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Chapter

Contribution of Aberrant Astrocytes to Motor Neuron Damage and Death in the SOD1G93A Rat Experimental Model of ALS

Gabriel Otero Damianovich, Olga Cristina Parada, Pablo Díaz-Amarilla, Eugenia Eloísa Isasi, Carmen Isabel Bolatto Pereira and Silvia Olivera-Bravo

Abstract

Amyotrophic lateral sclerosis (ALS) is an incurable paralyzing disease characterized by motor neuron death and glial reactivity. Superoxide dismutase 1 (SOD1) are among the most frequent alterations found in around 15–20% of ALS inheritable forms. Mutant SOD1 murine models mimic main human ALS features and allow purposing that pathological mechanisms include defective communication between neural cells together with astrocyte preponderant roles in disease progression. Years ago, a subset of the most neurotoxic aberrant astrocytes (AbAs) was obtained from spinal cords of SOD1G93A rats. AbA cultures show an exponential growing yield since the early symptoms of the disease up to the terminal stages. In cultures, AbAs present unprecedented toxicity to motor neurons, increased proliferation, loss of mature astrocyte markers, as well as extreme ER stress and abundant extracellular matrix components. Strikingly, AbA phenotype seems to be changing along few passages suggesting its signaling and features may accompany disease progression. However, the link between main AbA features and their highest motor neuron toxicity is not yet completely understood. Here, we reviewed ALS underlying pathological mechanisms in association to AbA phenotype, to collaborate with identification of the most relevant processes that seem crucially involved in the triggering or maintenance of neurotoxicity.

Keywords: aberrant astrocytes, motor neuron death, non-cell autonomous disease

1. Introduction

This chapter will discuss the pathogenic contribution of a subtype of aberrant glial phenotype into the progression and output of the neurodegenerative disease amyotrophic lateral sclerosis (ALS). Complete understanding of neuronal and glial cells roles and communication is necessary to unravel disease processes and

mechanisms. This will further allow the improvement of more focused therapeutic interventions aimed at reducing disease severity and positively impact on diagnosis, therapeutic management, and patients' care.

2. ALS

ALS is an adult onset neurodegenerative disease characterized by progressive loss of spinal, brain stem, and cortical motor neurons, leading to fatal paralysis within 1–5 years since the onset of symptoms that include tremor, muscle weakness, and spasticity [1–3]. ALS affects up to 2:100,000 persons per year; has a life risk around 1:500–1:1000; and exhibits a little predominance of men over women affected [4]. Although ALS is a sporadic multifactorial disease resulting from yet unknown interactions among environment, genes, and epigenetic modifications, genetics seemed to be the predominant factor for the risk of developing the disease [5], and more than 10% of ALS patients are linked to inheritable genetic abnormalities. Dominant mutations in the mitochondrial enzyme Cu/Zn superoxide dismutase-1 (SOD1) seem responsible for up to 1% of the total ALS cases and about 20% of the familial types [4, 6, 7]. Missense mutations in the 43 kDa transactive response DNA/RNA-binding protein (TDP-43) [8] and in fused in sarcoma/translocated in liposarcoma (FUS/TLS) accounted each one for up to 5% of dominantly inherited familial ALS cases [9, 10]. Mutations in the open reading frame 72 on chromosome 9 (C9ORF72) that results in up to thousands of G4C2 hexanucleotide repeats in one allele are found in up to 40 and 7% of the ALS familial and sporadic cases, respectively [11]. There are other genes involved in ALS familial subtypes, but its contribution to the disease is significantly lower in terms of the affected individual number. Regarding to the pathological pathways linking genetic abnormalities to ALS, SOD1 mutations seem to be related to neuronal damage because of abnormal protein folding causes unstable conformations, intracellular inclusion bodies or toxic oligomers, as well as pathological interactions with several proteins [3]. TDP-43 and FUS/TLS mutations are linked to altered RNA processing, transport, and quality control; whereas, G4C2 repeats might sequester RNA-binding proteins impairing the regulation of the RNA targets [12, 13] or causing epigenetic changes that decreased C9ORF72 expression [14, 15]. However, up to now, it is not completely understood how single mutations in one protein could elicit the ALS pathological cascades and how these cascades may finally cause a common neuropathological hallmark that is characterized by aggregation and accumulation of neuronal proteinaceous inclusions that in addition, are found in other neurodegenerative conditions including Alzheimer disease.

