Review Article

Altered Gene Expression, Mitochondrial Damage and Oxidative Stress: Converging Routes in Motor Neuron Degeneration

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Motor neuron diseases (MNDs) are a rather heterogeneous group of diseases, with either sporadic or genetic origin or both, all characterized by the progressive degeneration of motor neurons. At the cellular level, MNDs share features such as protein misfolding and aggregation, mitochondrial damage and energy deficit, and excitotoxicity and calcium mishandling. This is particularly well demonstrated in ALS, where both sporadic and familial forms share the same symptoms and pathological phenotype, with a prominent role for mitochondrial damage and resulting oxidative stress. Based on recent data, however, altered control of gene expression seems to be a most relevant, and previously overlooked, player in MNDs. Here we discuss which may be the links that make pathways apparently as different as altered gene expression, mitochondrial damage, and oxidative stress converge to generate a similar motoneuron-toxic phenotype.

1. Introduction

Motor neuron diseases (MNDs) are a rather heterogeneous group of diseases, with either sporadic or genetic origin or both, all characterized by the progressive degeneration of motor neurons. All MNDs are primarily axonopathies of the motor neurons in which neuromuscular synapses are early targets of damage and death of motor neurons probably occurs following loss of the neuromuscular junctions [1]. MNDs may manifest as weakness, atrophy of muscles, difficulty in breathing, speaking, and swallowing, with symptoms and severity varying as a consequence of the different involvement of upper or lower motor neurons or both.

The most common and studied form in adults is Amyotrophic Lateral Sclerosis (ALS), followed by Progressive Bulbar Palsy (PBP), the rarer forms being Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis (PLS). These conditions seem to form a continuum of diseases since only part of patients have a "pure" phenotype, while others with PBP or PLS eventually develop the widespread symptoms common to ALS [2]. In all these MNDs, onset of symptoms occurs mainly in people aged 40–70. Life expectancy is between 2 to about 5 years after onset in ALS and 6 months to 3 years in PBP, while pure PLS patients may have a normal or near-to-normal life duration. MNDs also include Spinal and Bulbar Muscular Atrophy (SBMA), in which age of onset and severity of manifestations vary from adolescence to old age, but longevity is usually not compromised. Infantile MNDs include Spinal Muscular Atrophy (SMA) with an infantile or juvenile onset and Lethal Congenital Contracture Syndrome (LCCS), causing prenatal death and thus being the most severe form of motor neuron disease.

2. Aetiology of MNDs

LCCS1 is an autosomal recessive condition found in communities of the northeastern part of Finland with a prevalence of 1 in 25,250 births [3]. LCCS manifests *in utero* with a marked atrophy of spinal cord motor neurons and fetal immobility due to lack of anterior horn motor neurons, severe atrophy of the ventral spinal cord, and hypoplastic skeletal muscles. It is characterized by total immobility of the fetus, detectable at the 13th week of pregnancy and invariably leading to prenatal

death before the 32nd gestational week. The defective gene for LCCS1 is a 16-exon gene coding for GLE1, an mRNA export mediator that is known to interact with the nuclear pore complex and is expressed in the neural tube of 11-day-old mice embryos, specifically in the ventral cell population from which the motor neurons differentiate, and later in other tissues including somites, from which skeletal muscle and bone tissue differentiate [3]. The most frequent mutation in LCCS1 (FinMajor) does not dramatically alter the stability or localization of the protein GLE1 but is predicted to introduce three aminoacid residues in a region that may be critical in the interaction between GLE1 and a motor neuron-specific protein [3].

SMA is the most frequent genetic cause of infant mortality and exists in various forms invariably caused by a genetic defect. Patients with the most common form (proximal SMA) are either deleted for the nine-exon gene *SMN1*, encoding the ubiquitously expressed protein SMN (Survival Motor Neuron) or carry small mutations in the same gene. However, SMA patients always carry at least one copy of the gene SMN2, which encodes the same protein as SMN1 and is only partially functional because of a critical, translationally silent single nucleotide C/T transition inside exon 7 that profoundly affects correct splicing. The clinical severity of SMA ranges from respiratory distress at birth associated with limited life expectancy (SMA1) to onset at older than 10 years and a normal life expectancy (SMA4) and is inversely related to the level of SMN2 compensating for SMN1 deletion [4].

SBMA (also called Kennedy's disease) is an X-linked recessive motor neuron disease in which only lower spinal cord and brain stem motor neurons are affected [5]. SBMA is caused by a polyglutamine expansion in the androgen receptor (AR) [6]; CAG repeat numbers range from 38 to 62 in SBMA patients, whereas healthy individuals have 10 to 36 CAG repeats. Symptoms appear in childhood or early adolescence [7]; SBMA is a rare disease, with the exception of some population in the Vasa region of Western Finland where it was estimated that the prevalence is 13 in 85,000 male inhabitants [8].

