



Mitochondrial Dysfunction, Neurogenesis, and Epigenetics: Putative Implications for Amyotrophic Lateral Sclerosis Neurodegeneration and Treatment

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Amyotrophic lateral sclerosis (ALS) is a progressive and devastating multifactorial neurodegenerative disorder. Although the pathogenesis of ALS is still not completely understood, numerous studies suggest that mitochondrial deregulation may be implicated in its onset and progression. Interestingly, mitochondrial deregulation has also been associated with changes in neural stem cells (NSC) proliferation, differentiation, and migration. In this review, we highlight the importance of mitochondrial function for neurogenesis, and how both processes are correlated and may contribute to the pathogenesis of ALS; we have focused primarily on preclinical data from animal models of ALS, since to date no studies have evaluated this link using human samples. As there is currently no cure and no effective therapy to counteract ALS, we have also discussed how improving neurogenic function by epigenetic modulation could benefit ALS. In support of this hypothesis, changes in histone deacetylation can alter mitochondrial function, which in turn might ameliorate cellular proliferation as well as neuronal differentiation and migration. We propose that modulation of epigenetics, mitochondrial function, and neurogenesis might provide new hope for ALS patients, and studies exploring these new territories are warranted in the near future.

Keywords: amyotrophic lateral sclerosis, epigenetics, mitochondria, neural stem cells, neurogenesis

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gherig's disease, is the third most common adult-onset neurodegenerative disease following Alzheimer's and Parkinson's diseases, with 90% of all cases being sporadic (i.e., without known associated genetic cause) (Zarei et al., 2015; Schiaffino et al., 2018). Despite that, mutations in more than two dozen genes have been thought to underlie, at least partially, the neuropathology of both familial ALS (fALS) and sporadic ALS (sALS). Some of the highly penetrant genes include Cu/Zn superoxide dismutase 1 (*SOD1*), Fused in Sarcoma (*FUS*)

(4% fALS and < 1% sALS), *C9orf72*, *CHCHD10*, TAR DNA-binding protein 43 (*TDP-43*) (5% fALS and < 1% sALS), and *Sqstm1/p62* (Seetharaman et al., 2009; Blair et al., 2010; Chio et al., 2011; Ludolph et al., 2012; Majounie et al., 2012; Gijssels et al., 2015; Webster et al., 2016; Carri et al., 2017; Collins and Bowser, 2017; Frick et al., 2018). Indeed, these genetic mutations correspond to ~68% of fALS cases, while 11% appear to be related to increased susceptibility to sALS (Bozzo et al., 2017; Webster et al., 2018). Mutations in the acetylcholine nicotinic receptors (Sabatelli et al., 2009) and in the charged multivesicular body protein 2b (*CHMP2B*) (Cox et al., 2010), previously known as chromatin-modifying protein 2b, are also frequent in sALS. However, it is estimated that ~20% of all fALS cases (and 1% of all sALS cases) are associated with mutations in *SOD1* (Carri et al., 2017). In agreement, more than 170 mutations have now been identified in this gene (Kodavati et al., 2020). However, it is also important to note that recent studies have demonstrated that the most prevalent mutation in ALS seems to be associated with the *C9orf72* gene (40% of fALS cases and 7% of sALS cases) (Carri et al., 2017; Stoccoro et al., 2018). Curiously, more than a hundred low-penetrance ALS loci have been identified, indicating that ALS pathology is also influenced by polygenic inheritance and environmental factors (van Rheenen et al., 2016; Ji et al., 2017; Stoccoro et al., 2018). Thus, ALS can be seen as the outcome of multiple genetic, physiological, and environmental factors, which may contribute to the phenotypic unpredictability associated with both sALS and fALS (Ajroud-Driss and Siddique, 2015).

ALS is characterized by the progressive degeneration of both upper motor neurons in the motor cortex and lower motor neurons in the spinal cord and brainstem (Kunst, 2004; Al-Chalabi et al., 2012; Vandoorne et al., 2018). As a consequence, there is gradual muscle denervation that leads to weakness, atrophy, and paralysis, culminating in lethal respiratory failure (Dupuis et al., 2011; Bucchia et al., 2015). It is reasonable to speculate that the various mechanisms implicated in the pathophysiology of ALS, including the numerous genetic mutations described so far, might affect not only neurons but also non-neuronal cells as well. Indeed, recent studies have shown that astrocytes, oligodendrocytes, and microglia might also play a role in ALS neuropathology (Chen H. et al., 2018). Such findings are reinforced by the presence of several genetic variants in individual ALS patients, suggesting that the interplay among the various mutations may determine disease onset (Cady et al., 2015) and that disease progression and outcomes can be influenced by a variety of factors (Jimenez-Pacheco et al., 2017). Moreover, the non-cell autonomous hypothesis is strengthened by studies involving transcriptome and histology (Chiu et al., 2013; Aronica et al., 2015; Gjonneska et al., 2015; Srinivasan et al., 2016), in which various markers of non-neuronal cells were recognized in induced pluripotent stem cells (iPSCs) from both sALS patients (Re et al., 2014) and *SOD1-G93A* mice (Nagai et al., 2007; Yamanaka et al., 2008; Ilieva et al., 2009; Chiu et al., 2013; Kang et al., 2013; van Rheenen et al., 2016; Krasemann et al., 2017). Within this scenario, it was also shown that the oligodendrocytic protein myelin-associated oligodendrocyte basic protein (MOBP) was a risk locus for ALS (van Rheenen et al., 2016), and that the expression of the astrocytic protein

excitatory amino acid transporter-2 (EAAT2) is reduced and its activity is decreased in the motor cortex and spinal cord of both ALS patients and *SOD1G93A* transgenic mice (Rothstein et al., 1995, 2005; Ganel et al., 2006; Pardo et al., 2006; Foran et al., 2011; Karki et al., 2015; Lee et al., 2016). Of note, the non-cell autonomous hypothesis has also been corroborated by several *in vitro* studies using cocultures of astrocytes expressing mtSOD1 (*G93A*) and neurons, cocultures of microglia and neurons, and cultures of motor neurons derived from embryonic stem cells (ESCell) from ALS patients (Di Giorgio et al., 2007; Nagai et al., 2007; Yamanaka et al., 2008; Ferraiuolo et al., 2011; Haidet-Phillips et al., 2011; K6nig et al., 2014; Endo et al., 2015; Johann et al., 2015).

Unfortunately, there is currently no effective treatment or cure for this devastating neurodegenerative disease, albeit some medications used to attenuate symptoms (Brito et al., 2019), such as RilutekTM (riluzole) and RadicavaTM (edaravone) (Martin et al., 1993; Sawada, 2017; Brito et al., 2019). On the other hand, to extend their life expectancy, ALS patients undergo tracheostomy-delivered assisted ventilation (Hayashi and Kato, 1989; Jimenez-Pacheco et al., 2017). Therefore, further elucidation of the neuropathological mechanisms that underlie this disorder is a recognized priority.

