mouse model of PD (Hashida et al. 2012).

Chronic MPTP/P injections in these mice led to an increased UPR (both ATF6α and PERK/eIF2α/ATF4 branches). MPTP/P injections in ATF6α$^{-/-}$ mice not only accelerated neurodegeneration and ubiquitin accumulation, but also strongly suppressed astrogliosis, with a reduction in the levels of BDNF and reduced expression of antioxidative stress genes (Hashida et al. 2012). Because nigrostriatal dopaminergic neurons have the lowest glia/neuron ratios in the brain (Damier et al. 1993), it has been suggested that a possible role of parkin in glial function could explain the selective vulnerability of dopaminergic neurons to parkin dysfunction in the SN, because consequences of glial dysfunction could be more critical in the SN than elsewhere in the brain (Mena and Garcia de Yebenes 2008). Interestingly, lowered parkin levels lead to increased susceptibility of astrocytes to cell death (MacCormac et al. 2004).

Reciprocal communication between astrocytes and neurons is important for the maintenance of neuronal health in PD, as exemplified by studies of the Wnt signaling pathway. Knockdown of astrocytic Wnt1 in the midbrain reduced astrocyte-mediated neuroprotection, and Fzd-1 receptor in mesencephalic neurons was required for this astrocyte-mediated neuroprotection (L'Episcopo et al. 2011). Furthermore, antagonist-mediated blockade of Fzd/β-catenin signaling in the SN-induced reactive astrogliosis and inhibited neuronal survival, and this effect could be prevented by pharmacological activation of β-catenin within the SN (L'Episcopo et al. 2011). Thus, Wnt1/Fzd-1/β-catenin defines an astrocyte-dopaminergic neuron autoprotective loop (L'Episcopo et al. 2011).

ASTROCYTES IN ALS

ALS is a progressive, invariably fatal neurodegenerative disease that selectively involves the death of upper and lower motor neurons in the brain and spinal cord (reviewed in Kiernan et al. 2011). Multiple aspects of motor neuron cellular physiology are perturbed and neuromuscular synapses are lost, causing the progressive paralysis of voluntary muscles. Death ultimately results from respiratory failure. Most cases (~90%) of ALS are sporadic, with no clear genetic component having been identified. Of the remaining (~10%) ALS cases that are inherited, ~40%–45% are associated with expansions of a hexanucleotide repeat sequence in *C9orf72*, and ~20%–25% are associated with dominantly inherited mutations in *SOD1* (the gene for cytosolic Cu/Zn superoxide dismutase). Overexpression pathogenic alleles of human *SOD1* in mice and rats recapitulates late-onset progressive neurodegenerative disease (Gurney et al. 1994; Wong et al. 1995; Bruijn et al. 1997; Nagai et al. 2001).

The fundamental pathological basis for ALS remains to be determined, as does the specific insult that targets only specific classes of motor neurons for death. However, relevant to this review, glial pathology is observed in all cases of familial and sporadic ALS (Neumann et al. 2007; Nishihira et al. 2008; Zhang et al. 2008; Seilhean et al. 2009; Hewitt et al. 2010; Yamamoto-Watanabe et al. 2010; Mackenzie et al. 2011; Robertson et al. 2011). Genes known to be linked to familial ALS are ubiquitously expressed, and ubiquitinated aggregates of ALS-causing mutant proteins (such as SOD1 or TDP-43) are found in both neurons and glial cells (Bruijn et al. 1997; Pasinelli et al. 2000; Stieber et al. 2000; Nishihira et al. 2008; Zhang et al. 2008; Forsberg et al. 2011).

Although ALS is a motor-neuron-specific disease, expression of human ALS-causing mutant genes solely in motor neurons is not sufficient to cause typical ALS-like disease in mice (Pramatarova et al. 2001; Lino et al. 2002; Boillee et al. 2006; Jaarsma et al. 2008). In addition, chimeric mouse experiments revealed that non-neuronal cells expressing mutant ALS-causing SOD1 transgenes can damage nearby WT motor neurons, whereas WT nonneuronal cells can delay degeneration of nearby neurons expressing the mutant *SOD1* gene (Clement et al. 2003). Thus, nonneuronal cells in the spinal cord can affect the viability of motor neurons in either a positive or negative manner, depending on the genotype of nonneuronal cells.

