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Review

Examining the relationship between astrocyte dysfunction and neurodegeneration in ALS using hiPSCs

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a complex and fatal neurodegenerative disease for which the causes of disease onset and progression remain unclear. Recent advances in human induced pluripotent stem cell (hiPSC)-based models permit the study of the genetic factors associated with ALS in patient-derived neural cell types, including motor neurons and glia. While astrocyte dysfunction has traditionally been thought to exacerbate disease progression, astrocytic dysfunction may play a more direct role in disease initiation and progression. Such non-cell autonomous mechanisms expand the potential targets of therapeutic intervention, but only a handful of ALS risk-associated genes have been examined for their impact on astrocyte dysfunction and neurodegeneration. This review summarizes what is currently known about astrocyte function in ALS and suggests ways in which hiPSC-based models can be used to more effectively study the role of astrocytes in neurodegenerative disease.

1. Introduction

The prevalence of age-related neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), continues to increase (Arthur et al., 2016; Heemels, 2016). Unfortunately, the primary mechanisms that drive the onset and progression of ALS are poorly understood, and current therapeutics provide minimal benefit. Here we present a case for increased focus on non-cell autonomous disease mechanisms arising from glial dysfunction in ALS (Pramatarova et al., 2001). Understanding the effect of ALS-specific mutations on astrocytes is paramount towards developing improved therapeutics.

Compared to neurons, astrocytes and other glial cells have been largely understudied (Barres, 2008). These cells play a crucial role in the maintenance of an extracellular environment that is suitable for neurons to function properly. Astrocytes remove neurotransmitters from the synapse, regulate local ion concentrations and pH homeostasis, supply glucose and other metabolites to neurons, remove metabolic waste, and aid in tissue repair after injury. They also help to regulate neuron excitability, synaptic strength, synaptogenesis, and the development of neuronal circuits (Reviewed by Clarke and Barres, 2013). Changes in normal astrocyte function can be toxic to neurons; it is becoming increasingly accepted that astrocytes play a key role in ALS and other neurodegenerative disorders.

Recent studies have revealed the complex genetic landscape underlying ALS risk, facilitating the development of improved animal models that more fully recapitulate key features of ALS pathology (Clement et al., 2003; Haidet-Phillips et al., 2013, p.; Qian et al., 2017). It remains to be seen whether inconsistent findings from these models is relevant to human disease or simply the shortcomings of mouse models. While some studies indicate that astrocytes harboring ALS-associated mutations can trigger disease onset, others show that they only impact the rate of disease progression, and others suggest that they have no effect on disease pathology (Gong et al., 2000; Lino et al., 2002; Nagai et al., 2007; Qian et al., 2017; Wang et al., 2011; Yamanaka et al., 2008). Moreover, the complex genetic nature of sALS (which constitutes approximately 90% of ALS patients) makes it difficult to generalize the conclusions drawn from monogenic mouse models, especially given that many ALS-associated genes are differentially expressed in rodents (Oberheim et al., 2009, 2012; Zhang et al., 2014, 2016). It is important to develop additional models that better capture complex

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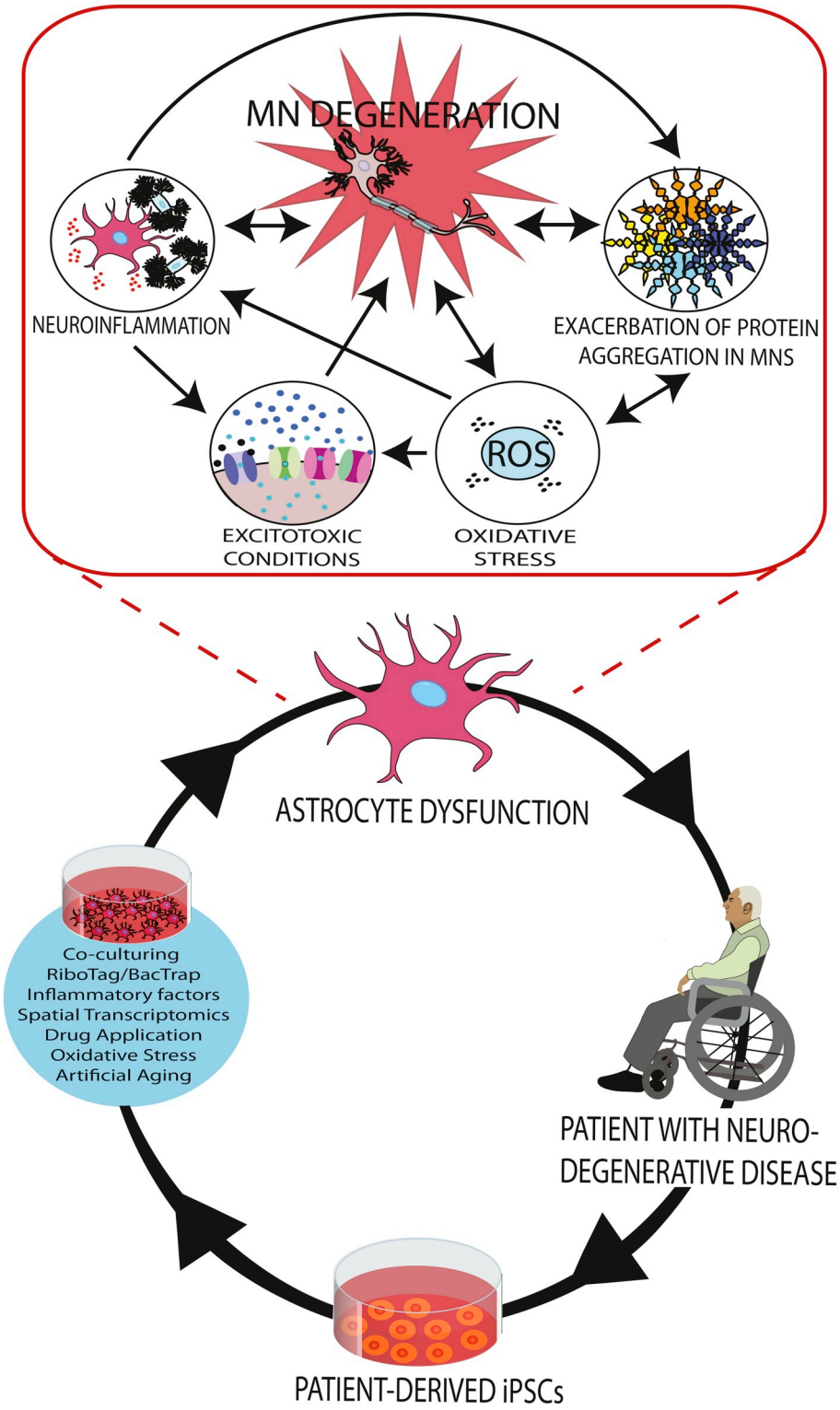

Fig. 1. Investigating astrocyte involvement in neurodegeneration. Astrocytes can drive neurodegeneration through several interrelated mechanisms, including neuroinflammation, oxidative stress, excitotoxicity, and the promotion of protein aggregation in affected neurons. These pathological hallmarks of astrocyte-mediated neurodegeneration are conserved across a number of neurodegenerative diseases. ALS patients, for example, exhibit all facets of astrocyte-related disease pathology, and a large portion of ALS risk genes are highly expressed in astrocytes. However, the high degree of interrelation among astrocyte-related pathological phenotypes, as well as between astrocyte dysfunction and MN degeneration in ALS, begs the question of "which came first?" hiPSC models offer a new perspective for further examination of the "chicken-or-egg" dilemma in astrocyte-mediated neurodegeneration. Able to capture the complex, polygenetic landscape of ALS pathology, these models have already begun to yield new insight into the genetic and cellular underpinnings of neurodegeneration. However, hiPSC-derived astrocytes remain an under-used tool in examining non-cell autonomous disease pathology.

human genetics. Recent advances in human induced pluripotent stem cell (hiPSC) modeling provides an *in vitro* system to model ALS in patient-derived cells.

Here we consider the critical role that astrocytes play in ALS pathology. First, we establish the repertoire of ALS-associated genes that, due to their relatively high level of expression in astrocytes, indicate a role for astrocytes in disease pathogenesis. We discuss the mechanisms by which dysfunctional astrocytes contribute to neurodegeneration, with an emphasis on the ways in which hiPSC models have increased our understanding of the genetic underpinnings of astrocyte-related ALS pathology (Fig. 1). Finally, we consider the implications for these findings in the context of other neurodegenerative diseases.

2. Genetic evidence of astrocyte involvement in ALS

Presently, approximately forty risk-associated genes have been identified in familial ALS, each of which is also mutated in a percentage of sporadic ALS cases (Chiò et al., 2012; van Es et al., 2010; Li et al.,

Table 1
ALS risk-associated genes highly expressed in astrocytes. Criteria for inclusion in table: FPKM for fetal/mature astrocytes greater than or equal to 10, unless gene was most highly expressed in fetal/mature astrocytes when compared to all brain cell-types (in which case, brain cell-types that showed similar gene expression levels were included). Genes for which hiPSC-derived astrocytes expressing disease-specific gene mutations have been generated and studied are written in red.