Up until a few decades ago, the mammalian brain was believed to be a static organ. However, it is now well established that the brain has the ability to adapt to new and different situations by several mechanisms of synaptic and structural plasticity (jointly referred to as neuroplasticity) that happen well into adulthood. One form of structural neuroplasticity relies on the self-renewal capacity of neural stem cells (NSCs) and neural progenitor cells (NPCs). These cells are now known to reside within restricted brain regions [the subventricular zone (SVZ)/olfactory bulb (OB) and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG), and a series of sequential events result in the generation of new neurons (Rodriguez and Verkhatsky, 2011a,b)].

In the past decade, several studies have implicated a deregulation of neurogenic function in the mechanisms that result in neurological dysfunction and neurodegeneration (Zhao et al., 2008; Le Grand et al., 2015; Liu and Song, 2016). Indeed, several reports have shown a reduction in neurogenesis in several models of neurodegenerative disorders (Thompson et al., 2008; Marxreiter et al., 2013; Winner and Winkler, 2015; Hollands et al., 2016). In agreement with these observations, various symptoms that are characteristic of the early stages of these neurodegenerative conditions, such as changes in affective behaviors (e.g., anxiety and depression), cognitive deficits, and olfactory disturbances, can be directly related to deregulation of adult neurogenesis. Interestingly, these alterations can be either in the hippocampal DG or in the OB, the two central regions in the adult mammalian brain that retain the capacity to generate new neurons into adulthood (Simuni and Sethi, 2008; Stout et al., 2011; Hinnell et al., 2012). However, these findings seem to vary not only with the brain region, but also with the stage of disease progression (Boekhoorn et al., 2006; Mirochnic et al., 2009) and the species evaluated (Jin et al., 2004; Curtis et al., 2005; Peng et al., 2008; Winner et al., 2008;

Kohl et al., 2010; Fedele et al., 2011; Simpson et al., 2011; van den Berge et al., 2011; Calió et al., 2014). Furthermore, these deficits in neurogenic function and affective/cognitive behaviors can both be modulated (i.e., attenuated) by environmental enrichment and physical activity (Chen et al., 2008; Mirochnic et al., 2009; Bossers et al., 2010).

Since the generation of new neurons is directly dependent on cellular energy levels, neurogenesis is considered an adenosine triphosphate (ATP)-dependent mechanism. In support, several studies have revealed the importance of maintaining mitochondrial function for the proliferation of NSCs as well as the survival and differentiation of new neurons (Calingasan et al., 2008; Kirby et al., 2009). In addition, neuronal growth, cytoskeleton remodeling, organelle transport, and the formation and maintenance of synapses also rely on ATP availability (Vayssiere et al., 1992; Bernstein and Bamberg, 2003; Sheng and Cai, 2012).

Considering that a deregulation of adult neurogenesis is a common feature of many neurodegenerative conditions, and taking into account that this is an energy-dependent process, in this mini-review we will discuss the relationship between mitochondrial function and adult neurogenesis in ALS. In addition, we will highlight how epigenetic modulation may be used as a therapeutic strategy to counteract ALS through an improvement of mitochondrial function and a consequent increase in neurogenic rate.

MITOCHONDRIAL DYSFUNCTION IN ALS

Mitochondria are essential organelles in eukaryotic cells, whose major function is the production of ATP through oxidative phosphorylation and thus meeting most of the cell's energy requirements (Nunnari and Suomalainen, 2012; Bernard-Marissal et al., 2018). Of note, several lines of evidence have indicated that the metabolic changes observed in several neurological diseases are the result of a disruption in mitochondrial function and a consequent reduction in ATP production (Herrero-Mendez et al., 2009; Requejo-Aguilar et al., 2014; Camandola and Mattson, 2017; Fiorito et al., 2018). In agreement, a large number of studies have shown that energy metabolism is deregulated in animal models of ALS as well in patients with either sporadic or familial forms of ALS (Bowling et al., 1993; Dupuis et al., 2004, 2011; Browne et al., 2006; Sasaki et al., 2007; Perera and Turner, 2016). Indeed, a decrease in the activity of the electron transport chain (Cozzolino et al., 2009; Crugnola et al., 2010; Kawamata and Manfredi, 2010) and a reduction in the activity of mitochondrial enzymes (Dupuis et al., 2004; De Vos et al., 2007; Gonzalez de Aguilar et al., 2008; Sotelo-Silveira et al., 2009; Bilsland et al., 2010) have been verified to occur in models of this incurable disease. For example, the mSOD1-G93A transgenic mouse model of ALS [which overexpresses the human *SOD1* with the Gly-93-Ala (G93A) substitution], has been revealed to display reduced activity of mitochondrial complex I (Jung et al., 2002; Coussee et al., 2011). Interestingly, the discovery of the G93A mutation

in the antioxidant enzyme SOD1 was the first known genetic cause of human ALS, and ~160 different mutations affecting the binding of Cu and Zn to the redox center of SOD1 have been identified (Lovejoy and Guillemin, 2014; Malik et al., 2019). There is also much evidence that transition metals, especially Cu, Zn, and Fe, can mediate mitochondrial dysfunction, DNA damage, telomere shortening, and neurodegeneration (Almeida et al., 2006; Lovejoy and Guillemin, 2014; Bertocini et al., 2016). In ALS patients, magnetic resonance imaging has presented a characteristic T2 shortening, which is attributed to the presence of Fe in the motor cortex. Increased Fe is also detected in the spinal cord of mSOD1 mouse models, and treatment with Fe-chelating drugs lowers levels of Fe in the spinal cord, preserves motor neurons, and extends the lifespan of these animals (Lovejoy and Guillemin, 2014).

Nevertheless, in addition to changes in cellular redox status, alterations in mitochondrial dynamics (Magrane et al., 2012), size (Liu et al., 2013; Wang et al., 2013; Deng et al., 2015; Pansarasa et al., 2018) and localization (Williamson and Cleveland, 1999; Higgins et al., 2002; Magrane et al., 2009, 2012; Zhou et al., 2010; Vande Velde et al., 2011) are also believed to contribute to the pathophysiology of ALS. Indeed, defects in mitochondrial dynamics and disruption of mitochondrial axonal transport have been described in ALS models (De Vos et al., 2007; Shi et al., 2010; Gao et al., 2018). Within this context, Joshi and colleagues have reported excessive mitochondrial fragmentation, mediated by hyperactivation of Drp1, in both fibroblasts derived from numerous forms of fALS and in *SOD1*-mutant motor neurons (Joshi et al., 2018). Accordingly, an improvement in motor performance and an increase in survival were reported in *SOD1* G93A mice exposed to a peptide that inhibits the interaction between Drp1 and Fis1 (Joshi et al., 2018). Both *in vivo* studies with the mSOD1-G93A transgenic mouse model and *in vitro* studies with the NSC34 motor neuron cell line (both of which overexpress mSOD1) have described mitochondrial abnormalities as well as altered axonal distribution of these organelles (Williamson and Cleveland, 1999; Magrane et al., 2009, 2012; Vande Velde et al., 2011). Meaningful, mSOD1 tends to accumulate within mitochondria, thus resulting in the accumulation of defective mitochondria (Jaarsma et al., 2001; Pasinelli et al., 2004; Vijayvergiya et al., 2005; Vande Velde et al., 2011; Tafuri et al., 2015). In agreement, studies using patients' samples have demonstrated the presence of clusters of mitochondria in the anterior region of the lumbar spinal cord (Sasaki and Iwata, 1996) as well as an increase in presynaptic mitochondrial volume in motor neurons (Siklos et al., 1996). Furthermore, mSOD1-G93A transgenic mice exhibited abnormal localization of mitochondria, which may further contribute to mitochondrial dysfunction (Higgins et al., 2002; Zhou et al., 2010). Additionally, Palomo and collaborators have shown that the degradation of dysfunctional mitochondria (i.e., mitophagy) is activated due to the recruitment of the autophagy receptor p62 in the spinal cord of *SOD1*-G93A mice (Palomo et al., 2018). Furthermore, Miro and Mfn2 (proteins involved in mitochondrial dynamics), Parkin (a ubiquitin ligase), as well as PGC1 α (the master regulator of mitochondrial biogenesis) are decreased in these mice (Palomo et al., 2018).