ALS astrocytes have been shown to directly contribute to motor neuron death in vitro. Pri-

mary astrocytes from the SOD1 G93A mouse model of ALS adversely affect motor neuron viability of both WT and ALS motor neurons (Di Giorgio et al. 2007; Nagai et al. 2007). Interestingly, this toxicity was selective to motor neurons, both primary neurons as well those derived from mouse embryonic stem (ES) cells, and the deleterious effects can be recapitulated by culture medium conditioned by the mutant astrocytes. Mutant mouse astrocytes are also similarly toxic to human ES-cell-derived motor neurons (Di Giorgio et al. 2008; Marchetto et al. 2008), and human astrocyte-like cells derived from both familial and sporadic ALS patients are toxic to mouse motor neurons (Haidet-Phillips et al. 2011; Meyer et al. 2014). Thus, the presence of ALS-associated mutant proteins in astrocytes leads to a motor-neuron-specific non-cell-autonomous toxicity. Of course, the loss of viability of motor neurons in these cell culture experiments could be because of a combination of the loss of positive support by astrocytes and the secretion of toxic factors. Consistent with this view, experiments in cell culture showed that there is extensive cross talk between motor neurons and astrocytes, mediated by an intricate network of signaling pathways, and that mutant protein expression in both neurons and glial cells synergizes to accelerate the death of ALS motor neurons exposed to ALS astrocytes (Phatnani et al. 2013).

In vivo experiments in mouse models of ALS in which the mutant *SOD1* transgene was deleted in a cell-specific manner revealed that reducing the levels of SOD1 expression in astrocytes was sufficient to delay disease onset and/or progression (Yamanaka et al. 2008; Ilieva et al. 2009; Wang et al. 2011). The same strategy was used to implicate mutant microglia (Boillee et al. 2006) and oligodendrocytes (Kang et al. 2013) in disease progression in the ALS mouse model. In contrast, reduction of SOD1 levels specifically in motor neurons delayed disease onset, but did not affect disease progression (Boillee et al. 2006). Thus, the pathophysiology of ALS depends on complex multicellular interactions in the spinal cord.

Transplanting precursors of mutant SOD1 astrocytes into the spinal cord of WT rats has also been shown to lead to the degeneration of motor neurons, which is thought to be mediated in part by the activation of host microglia (Papadeas et al. 2011). Conversely, transplanting precursors of WT astrocytes into ALS rats not only reduced microgliosis in the spinal cord, but also reduced motor neuron loss and extended survival (Lepore et al. 2008). Thus, ALS astrocytes can be toxic to motor neurons in vivo, either directly and/or indirectly, by acting through microglia.

Astrocyte Dysfunction in ALS

Astrocytes from the SOD1 mouse model have been shown to be defective in the uptake of glutamate. The resulting extracellular accumulation of glutamate has been proposed to lead to motor neuron death through excitotoxicity (Rothstein et al. 1992, 1995; Howland et al. 2002; Guo et al. 2003; Pardo et al. 2006). Astrocytes are also thought to exacerbate the vulnerability of motor neurons to excitotoxicity by regulating their ability to modulate expression of the GluR2 subunit of AMPA receptors (Van Damme et al. 2007). ALS astrocytes have also been shown to have dysfunctional mitochondria (Cassina et al. 2008). In vitro and in vivo studies using ALS mice have provided evidence of metabolic dysfunction in ALS astrocytes, particularly in the transporter responsible for the efflux of lactate, an important metabolite for neurons (Ferraiuolo et al. 2011). These astrocytes have also been shown to activate pro-nerve growth factor p75–receptor signaling in motor neurons, and thereby contribute to their demise (Ferraiuolo et al. 2011).

ALS causing mutant proteins may also be toxic to the astrocytes themselves. Astrocytes bearing ubiquitin-positive inclusions and an abnormal morphology, and containing ubiquitin-positive inclusions, have been detected in close proximity to motor neurons before symptom onset (Pun et al. 2006; Rossi et al. 2008; Martorana et al. 2012). Interestingly, glutamate may contribute to astrocyte degeneration, via signaling through its metabotropic receptor mGluR5, leading to persistent Ca^{2+} release and apoptosis (Rossi et al. 2008; Martorana et al.

2012). Finally, astrocytes generated from human iPS cells bearing a familial mutation in TDP43 showed decreased survival (Serio et al. 2013). However, neither iPS-derived TDP-43 mutant astrocytes nor mutant-TDP43 overexpressing mouse astrocytes displayed toxicity toward iPS- or ES-derived motor neurons in cell culture. In addition, transplanting precursors of mutant TDP43-overexpressing mouse astrocytes into WT rat spinal cords did not affect motor neuron survival (Haidet-Phillips et al. 2013; Serio et al. 2013). Although it has been argued that this lack of toxicity may be because of a difference between mutations in SOD1 and TDP43, transgenic rats expressing human mutant TDP43 in astrocytes did display non-cell-autonomous motor neuron death (Tong et al. 2013). Thus, the lack of toxicity of iPS-generated human astrocytes in these experiments could be a consequence of differences between primary and iPS-generated astrocytes in the only cases thus far reported.