2.1 Animal models and non-cell autonomous mechanisms in ALS

To understand the different pathological mechanisms involved in ALS, many experimental models from yeast to rodents have been developed. Whereas, models in lower animals are powerful genetic tools and offer advantages related to short life span and easy handling, distance with mammal nervous systems constitute major limitations when studying human neurodegeneration [16, 17]. Mice and rats are closer to human brain anatomy and complexity, but are not good genetic tools and their lifespan makes necessary the over-expression of mutant human proteins several-fold times to mimic the disease [4], causing the risk that the number of copies over-expressed influence the model by itself. In spite of this, animal models appear as the best approaches to study ALS patho-mechanisms, at least until the employment of inducible pluripotent cells obtained from human patients becomes a well-known and controlled technology.

The first successful ALS models, yet under current extensive use, were developed over-expressing different single mutations of human SOD1 (SOD1G93A, SOD1G37R, and SOD1G85R) in mice or rats [18–20]. Most of the models that overexpress SOD1 present an age-dependent progressive motor syndrome that mimics some pathological features of the human disease [4, 20]. In addition, it seems that pathological features elicited do not derive from the loss of SOD1 catalytic activity but from a yet unknown gain-of-function [4, 20]. Among the highest contributions of murine SOD1 models to the ALS knowledge is the introduction of the non-cell autonomous mechanism concept in which the exclusive neuronal presence of mutant SOD1 did not cause motor neuron death. This implies that motor neuron disease results from the involvement of at least two different cell types. Therefore, a defective cell-cell communication between motor neurons and surrounding glial cells seems actively participating in motor neuron death through not completely understood mechanisms. Pioneer works made in *LoxSOD1G37R/GFAP-Cre⁺* mice [21] or specifically excising the mutant SOD1 transgene from different glial cell types in mice [22, 23] showed that astrocytes [21] and microglial cells [22] play active roles in ALS progression. In support of the non-cell autonomous mechanisms in SOD1 models, reactive astrocytes obtained from transgenic rats or mice [24–26], and from patients of sporadic and familial motor neuron diseases [27, 28] caused neurotoxicity to motor neurons even in cases in which SOD1 is not involved [28].

Other ALS models in rodents were not as clear as those over-expressing mutated SOD1. Transgenic animals expressing mutations of TDP-43-, FUS/TLS-, or C9ORF72-linked ALS produced controversial results without a clear association between each mutation and motor neuron disease, in spite of having motor neuron damage, proteinaceous inclusions, and astrogliosis [29, 30]. Despite these drawbacks, ALS models valuably contribute to make the concept that disruption at systemic, cellular, and molecular levels likely result in many different interacting mechanisms and multiple factors, and that a particular combination of factors and mechanisms likely determine the singularity of each case thus explains the heterogeneity of the human disease.

3. Contribution of aberrant glial phenotypes to ALS pathogenesis

SOD1 models support the concept of ALS as a non-cell autonomous disease in which the reactive astrocyte phenotypes that are produced in the injuring environment greatly contribute to motor neuron death. Astrocytes are the most abundant glial cells in the mammal brain and those responsible for the maintenance of CNS homeostasis [31–34]. During injury, CNS homeostasis is lost and astrocytes respond in a process usually called astrogliosis, in which cells became reactive, highly proliferative and with morphological and functional changes that usually result in decreased protection together with activation of injuring cascades to neurons and oligodendrocytes, further affecting the whole CNS [31–37]. Depending on the injury type and context, astrocyte response can become chronic causing a long lasting state characterized by glial scar, structural tissue rearrangement and impeded repair, as well as a permanent imbalance among homeostatic supportive and gain of neurotoxic functions, all potentially participating in the triggering and progression of several neurological diseases [3, 31–35, 37, 38]. Remarkably, astrocytes also contribute to maintain astrogliosis through autocrine and paracrine signaling [35, 38, 39], thus causing a positive feedback that widespread reactivity and dependent injuring cascades perpetuating CNS damage.