Gene symbol	Protein	Human cell type specific expression [see (Zhang et al., 2014)]	Normal protein function / Implicated pathways	Number of disease-related mutations	Possible pathological mechanism	References
*ALS2**	Alsin (Amyotrophic lateral sclerosis 2)	Fetal Astrocytes (FPKM > 4, < 8) Neurons (FPKM ~5.5)	RAB5 GEF; Cytoskeletal maintenance; Vesicle and endosomal trafficking; Protein transport; Cell signaling; Glut4 trafficking	≥40	Endosomal dynamics; Oxidative stress	(Zhang et al., 2014) (Chen et al., 2018) (Ince et al., 2011) (Zufiría et al., 2016) (Cirulli et al., 2015) (Morgan et al., 2015) (Sato et al., 2018)
*ANG**	Angiogenin	Fetal Astrocytes (FPKM > 0.75, < 3.5) Microglia/Macrophage (FPKM > 1.5, < 3)	Ribonuclease; RNA transcription; Angiogenesis	> 10	Stress granule formation; TDP-43 aggregate formation	(Zhang et al., 2014) (Chen et al., 2018) (Ince et al., 2011) (Zufiría et al., 2016) (Taylor et al., 2016)
ATXN2	Ataxin 2	Mature Astrocytes (FPKM > 11, < 20) Fetal Astrocytes (FPKM > 11, < 20) Neurons (FPKM ~10)	Endocytosis; RNA metabolism	CAG trinucleotide repeat expansion (27-33 repeats)	TDP-43 toxicity modifier; Protein cleavage increases with length of polyglutamine repeat: truncated peptides potentially toxic to cells	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Guerreiro et al., 2015) (Robberecht and Philips, 2013)
C21ORF2	C21ORF2	Fetal Astrocytes (FPKM > 0.5, < 2.5)	Ciliome component; Possibly cytoskeletal dynamics; Possibly DNA repair	≥1	Mitochondrial dysfunction; Primary cilia loss; DNA repair insufficiency	(Zhang et al., 2014) (Chen et al., 2018) (Van Rheenen et al., 2016)
C9ORF72	C9ORF72	Microglia (FPKM > 20, < 30) Neurons (FPKM ~12) Fetal Astrocytes (FPKM > 7, < 15)	RAB(8a/39b) GEF (experimentally); Possibly cytoskeletal dynamics and endosomal trafficking; Possibly lysosomal autophagy pathway; nucleocytoplasmic transport	Intronic GGGGCC repeat (> 30 repeats) (5 known Dipeptide Protein Repeat Sequences)	Altered C9ORF72 RNA splicing; Toxic RNA or repeat dipeptide aggregation (due to reduced C9ORF72 expression); Ubiquitin and p62 aggregate formation; Neuro-inflammation; Formation of RNA foci; transcription inhibition; histone modification; accumulation of double stranded RNA	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Almad et al., 2016) (Meyer et al., 2014) (Selvaraj et al., 2017) (Zhang et al., 2015) (Kwon et al., 2014) (Spang et al., 2014) (Gomez-Deza et al., 2015) (Allen et al., 2019) (Zhang et al., 2019)
CCNF	Cyclin F	Fetal Astrocytes (FPKM > 0.6, < 1.4)	E3 ubiquitin-protein ligase complex component; Protein degradation	≥10	Abnormal ubiquitination; Ubiquitinated protein aggregation (including TDP-43 and $SCF^{Cyclin\ F}$ substrate)	(Zhang et al., 2014) (Chen et al., 2018) (Maurel et al., 2018) (Williams et al., 2016)
CHCHD10	Coiled-coil-helix-coiled-coil helix domain containing 10	Mature Astrocytes (FPKM > 1.75, < 3.5)	Mitochondrial protein of unknown function	≥2	Mitochondrial function	(Zhang et al., 2014) (Chen et al., 2018) (Taylor et al., 2016) (Guerreiro et al., 2015) (Ajroud-Driss et al., 2015)(Perrone et al., 2017)(Che et al., 2017)
DCTN1	Dyactin subunit $p150^{glued}$	Fetal Astrocytes (FPKM > 3.5, < 8) Oligodendrocytes (FPKM > 2.3, < 3.2) Neurons (FPKM ~2.5) Mature Astrocytes (FPKM > 1.5, < 2.25)	Dynein motor complex component; Vesicle trafficking; Cytoskeletal dynamics	≥10	Protein transport	(Zhang et al., 2014) (Chen et al., 2018) (Taylor et al., 2016) (Guerreiro et al., 2015) (Boillée et al., 2006)
ERLIN2	ER lipid raft associated 2	Mature Astrocytes (FPKM > 9, < 12)	ER lipid raft formation	≥1	Lipid raft functioning	(Zhang et al., 2014) (Guerreiro et al., 2015)
FUS	FUS	Fetal Astrocytes (FPKM > 6, < 8) Microglia/Macrophage (FPKM < 4.5, > 7)	Transcriptional regulator; UPS pathway	≥35	Altered RNA processing resulting in FUS aggregates	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Maurel et al., 2018)
GLE1	GLE1 RNA export mediator	Fetal Astrocytes (FPKM > 1.75, < 3.5) Mature Astrocytes (FPKM > 2, < 2.5) Neurons (FPKM ~2.2)	RNA metabolism	≥3	RNA metabolism	(Zhang et al., 2014) (Zufiría et al., 2016) (Guerreiro et al., 2015) (Kaneb et al., 2015)

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Table 1 (*continued*)

Gene symbol	Protein	Human cell type specific expression [see (Zhang et al., 2014)]	Normal protein function / Implicated pathways	Number of disease-related mutations	Possible pathological mechanism	References
GLT8D1	Glycosyltransferase 8 domain containing 1	Neurons (FPKM > 12) Mature Astrocytes (FPKM > 9, < 12)	Unknown; Possibly involved in sugar metabolism and cell adhesion	5	Unknown	(Cooper-Knock et al., 2019; Zhang et al., 2014)
HNRNPA1	Heterogeneous nuclear ribonucleoprotein A1	Fetal Astrocytes (FPKM > 70, < 140) Oligodendrocytes (FPKM > 80, < 115) Microglia/Macrophage (FPKM > 70, < 90) Neurons (FPKM ~70) Mature Astrocytes (FPKM > 25, < 40)	RNA-binding protein; Directly interacts with TDP-43; RNA metabolism; transport of poly (A) mRNA from nucleus to cytoplasm	3	Strengthened 'steric zipper' motif in PrLD; Accelerated formation of fibrils that self-seed and cross-seed polymerize with wildtype hnRNP	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Hutten and Dormann, 2016)
HNRNPA2b1	Heterogeneous nuclear ribonucleoprotein A2/B1	Fetal Astrocytes (FPKM > 60, < 100) Microglia/Macrophage (FPKM > 60, < 90) Neurons (FPKM ~65) Oligodendrocytes (FPKM > 50, < 80) Mature Astrocytes (FPKM > 40, < 50)	RNA-binding protein; Directly interacts with TDP-43; RNA metabolism	≥1	Strengthened 'steric zipper' motif in PrLD; Accelerated formation of fibrils that self-seed and cross-seed polymerize with w hnRNP; Widespread changes in alternative splicing (mechanism unknown)	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Guerreiro et al., 2015) (Kaneb et al., 2015)
MATR3	Matrin 3	Neurons (FPKM ~75) Fetal Astrocytes (FPKM > 35, < 50) Oligodendrocytes (FPKM > 25, < 40) Microglia/Macrophage (FPKM > 25, < 35) Mature Astrocytes (FPKM > 15, < 20)	RNA-binding protein; RNA metabolism	4	Interaction with TDP-43 to regulate transcription (in MNs)	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016)
NEK1	Never-in-mitosis A (NIMA-) related kinase 1	Mature Astrocytes (FPKM > 5, < 7) Fetal Astrocytes (> 3, < 4)	Centrosomal complex component; Mitotic protein kinase; Cytoskeletal dynamics; Genotoxic stress response	≥120	DNA damage accumulation	(Zhang et al., 2014) (Chen et al., 2018) (Higelin et al., 2018) (Chen et al., 2011) (Pelegrini et al., 2010) (Kenna et al., 2016)
PFN1	Profilin-1	Microglia/Macrophage (FPKM > 25, < 65) Fetal Astrocytes (FPKM > 25, < 40) Oligodendrocytes (FPKM > 15, < 25) Mature Astrocytes (> 12, 20)	Actin-binding protein; Cytoskeletal dynamics; regulator of actin polymerization	5	Cytoskeletal pathways disruption	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016)
SIGMAR1	Sigma1R	Fetal Astrocytes (FPKM > 6, < 9) Mature Astrocytes (FPKM > 5, < 7) Neurons (FPKM ~6)	Regulator of Ca^{2+} transport from ER to mitochondria through IP_3R; Protein degradation; receptor protein involved in endocrine and immune signaling	≥1	Aberrant potassium channel (Kv1.4) activity; Mitochondria-associated membrane collapse	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Watanabe et al., 2016) (Shinoda et al., 2015)

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Table 1 (*continued*)