Although most studies that have assessed mitochondrial function in animal models of ALS have primarily used *SOD1* genetic models, it has also been shown that TARDBP, C9orf72, TDP-43, and FUS can also impact this organelle. Fibroblasts with the *TARDBP* (*p.A382T*) mutation present a fragmented mitochondria network as well as changes in mitochondria ultrastructure (Onesto et al., 2016). Moreover, *TARDBP* fibroblasts exhibit a decrease in mitochondrial membrane potential, while *C9orf72* fibroblasts show mitochondrial hyperpolarization as well as an increase in ATP, mitochondrial DNA content, mitochondrial mass, PGC1- α protein, and reactive oxygen species (ROS) levels (Onesto et al., 2016). These results suggest that both *TARDBP* and *C9orf72* mutations can lead to cell death by mechanisms other than RNA metabolism impairment (Onesto et al., 2016). An imbalance between fission and fusion was also observed in *C9orf72* human fibroblasts, as a consequence of increased Mfn1 levels and alterations in mitochondrial shape (Onesto et al., 2016). *C9orf72* was also shown to induce mitochondrial hyperpolarization, in addition to an increase in mitochondrial content and mass, mitochondrial fragmentation, and a loss of mitochondrial cristae (Dafinca et al., 2016; Lopez-Gonzalez et al., 2016). With regard to *TDP-43*, it has been described that the full-length protein can interfere with the mobility of animals (Davis et al., 2018). Curiously, some targets of *TDP-43* include prohibitin 2 (PHB2), a mitochondrial chaperone and mitochondrial degradation receptor, voltage-gated anion channel 1 (VDAC1), and the fusion protein mitofusin 2 (MFN2) (Davis et al., 2018). Furthermore, it has also been shown that the expression of *TDP-43* could lead to the phosphorylation of serine 637 of the DRP1 protein, thus abolishing mitochondrial fission (Davis et al., 2018). Finally, *TDP-43* was also shown to bind to ND3 and ND6 mitochondrial mRNA, thus inhibiting the activity of complex I of the mitochondrial respiratory chain and, consequently, oxidative phosphorylation (Wang et al., 2016). Changes in mitochondrial function have also been documented in *FUS*-associated ALS. Indeed, it has been shown that *FUS* can induce defects in DNA break-ligation mediated by DNA ligase 3 (LIG3), a crucial enzyme for the replication and repair of mtDNA (Kodavati et al., 2020). Furthermore, both R521G and R521H mutations of *FUS* have been associated with smaller mitochondria in motor neurons, deficits in axonal transport, and disruptions in the transference of vesicles between endoplasmic reticulum and mitochondria in iPSC-derived neurons from ALS patients (Tradewell et al., 2012). Moreover, an increase in mitochondrial *FUS* was shown to induce an increase in Fis1 and, as a result, an intensification of mitochondrial fragmentation and ROS production, in addition to mitochondrial depolarization, abnormal mitochondria transport along axons, and a decrease in ATP synthesis (Deng et al., 2020). Together, these studies suggest that unbalanced mitochondrial dynamics may be a common feature in ALS and this can, in turn, lead to a reduction in cell survival.

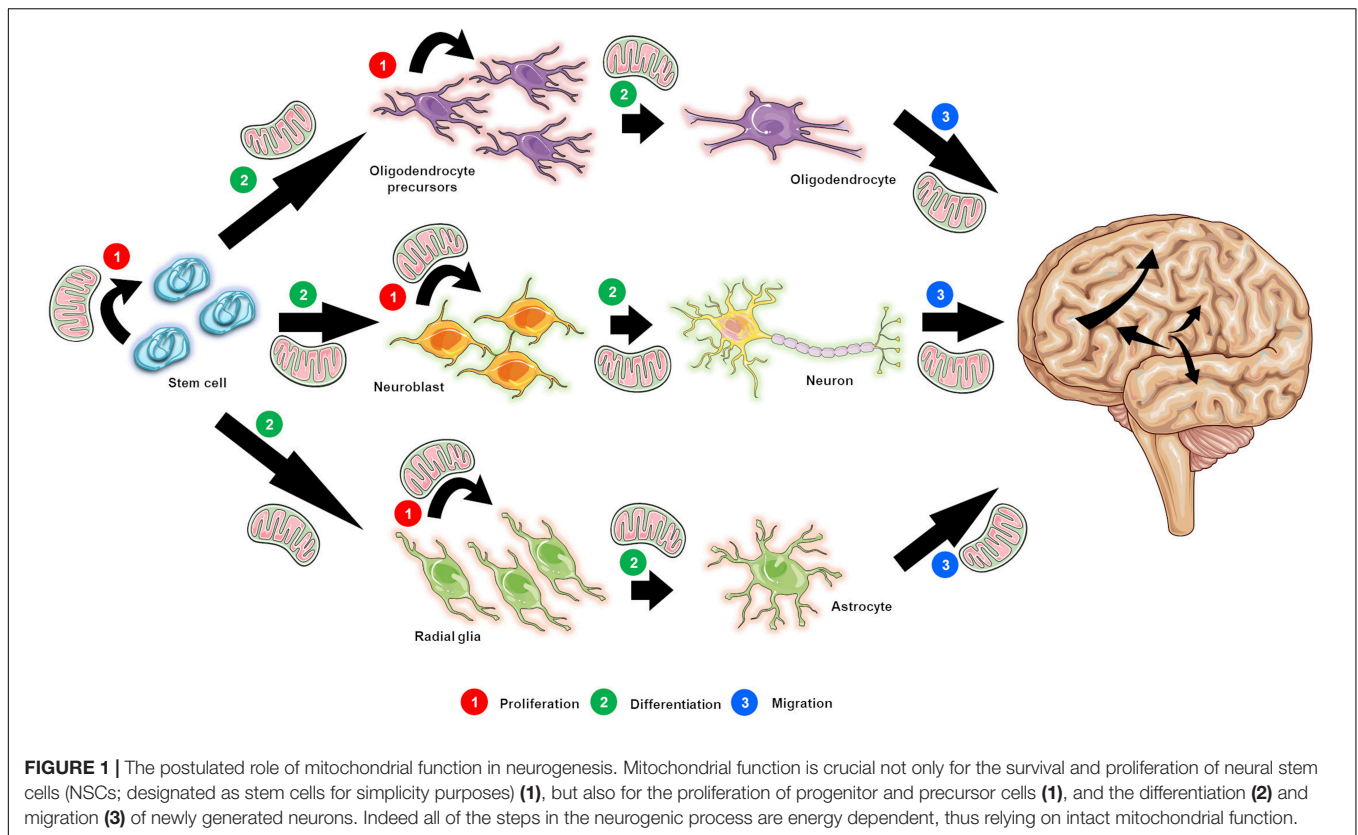
Though small modifications in the mitochondrial genome can represent a risk factor for neurodegenerative diseases, the sole presence of a few mitochondrial DNA (mtDNA) mutations is not enough to directly lead to neurodegeneration *per se* (Gerschütz et al., 2013; Perier et al., 2013; Parkinson et al., 2014;