A striking question that remained unanswered until recently was to know if all of the astrocytes that share the same injuring environment respond in the same way or if some of them adopt the worse aberrant phenotypes that account for most of the neurotoxic effects. Trying to unravel this question, when we were studying spinal cord astrocyte phenotypes along the symptomatic phase of the rat SOD1G93A ALS experimental model, we isolated a novel type of aberrant astrocyte-like cells (AbAs) from the spinal cord of paralytic animals whose number exponentially increased toward the terminal stages of the disease [40]. AbAs proliferated faster than astrocytes from neonates or adult wild-type rats and were exceptionally toxic to embryonic motor neurons grown in culture, suggesting a link between their emergence and progression of the paralysis that is a characteristic in the SOD1G93A ALS rat model. Moreover, AbAs did not express distinctive markers that clearly allow distinguishing from typical astrocytes; but present peculiar functional and ultrastructural features that suggest a distinctive phenotype. Among the most remarkable features that AbAs possess, Jiménez-Riani et al. [41] describe their permanent absence of contact inhibition that allowed them to grow in multiple layers and arrange in 3D-cell aggregates that adopt a helicoidal pattern with a central core of extracellular matrix surrounded by cells. In addition, AbAs cytoskeleton does not have intermediate filaments but a significant abundance of microtubules and mitochondria, and ER stress have a restricted perinuclear location suggesting disturbed organelle trafficking that may be associated to alteration in microtubule network or Golgi fragmentation [42]. Furthermore, mitochondria from AbAs are small, electron dense matrix and with few crests; all, comparable to what was described early in models and human ALS [43, 44]. AbAs also have prominent ER with extremely swollen cisternae, some of them degenerating, and express high levels of some ER stress markers [45–47], as well as abundant lipid droplets close to ER and to mitochondria. Their cytoplasm is enriched in diverse vesicles with abundant signs of secretion including extracellular vesicles that can be distinguished by MET and SEM in cultures as well as expression of protein that marks secretion granules [41, 48, 49]. AbAs are also highly positive to the autophagy marker LC3B [50] and present cells' autophagic vesicles and residual bodies [51, 52], likely showing signs of increased autophagy that may allow cells coping with ER stress by favoring the clearance of misfolded proteins [53].

Recently, we confirmed that AbAs were not isolated from the cervical spinal cord of paralytic animals. Instead, the cultures obtained from the cervical spinal cord were similar to the age-matched wild type non-transgenic rats, sharing a low rate of proliferation and resembling a phagocytic microglia morphology that persists throughout the cell culture. Similarities also include low survival along few passages together with absence of complete phenotypic transition to flat cells like astrocytes (**Figure 1**). Therefore, AbAs might result as a local lumbar response to damage, acting similar to astrocytes when react stereotypically depending on injury type, location, and signaling [32].

In addition, we have found that some AbAs critical features are changing during few passages, as occurring with their most prominent markers S100 β and glial glutamate transporter GLT1. Meanwhile, there were no evident morphological differences between low (LP) (~4–7) and high passages (HP) (~14–18) (**Figure 2A**), since cultured AbAs proliferated without replicative senescence, S100 β expression levels decreased \cong 98% (**Figure 2B**), suggesting that this aberrant phenotype may exhibit some plasticity along time. S100 β is a well-known danger-associated molecular pattern (DAMP) which downstream trigger the transcription of nuclear factor NF κ B that further may elicit increased expression and release of pro-inflammatory cytokines [54, 55]. Given that S100 β appears to integrate AbAs