Gene symbol	Protein	Human cell type specific expression [see (Zhang et al., 2014)]	Normal protein function / Implicated pathways	Number of disease-related mutations	Possible pathological mechanism	References
SPG11	Spatacsin	Mature Astrocytes (FPKM > 6.5, < 8) Fetal Astrocytes (FPKM > 4.5, < 6.5) Microglia/Macrophage (FPKM > 5.25, < 6.5) Oligodendrocytes (FPKM > 5, < 6) Neurons (FPKM ~5.3)	Possibly implicated in gene expression control, protein transport, and/or DNA damage repair	≥21	DNA damage repair	(Zhang et al., 2014) (Chen et al., 2018) (Morgan et al., 2015) (Nakamura et al., 2016)
SOD1	Cu/Zn superoxide dismutase	Neurons (FPKM ~190) Mature Astrocytes (FPKM > 100, < 125) Oligodendrocytes (FPKM > 75, < 115) Fetal Astrocytes (FPKM > 25, < 65) Microglia/Macrophage (FPKM > 20, < 35)	Nuclear/cytosolic protein; Superoxide radical break-down; UPS/ chaperone network	> 200	SOD1 and p62 protein/RNA aggregate formation; Gain in redox function; Axonal transport	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Almad et al., 2016) (Meyer et al., 2014) (Maurel et al., 2018)
SQSTM1	p62	Microglia/Macrophage (FPKM > 15, > 30) Mature Astrocytes (FPKM > 15, < 20) Oligodendrocytes (FPKM > 10, < 20) Neurons (FPKM ~18)	Autophagy adaptor; Glucose metabolism regulation; ERAD pathway; NF-kB pathway	≥10	Autophagy	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Maurel et al., 2018)
TARDBP	TAR DNA-binding protein	Neurons (FPKM ~32) Fetal Astrocytes (FPKM > 17, < 30) Oligodendrocytes (FPKM > 25, < 30) Microglia (FPKM > 20, < 25) Mature Astrocytes (FPKM > 15, < 18)	RNA-binding protein; RNA splicing; Autophagy; transcriptional regulator	≥60	DNA/RNA metabolic changes; Ubiquitin, p62, and TDP-43 aggregate formation	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Maurel et al., 2018) (Serio and Patani, 2018)
TIA1	T-cell restricted intracellular antigen 1	Fetal Astrocytes (FPKM > 14, < 20) Neurons (FPKM ~12)	RNA binding protein; Stress granule (SG) component	≥1	Enhanced phase separation of membrane-less organelles; Delayed SG disassembly; TDP-43 aggregate formation	(Zhang et al., 2014) (Chen et al., 2018) (Mackenzie et al., 2017)
VAPB	VAMP-associated membrane protein B	Fetal Astrocytes (FPKM > 0.15, < 0.32)	Vesicular trafficking; Unfolded protein response pathway	4	Altered binding to mitochondrial proteins; Elevated mitochondrial calcium; TDP43 aggregate formation	(Zhang et al., 2014) (Zufiría et al., 2016) (Maurel et al., 2018) (Boillée et al., 2006) (Kim et al., 2016) (Tsuda et al., 2008)
VCP	Valosin-containing protein (Transitional endoplasmic reticulum ATPase)	Fetal Astrocytes (FPKM > 18, < 14) Neurons (FPKM ~10) Microglia/Macrophage (FPKM > 6, < 14)	Ubiquitin segregase; Protein degradation; UPS/autophagy/ERAD pathways	5	Autophagy; Proteasomal degradation; TDP-43 aggregate formation	(Zhang et al., 2014) (Chen et al., 2018) (Zufiría et al., 2016) (Taylor et al., 2016) (Guerreiro et al., 2015) (Maurel et al., 2018) (Hall et al., 2017)

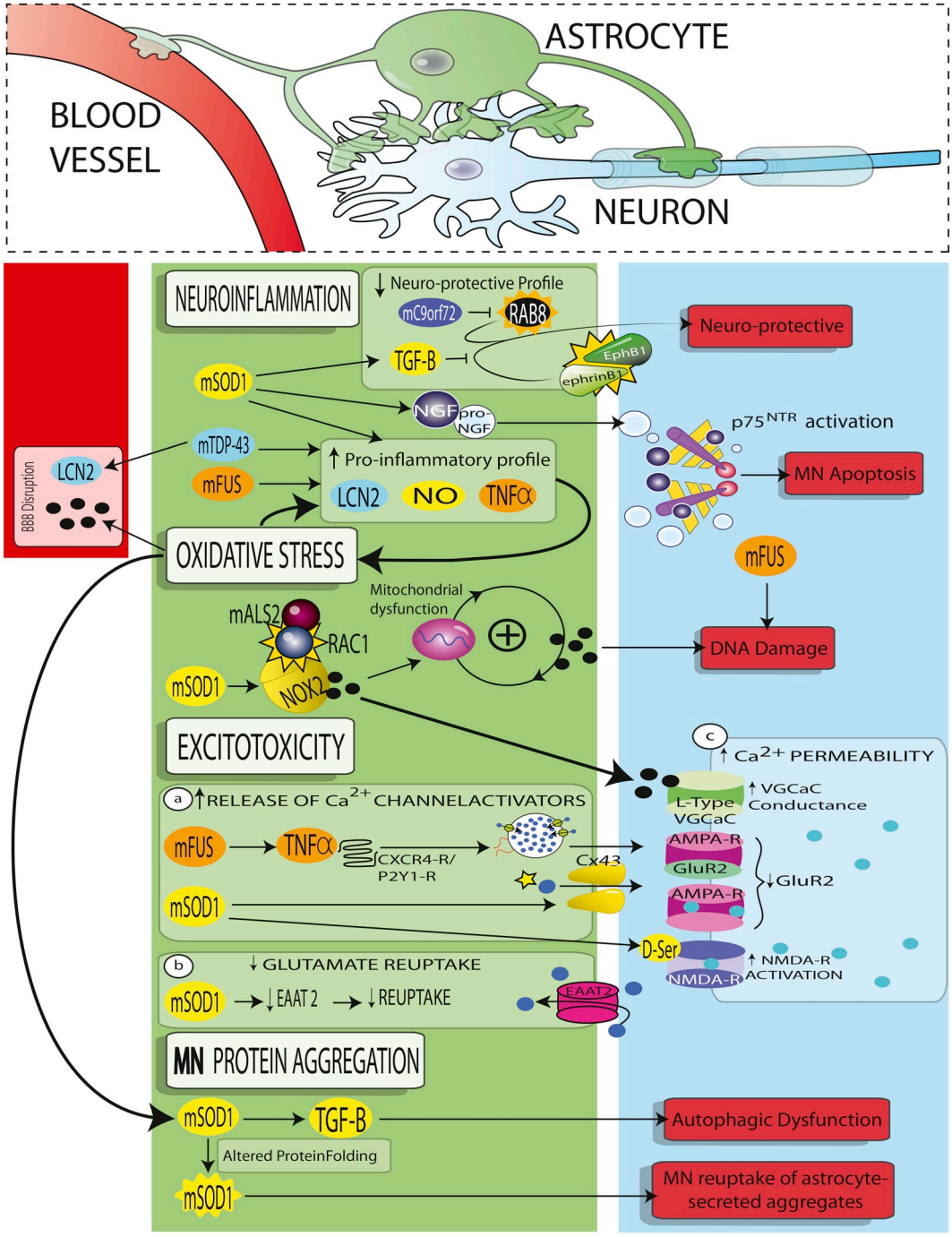

Fig. 2. Mechanisms implicating astrocytes in ALS-related neurodegeneration. (1) Patient astrocytes show enhanced reactivity and heightened neuroinflammation, with astrocytes favoring pro- over anti-inflammatory phenotypes. In addition to being directly toxic to MNs, neuroinflammatory factors promote cytotoxic protein aggregation (i.e. via TGF-Beta) and dysregulate astrocytic control of synaptic glutamate levels (i.e. via TNF-alpha). (2) By generating a number of reactive oxygen and nitrogen species (black dots), diseased astrocytes provoke oxidative stress, which can directly kill MNs via the oxidation of key macromolecules. Oxidative species can also promote further neurodegeneration by disrupting mitochondrial functions (in both astrocytes and MNs) and enhancing astrocytic neuroinflammation. Reactive oxygen species can also drive pathological protein aggregation in MNs and lower MN defenses against excitotoxic death. (3) Due to enhanced Cx-43 expression and increased vesicular release of glutamate-containing vesicles, patient astrocytes show heightened glutamate release (purple dots) (3-a). Together with a decrease in glutamate re-uptake (3-b), this drives the build-up of glutamate at the synapse. The effects of glutamate accumulation are subsequently compounded by the astrocyte-driven enhancement of Ca2+ (blue dots) conductance in MNs (3-c). (4) Astrocytes also incite protein aggregation in MNs by inhibiting MN autophagic capacity and by secreting prion-like protein aggregates.