Smith et al., 2019). Nevertheless, sporadic rearrangements of mtDNA and hereditary mtDNA point mutations have indeed been indirectly linked to neurodegenerative processes (Chinnery and Hudson, 2013; Pinto and Moraes, 2014; Cha et al., 2015; Keogh and Chinnery, 2015; Nissanka and Moraes, 2018). In ALS, in particular, it is known that the amount of mtDNA, a marker for mitochondrial copy number, is reduced in the spinal cord of patients with either familial or sporadic forms of the disease (Wiedemann et al., 2002). Nuclear DNA (nDNA) mutations in genes responsible for mitochondrial proteins have also been connected to ALS (Smith et al., 2019). Taken together, these studies suggest that a decrease in mitochondrial biogenesis may indeed contribute to the pathogenesis of this disorder.

Interestingly, mitochondria are also involved in the buffering of calcium, and a deregulation of mitochondrial-dependent calcium handling has also been linked to neurodegeneration (Rosenstock et al., 2004, 2010a,b; Tang et al., 2005; Damiano et al., 2006; Pelizzoni et al., 2008; Cali et al., 2012; Naia et al., 2014; Carri et al., 2017; Salvatori et al., 2017). Indeed, a disruption of intracellular calcium homeostasis has been revealed to accompany changes in oxidative phosphorylation and ATP synthesis in various neurodegenerative processes, including ALS (Coussee et al., 2011; Ravera et al., 2018).

MITOCHONDRIAL (DYS)FUNCTION AND NEUROPLASTICITY

It is well established that both structural and synaptic neuroplasticity, including cell proliferation, neuronal differentiation, and migration, as well as formation and maintenance of functional synapses, are processes that require energy (i.e., ATP) (**Figure 1**), and therefore rely on mitochondrial content (Vayssiere et al., 1992; Mattson et al., 2008; Petanjek et al., 2011; Agostini et al., 2016; Lin-Hendel et al., 2016). In support, an increase in the content (i.e., levels) of mitochondrial proteins as well as of transcription factors, which are known to promote an increase in mitochondrial mass, has been detected during early neuronal differentiation (Cordeau-Lossouarn et al., 1991; Vayssiere et al., 1992); these data indicate that mitochondrial content varies during neuronal development. Moreover, in the SVZ niche, mitochondrial genes are the most affected as NSCs progress from quiescent to activated (Mu et al., 2010). In agreement, numerous studies have shown that in addition to requiring appropriate growth factors (Ramasamy et al., 2013) and adequate surfaces (Faissner and Reinhard, 2015), NSCs and their daughter cells undergo various changes concerning their intracellular metabolic machinery in order to proliferate and differentiate (Rafalski and Brunet, 2011; Folmes et al., 2012; Gage and Temple, 2013). Notably, these changes are likely to be correlated with the stage of neuronal differentiation, rather than with simple progression to the postmitotic phase (Vayssiere et al., 1992). Additionally, it has been presented that p53 translocates to mitochondria during the early stages of neuronal differentiation in an attempt to attenuate oxidative stress and decrease mitophagy and cytochrome *c* release, thus contributing to the survival of the newly born neurons and the



growth of neuritis, further promoting neuronal differentiation and maturation (Xavier et al., 2013).

Mitochondria are also important for neuronal structure, including axonal and dendritic formation (axonal growth cone and filopodia, respectively); interestingly, both growing axons and dendrites are enriched in these organelles (Cunniff et al., 2016; Han et al., 2016; Sainath et al., 2017; Sheng, 2017; Shneyer et al., 2017; Gershoni-Emek et al., 2018; Smith and Gallo, 2018). Once neurons mature, mitochondrial function (i.e., energy production and supply) is absolutely required for neuronal synaptic plasticity and the formation and maintenance of synapses. Indeed, ATP is necessary for both synaptic vesicle recruitment and neurotransmitter release, as well as the maintenance of ionic and electric gradients across the cell membrane (Tang and Zucker, 1997; Bindokas et al., 1998; Zenisek and Matthews, 2000; Billups and Forsythe, 2002; Kann et al., 2003; Levy et al., 2003; Yang et al., 2003; Verstreken et al., 2005). Consequently, pre- and postsynaptic terminals and nodes of Ranvier have an increased number of mitochondria in comparison to other cellular areas (Fabricius et al., 1993; Li et al., 2004; Zhang et al., 2010).

Noteworthy, disturbances in intracellular calcium buffering by the mitochondria and mitochondrial ROS production can also affect synaptic formation and function. For example, synaptotagmin-1, a protein involved in synaptic vesicle formation, is activated by calcium (Choi, 1985; Schinder et al., 1996; David et al., 1998), and therefore changes in intracellular calcium levels can affect its function. On the

other hand, neuronal pruning can be modulated and affected by ROS (Sidlauskaite et al., 2018). Indeed, an increase in mitochondrial ROS production has been observed in inactive synapses, and the presence of ROS in these “weak” synapses may constitute a signal or trigger for their subsequent elimination (Sidlauskaite et al., 2018).

CHANGES IN NEUROGENIC FUNCTION IN ALS

As ALS is a multifactorial disorder (where both genetic predisposition and environmental factors may contribute to its etiology) (Bilsland et al., 2008; Haidet-Phillips et al., 2011; Brites and Vaz, 2014; Nikodemova et al., 2014; Beeldman et al., 2016; Matias-Guiu et al., 2016; Martinez-Merino et al., 2018; Nonneman et al., 2018), changes in neuroplasticity (including altered neurogenic function) may contribute to the pathogenesis of this disease.

To date, various studies have assessed neurogenic function in ALS animal models (Table 1), namely in transgenic mice and rats expressing the mutation in the *SOD1* gene (Warita et al., 2001; Chi et al., 2006, 2007; Liu and Martin, 2006; Murphy, 2009; Li et al., 2012; Khalil and Lievens, 2017). Within this scenario, Li et al. (2012) have reported that mSOD1-G93A rats show a significant reduction in fetal tissue derived NSCs proliferation (Li et al., 2012). In agreement, Liu and Martin (2006) have also observed altered proliferative capacity in all neurogenic

TABLE 1 | Summary of studies that have assessed adult neurogenesis in ALS animal models.