While SMA, SBMA, and LCCS1 are invariably familial diseases, adult-onset MNDs are both sporadic and familial. PBP, PMA, and PLS are usually sporadic. ALS occurs sporadically in the majority of cases [9]. Proposed risk factors for ALS include ingestion of high concentrations of β-methyl-amino-L-alanine [10], use of cholesterol-lowering drugs [11], intensive physical exercise [12] including football playing [13, 14] and service in the USA Army [15], possibly linked to intermittent occupational hypoxia [16] or to head injury [17–19]. Environmental factors also include cigarette smoking [18, 20], exposure to heavy metals [21], and pesticides or herbicides [22–24]. Approximately 10% of ALS cases is inherited, with multiple autosomal dominant and recessive forms that have been ascribed to mutations in a number of different genes, each of them accounting for a different percentage of cases (Table 1). Interestingly, ALS-associated mutated proteins are implicated in a wide range of cellular processes, from antioxidant response to axonal and vesicular transport, angiogenesis, endoplasmic reticulum (ER) stress and unfolded protein response (UPR), and, most noticeably, to RNA metabolism.

3. Multifactoriality of MNDs: The Role of Altered Gene Expression

At the cellular level, MNDs share features such as protein misfolding and aggregation, mitochondrial damage and energy deficit, excitotoxicity, and calcium mishandling [1], a condition often indicated as multifactoriality. This is particularly well demonstrated in ALS, where both sporadic and familial forms share the same symptoms and pathological phenotype, that are recapitulated in available animal and cell models, with a prominent role for mitochondrial damage and resulting oxidative stress (for an extended Review, see [25]). Oxidative stress is reported also in SMA [26] and reactive oxygen species (ROS) inhibit assembly and activity of SMN complex in a dose-dependent manner [27]. Mitochondrial damage seems to be invariably present in neurodegenerative conditions [28] including SMA [29–32] and SBMA [33], in which mitochondrial dysfunction may be due to the interaction between AR and cytochrome c oxidase subunit Vb (COXVb) [34].

Based on recent data, however, altered control of gene expression seems to be a most relevant, and previously overlooked, player in MNDs.

Several studies addressing epigenetic modifications, transcriptomics, and proteomics of models and tissues from patients indicate that the overall pattern of gene expression is modified in MNDs. Because of the known non-cell autonomous mechanism of death of motor neurons, studies in ALS have been performed in tissues [35, 36] and in neuronal and in nonneuronal cultured cells (astrocytes, muscle) and revealed that most of the deregulated genes are involved in defense responses, cytoskeletal dynamics, protein degradation system, and mitochondrial dysfunction in neurons [37], while the insulin-like growth factor-1 receptor and the RNA-binding protein ROD1 are the most downregulated genes in glia [38]. The pattern is altered also in muscle, in which many of deregulated genes are the same found in surgically denervated muscles, while others appear to be ALS-specific and include proteins clearly involved in the redox response (e.g., metallothionein-2 and thioredoxin-1) [39, 40]. In a recent proteomic study on embryonic stem cell from a severe SMA mouse model differentiated into motor neurons in vitro, Wu et al. reported that 6 proteins are downregulated and 14 upregulated in this model. Most of these proteins belong to the same categories altered in ALS models, that is, are involved in energy metabolism, cell stress response, protein degradation, and cytoskeleton stability [41].

As in other neurodegenerative conditions, alterations of transcription in MNDs may follow altered epigenetic control due to an unbalance between histone acetyl transferases (HATs) and histone deacetylases (HDACs, including sirtuins, SIRTs) activities [42]. These enzymes catalyze forward and reverse reactions of lysine residue acetylation; thus, HATs modify core histone tails thereby enhancing DNA accessibility to transcription factors (TFs), while HDACs activity in general results in transcriptional repression and gene silencing. Interestingly, various TFs, like RelA, E2F, p53, and GATA1, which form part of the transcription initiation complex, are themselves substrates susceptible to the action of HATs and HDACs.

Table 1: Genes involved in MNDs.