1988). The 5-10% of ALS patients with a family history of ALS are symptomatically indistinguishable from those presenting with sporadic ALS; 95% of all ALS patients develop TDP-43 aggregates. While ALS patients are genetically diverse, known ALS risk genes converge on several main cellular functions (Table 1, Fig. 2) (Farg et al., 2013; Hart and Gitler, 2012; Kim et al., 2010; Nihei et al., 2012). For example, *ALS2*, *C21ORF2*, *C9ORF72*, *DCTN1*, *NEFH*, *NEK1*, *OPTN*, *PFN1*, *PRPH*, *TUBA4A*, and *VAPB* are implicated in the maintenance of cytoskeletal dynamics/vesicular trafficking and release (Table 1). Many of the remainder are implicated in transcriptional regulation (*ANG*, *FUS*, *SETX*,

SPG11, *TARDBP*), RNA metabolism/transport (*ATXN2*, C9ORF72, *GLE1*, *HNRNPA1*, *HNRNPA2b1*, *MATR3*, *SMN1*, *TARDBP*, *TIA1*), DNA repair (*C21ORF2*, *NEK1*, *SPG11*), protein trafficking/degradation (*CCNF*, *CHMP2B*, *DCTN1*, *ERLIN2*, *FUS*, *SIGMAR1*, *UBQLN2*, *VCP*), mitochondrial function (*CHCHD10*, *SIGMAR1*), endocytosis (*ATXN2*, *CHMP2B*), cell signaling (*ALS2*), and autophagy (*SQSTM1*, *TARDBP, TBK1, VCP, OPTN*). Expression of mutant genes can affect the relative abundance of other genes with similar cellular functions. For instance, expression of *mSOD1*(G93A) in astrocytes results in downregulation of *Igf-1R* (transcriptional regulation; pro-survival), and *Rod1* (RNA metabolism/transport), and upregulation of *Dcn1* (cytoskeletal dynamics/protein transport), *Cx43* (cell signaling), and *Nox2* (autophagy/endocytosis) (Almad et al., 2016; Marchetto et al., 2008; Marden et al., 2007; Vargas et al., 2008b). Still, the mechanisms by which mutations in these genes leads to the selective loss of motor neurons in an age-dependent manner is unclear.

RNAseq data from human neural cell subtypes indicate that many of the genes that have been associated with ALS are expressed in astrocytes at similar or higher levels than in neurons (Table 1) (Zhang et al., 2014). While the majority of previous work examining these genes has focused on MNs, given the range of essential cellular functions that these mutated proteins perform, it seems likely that astrocyte function is also impacted. Astrocyte dysfunction may affect the onset and/or progression of neurodegeneration via several possible, non-mutually exclusive mechanisms: the increased production of neurotoxic inflammatory factors and reactive oxygen species (ROS), the disruption of astrocyte-mediated MN homeostasis, the establishment of astrocyte-mediated excitotoxic conditions coupled with enhanced neuronal susceptibility to excitotoxic death, and the accumulation of pathological protein aggregates (Fig. 2).

3. Astrocyte dysfunction in ALS

The role of astrocytes in ALS onset and progression remains unclear. Early models suggested that astrocytic dysfunction was secondary to neuronal death (Alexianu et al., 2001; Cassina et al., 2008; Simpson et al., 2004; West et al., 2004; Wilms et al., 2010; Yoshihara et al., 2002). The onset of neurodegeneration was thought to arise from neuron cell-autonomous mechanisms, with astrocytes only implicated in further disease progression. Consistent with this, specific removal of mutant SOD1 from astrocytes in the SOD1(G37R) ALS mouse model slows disease progression, but does not impact disease onset (Yamanaka et al., 2008). In contrast, deletion of mutant *SOD1* from astrocytes in the *SOD1*(G85R) mouse delays disease onset and progression (Lino et al., 2002; Wang et al., 2011). Moreover, chimeric mouse studies using SOD1(G93A) demonstrated that neighboring wildtype glia extend the survival of SOD1 mutant (mSOD1) MNs (Clement et al., 2003). These observations are supported by *in vitro* studies of astrocytes expressing disease-specific mutations in *SOD1*—including G93A (Di Giorgio et al., 2007; Nagai et al., 2007), A4V (Haidet-Phillips et al., 2011), and G37R (Marchetto et al., 2008)—as well as astrocytes from sporadic ALS (sALS) patients (Haidet-Phillips et al., 2011; Qian et al., 2017). Taken together, these findings suggest that MN death may be initiated in a non-cell autonomous astrocyte-dependent manner. Similar inconsistencies regarding astrocytic involvement in disease pathogenesis have also been noted upon examination of other ALS-associated genes—including TARDBP and C9ORF72 (Allen et al., 2019; Haidet-Phillips et al., 2013; Koppers et al., 2015; Lagier-Tourenne et al., 2013; Meyer et al., 2014; Tong et al., 2013; Waite et al., 2014). The disparity between these results may be attributable to differences between models (e.g. promotors used to drive mutant gene expression, the use of different disease-associated mutants of the same gene, etc.). More work must be done in order to understand the extent to which astrocytes can be an initial driver of ALS.

Given that astrocyte dysfunction is evident in ALS pathology, understanding the mechanisms by which astrocytes contribute to disease could have major implications for potential drug targets. Importantly, these mechanisms are not isolated from each other, but rather are highly interconnected, often amplifying one another through a series of positive feedback loops. For example, the initiation of the inflammatory response results in the release of ROS from astrocytes, which in turn induces further reactivity in astrocytes, acts as a signaling molecule that affects neuronal susceptibility to excitotoxic stressors, and induces further ROS release from degenerating MNs and newly activated glial cells (Fig. 1). The highly responsive nature of the positive feedback loops implicated in astrocyte-driven neurodegeneration has made it difficult to distinguish between the initiating and progressive causes of neurodegeneration.

4. The utility of hiPSCs in examining astrocyte-related ALS pathology

Murine ALS models have significantly enhanced our understanding of several risk-associated mutations, but fail to capture the complexity of human genetics. Specifically, the structural and functional differences between human and rodent astrocytes make it difficult to generalize conclusions pertaining to astrocyte-related pathology that are drawn from rodent models. Human astrocytes, for example, are larger and have 10-fold more glial fibrillary acidic protein (GFAP)-positive primary processes than astrocytes found in rodents (Oberheim et al., 2009). Unlike rodent astrocytes, human astrocytes respond to glutamatergic and purinergic receptor agonists with a transient increase in cytosolic Ca^{2+}. Rodent astrocytes are also less structurally and functionally diverse than human astrocytes (Oberheim et al., 2009, 2012). This is a significant detriment to rodent models, as this diversity may explain the highly localized nature of neuronal death that is observed in many neurodegenerative diseases (reviewed by Schitine et al., 2015). Finally, in the context of ALS, it is important to note that human and rodent astrocytes also differ in the relative expression of several ALS-related genes when compared with neurons (Oberheim et al., 2009, 2012; Zhang et al., 2014, 2016). When combined with CRISPR-mediated genome editing, patient-derived hiPSCs represent a powerful tool for assessing the impact of ALS-specific mutations in varied genetic backgrounds. Patient-derived hiPSCs can also be used to study those sporadic ALS cases in which no known mutations have yet been identified. Thus, hiPSCs represent a valuable tool in the study of astrocyte-related ALS pathology.

Many protocols have been established for the generation of astrocytes from patient-derived hiPSCs and neural progenitor cells (NPCs) (Emdad et al., 2011; Santos et al., 2017; Shaltouki Atossa et al., 2013; Tcw et al., 2017). The earliest protocols, which took as long as 180 days, generated relatively uniform populations of astrocytes by progressing through neuroepithelial cell intermediates that were patterned with anterior/posterior/ventral (fibroblast growth factor 8/retinoic acid/sonic hedgehog) patterning molecules (Emdad et al., 2011; Krencik et al., 2011). Conversely, more recent protocols yield functional astrocytes in as little as 30 days, though these methods are as yet unable to produce pure populations of distinct astroglial subtypes (Shaltouki Atossa et al., 2013; Tcw et al., 2017). Most recently, via the overexpression of two transcription factors (*SOX9* and *NFIB*), astrocytes can be generated in as little as 2 weeks (Canals et al., 2018). hiPSC-derived astrocytes display several astrocyte-specific and disease-relevant functionalities, such as phagocytic ability and neuroinflammatory response (Tcw et al., 2017; Santos et al., 2017).

To date, hiPSCs have been generated from patients with a variety of mutations in ***SOD1*** (Bhinge et al., 2017; Chen et al., 2014; Jeon et al., 2018; Kiskinis et al., 2014; Li et al., 2015; Wainger et al., 2014; Wang et al., 2017), ***C9ORF72*** (Donnelly et al., 2013; Egawa et al., 2012; Haeusler et al., 2014; Li et al., 2015; Liu et al., 2017; Madill et al., 2017; Meyer et al., 2014; Sareen et al., 2013; Wen et al., 2014; Westergard et al., 2016), ***TARDBP*** (Alami et al., 2014; Barmada et al., 2014; Bilican et al., 2012; Serio et al., 2013; Zhang et al., 2013), ***FUS*** (Ichiyanagi

et al., 2016; Japtok et al., 2015; Lenzi et al., 2015, 2016; Li et al., 2015; Wainger et al., 2014; Wang et al., 2017), ***ANG*** (Li et al., 2015), ***FIG4*** (Li et al., 2015), ***VAPB*** (Mitne-Neto et al., 2011), and ***VCP*** (Hall et al., 2017; Li et al., 2015). A smaller number of these hiPSCs have yet been differentiated into astrocytes: ***mSOD1*** (Almad et al., 2016; Tyzack et al., 2017), ***mC9ORF72*** (Donnelly et al., 2013; Liu et al., 2017; Madill et al., 2017; Meyer et al., 2014), ***mTARDBP*** (Barmada et al., 2014; Serio et al., 2013), ***FUS*** (Qosa et al., 2016), and ***VCP*** (Hall et al., 2017). The results of these studies, which will be discussed throughout the following sections, have already begun to inform our understanding of astrocyte-related processes in ALS.