Authors (year of publication)	Model	Main finding
Warita et al. (2001)	mSOD1-G93A mice	Progressive expression of PSA-NCAM
Liu and Martin (2006)	mSOD1-G93A mice	Alterations in proliferation capacity in SVZ, OB, and DG
Chi et al. (2007)	mSOD1-G93A mice	Augmentation in NSC levels
Lee et al. (2011)	mSOD1-G93A mice	Decrease in functional capacities of neural progenitor cells
Li et al. (2012)	mSOD1-G93A rats	Reduction in NSC proliferation
DiFebo et al. (2012)	Murine model of motor neuron degeneration	Lower NSC proliferation
Marcuzzo et al. (2014)	mSOD1-G93A mice	epSPCs differed more into neurons than into astrocytes
Galán et al. (2017)	Patients	Increase in the neurogenesis in the SVZ, but a decrease of it in the SGZ

niches (SVZ, OB, and hippocampal DG) of the mSOD1-G93A transgenic mouse model. Interestingly, these changes in neurogenic activity can be detected during the presymptomatic phase, before the onset of motor neuron degeneration and subsequent motor paralysis, suggesting that a disruption of the neurogenic process may somewhat contribute to the progression of the disorder in this ALS model (Liu and Martin, 2006). These findings also suggest that ALS-induced alterations in the neurogenic microenvironment (i.e., neurogenic niche) can permanently alter the proliferative capacity of NSCs and NPCs (Lee et al., 2011). Curiously, in 25-week-old mSOD1-G93A transgenic mice, the progressive expression of polysialylated neural cell adhesion molecule (PSA-NCAM, a protein expressed during the maturation and migration of immature neurons and during synaptogenesis) (Rutishauser and Landmesser, 1996; Rutishauser, 2008) has been noted in surviving motor neurons. This outcome suggests that the expression of this protein may dictate, or at least contribute, to the survival of motor neurons in ALS (Warita et al., 2001).

NSC proliferation and degeneration of spinal cord motor neurons were also evaluated in a bi-transgenic mouse (Bi-Tg) expressing both mSOD1-G93A and a Nestin enhancer gene (Chi et al., 2007). In this study, Chi and collaborators described an increase in NSC levels in the motor cortex of bi-transgenic animals at the beginning of disease progression when compared with age-matched wild-type controls (Chi et al., 2007). However, as disease progressed, a decrease in NSCs in the lateral ventricles of Bi-Tg was observed, although no changes in the number of NSCs in the hippocampal DG were detected (Chi et al., 2007). Hence, it seems that at least in this model, ALS progression is only related to a decrease in neurogenic function in the SVZ neurogenic niche.

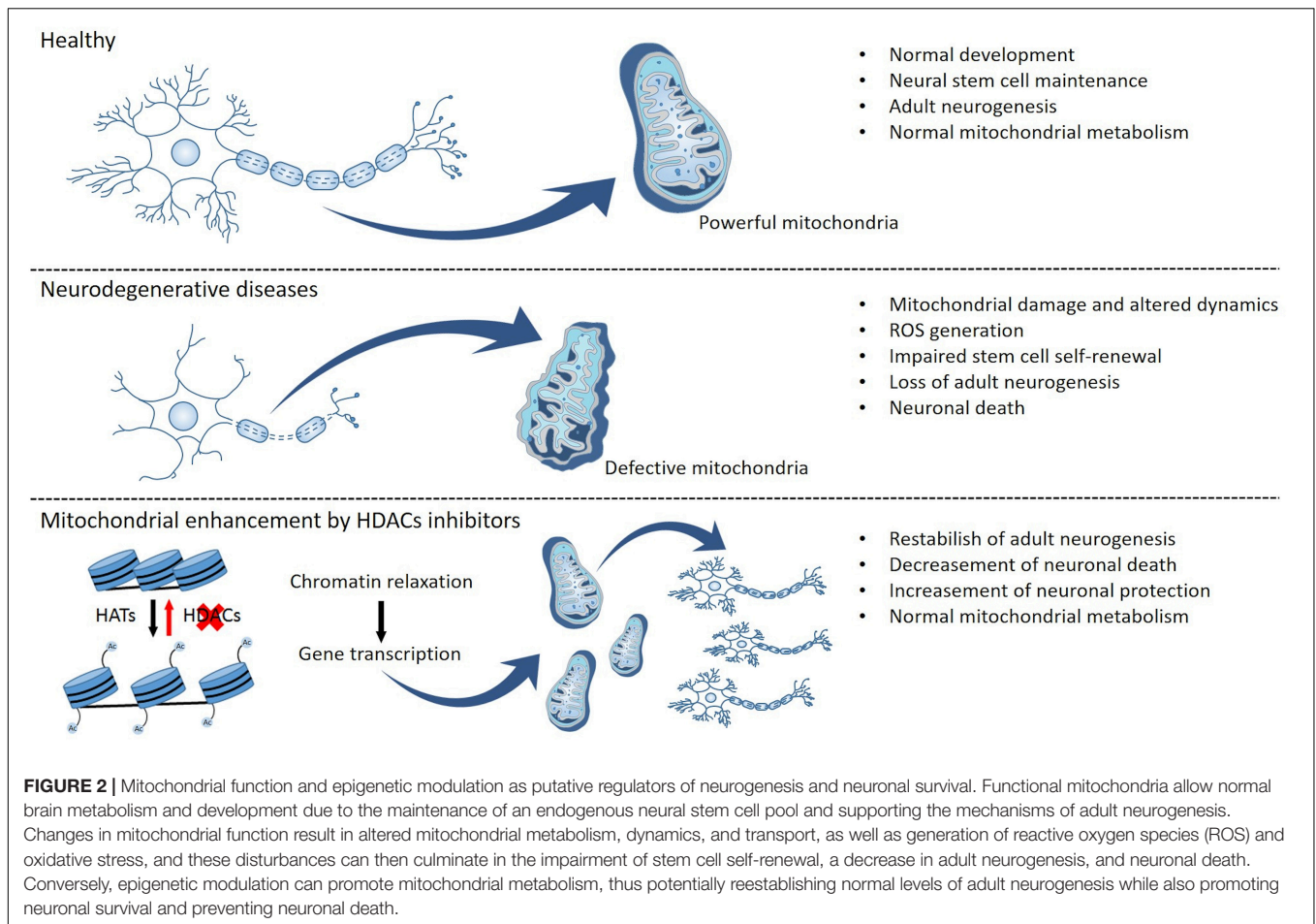
Various *in vitro* studies have also assessed proliferation and differentiation of stem cells derived from animal models