Candidates for Astrocyte-Mediated Toxicity in ALS

Defects in the astrocyte-specific glutamate transporter EAAT2 (GLT-1) have been identified in ALS patients (Rothstein et al. 1992, 1995). In addition, studies in animal models have revealed a number of astrocyte toxic effects, including (1) the focal loss of the EAAT2 transporter, which is coincident with reactive gliosis and occurs before the loss of motor neurons or onset of symptoms in SOD1 rats (Howland et al. 2002); (2) transplanted ALS astrocytes induced reactive astrocytosis and decreased GLT-1 expression in the spinal cords of WT animals (Papadeas et al. 2011); (3) D-serine, coagonist for the NMDA receptor, has been proposed to be a glia-derived enhancer of glutamate toxicity (Sasabe et al. 2012); and (4) levels of D-serine and serine racemase, the enzyme that produces D-serine, increase with disease progression in ALS mice, predominantly in glia (Sasabe et al. 2007). However, increasing the expression of EAAT2 (GLT-1) in ALS mice did not delay the onset of paralysis or extend survival, despite protecting neurons from L-glutamate-induced cytotoxicity and cell death in vitro (Guo et al. 2003).

Mitochondrial dysfunction accompanied by an increase in reactive oxygen species (ROS) from ALS astrocytes has also been proposed as a mechanism that contributes to neurotoxicity (Cassina et al. 2008). Mitochondria from rat ALS astrocytes are defective in respiratory function, show increased superoxide radical formation, and defects associated with nitro-oxidative damage, whereas treatment of WT astrocytes with mitochondrial inhibitors are toxic to motor neurons in vitro (Cassina et al. 2008). Antioxidants and nitric oxide synthase inhibitors ameliorated motor neuron death in vitro (Cassina et al. 2008; Marchetto et al. 2008), and stimulation of the astrocytic oxidative stress response in ALS mice delayed disease onset and extended survival (Vargas et al. 2008).

Among the several inflammatory mediators (prostaglandin D2, IFN-γ, and TGF-β) that have been implicated in astrocyte–neuron communication in ALS (Di Giorgio et al. 2008; Aebischer et al. 2011; Phatnani et al. 2013), IFN-γ has been proposed to induce motor neuron-selective cell death via activation of the lymphotoxin-β receptor (LT-βR) by LIGHT (Aebischer et al. 2011). IFN-γ was shown to be preferentially expressed by astrocytes as well as motor neurons in ALS mice and genetically ablating LIGHT slows disease progression and extends life span (Aebischer et al. 2011). Interestingly, studies examining the localization of glial IFN-γ receptors in the human CNS showed that most IFN-γ-receptor-positive cells are GFAP-positive astrocytes in human ALS spinal cords (Hashioka et al. 2010). In addition, IFN-γ-treated human astrocytes have been shown to be neurotoxic (Hashioka et al. 2009), likely via a STAT3-dependent pathway. Activation of STAT3 has been observed in spinal cords from sporadic ALS patients (Shibata et al. 2009), and activated STAT3 was found to accumulate in the nucleus of motor neurons, reactive astrocytes, and activated microglia in ALS mice (Shibata et al. 2010). In addition, STAT3 inhibitors attenuate the neurotoxicity of human astrocytes (albeit toward SH-SY5Y cells; therefore, specificity toward motor neurons is unclear) (Hashioka