Critically, as with other hiPSC-derived cell-types, hiPSC-derived astrocytes display fetal transcriptional profiles (Reviewed by Ravaioli et al., 2018). This complicates the application of hiPSCs for the study of age-related disorders such as ALS. While methods to address this issue do exist, they are limited in their ability to properly recapitulate the normal aging process. For example, progerin-overexpression induces some age-related phenotypes, but does not facilitate maturation of neural cell types (Miller et al., 2013). While extended culture can improve the maturity of hiPSC-derived astrocytes, even organoid-based differentiations of up to a year only approach neonatal transcriptomic profiles (Sloan et al., 2017). Alternatively, transcription-factor induction from fibroblasts maintains epigenetic age, and have been applied to studies of MNs in ALS (Liu et al., 2016; Son et al., 2011; Zhang et al., 2017a, b); similar protocols for astrocyte induction have been reported but not yet applied to ALS (Caiazzo et al., 2014; Tian et al., 2016). Nonetheless, hiPSC models well capture the genetic elements of disease risk (if not the disease state itself) and yield useful insight into the origins of ALS.

5. The neurotoxic effects of neuroinflammation

In healthy brain tissue, neuroinflammation occurs as part of a protective homeostatic reaction to acute states. For example, the activation of the immune response following an infection or injury can trigger the onset of neuroinflammation (reviewed by Dantzer et al., 2008 & Tohidpour et al., 2017). This communication between the peripheral immune system and the brain is crucial for the induction of normal, adaptive responses to infection or injury (e.g. fever, fatigue, etc.) that are necessary for recovery (Serrats et al., 2010; Hansen et al., 2001; Laflamme et al., 1999; Ching et al., 2007). Moreover, neuroinflammation coincides with the onset of tissue repair responses. However, the neuroinflammation that results from immune activity – characterized by the short-lived activation of both astrocytes and microglia – is highly-regulated and transient (Norden et al., 2016).

Neuroinflammation can be identified by increased abundance of pro-inflammatory biomarkers, such as cytokines (IL-1β, IL-6, and TNF-α), chemokines (CCL2, CCL5, and CXCL1), and secondary messengers such as Nitrous Oxide (NO), prostaglandins, and ROS, in CNS tissue (Chao et al., 1996; Meeuwsen et al., 2003). At the cellular level, the initiation, maintenance, and regulation of neuro-immune responses is accomplished by activated microglia and astrocytes, each contributing to distinct and complementary aspects of inflammation. The development of *reactive gliosis* – the accumulation of the morphologically and functionally altered glial cells that are involved in the neuro-immune response – is a key feature of neuroinflammation. During an acute neuro-immune response, microglia can adopt an “M1” pro-inflammatory phenotype or “M2” protective/anti-inflammatory function depending on the type of insult (Reviewed by Cherry et al., 2014). Similarly, reactive astrocytes can both contribute to (“A1”) and prevent (“A2”) damage from inflammation, and the specifics of destructive and protective reactive astrocytes will be discussed presently (Brambilla et al., 2005; Colombo et al., 2012; Hindinger et al., 2012; Linker et al., 2010; Nobuta et al., 2012).

5.1. Neuroinflammation contributes to neurodegeneration

Despite its contribution to cell repair mechanisms, rampant neuroinflammation is observed in several neurodegenerative diseases, including Alzheimer’s disease (AD), multiple sclerosis (MS), Parkinson’s disease (PD) (Ellwardt and Zipp, 2014; Heneka et al., 2015; Tansey and Goldberg, 2010), and ALS (Morello et al., 2017). Such neuroinflammation is not evident in asymptomatic individuals carrying ALS-associated mutations, demonstrating that it is a characteristic that is necessarily linked to disease development (Oeckl et al., 2018). Damaging pro-neuroinflammatory molecules, such as NO and ROS, can indirectly induce MN degeneration via activation of intracellular signaling cascades that alter key cellular functions (Pintado et al., 2017). These findings suggest that alterations to the regulated balance between the inflammatory and protective components of neuroinflammation can result in a cytotoxic microenvironment and subsequent neurodegeneration (Chao et al., 1996; Downen et al., 1999; McCoy et al., 2006).

A prominent hypothesis regarding the role of neuroinflammation in neurodegeneration is that neurotoxic inflammation results, in part, from a high ratio of M1/M2 reactive microglial populations—a trait that occurs even in normal aging (Frank et al., 2006; Kigerl et al., 2009; Kumar et al., 2013; Zhang et al., 2017a, b). Astrocytes display a similar imbalance between cellular phenotypes in disease pathology (Liddelow et al., 2017). Consequently, deactivation of the pro-inflammatory astrocyte signaling cascade (NF-kB inhibition) minimizes the extent of tissue injury following an inflammatory response (Brambilla et al., 2005, 2009, 2012). However, it remains unclear whether this aberrant inflammatory response is self-generated or initiated following neuronal damage of unknown origin. Regardless, it is clear that neurodegeneration and inflammation promote each other through a positive feedback loop: inflammatory cytokines induce neurodegeneration, while MN decay incites further inflammation (Fig. 1) (Meeuwsen et al., 2003). This feedback mechanism may contribute to the progressive nature of ALS. However, the presence of reactive astrocytes and microglia before the onset of motor symptoms in mouse models of ALS suggests that astrocyte dysfunction plays a more inciting role in disease pathology (Bruijn et al., 1997; Levine et al., 1999). For example, astrocytes can induce neuroinflammation through the release of pro-inflammatory factors that increase blood-brain barrier (BBB) and blood-spinal cord barrier (BSCB) permeability, indicating a potential mechanism for astrocyte involvement in disease onset (Abbott, 2000; Winkler et al., 2014).

5.2. Toxic gain-of-function mutations contribute to neuroinflammation in ALS

Several ALS-associated genes that are expressed in astrocytes are implicated in hyperactive neuroinflammatory responses in ALS patients. Astrocytes expressing *mSOD1*, for instance, display an enhanced release of neurodegenerative inflammatory factors and pro-inflammatory mediators (Chao et al., 1996; Dawson et al., 1993; Gong et al., 2000; Meeuwsen et al., 2003; Pintado et al., 2017). Interestingly, gliosis is suppressed when autophagy is conditionally knocked out in MNs in the SOD1 G93A mouse model (Maniatis et al., 2019; Rudnick et al., 2017), suggesting a possible mechanism for MNs to promote inflammation in neighboring glia. *SOD1* mutations attenuate neuronal responses to protective aspects of inflammation through altered TGF-β signaling, which is observed in *SOD1*(G93A) mice (Phatnani et al., 2013) as well as in ALS patients (Endo et al., 2015). Prolonged release of TGF-β1 from chronically reactive astrocytes (both wildtype and ALS-related SOD1 mutant) drives the development of ALS-like protein inclusions *in vitro* and induces cell death in otherwise healthy MNs (Tripathi et al., 2017). Furthermore, reactive murine astrocytes harboring the *SOD1*(G93A) mutation release increased levels of nerve-growth factor (NGF) (Ferraiuolo et al., 2011). Although NGF is neuroprotective in non-pathological conditions, its low-affinity binding to

p75 neurotrophin receptors ($p75^{NTR}$) induces apoptosis. Interestingly, aberrant NGF processing in mSOD1 astrocytes leads to $p75^{NTR}$ upregulation in nearby neurons, an outcome that is also noted in spinal MNs from ALS patients (Ferraiuolo et al., 2011). Subsequent apoptosis can be prevented by application of NGF or $p75^{NTR}$ blocking-antibodies (Pehar Mariana et al., 2004; Turner et al., 2004, p. 7). Still, these toxic effects of SOD1 mutations are not ubiquitous—not all SOD1 mutations, when selectively expressed in astrocytes, are enough to drive MN degeneration (Gong et al., 2000; Nagai et al., 2007). Finally, by using hiPSC-derived astrocytes harboring the *SOD1*(A4V) mutation to model intercellular interactions at the BBB, it has been demonstrated that patient astrocyte dysfunction may induce alterations to the BBB (Qosa et al., 2016). Interestingly, hiPSC-derived astrocytes expressing *FUS* (H517Q) induced similar effects (Qosa et al., 2016).

Selective expression of mutant TDP-43 (Q331K) in glial cells promotes an increased level of age-dependent astrocyte activation (Ditsworth et al., 2017), but the mechanism for this enhanced neuroimmune response is unclear. TDP-43 is involved in transcriptional regulation and RNA metabolism, and one explanation is that TDP-43 mutants favor expression of pro-inflammatory genes (Table 1) (Reviewed by Lagier-Tourenne et al., 2010; Swarup et al., 2011). Lipocalin 2 (Lcn2) protein is one such pro-inflammatory factor that is secreted by reactive astrocytes expressing the patient-specific TDP-43(M337V) mutant (Tong et al., 2013), is toxic to neurons in a non-specific manner (Song et al., 2014), and linked to neuro-inflammatory response (Jin et al., 2014). Lcn2 also promotes permeabilization of the BBB (Egashira et al., 2016). However, Lcn2 secretion from reactive astrocytes has, thus far, only been observed in rodent models (Lee et al., 2009). Given that hiPSC-derived astrocytes harboring *TARDBP* mutations do not induce MN degeneration, future studies should examine whether LCN2 secretion is observed from $mTARDBP^{+}$ patient-derived astrocytes (Serio et al., 2013).