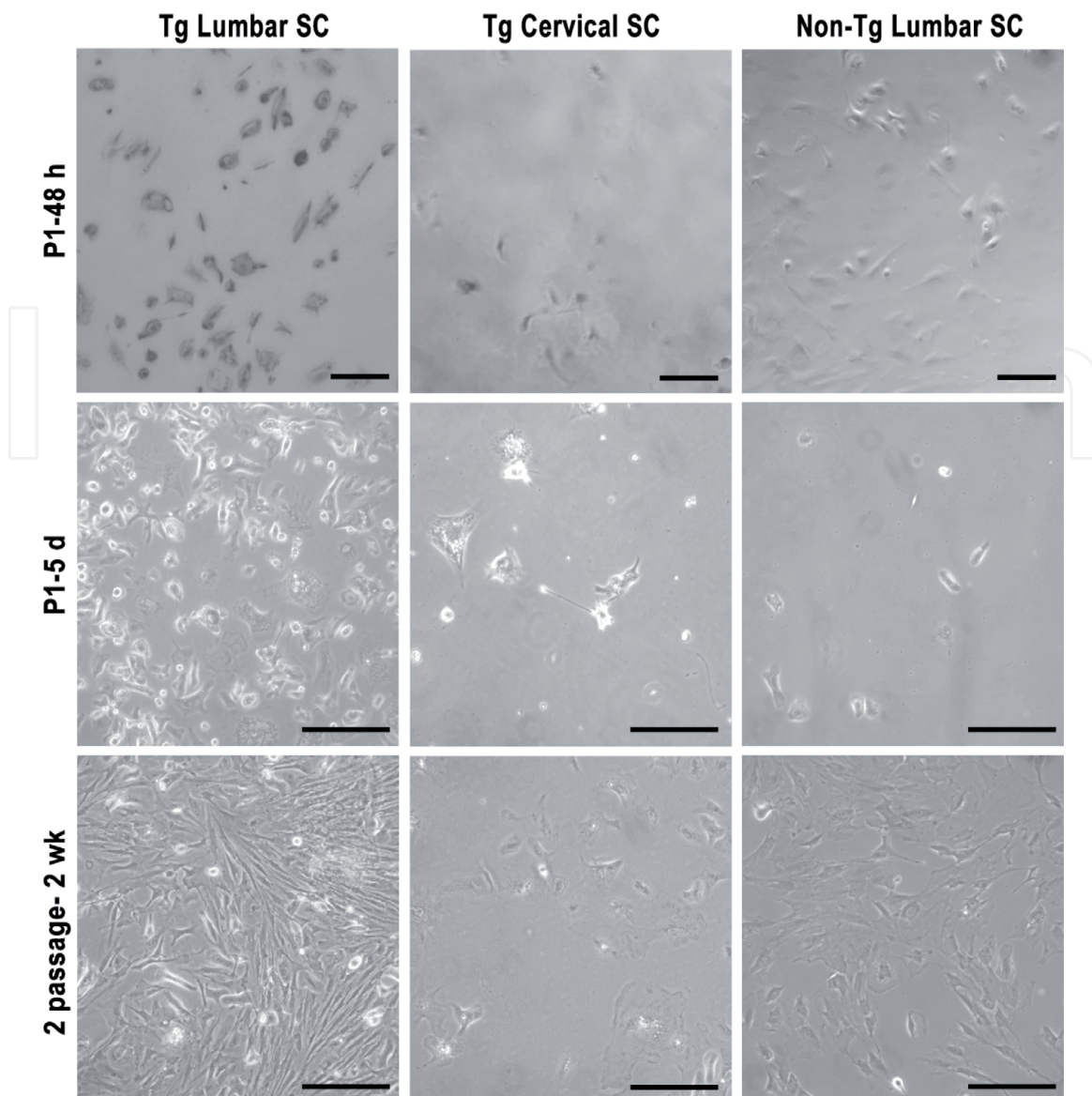


Figure 1.

Morphological appearance of AbAs throughout the cell culture. Light microscopy examination of cells isolated from symptomatic cervical and lumbar spinal cord of transgenic (Tg cervical SC and Tg lumbar SC) or age-matched non-transgenic animals (No Tg lumbar SC) at 48 h, 5 days and 2 weeks after dissection. Note that AbA cells are recovered only from the lumbar spinal cord of transgenic animals whereas the cultures obtained from the cervical spinal cord of the same animals have similar characteristics to the age-matched wild type non-transgenic rats. Adherent cell population is heterogenous with very bright cells that resemble microglial cells and others elongated similar to astrocytes. Scale bar = 150 μm (first line) and 100 μm (second and third lines).

cytoskeletal elements, we cannot discard that S100 β downregulated expression may cause cytoskeleton instability, a characteristic that is linked to exacerbated proliferative capacity as found in AbAs [56]. Thus, decreasing S100 β might constitute a reinforcing proliferation feedback that may underlie AbAs invasive properties as disease progressed. We have also found that GLT1 expression levels also decreased strongly along AbAs passages ($\cong 94\%$, **Figure 2B**), worsening its poor expression which can also aggravated excitotoxic damage [31].

Concurrence of all of the features makes AbAs a unique aberrant phenotype with unprecedented neurotoxicity, which may rely in the yet unknown combination of ER stress, lipid droplet accumulation, abundant extracellular matrix, secretory granules, and exacerbated proliferation. Likely, all these events causing the active production of proteinaceous or lipidic soluble factors that act by itself or reinforce the defective cell-contact properties produced by loss of contact inhibition [41].