of ALS. Marcuzzo et al. (2014) assessed the proliferating and differentiating capacity of ependymal stem progenitors (epSPCs) from the spinal cord of wild-type control, asymptomatic, and symptomatic mSOD1-G93A transgenic mice (Marcuzzo et al., 2014). Surprisingly, these authors found an increase in the number of epSPCs-derived neurons (and a corresponding decrease in the number of epSPCs-derived astrocytes) in mSOD1-G93A transgenic cell populations when compared with wild-type control cells. Oddly, the proportions of oligodendrocytes were similar between both populations. However, G93A-SOD1 epSPCs-derived neurons were smaller than epSPCs-derived wild-type control neurons, whereas G93A-SOD1 epSPCs-derived astrocytes presented an activated phenotype. These marks demonstrate that although SOD1-G93A epSPCs have the potential to differentiate into the three distinct neural lineages (neurons, astrocytes, and oligodendrocytes) *in vitro*, the newly generated transgenic cells are morphologically and physiologically different, and such differences might contribute, at least in part, to the neurodegenerative mechanisms underlying this neurological disorder. The neurogenic capacity of SVZ-derived NSCs and its relationship with motor neuron degeneration was also evaluated in the wobbler mouse model, a murine model of motor neuron degeneration characterized by increased cortical hyperexcitability (DiFebo et al., 2012). *In vitro* experiments demonstrated that the rate of wobbler-derived NSC proliferation was significantly lower than in control healthy mice. On the contrary, the number of NSCs exhibiting early neuronal commitment was significantly higher for wobbler-derived NSCs when compared to NSCs from control animals.

So far, only one study has assessed neurogenic capacity in ALS patients. In this study, while an increase in SVZ neurogenesis was observed, a decrease in SGZ neurogenesis was detected in the hippocampal DG of ALS patients (Galán et al., 2017). While the observed increase in SVZ neurogenesis may be part of an endogenous compensatory mechanism to counteract the underlying neurodegenerative process, the real impact of this increase is currently unknown, and future studies are warranted to determine whether the newly generated cells can fully differentiate and migrate toward the areas of ongoing degeneration, or whether they die before becoming fully functional (Galán et al., 2017). Similarly, the impact of the observed reduction in hippocampal DG neurogenesis is unexplained and further investigations are thus necessary to determine its functional implications. **Table 1** further summarizes the studies described in this section.

REGULATION OF NEUROGENIC FUNCTION IN ALS THROUGH EPIGENETIC MODULATION: POSSIBLE THERAPEUTIC AVENUES

Despite considerable scientific progresses regarding the identification of the molecular underpinnings of ALS pathophysiology, the genesis of this devastating neurological



disorder and the factors that dictate its progression remain, for the most part, unknown. As a consequence, no effective treatments are currently available for individuals afflicted with this disease (Mancuso et al., 2014), which makes the search of potential disease-modifying therapies capable of altering the rate of disease progression a recognized priority (Al-Chalabi and Hardiman, 2013). Within this scenario, several lines of evidence have suggested that interventions capable of promoting an increase of neurogenesis may lead to better functional recovery (Marsh and Blurton-Jones, 2017; Kameda et al., 2018; Schiaffino et al., 2018). Indeed, neurogenesis can be modulated by numerous intrinsic and extrinsic factors, including epigenetic modifications, thus suggesting that epigenetic factors may be used as potential targets to promote neurogenic function in models of neurodegeneration. Even though epigenetic modifications are not genetically transmitted, they can be pharmacologically manipulated, making them potential marks for medical intervention (Hwang et al., 2017). In reality, several lines of evidence suggest that epigenetics might not only facilitate the identification of effective therapeutic targets, but also assist with ALS diagnosis and follow-up, since the expression of numerous genes can be modulated by epigenetic mechanisms (Chestnut et al., 2011; Jimenez-Pacheco et al., 2017; Young et al., 2017; Coppedè et al., 2018; Masala et al., 2018).

Epigenetic modifications are mediated through gene-environment interactions (Mehler, 2008; Al-Chalabi and Hardiman, 2013) and result in heritable changes in gene expression that are independent of alterations in DNA sequence (Probst et al., 2009; Bonasio et al., 2010; Rosenstock, 2013). Examples include DNA methylation, posttranslational histone modifications such as methylation, acetylation, phosphorylation, ubiquitination, and isomerization of histones, as well as RNA editing (and non-coding RNA modulation) (Rosenstock, 2013; Bowman and Poirier, 2015; Javaid and Choi, 2017; Jimenez-Pacheco et al., 2017; Koreman et al., 2018; Bennett et al., 2019). Within this scenario, it was demonstrated that miRNA can regulate up to 60% of all protein-coding genes (Friedman et al., 2009). In the context of ALS, it was shown that numerous miRNAs are upregulated, namely miR-155, miR-22, miR-125b, miR-146b, and miR-365, in SOD1-G93A mice and in the spinal cord of ALS patients (Butovsky et al., 2012; Koval et al., 2013; Parisi et al., 2013, 2016). Of interest, it was also described that the processing and biogenesis of miRNAs can be modified by several proteins, including TDP-43 (Buratti et al., 2005; Kawahara and Mieda-Sato, 2012; Paez-Colasante et al., 2015).

Posttranslational histone modifications can alter the accessibility of DNA to transcription regulators by inducing changes in the structural configuration of nucleosomes

(Feng et al., 2015). In particular, histone acetylation is catalyzed by histone acetyltransferases (HATs), and this process results in the loosening of the chromatin structure, which in turn allows for transcriptional activation; on the other hand, histone deacetylases (HDACs) exert the opposite effect (Probst et al., 2009; Feng et al., 2015; Li et al., 2016), and therefore, overexpression of HDACs can have a deleterious effect. In agreement, reduced histone acetylation is a common feature observed in several models of neurodegenerative diseases (Lagali and Picketts, 2011; Naia et al., 2017), and an imbalance between HATs and HDACs activities has been described in ALS (Rouaux et al., 2003; Schmalbach and Petri, 2010). Several *in vivo* studies using ALS animal models and postmortem human tissue have addressed the role of HDACs in modulating disease progression. Of note, an increase in HDAC2 mRNA and a reduction in HDAC11 mRNA (Janssen et al., 2010) has been detected in postmortem spinal cord and brain tissue from ALS patients. Furthermore, disease progression was shown to be associated with an increase in the expression of HDAC4 in muscles in ALS patients (Bruneteau et al., 2013). In agreement, changes in levels of HDACs appear to be correlated with decreased cell death and a delay in disease onset (Rouaux et al., 2003; Yoo and Ko, 2011). On the other hand, preclinical *in vivo* studies with mSOD1-G93A transgenic mice demonstrated that trichostatin A, an inhibitor of HDACs, attenuated motor neuron loss, gliosis, muscular atrophy, and neuromuscular junction denervation, while increasing the survival of transgenic mice (Mancuso et al., 2014). ACY-738, an HDAC inhibitor, was equally able to ameliorate the motor phenotype, spinal cord metabolism, and the life span of a *FUS*-transgenic mouse model (Rossaert et al., 2019). *In vitro* studies have also revealed that inhibition of HDAC class II enhanced the transcription of the glutamate transporter excitatory amino acid transport 2 (EAAT2) and reestablished its expression in *SOD1* animal models (Lapucci et al., 2017). Notably, non-selective HDAC inhibitors can also activate the promoters of the brain-derived neurotrophic factor (*bdnf*) and glial cell line-derived neurotrophic factor (*gdnf*) genes (Wu et al., 2008). Treatment of *SOD1* transgenic animals with a combination of riluzole and an HDAC inhibitor resulted in a 20% increase in survival rate when compared to mice treated with only riluzole, in addition to diminishing the levels of astrogliosis and the death of motor neurons (Del Signore et al., 2009).