The *C9ORF72* hexanucleotide repeat expansion—the most pervasive risk-associated gene in ALS pathology—has also been implicated in the dysregulated neuroinflammation seen in ALS patients (DeJesus-Hernandez et al., 2011; Renton et al., 2011). C9ORF72 is thought to play a role in endosomal trafficking and the lysosomal autophagy pathway (Table 1). It acts as a guanidine nucleotide exchange factor (GEF) for Rab8, which is also highly expressed in astrocytes (fetal) (Sellier et al., 2016; Zhang et al., 2014) and involved in protective, non-inflammatory signaling (Wall et al., 2017). In general, C9ORF72 expansions may promote neurodegeneration through two possible mechanisms: 1) haploinsufficiency of the C9ORF72 gene (loss-of-function, LOF) (DeJesus-Hernandez et al., 2011; Waite et al., 2014), and/or 2) toxicity of transcribed and/or translated elements of the mutant intronic region of the gene (GOF) (Reviewed by La Spada and Taylor, 2010). Unlike GOF phenotypes that can directly induce neurotoxicity, *C9ORF72* LOF appears to be more relevant to the neuroinflammatory component of ALS, gradually altering the extracellular environment over the course of an animal's lifetime. For example, complete KO of *C9ORF72* in mice results in heightened age-related inflammation, including neuroinflammation (Atanasio et al., 2016; Koppers et al., 2015; O'Rourke et al., 2016). The widening gap between patients' and controls' neuroinflammatory responses with age may be relevant in considering the age-related nature of ALS pathology.

The exact role neuroinflammation plays in the pathogenesis of ALS remains unclear even as evidence of its involvement increases. Neuroinflammation may be a byproduct of tissue damage from the disease, or may even be protective, attempting to promote tissue repair early in disease progression (Endo et al., 2015; Hu et al., 2012). The bifunctional roles of neuro-immune cells may well explain the emergence of such diametrically contrasting conclusions, and it is possible that reactive astrocytes play dual roles in disease pathology given the differences in function between inflammatory A1 and protective A2 astrocyte populations. The increased presence of A1 astrocytes in postmortem CNS tissue in ALS (Liddelow et al., 2017) is consistent with neuroinflammation that could lead to MN death. As the disease progresses, the relative decrease in cells displaying A2 protective phenotypes compounds the directly neurotoxic effects of A1 cells.

Experiments using hiPSC-derived cells indicates that specific ALS-related mutations can either block protective A1 phenotypes or generate toxic A2 phenotypes. For example, upregulation of EphB1 in degenerating MNs induces astrocytes to take on protective phenotypes (Tyzack et al., 2017). Disruptions in the EphB1-ephrin-B1 pathway in hiPSC-derived astrocytes from patients harboring *SOD1*(D90A) mutations result in a relative decrease in the number of reactive astrocytes with neuroprotective phenotypes. In accordance with this, hiPSC-derived astrocytes from sporadic ALS patients transplanted into mice display neuroinflammatory reactive phenotypes and are toxic to surrounding neurons, whereas control astrocytes do not (Qian et al., 2017). However, because the resultant neurodegeneration was ubiquitous, this did not explain the selective toxicity observed in MN populations. Thus, future work using hiPSC-derived astrocytes should focus on protocols that generate astrocytes that closely mimic the A1 and A2 phenotypes observed *in vivo*, and whether mutations implicated in ALS fundamentally alter the function of these distinct astrocyte populations.

6. The generation and proliferation of oxidative stress

Endogenous ROS are generally a byproduct of mitochondrial enzymes (Cadenas et al., 1977). In small amounts, free radicals serve as important signaling molecules in the establishment of long term potentiation (LTP), the myelination of highly active neurons, and angiogenesis in damaged brain tissue (Atkins et al., 1997; Atkins and Sweatt, 1999; McCann and Roulston, 2013; Wang et al., 2004; Zimmerman et al., 2005). In large quantities, however, ROS are cytotoxic – capable of oxidizing proteins, DNA, and other essential molecules. ROS contribute to neurodegeneration by driving inflammation, pathological protein aggregation, mitochondrial dysfunction, activation of apoptotic pathways, and disruption the BBB (Fig. 2) (Cassina et al., 2008; Cohen et al., 2012; Haorah et al., 2007; Javed et al., 2012; Ryter et al., 2007; Shodai et al., 2013). Finally, by reacting with pro-inflammatory NO, which increases as part of the hyper-active neuroinflammatory response, ROS can be converted into cytotoxic reactive nitrogen species (RNS) (Kempuraj et al., 2016). Thus, the balance between the production and breakdown of ROS is crucial.

6.1. ROS are associated with aging and neurodegeneration

Oxidative damage is a nearly ubiquitous feature in post mortem brain and spinal cord samples from ALS patients (Shaw et al., 1995a, 1995b; Shibata et al., 2001). Accordingly, disease models have demonstrated that ROS increase with age and are direct drivers of MN death (Cassina et al., 2008; Cohen et al., 2012; Haorah et al., 2007; Javed et al., 2012; Ryter et al., 2007; Shodai et al., 2013). DNA damage resulting from oxidative stress, as measured by 8-hydroxy-2′-deoxyguanosine (8-OHdG) accumulation, has been observed in postmortem spinal cord and motor cortex from ALS patients (Ferrante et al., 1997). Moreover, 8-OHdG accumulation in cerebrospinal fluid and urine increases during the course of disease. It has been proposed that DNA damage contributes to fALS and sALS pathogenesis (Reviewed by Coppedè and Migliore, 2015). Indeed, alterations to DNA damage response signaling pathways causes neurodegeneration in hiPSC-derived motor neurons (Naumann et al., 2018). However, whether the increase in ROS occurs before disease onset or is secondary to initial MN degeneration remains uncertain. It is important to note that ROS-induced mitochondrial dysfunction promotes further ROS production, initiating a positive feedback loop, suggesting that the accumulation of ROS contributes to the progressive nature of ALS (Fig. 2).

6.2. Astrocyte dysfunction contributes to ROS Build-up

Paradoxically, reactive astrocytes contribute to the production of ROS while also scavenging ROS (Schreiner et al., 2015), suggesting that a balance between protective and inflammatory reactive astrocyte phenotypes may be crucial for the maintenance of a neuron-friendly extracellular environment. A deeper investigation into how astrocytes contribute to the normal age-related increase in ROS production, and how this differs between patients and controls, may offer further insight into how and why ROS increase with aging and in ALS pathology. Present theories mainly highlight mitochondrial dysfunction in patient cells as a potential explanation for the disease-related increase in ROS production. Interestingly, much like ROS production, mitochondrial dysfunction is progressively enhanced over the course of normal aging, and is exacerbated in ALS and other neurodegenerative diseases (Cassina et al., 2008; Corral-Debrinski et al., 1992; Johri and Beal, 2012; Said Ahmed et al., 2000). Drug-induced mitochondrial disruption in wildtype astrocytes incites MN degeneration upon co-culture (Cassina et al., 2008), and the stimulation of antioxidant pathways in astrocytes delays symptomatic onset, and extends survival in animal models (Vargas et al., 2008a). Further examination of these pathways in hiPSC-astrocytes may clarify whether patient lines inherently produce more ROS and/or are more prone to DNA damage, as well as the impact patient astrocytes have on motor neuron function.

6.3. Risk-Associated Genes and Astrocyte contribution to ROS accumulation

Several ALS-associated genes have been implicated in disease-related mitochondrial dysfunction. For example, the SOD1 enzyme, which typically functions as a potent antioxidant (Reviewed by Kim, 2014), aberrantly accumulates in the mitochondria of neural cells from ALS patients and murine models. The extent of such SOD1 accumulation increases with age, and incites mitochondrial dysfunction and increased ROS production (Liu et al., 2004; Takeuchi et al., 2002; Velde et al., 2008; Zetterström et al., 2007). Interestingly, an over-oxidized form of wildtype SOD1, which damages mitochondria and is prone to aggregation, has been observed in a subset of sporadic ALS patients (Guareschi et al., 2012). Thus, post-translational modifications may drive aggregation of SOD1 (Bosco et al., 2010; Ezzi et al., 2007; Guareschi et al., 2012; Schmitt and Agar, 2017), indicating that the localization and/or oxidation state of SOD1 may incite mitochondrial dysfunction (Said Ahmed et al., 2000; Xu et al., 2018).