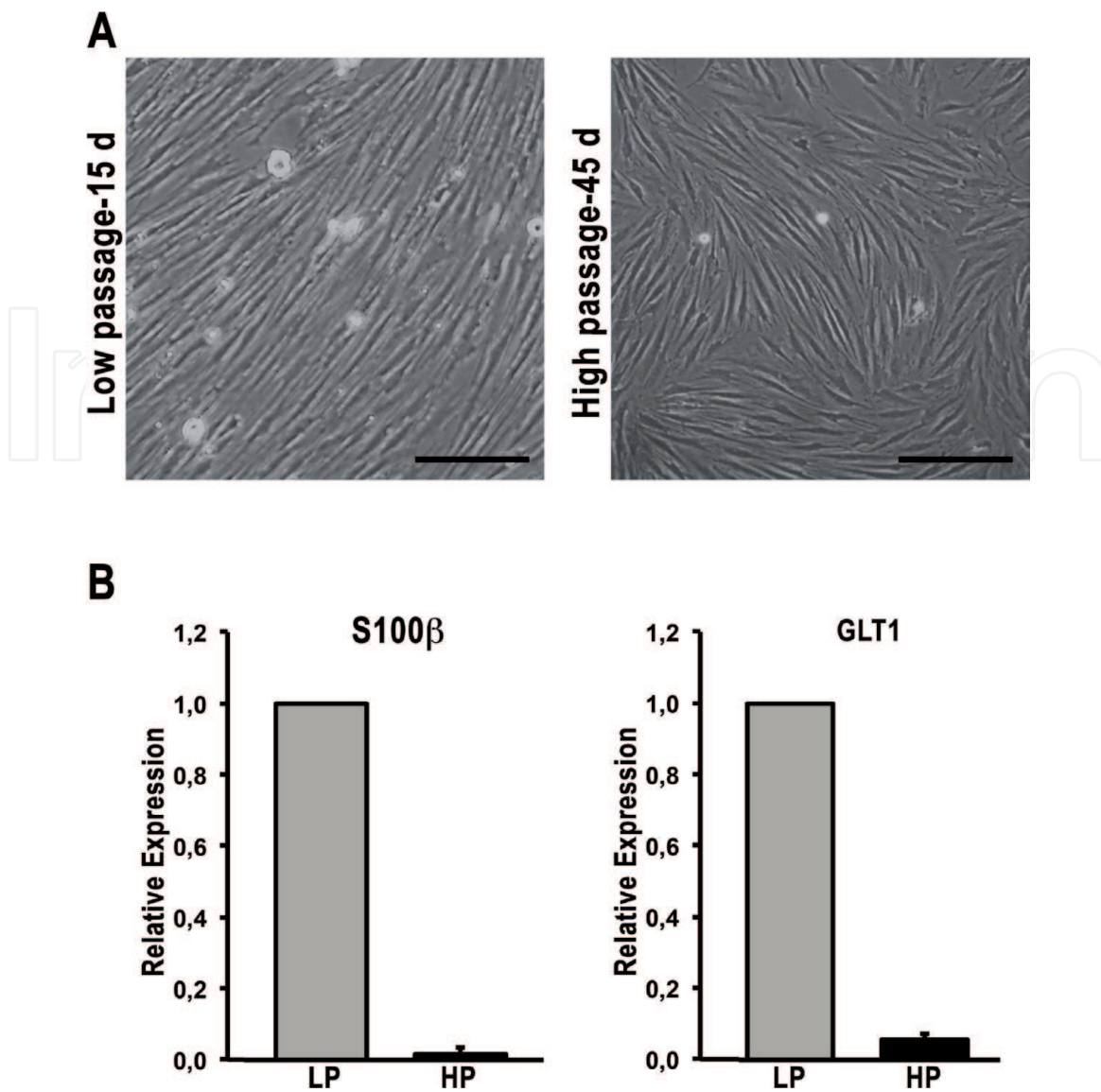


Figure 2.

Morphology and gene expression in AbAs at low and high cell passages. A. Representative light microscopy images of low (LP, left) and high (HP, right) passage cells from transgenic lumbar spinal cords showing their distinctive appearance of flatted elongated cells that appear very similar to astrocytes. Note the low number of bright microglial-like cells. Scale bar = 100 μ m. B. Gene expression analysis in AbA cell cultures showing a down-regulation of S100 β (left) and glutamate transporter GLT1 (right) in HP cells compared with LP cells (control). The expression levels for each gene were obtained by SYBR green qPCR and normalized to the actin transcripts. Data represent the mean \pm the standard deviation for each group.

3.1 Mechanisms that might link AbA to ALS pathogenesis

The most important cellular processes implicated in ALS pathophysiology include ER stress and protein clearance, neuron-glia metabolic coupling, and energy homeostasis [57, 58]. Among their most remarkable features, AbAs exhibit a hardly coping extreme ER stress, as well as lipid droplets and disturbed mitochondrial morphology and trafficking [41]. ER stress is produced by the lack of balance between protein synthesis, folding, and degradation rates [59]. To recover ER homeostasis, cells activate the unfolded protein response (UPR) that orchestrates pro-adaptive and pro-death cellular responses that include protein synthesis decrease except for the effectors that mediates UPR [59–61]. ER stress's final outcome depends on stress duration, strength, and cell targets, and if not resolved, it becomes chronic and as one of the earliest perturbations in several neurodegenerative diseases [59]. Interestingly, ER stress is present in ALS

experimental models, and is described as a predominant mechanism underlying motor neuron death in patients from sporadic and familial cases [46, 59, 62–66]. Furthermore, active UPR in AbAs may down regulate the expression of peptides and proteins that collaborate with neuron survival such as the most important cellular antioxidant defense glutathione or neurotrophins [3, 32]. Thus, although ER stress in AbAs did not cause their own death, it is highly probable that it affects neuron and oligodendrocyte survival in view of their high dependence on astrocyte support.