The importance of HDACs to ALS is not limited to classic HDACs (classes I, II, and IV) (Gal et al., 2013; Taes et al., 2013; Valle et al., 2014); sirtuins (SIRT1), which are HDACs class III, have also been presented to play an important role in the pathogenesis of this disorder (Giralt and Villarroya, 2012; Rosenstock, 2013; Song et al., 2013; Salvatori et al., 2017). Indeed, studies have demonstrated that Resveratrol (*trans*-3,4,5-trihydroxystilbene), a natural polyphenol found in grapes, enhanced the enzymatic activity of SIRT1, thus exerting a neuroprotective effect on motor neurons and on muscular fibers (Pasinetti et al., 2013; Song et al., 2014). Furthermore, SIRT1 overexpression in mSOD1-G93A transgenic mice counteracted the toxic effect of mutated *SOD1* in neuronal cultures derived from this transgenic mouse model (Kim et al., 2007). In agreement, administration of resveratrol has also been reported to increase the lifespan of ALS murine models

(Douglas and Dillin, 2010; Song et al., 2014), an effect that seems to be related to the expression and activation of several pathways involving not only SIRT1, but also 5'-AMP-activated protein kinase (AMPK) (Mancuso et al., 2014; Song et al., 2014).

Noteworthy, since HDAC can regulate the acetylation of several proteins in addition to histones, numerous pathways other than transcription regulation can be modulated by this class of enzymes (Xiong and Guan, 2012). For example, cellular and, in particular, mitochondrial metabolism can be affected by HDAC activity. Indeed, since ~99% of all mitochondrial proteins are codified by the nuclear genome, alterations in nuclear DNA triggered by HDAC modulation and epigenetic modifications may in turn affect mitochondrial function (Devall et al., 2016). In support of this hypothesis, it has already been described that SIRT3 (considered the most important deacetylase of mitochondrial proteins) (Lombard et al., 2007) can control not only the levels of mitochondrial phosphorylation, but also the production of ROS and, therefore, levels of oxidative stress (Giralt and Villarroya, 2012) and mitochondrial fragmentation in cortical neurons in the presence of mSOD1 (Song et al., 2013).

Along with mitochondrial function control, it has also been revealed that HDAC modulation regulates autophagy, the main pathway responsible for the degradation of aggregated proteins and deregulated mitochondria (Corcoran et al., 2004; Olzmann et al., 2008; Trüe and Matthias, 2012; Liang et al., 2013). Within this scenario, it has been shown that HDAC1 inhibition induces autophagy (Oh et al., 2008), mitophagy (known to be essential for the maintenance of mitochondrial integrity and function) (Green et al., 2011; Andreux et al., 2013) is increased by overexpression of Sir2 (Koh et al., 2012), and that HDAC6 controls autophagosome and lysosome fusion (Lee et al., 2010). Moreover, in the *SOD1*-G93A transgenic model of ALS a decrease in HDAC6 expression was found both at the onset and the end stage of disease progression, and the upregulation of this HDAC could increase the life expectancy of these transgenic animals (Chen et al., 2015). However, it was also shown that HDAC6 deficiency could induce an upregulation of tubulin acetylation, which was related to an increase in cell viability (Gal et al., 2013; Taes et al., 2013). More recently, HDAC6 inhibition was suggested to be neuroprotective, since its ablation improves axonal transport and decreases protein aggregation, thus enhancing the clearance of cytosolic proteins (Jimenez-Pacheco et al., 2017). In accordance, Kim and collaborators demonstrated that the TDP-43 and the *FUS* proteins are able to enclose HDAC6 mRNA (Kim et al., 2010). Given these discrepant results, future studies are warranted to further elucidate the exact role of HDAC6 on the neuropathology of ALS. On the other hand, genetic and pharmacological induction of the mitophagy receptor Nip3-like protein X (NIX) was recently shown to prevent mitochondrial degradation in cells derived from Parkinson's disease individuals (Koentjoro et al., 2017; Sarkar et al., 2018). Future studies are warranted to determine whether strategy can also be beneficial in models of ALS.

Because epigenetic deregulation may be triggered by the same long-term environmental factors that underlie an increased risk of developing this neurodegenerative disorder, the accumulation of epigenetic modifications throughout life might contribute

to the onset and progression of ALS (Paez-Colasante et al., 2015). Indeed, it has been proposed that the silencing of genes that are vital for motor neuron function by epigenetic modifications could underlie, at least in part, sALS. However, several studies revealed an absence of methylation in the promoter region of several ALS-related genes, such as *SOD1*, vascular endothelial growth factor (VEGF), and glutamate type I transporter (GLT1) (Morahan et al., 2007; Oates and Pamphlett, 2007; Yang et al., 2010). However, an increase in DNA methylation was found in the blood of ALS subjects, regardless of the time of onset of the disorder (Tremolizzo et al., 2014). Moreover, total cytosine hydroxymethylation has been found in the brains of end-stage *SOD1* transgenic animals (Figueroa-Romero et al., 2019), while altered levels of DNA methylation have been reported in postmortem brains from sALS individuals when compared to age-matched controls (Morahan et al., 2009). Curiously, 60% of the genes affected by such changes are involved in neurotransmission, oxidative stress, and calcium handling, mechanisms that are thought to be disrupted in ALS (Morahan et al., 2009). Further supporting a role for DNA methylation in ALS is the fact that DNA-(cytosine-5)-methyltransferase 3A (DNMT3A) was shown to be overexpressed in the brain and spinal cord of ALS patients, and this overexpression seems to be related to cell death in motor neuron like cells *in vitro* (Chestnut et al., 2011). In addition, *TDP-43* has been related to uncommon DNA methylation (Appleby-Mallinder et al., 2020). However, methylation of the *C9orf72* gene promoter is still controversial (Gijssels et al., 2015; Bauer, 2016).

Several other epigenetic alterations have also been described in different cellular and animal models of ALS, including models based on mutations in *Sod1* (G93A or H80R), *Tardbp*, and *Fus*. These alterations comprise changes in phosphoacetylation of serine 10 and lysine 14 on the H3 tail (H3K14ac-S10ph), dimethylation of lysine 4 on the H3 tail (H3K4me2), and trimethylation of lysine 9 on the H3 tail (H3K9me3) (Jimenez-Pacheco et al., 2017; Masala et al., 2018). It has also been shown that *FUS* can abrogate histone 4 (H4) methylation in arginine residues by inhibiting methyltransferase *PRMT1* (Tibshirani et al., 2015), and that overexpression of human *FUS* in yeast diminishes H3 acetylation in two different residues, lysine 14 and lysine 56 (H3K14 and H3K56) (Chen K. et al., 2018). In addition, *FUS* was shown to inhibit *CBP/p300* HAT after binding to it, leading to a hypoacetylation state (Alao, 2007; Wang et al., 2008). Of note, the effects of *FUS* and *TDP-43* on epigenome alterations seem to be associated with specific variants of the disease (Masala et al., 2018). In addition, it was recently reported that astrocytes and neurons from *C9orf72* BAC mice showed a decrease in H3K9me3 and this was associated with cell death and memory deficiency (Jury et al., 2020).