Other ALS-related genes code for proteins that are critical for proper mitochondrial function (*C21ORF2*, *CHCHD10, SIGMAR1*, and *VAPB* - Table 1). CHCHD10 is a key regulator of potentially ROS-generating mitochondrial oxidative phosphorylation reactions (Purandare et al., 2018). The endogenous expression or forced overexpression of mutant *CHCHD10* (*mCHCHD10*) (S59L) in HeLa cells and patient fibroblasts disrupts mitochondrial structure (Bannwarth et al., 2014; Genin et al., 2016). *CHCHD10* disease variants (G66V and P80L) also display faulty interactions with cytochrome c oxidase and other mitochondrial proteins, resulting in reduced respiration and increased ROS. To the same effect, mutations in *SIGMAR1* disrupt mitochondrial function, leading to an increase in ROS production and autophagic cell death (Fukunaga et al., 2015; Shinoda et al., 2015; Watanabe et al., 2016). As a receptor that is enriched at the mitochondrial-associated endoplasmic reticulum membrane, SIGMAR1 is important for mitochondrial homeostasis (Hayashi and Su, 2007; Pal et al., 2012). VAPB, which is also enriched at the mitochondrial-associated endoplasmic reticulum membrane, is involved in mitochondrial Ca^{2+} uptake (De Vos et al., 2012). The expression of ALS mutant VAPB (P56S) results in mitochondrial damage. Importantly, the relatively high expression of SIGMAR1 and VAPB in fetal astrocytes suggests that further study of mutations in these genes may shed light on the developmental underpinnings of mitochondrial dysfunction in ALS. Finally, although not mitochondrial proteins, the mTDP-43 and C9ORF72 repeat has also been associated with mitochondrial dysfunction and the upregulation of oxidative stress markers (Braun et al., 2011; Duan et al., 2010; Lopez-Gonzalez et al., 2016; Zhan et al., 2015).

In hiPSC-derived MNs, dipeptide repeat proteins (DPRs)—encoded by the C9ORF72 hexanucleotide repeat expansions—preferentially bind to mitochondrial ribosomal proteins (Lopez-Gonzalez et al., 2016) thereby compromising mitochondrial function; it is likely DPRs have similar effects in astrocytes. Mutations in VCP (both ALS- and non-ALS-related) alter mitochondrial function in hiPSC-derived cortical neurons (Ludtmann et al., 2017) and increase ROS production in hiPSC-derived glial progenitor cells (Hall et al., 2017). Finally, the dysregulation of several mitochondrial genes in hiPSC-derived MNs from sALS patients suggests that mitochondrial dysfunction is a feature observed across ALS patient subgroups, though additional work must be done in order to establish whether this is also the case in astrocytes (Alves et al., 2015).

The pathological accumulation of ROS may not be solely due to mitochondrial dysfunction. For example, ROS produced by NADPH oxidase 2 (NOX2) enzymes is heightened in ALS patients, as NOX2 expression is progressively upregulated over time in *SOD1(G93A)* mice (Marden et al., 2007; Wu et al., 2006). Heterozygous deletion of NOX2 in *SOD1(G93A)* mice slows the progression of ALS-like phenotypes and increases animal survival, indicating that NOX2 suppression is a potential therapeutic target to slow disease progression (Reviewed by Bedard and Krause, 2007; Marden et al., 2007; Wu et al., 2006). The upregulation of NOX2 in SOD1 ALS mouse and primary astrocyte models (Marchetto et al., 2008; Wu et al., 2006) induces astrocyte reactivity and selective MN toxicity (Marchetto et al., 2008). Moreover, mSOD1 can also promote NOX2 activity by inhibiting Rac1 GTPase activity (Harraz et al., 2008). Interestingly, *ALS2*, which has been associated with juvenile ALS, is also a potent activator of RAC1 (Topp et al., 2004; Yang et al., 2001), although the effect of mutant *ALS2* in astrocytes has not been examined.

These findings suggest that heightened ROS production is genetically encoded, and may even precede neurodegeneration (Park et al., 2009). Unfortunately, many of these genes, with the exception of *SOD1* and *VCP*, have not yet been examined for their specific impact on astrocyte ROS production. This is especially crucial as mitochondrial proteins may display cell-type-specific heterogeneity in their contribution to ROS-related toxicity (Liu et al., 2004). Given that the aforementioned genes are relatively highly expressed in astrocytes, hiPSC models may enhance our understanding of how alterations to the functional development of astrocytes lays the foundation for ROS pathology later in life.

7. Excitotoxicity in ALS

Excitotoxic death is typically driven by the prolonged exposure of neurons to high levels of glutamate. The effects of excitotoxicity are mediated through Ca^{2+}, which can be cytotoxic in large quantities. Accordingly, blocking Ca^{2+} signaling protects motor neurons (Beers et al., 2001; Van Den Bosch et al., 2002). Because of its ability to promote cell death in highly localized regions, the impact of excitotoxic mechanisms on ALS pathology is of particular interest, given that cell death is largely restricted to a particular neuronal population.

7.1. Astrocyte dysfunction contributes to excitotoxic conditions

Astrocytes are involved in the homeostatic-maintenance of extracellular ion and glutamate concentrations, which are crucial for ensuring normal neuronal excitability (Dehnes et al., 1998; Karwoski et al., 1989). In ALS pathology, this key function of astrocytes may be disrupted (Shaw et al., 1995a, 1995b; Spreux-Varoquaux et al., 2002). Taken together with the fact that the only medication to date that is prescribed for the treatment of ALS is Riluzole—an inhibitor of

presynaptic glutamate release—this highlights that excitotoxic cell death is involved in ALS-related neurodegeneration. Of course, given that Riluzole is limited in its capacity to delay disease progression, this is likely not the only factor involved in MN death (Bensimon et al., 1996).

Astrocytes may promote excitotoxic conditions through decreased capacity for glutamate reuptake (Guo et al., 2003; Howland et al., 2002; Rothstein et al., 1992, 1995) or by glutamate release (Bezzi et al., 1998; Porter and McCarthy, 1996). Decreased expression of the astrocyte glutamate transporter EAAT2 has been observed in the brains and spinal cords of ALS patients (Fray et al., 1998; Rothstein et al., 1992, 1995). Gliotransmission, the astrocytic release of glutamate, may be altered in ALS patients. In the healthy brain, gliotransmission is thought to bolster synaptic plasticity (Reviewed by Schipke and Kettenmann, 2004), although the extent to which gliotransmission occurs in humans remains in question (Sloan and Barres, 2014). *In vitro* animal models suggest several potential mechanisms of glutamate release by astrocytes (Bezzi et al., 2001, 2004; Duan et al., 2003; Kimelberg et al., 1990; Takano et al., 2005; Ye et al., 2003) (Fig. 2). For example, the activation of astrocytic CXCR4 chemokine receptors or purinergic $P2Y_1$ receptors by pro-inflammatory mediators—including those produced by astrocytes, such as TNFα—induces Ca^{2+}-mediated glutamate exocytosis in astrocytes (Bezzi et al., 1998, 2001; Domercq et al., 2006; Santello et al., 2011). In accordance with this mechanism, the overproduction of pro-inflammatory factors, as is seen in pathological neuroinflammation, is accompanied by an overall shift in synaptic glutamate regulation (Bezzi et al., 1998, 2001). Astrocytes can also release glutamate—as well as ATP—through connexin-43 (Cx-43) hemichannels (Ye et al., 2003). In addition to the obvious implications of this on excitotoxicity, glutamate and ATP released from astrocytes function together to increase permeability of neuronal pannexin-1 hemichannels for ATP, subsequently inducing apoptotic cell death in MNs (Almad et al., 2016; Orellana et al., 2011). Importantly, ALS patients show heightened levels of Cx-43 in CNS tissue, and these results have been recapitulated in mice harboring the *SOD1*(G93A) mutation (Almad et al., 2016).

MNs may be more susceptible to excitotoxicity than other neurons even in healthy controls. There are a number of reasons for this, including a relatively low expression of GluR2-containing AMPA/kainate channels, rendering MNs more permeable to Ca^{2+}. MNs also express sparse levels of intracellular Ca^{2+}-buffering proteins (Ince et al., 1993; Takuma et al., 1999; Van Damme et al., 2002; Vandenberghe et al., 2000). Under non-pathological conditions, astrocytes modulate MN excitability, in part by regulating the number of GluR2-containing AMPA receptors expressed by MNs (Van Damme et al., 2007). Yet ALS patients display enhanced MN hyper-excitability, even in the pre-symptomatic and early stages of ALS pathology, suggesting a loss of such astrocytic modulatory input (Van Damme et al., 2007; Vucic et al., 2008; Vucic and Kiernan, 2006). Moreover, the heightened release of D-serine—an endogenous co-activator of NMDA receptors that is elevated in familial and sporadic ALS patients—by diseased astrocytes further enhances Ca^{2+} influx into MNs (Mitchell et al., 2010; Sasabe et al., 2007, 2012). Finally, NOX2-derived ROS (e.g. from astrocytes) can increase the conductance of L-type voltage gated calcium channels and contribute to MN hyperexcitability (Wang et al., 2004; Zimmerman et al., 2005). Thus, it appears that astrocytes are not only pertinent to the generation of excitotoxic conditions, but also are associated with increased MN sensitivity upon exposure to these conditions.