In close relationship with ER stress, AbAs are also much enriched in lipid droplets that appear near to mitochondria or ER cisternae [41]. Lipid droplets originate from the ER and are described as having a role in ER stress and clearance of protein aggregates as well as in energy homeostasis [67]. Protein turnover is critical for ALS because a number of mutations linked to ALS affect genes directly involved in protein clearance and homeostasis [58]. Lipid droplets appear associated with some of these proteins into the cytoplasm or the nucleus [67, 68], where they appear close and likely associated with the nuclear-naked organelles that control transcriptional activity, cell senescence, and protein degradation named as promyelocytic leukemia nuclear bodies [67, 69, 70], which in addition are found in cell nuclei of ALS patient brains co-localizing with ubiquitin and proteasome components in nuclear inclusions [71].

In brain, lipid droplets are found mainly in glial cells and help to provide fuel for neurons when energy is needed and glucose is scarce. At this time, lipid droplets turned over by cytoplasmic lipases and autophagy, providing fatty acid fuel for ATP production [67], thus playing a crucial role in the anaplerotic support [72]. However, overabundance of lipid droplets as seen in AbAs may suggest a disrupted lipid metabolism in which lipid droplets may not be digested thus decreasing the energy intermediate shuttle to neurons, which can influence motor neuron survival through limited anaplerosis. Lipidic dysfunction could also indirectly impact motor neuron survival as shown in mice over-expressing TDP-43, that beside displaying neurological symptoms and motor deficits, also present increased fat accumulation and adipocyte hypertrophy [73]. Conversely, TDP-43 depletion causes body fat reduction, increased fatty acid consumption, and rapid death [74], likely, because TDP-43 depletion blocks insulin-induced trafficking of glucose transporter Glut4 to the plasma membrane thus impairing glucose uptake and inducing a metabolic switch toward lipids for energy production. This has also been reported in SOD1 mouse models in which spinal cord neurons display decreased glucose usage [75], and a fat-rich diet restores body mass, delays disease onset, and extends life expectancy [57]. Moreover, excessive accumulation of lipid droplets in glial cells is a hallmark in many models of neurodegeneration, and it is usually linked to mitochondrial dysfunction and disease progression [72, 76, 77]. It also seemed enough to promote neurodegeneration by itself [76], therefore indicating that overabundance of lipid droplets in AbAs may have dual functions: for one side not only helping to the clearance of abnormal proteins, but also impairing anaplerotic support to neurons or even having direct neurotoxicity.

AbAs also show evidences of a high secretory activity, which also is described as being crucial to ALS neuronal damage. Although secretory granules seem a conserved protective response to conserve energy and allow recovery under stress conditions, sustained secretory activity of stress granules seems crucial to ALS pathogenesis [78]. Moreover, it has been demonstrated that chromogranins interact and co-localize with mutated misfolded SOD1 [79]; and can eventually act as chaperones to promote secretion of SOD1 mutants that once released may trigger microgliosis and neuronal death [79].

Absence of contact inhibition and exacerbated proliferation are other of the relevant features related to AbAs neurotoxic capacity. Contact inhibition that occurs when dividing normal cells contact adjacent ones is crucial to maintain tissue homeostasis [80, 81], thus constituting an important anticancer mechanism which lack unleashes cells to proliferate virtually unchecked. Although underlying mechanisms are mostly unknown, cell contact inhibition seems to occur when injury disrupts intercellular contacts achieving a proliferative status leading to an aggressive state associated with neoplasia [82] and malignant transformation [81]. Thus, AbAs, absence of contact inhibition seemed directly related to their exacerbated proliferation and invasive behavior during the final stages of the disease. In addition, abundance of EM components secreted by AbA cells may create a non-permissive microenvironment that potentiates invasive behavior apart from having a direct neurotoxic influence to motor neurons, as described in ALS astrocytes [83–85]. No one of each proposed mechanisms seem enough to explain AbAs unprecedented neurotoxicity. Instead, it likely results from the concurrence of many pathological pathways. However, it is also possible that one or two underlying mechanisms prevail over the rest and elicit most of AbAs deleterious effects. Identification of these prevalent mechanisms will be a valuable aid to design the best ALS treatment (**Table 1** and **Figure 3**).