Given that epigenetics plays a role in the pathogenesis of ALS, we can hypothesize that modulation of neurogenic function through epigenetic modifications may influence disease progression and neurodegeneration in ALS. In support of this hypothesis, recent studies have demonstrated that epigenetic modulation can determine cell type and influence the differentiation of NSCs, during both development and the

postnatal period (Chen et al., 2019; Desai et al., 2019). For example, it was verified that moderate changes in the redox status of *SIRT1* can suppress NSC proliferation and direct its differentiation toward the astrocytic phenotype, suggesting the existence of a still unidentified metabolic master switch that can determine the fate of neural progenitors (Prozorovski et al., 2008). In addition, inhibition of HDACs is known to prompt neuronal differentiation in NSCs derived from the adult hippocampal DG (Hsieh et al., 2004). Furthermore, valproic acid, a well-known anticonvulsant and mood stabilizer (Henry et al., 2011), was presented to induce neural differentiation of embryonic hippocampal neural progenitor cells *in vitro* and *in vivo* by decreasing proliferation and increasing neuronal differentiation through a mechanism that involves acetylation of histone 3 and 4 (Yu et al., 2009). Valproic acid also seems to inhibit astrocytic and oligodendrocytic differentiation by inducing the expression of neurogenic differentiation factor 1 (*NeuroD*) (Hsieh et al., 2004).

The role of HAT modulation on neurogenesis is equally promising. It has already been described that a deficiency of HATs reduces the ability of SVZ NSCs to self-renew and differentiate (Merson et al., 2006). For example, an absence of the HAT lysine acetyltransferase 6B (*KAT6B*) has been shown to result in a reduction in the number of migrating neuroblasts in the rostral migratory stream (RMS) and, consequently, a considerable reduction in the number of new interneurons in the OB (Merson et al., 2006). Increasing evidence has also revealed that histone modification and non-coding RNA expression are closely associated with multiple aspects of the different stages of the adult neurogenesis process (Yao et al., 2016), and histone acetylation in particular is known to affect the differentiation of NSCs (Hsieh et al., 2004; Mu et al., 2010; Kameda et al., 2018).

More recently, a few studies have also assessed whether epigenetic modifications in mtDNA also occur in the context of ALS (Jimenez-Pacheco et al., 2017; Stocco et al., 2018). Within this scenario, an increase in mitochondrial DNA methylation and in the levels of *DNMT3A* were found in the spinal cord and muscles of an animal model of ALS (Maekawa et al., 2001). In agreement, an up-regulation of *DNMT3A* was also seen in postmortem mitochondrial fractions from the motor cortex of ALS patients (Chestnut et al., 2011). In addition, changes in 5mC and *DNMT1* have also been noted in neuronal mitochondria from ALS patients (Chestnut et al., 2011). Given these findings, epigenetic modulation of mtDNA might also contribute to the pathogenesis of ALS and play a role in determining disease onset, as well as environmental vulnerability and response to toxicity (Iacobazzi et al., 2013).

Of note, an increase in mtDNA copy number has been reported in ALS patients, particularly in individuals with the *SOD1* and *C9orf72* mutations. However, subjects with the *SOD1* mutations also present a reduction in methylation levels in the D-loop region (Stocco et al., 2018). Since this region is critical for mtDNA replication and transcription, such demethylation might indicate a compensatory mechanism to counteract the overall upregulation of mtDNA (Stocco et al., 2018). Curiously, an increase in the mitochondrial gene responsible for the

methylation of 16S rRNA was observed in spinal cord neurons and skeletal muscle of ALS transgenic mice (Wong et al., 2013).

Given the foregoing evidence, HDAC modulation, resulting in epigenetic modifications and consequent alterations of gene expression, mitochondrial function, and autophagy/mitophagy may exhibit a broad influence on neurogenesis. However, to date only a few studies (five at the date of revision of this article) have investigated the relationship among epigenetic modifications, mitochondrial function/bioenergetics, and neurogenesis. Nevertheless, one of these recently published studies has elegantly presented that cellular reprogramming by alterations in cellular metabolism is the main mechanism underlying changes in morphogenesis and that NSC differentiation can be modulated by mitochondrial function (Xie et al., 2019). Future studies are clearly necessary in order to elucidate the underpinnings of the relationship among epigenetics, mitochondrial function, and neurogenesis, and whether modulation of this relationship can alter the course of neurodegenerative diseases such as ALS.

CONCLUSION

Various lines of evidence primarily from preclinical studies performed in animal models of ALS suggest that preservation and/or an increase in mitochondrial function and metabolism could be beneficial in altering the course of this devastating neurodegenerative disease. In addition, increased mitochondrial function also has the potential to enhance adult neurogenesis, which is known to be altered by neurodegenerative processes. Thus, one postulates that improving mitochondrial function may promote NSC viability and proliferation, as well as neuronal differentiation and migration. As such, modulation of mitochondrial function may be an attractive beneficial strategy not only by promoting bioenergetics and reducing oxidative stress but also by facilitating pro-neurogenic processes in regions of the brain (and CNS) particularly affected by neurodegeneration. NSCs differentiation can be modulated by mitochondrial function and/or responsible for the signs and symptoms of the disease (Figure 2). Future studies using postmortem brain tissue from patients afflicted with ALS are thus essential to further elucidate the relationship between mitochondrial (dys)function and neurogenesis in the ALS brain. Moreover, additional preclinical studies using *in vivo* ALS animal models are needed in order to determine whether therapeutic

manipulations aimed at modulating mitochondrial function can impact not only neurogenic function but also disease severity and progression.

Finally, although progress has been made with regard to characterizing the contribution of epigenetics for the pathogenesis of ALS, the possibility that epigenetic modifications can indeed alter mitochondrial function and neurogenesis in ALS is still a matter of debate. Additional studies are clearly required in the near future to answer this challenging question and deepen our current understanding of ALS pathogenesis. Elucidating the relationships among epigenetics and mitochondrial function may not only provide the missing link in the understanding of the mechanisms underlying neurodegeneration in sporadic diseases such as ALS, but also might in turn open new doors in the search for effective disease-modifying treatments for these devastating neurological disorders.

THE INTEGRITY OF RESEARCH AND REPORTING

This is a review manuscript and therefore does not report original preclinical (i.e., animal) or clinical (i.e., human) data.

AUTHOR CONTRIBUTIONS

MC and TR drafted the initial version of the review. EH and AS helped with the formatting and figures. CB and JG-M collaborated in the revision of the version. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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