Hyperexcitability of MNs has been recapitulated in hiPSC-derived MNs from patients with SOD1, FUS, and C9ORF72 mutations (Wainger et al., 2014; Selvaraj et al., 2018). However, whether astrocytes contribute to hyperexcitability of hiPSC-derived MNs *in vitro* remains relatively unexplored. Systematic analysis of MN excitability when co-cultured with hiPSC-derived astrocytes from various ALS patient backgrounds could elucidate which mutations impact MN excitability through a non-cell autonomous mechanism.

8. Protein aggregation in ALS

The presence of protein aggregates (also referred to as inclusions) is a well-documented pathological feature of ALS and other neurodegenerative diseases (Durham et al., 1997; Jang et al., 2017; Johnson et al., 2009; Jucker and Walker, 2013; Mori et al., 2013; Schwartz et al., 2014). Indeed, up to 95% of all ALS patients have ubiquitinated inclusions that contain TDP-43 in the CNS (Naumann et al., 2006); protein inclusions are observed in both neurons and glia in human postmortem tissue (Forsberg et al., 2011; Mackenzie et al., 2007; Nishihira et al., 2008). TDP-43 is a ubiquitously expressed heterogeneous nuclear ribonucleoprotein (hnRNP) important for RNA metabolism. Mislocalization of TDP-43 from the nucleus to the cytoplasm and its subsequent sequestration within aggregates has been proposed as loss-of-function mechanism that disrupts its function in RNA metabolism (Scotter et al., 2015). Inclusions may also contain other RBPs and related hnRNPs (Conlon et al., 2018). Innovative computational approaches have proposed several new RBPs that could be mislocalized in ALS (Bakkar et al., 2018), all of which could be tested in hiPSC models.

The genesis and spread of inclusions remain an intensely studied topic and is beyond the scope of this review. However, recent studies suggest several possibilities. First, protein aggregation may be mediated by the interaction of so-called low complexity domains (LCDs) involved in liquid-liquid phase transitions necessary for membrane-less organelle formation (reviewed by Taylor et al., 2016). P bodies, stress granules, and RNA transport granules are all examples of membrane-less organelle structures that assemble and disassemble in response to stimuli. These highly dynamic structures are critical components of normal RNA metabolism. LCDs are common in RNA binding proteins (e.g. FUS, TDP-43, hnRNPs), which may render them more susceptible to persistent and aberrant aggregation (Purice and Taylor, 2018). Second, ALS mutations identified in genes involved in autophagy (Table 1) indicate that dysregulation of protein homeostasis contributes to aggregation. Autophagy, a major pathway for breaking down organelles, is important for the normal recycling of stress granules. Lastly, protein aggregates may be nucleated by DNA damage. DNA breaks have been linked to the mislocalization and aggregation of FUS in hiPSC-derived motor neurons (Naumann et al., 2018). Persistent protein aggregates may be toxic to cells; several mechanisms have been proposed (Gao et al., 2018; Scotter et al., 2015) that result in alterations to key components of cellular homeostasis, gene expression, and signal transduction (reviewed by Kim and Taylor, 2017).

8.1. Aggregation in hiPSC-derived motor neurons and astrocytes

ALS-related protein aggregation phenotypes observed in mice and human postmortem tissue have been difficult to recapitulate in hiPSC-derived MNs (reviewed in Lee and Huang, 2017). Even when using patient lines harboring mutations in TDP-43, TDP-43 inclusions in hiPSC-derived MNs are inconsistent across studies (Egawa et al., 2012; Fujimori et al., 2018; Seminary et al., 2018). However, inclusions have been observed in C9ORF72 (Donnelly et al., 2013; Sareen et al., 2013), SOD1 (Chen et al., 2014), and FUS (Purice and Taylor, 2018) patient lines. Repeat-associated non-ATG (RAN) translation of RNA from the C9ORF72 repeat produces several dipeptide repeat proteins (DPRs) that are aggregation-prone and proposed to interfere with nucleocytoplasmic transport (Reviewed by Yuva-Aydemir et al., 2018) and heterochromatin structure (Zhang et al., 2019). Consistent aggregation phenotypes, particularly in cells derived from sALS patients, may require more 'aged' cells (discussed in Future Directions) or other manipulation to mimic age-related phenotypes.

Few studies have examined whether aggregation occurs in glia derived from ALS hiPSCs. Cytoplasmic mislocalization of M337V TDP-43 has been observed in patient hiPSC-astrocytes as well as control astrocytes transduced with other mutant TDP-43 (Serio et al., 2013). These astrocytes showed decreased viability, but unlike SOD1

astrocytes, they did not impact MN survival in co-culture experiments. Given the divergent function of MNs and astrocytes, the repertoire of RNAs and LCD-containing RNA binding proteins found within membrane-less organelles in astrocytes may be different than in MNs. Unlike motor neurons that ultimately die during the course of disease, astrocytes proliferate and contribute to an inflammatory response. Thus, hiPSC-astrocytes could be used to model perturbations in astrocyte function as a result of intrinsic protein aggregation. For example, protein aggregate formation might induce a more toxic astrocyte state rather than cell death.

Murine models of ALS indicate astrocyte-dependent, non-cell autonomous impacts on MN degeneration *in vivo* (Clement et al., 2003) and *in vitro* (Phatnani et al., 2013). hiPSCs provide an ideal platform to investigate non-cell autonomous effects *in vitro* and have largely supported observations from murine models (Haidet-Phillips et al., 2011; Marchetto et al., 2008; Meyer et al., 2014). How inclusions observed in astrocytes exert effects on MNs is unclear. Endocytosis of SOD1 aggregates and subsequent toxicity to hiPSC-MNs supports a prion-like spread of disease (Benkler et al., 2018). Whether these aggregates originate and can be secreted by glia or MNs remains an open question. However, micro-RNAs secreted by C9ORF72 hiPSC-derived astrocytes that reduce MN viability *in vitro* have been observed (Varcianna et al., 2019). C9ORF72 hiPSC-MNs display cell-to-cell spreading of aggregates (Westergard et al., 2016). Additionally, SOD1 aggregates released by primary mouse astrocytes harboring the *SOD1*(G93A) mutation are taken up by MNs in co-culture and induce MN cell death, indicating a potential mechanism by which protein aggregation in astrocytes can promote neurodegeneration (Basso et al., 2013). TDP-43 aggregates are also transferred from cell-to-cell via exosomes, though it is unclear if TDP-43 containing exosomes could be astrocytic in origin (Nonaka et al., 2013). hiPSC-derived three-dimensional culture systems, which contain networks of neurons and glia, recapitulate aspects of Alzheimer's disease pathology, including phosphorylated tau aggregates (Choi et al., 2014), and so may provide a system for investigating TDP-43 proteinopathy and the intercellular spread of inclusions.

9. Future directions and concluding remarks

Due to their ability to recapitulate the complete genetic profile of the original donor fibroblast, hiPSC models allow for a new perspective in examining complex genetic diseases such as ALS. Unfortunately, despite the fact that a large portion of ALS-associated genes are highly expressed in astrocytes, only a handful of studies have applied this technique to study astrocyte involvement in ALS pathology. This is in contrast to hiPSC-derived MNs, which have been extensively modeled since the advent of hiPSCs. Moreover, of the studies that have been conducted, very few have examined those less penetrant genes that, unlike *SOD1* and *C9ORF72*, are understudied in animal models. In particular, genes that have been associated with ALS pathology and are relatively highly expressed in fetal astrocytes are particularly well-suited for hiPSC modeling, due to the fetal expression profile of hiPSC-derived cells.

Still, the immature expression profile of hiPSC-derived cells brings into question the utility of hiPSC-derived astrocytes to model age-related disease pathology. One possible solution may be the development of protocols for the direct induction of specific cell types from patient fibroblasts, which would bypass stem-cell reprogramming and the resultant loss of age-related epigenetic markers. Therefore, the further development of artificial-aging and direct-induction protocols would enhance the utility of hiPSC-based systems to study disease pathology (Reviewed by Cornacchia and Studer, 2017). As the current understanding of astrocyte heterogeneity and patterning continues to improve (Reviewed by Farmer and Murai, 2017), the development of novel hiPSC differentiation techniques to better specify astrocyte subpopulations will be an important step towards improving hiPSC modeling of ALS. Although astrocytes have the capacity to alternate between protective and toxic phenotypes *in vivo*, this feature has yet to be accounted for in either hiPSC models. Future iPSC-derived astrocyte models, then, should profile astrocytes as they mature in co-culture, with a particular focus on understanding the relative abundance of protective versus toxic astrocytes present in culture. Conversely, controlling for this phenotype, perhaps by artificially driving the NF-kB or STAT3 pathways in patient-derived astrocytes, may enhance the reproducibility of *in vitro* ALS astrocyte models.

A better understanding of the relationship between astrocytes and ALS pathology may shed some light on other age-related neurodegenerative diseases. Patients with Alzheimer's disease and Parkinson's disease also frequently present with heightened levels of neuro-inflammation (Heneka et al., 2015; Wang et al., 2015). Even more specifically, certain disease-related phenotypes, such as the upregulation of Cx-43, have been noted in these diseases as well, suggesting that potential pathological spread of disease via astrocyte gap junctions may be shared (Kawasaki et al., 2009, p. 43; Yi et al., 2016). Overall, consideration of astrocyte-mediated roles in neurodegeneration could increase the number of potential therapeutic targets for these diseases.

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