(i) Absence of contact inhibition
<ul style="list-style-type: none"> • Invasive phenotype [40, 41] • Lack of replicative senescence [40, 86] • Exacerbated proliferation [40, 86, 87]
(ii) Immature phenotype
<ul style="list-style-type: none"> • Lack of gliofilaments [40, 41] • Defective differentiation [40, 41, 88]
(iii) Oxidative and ER stress
<ul style="list-style-type: none"> • Mitochondrial dysfunction [89, 90] • Mitochondrial morphological alterations [41] • Defective oxidative phosphorylation [89, 90] • Dysfunction in energy homeostasis [24, 89, 91] • Dilated ER and degenerating ER cisternae [41] • Elevated expression of ER stress markers [41]
(iv) Altered lipid metabolism
<ul style="list-style-type: none"> • Abundant lipid droplets close to mitochondria & ER [41] • Altered anaplerotic support [88]
(v) Intracellular inclusions
<ul style="list-style-type: none"> • Intranuclear and intramitochondrial deposits [41] • Abundance of autophagic bodies [41]
(vi) Aberrant signaling
<ul style="list-style-type: none"> • Extremely neurotoxic conditioned media [40] • Neurotoxic exosomes [90] • Abundance of secretory vesicles and secretory body markers [41]

Table 1.

A summary of AbAs potential pathogenic contribution to the main ALS hallmark. All of ALS main features are listened as (i)–(vi) together with each specific AbAs potential participation.

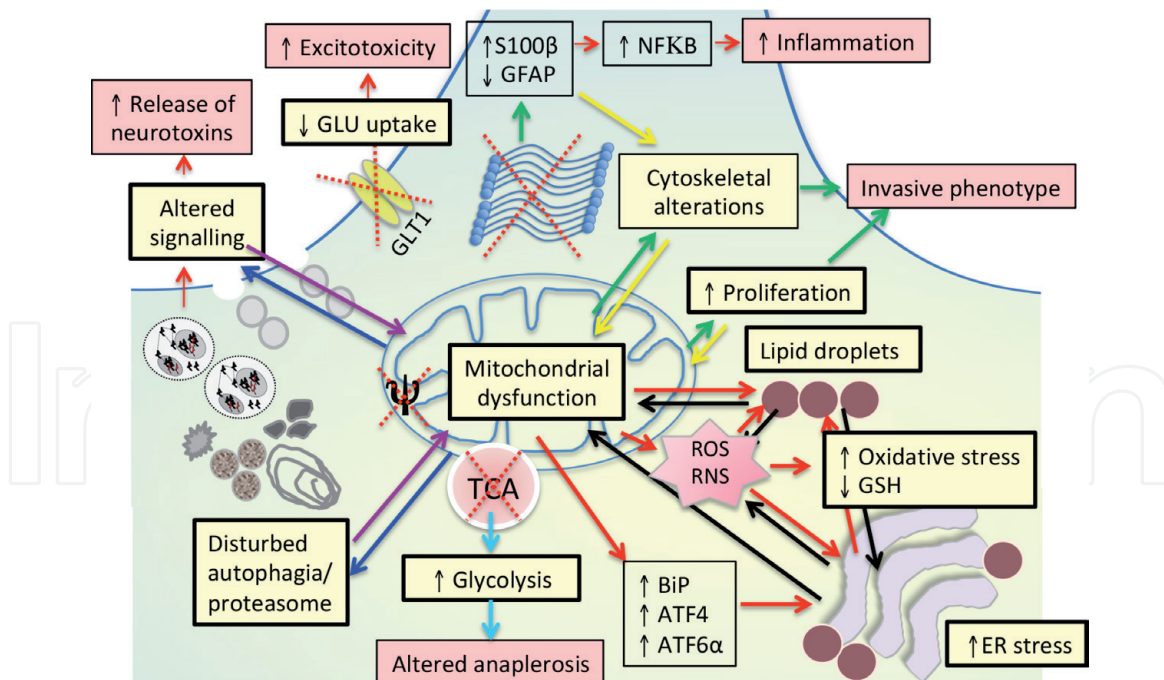


Figure 3. *AbAs: Cytotoxic effects and pathological events. AbAs present mitochondrial dysfunction associated to oxidative stress and ER stress as well as accumulation of lipid droplets, all causing a positive feedback that elicit and perpetuate cell damage (red and black arrows). Mitochondrial abnormalities together with cytoskeletal alterations are also involved in AbAs exacerbated proliferation and cytoskeleton instability both likely underlying the absence of contact inhibition and invasive phenotype as well as S100β-dependent inflammation cascades (green and yellow arrows). Progressive loss of the glutamate transporter GLUT1 causes decreased glutamate uptake becoming neurons more expose to glutamate excitotoxicity. Altered signaling and disturbed autophagia and proteasome functions caused the release of stress granules and soluble neurotoxins as well as the accumulation of cell detritus and inclusion bodies (violet and blue arrows). Finally, the lack of mitochondrial potential (represented as Ψ) caused increased glycolysis and deficient anaplerosis that alters the trophic and energetic support to neurons and oligodendrocytes (light blue).*