Table 1. Summary of astrocyte dysfunction in disease

Signaling molecules/pathways/functions	Disease
Rosenthal fibers (intra-astrocytic protein aggregates comprising mutant GFAP, Hsp27, and α/β crstallin)	Alexander disease (Brenner et al. 2001; Li et al. 2005; Quinlan et al. 2007)
Intra-astrocytic accumulation of osmotically active glutamine leading to changes in levels of GLT-1, Aqp4, GLUT1, and GFAP	Hepatic encephalopathy (Felipo and Butterworth 2002; Haussinger and Schliess 2008; Butterworth 2010)
Inflammatory signaling through STAT3	Neuroprotective in SCI (Okada et al. 2006; Herrmann et al. 2008); Neurotoxic in ALS? (Hashioka et al. 2009; 2011; Shibata et al. 2009, 2010)
Inflammatory signaling through NF-κB	Neurotoxic in SCI (Brambilla et al. 2005); implicated in HD (Hsiao et al. 2013); EAE (Brambilla et al. 2009b)
Altered connectivity through gap junctions	AD (Nagy et al. 1996; Mei et al. 2010)
Increased glutamate and ATP release in vitro	AD (Orellana et al. 2011a,b)
Perturbed energy metabolism and oxidative stress	AD (Allaman et al. 2010)
Activation of neutral sphingomyelinase	AD (Jana and Pahan 2010)
Overexpression of S100β	AD (Mori et al. 2010)
Maintenance of K^+ homeostasis	HD (Khakh and Sofroniew 2014; Tong et al. 2014)
Impaired glutamate transport	HD (Faideau et al. 2010); ALS (Rothstein et al. 1992, 1995)
Enhanced Ca^{2+}-dependent glutamate release	HD (Lee et al. 2013b)
Loss of GABA release through GAT-3	HD (Wojtowicz et al. 2013)
Enhanced coupling through gap junctions	HD (Vis et al. 1998)
Cannabinoid signaling through CB2 receptors	HD (protective) (Sagredo et al. 2009)
Defects in TGF-β1 production	HD (Battaglia et al. 2011)
Mitochondrial dysfunction	HD (Oliveira 2010; Schon and Przedborski 2011); ALS (Cassina et al. 2008)
Decreased trophic factor release	HD (Chou et al. 2008; Arregui et al. 2011; Wang et al. 2012)
Aberrant cholesterol production	HD (Valenza et al. 2010)
Disruption of glutamate transporters	PD (Gu et al. 2010)
Disrupted regulation of the blood–brain barrier	PD (Gu et al. 2010)
Dysregulation of astrocyte-specific functions of DJ-1 and parkin	PD (Ledesma et al. 2002)
Nrf2-ARE pathway	Many diseases (Johnson et al. 2008)
Wnt1/Fzd-1/β-catenin autoprotective loop	PD (L'Episcopo et al. 2011)
Modulation of neuronal expression of GluR2 subunit of AMPA receptors	ALS (Van Damme et al. 2007)
Impaired lactate transport	ALS (Ferraiuolo et al. 2011)
Activation of p75-receptor signaling in motor neurons	ALS (Ferraiuolo et al. 2011)
Glutamate signaling through mGluR5, leading to persistent Ca^{2+} release and apoptosis	ALS (Rossi et al. 2008; Martorana et al. 2012)
Decreased GLT-1 expression	ALS (Papadeas et al. 2011)
Increased levels of D-serine and serine racemase	ALS (Sasabe et al. 2007)
Inflammatory mediators (prostaglandin D2, IFN-γ, and TGF-β)	ALS (Di Giorgio et al. 2008; Aebischer et al. 2011; Phatnani et al. 2013)
Neurotoxic cocktail released by IFN-γ-treated astrocytes in vitro (IL-6, proteases, oxygen free radicals, prostaglandin, and glutamate)	(Lee et al. 2013a)

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ATP, adenosine triphosphate; EAE, experimental autoimmune encephalomyelitis; GFAP, gene fibrillary acidic protein; GLT-1, glutamate transporter EAAT2; IFN-γ, interferon-γ; IL-6, interleukin-6; PD, Parkinson's disease; SCI, spinal cord injury; TGF, transforming growth factor.

et al. 2011). The neurotoxicity of IFN-γ-treated human astrocytes has been attributed to the release of a "cocktail" of neurotoxins. When inhibitors targeted to IL-6, proteases, production of oxygen free radicals by NADPH oxidase, prostaglandin production, and glutamate (by treatment with glutamate decarboxylase) were added together, the toxicity of the conditioned medium from the astrocyte culture was reduced by >90% (Lee et al. 2013a).

CONCLUDING REMARKS

The involvement of astrocytes in the pathology of neurodegenerative diseases is likely caused by a combination of the loss of their normal homeostatic functions and the gain of toxic functions in disease (Table 1). Intracellular aggregates are found in astrocytes in various neurodegenerative diseases. The presence of these aggregates perturbs normal astrocytic functions in various ways that can prove harmful to neuronal viability. The outcome of disrupted astrocyte–neuron communication likely depends on the context, as both astrocytes and neurons are regionally specialized in terms of their morphology and physiology (Kimelberg 2004; Zhang and Barres 2010; Molofsky et al. 2012; Tsai et al. 2012). For example, neurons may differ in their reliance on astrocytes, depending on their location in the CNS. Because nigrostriatal dopaminergic neurons have the lowest glia/neuron ratios in the brain (Damier et al. 1993), it has been hypothesized that consequences of glial dysfunction could be more critical in the SN than elsewhere in the brain (Mena and Garcia de Yebenes 2008). Neurons may also have specialized requirements, or affect astrocytes in distinct and specific ways, depending on neuronal type. For example, motor neurons secrete angiogenin, which can be endocytosed by glia, induce RNA cleavage, and alter the astrocyte secretome. An ALS-associated mutant of angiogenin can be endocytosed but fails to induce RNA cleavage (Skorupa et al. 2012, 2013). Better in vivo tools will certainly be required to assess different types of neurons and their associated, regionally specialized astrocytes in vivo. Although great strides have been made toward understanding how neurons and glia work in concert and how these interactions are disrupted in disease, there is still a long way to go.

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