4. ALS therapeutics focused on aberrant astrocytes

ALS is an old disease with a narrow offer of pharmacological approaches. Riluzole, an anti-glutamatergic drug, was the first compound authorized to be used in ALS, providing around of 3-month improvement in survival [92]. Recently, FDA approved the free radical scavenger edaravone, as the second compound to treat ALS, that seemed to have beneficial effects only on patients in an early stages of the disease that in addition satisfy a number of restricted criteria. In that population, edaravone showed a significantly smaller decline of Revised ALS Functional Rating Scale score compared with placebo [93]. A randomized phase III clinical trial that tested the effect of the tyrosine kinase inhibitor masitinib in ALS patients showed an improving in the functioning of ALS patients, and the combination with riluzole caused a delayed disease progression without adverse effects [94]. However, the narrow temporal windows that the two compounds approved offer obligates to search alternative avenues to treat the disease.

As astrocytes and microglial cells develop both protective and pathological functions its pharmacological targeting must be carefully evaluated. However, in view of the distinctive phenotype of AbAs, it seems rational to direct therapeutic treatments toward the control of this population during disease progression and ideally trying to inhibit their emergence during asymptomatic stages. AbAs expression of S100β at levels higher than wild type astrocytes may imply that they have a role in the amplification of the inflammatory response, therefore new anti-inflammatory drugs targeting the production of pro-inflammatory cytokines

by a blockade of NF κ B activation may have positive results, moreover because NF κ B is downstream to S100 β [54]. For example, FDA has been approved a drug called mitoxantrone for multiple sclerosis treatment because it inhibited production of IL-12 and IL-23 and suppressed the expression of C-reactive protein by astrocytes in culture and LPS induction of NF κ B DNA-binding activity in primary astrocytes, suggesting a novel mechanism that suppresses the expression of astrocytic pro-inflammatory molecules helping to modulate inflammatory diseases [95]. However, as AbAs seem to lose S100 β at higher passages, neuroprotection by targeting this via might be successful only during asymptomatic stages. Targeting neuroinflammation, recently, it has been shown that the tyrosine kinase inhibitor (masitinib) that is used to control cancer cell proliferation reduced the emergence of aberrant glial cells in the degenerating spinal cord of SOD1G93A paralytic rats and delay disease progression [87]. Authors proposed that masitinib acts preventing the appearance of aberrant glial phenotypes, likely through the inhibition of CSF-1R kinase which activation potentiates inflammatory phenotypes and glial reactivity, and that are particularly effective on proliferating but not on post-mitotic cells [96]. Furthermore, masitinib also prevented astrocyte-induced motor neuron death in cell cultures [97], suggesting that neuroprotection can be achieved through different pathways. In accordance, other report has shown that CSF-1R blockade with the drug GW2580 administered to ALS mice several weeks before paralysis onset decreased both microgliosis and slowed disease progression [98], thus opening a wider avenue to treat aberrant glial phenotypes. Finally, although molecular genetic techniques devoted to switch genes on or off, or to edit their nucleotide sequences, once developed and approved can be effective therapeutic tools to the inherited ALS forms, pharmacological approaches directed against aberrant glial phenotypes may help to control disease progression in a wider range of patients.

5. Conclusions

All data reviewed here suggest that aberrant astrocytes or more generally, aberrant glial cells, are among the most important players in CNS damage causing deleterious effects through many potential patho-mechanisms, mostly sustained on their exacerbated proliferation together with their unprecedented neurotoxicity. Therefore, controlling these populations seems at least equally important than maintenance or restoration of homeostatic astrocyte functions to achieve CNS protection and repair. Moreover, AbAs seemed a better pharmacological target than astrocytes, since therapeutic approaches focused on astrocytes have to be carefully tailored taking into account their multiple faces, moreover in the context of neurodegeneration where several cell types are involved. Future investigation should aim to elucidate if AbAs can indeed be feasible targets to avoid initiation, progression or outcome of neurodegeneration.

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Conflict of interest

There is no conflict of interest.

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