Gene	Protein	MND	Main known function
SOD1	Cu, Zn superoxide dismutase	ALS1	Antioxidant enzyme
ALS2	Alsin	ALS2	guanine nucleotide exchange factor for GTPases
SETX	Senataxin	ALS4	DNA/RNA metabolism and repair
SPG11	Spataxin	ALS5	Neuron differentiation and axonal transport
FUS/TLS	Fused in sarcoma	ALS6	RNA binding protein
VAPB	VAMP-associated protein B	ALS8	Trafficking between the endoplasmic reticulum and Golgi apparatus
TDP-43	TAR-DNA-binding protein-43	ALS9	DNA- and RNA-binding protein
ANG	Angiogenin	ALS10	Angiogenesis in response to hypoxia; possibly RNA metabolism
FIG4	PI(3,5)P(2)5-phosphatase	ALS11	Metabolism of phosphatidyl inositol bisphosphate and vesicle dynamic
OPTN	Optineurin	ALS12	Vesicular trafficking
nAChR	Neuronal nicotinic acetylcholine receptor	ALS	Glutamatergic pathway
CHMP2B	Charged multivesicular protein 2B	ALS	Chromatin-modifying protein/charged multivesicular body protein family
VCP	Valosin-containing protein	ALS	Membrane trafficking, organelle biogenesis, maturation of ubiquitin-containing autophagosomes
DAO	D-aminoacid oxidase	ALS	Oxidative deamination of D-aminoacid
UBQLN2	Ubiquilin2	ALS	Ubiquitin-proteasome response
Sig-1R	Sigma-1 receptor	ALS	ER chaperone, modulates calcium signaling through the IP3 receptor
C9ORF72	Unknown	ALS	Unknown
AR	Androgen receptor	SBMA	Androgen receptor
SMN	Survival Motor Neuron	SMA	RNA processing
GLE1	Nucleoporin GLE1	LCCS1	Export of mRNAs containing poly(A)

Evidence for the involvement of this kind of regulation in MNDs is accumulating, although still far from definitive, and unspecific HDAC inhibitors such as sodium phenylbutyrate, trichostatin A, and valproic acid have been tested as neuroprotective drugs for the treatment of ALS with some positive result [43–47]. It is interesting to note that valproic acid is also endowed with antioxidative and antiapoptotic properties. However, most likely only selected HDACs participate to onset or propagation of motor neuron damage and thus must be targeted for an effective therapy. This concept is strengthened by the observation that complexes formed by ALS-linked proteins TDP-43 and FUS/TLS control the expression level of HDAC6 [48].

The SMN gene has a reproducible pattern of histone acetylation that is largely conserved among different tissues and species [49] and several HDAC pan-inhibitors such as suberoylanilide hydroxamic acid (SAHA) [50], trichostatin A [51], and the benzamide M344 [52] increase SMN2 transcript and protein levels. Valproic acid is currently tested in phase I and II clinical trials for the treatment of SMA (http://clinicaltrials.gov/). However, valproic acid has also serious adverse effects in cell and mice models for SMA [53, 54] pointing again to the need of inhibition of selected HDACs in MNDs, especially in the light of a recent report that the SMN2 gene is differentially regulated by individual HDAC

proteins and silencing of HDAC5 and 6 enhances inclusion of an alternatively spliced exon in SMN2 [55]. Finally, oral administration of the HDAC inhibitor sodium butyrate has been tested also in a transgenic mouse model of SBMA with some positive outcome but only within a narrow range of drug dosage [56].

Epigenetic control of transcription may also occur via methylation by DNA methyltransferases (DNMTs) or histone methyltransferases (HMTs), both using S-adenosylmethionine (SAM o AdoMet) as the methyl donor. DNA methylation in eukaryotes occurs by the covalent modification of cytosine residues (on the fifth carbon) in CpG dinucleotides, leading to gene silencing. Methylation of histones (as well as transcription factors) occurs on lysine or arginine. Methylated lysine residues can carry up to three methyl moieties on their amine group, whereas arginine can be mono- or dimethylated on the guanidinyl group. Lysine methylation of histones is associated with activation or repression of transcription, depending on the degree of methylation and on the residue location [57].

Methylation may be extremely relevant in MNDs if one considers, for instance, that recognition of some Sm proteins by the SMN complex (that mediates the assembly of the Sm proteins onto snRNAs involved in pre-mRNA splicing and histone mRNA processing) is dependent on symmetrical

dimethyl arginine modifications of their RG-rich tails [58, 59]. This methylation is achieved by PRMT (protein arginine methyltransferase) 5 or by PRMT7, two enzymes that function nonredundantly [60] and utilize SAM as methyl donor. Furthermore, the SMN2 gene is subject to gene silencing by DNA methylation and some HDAC inhibitors including vorinostat and romidepsin are able to bypass SMN2 gene silencing by DNA methylation, while others such as valproic acid and phenylbutyrate are not [61].

Other observations support the concept that MNDs may be considered as "RNA dysmetabolisms" [62]. As reported in Table 1, several of the genetic factors involved in MNDs encode proteins with a role in RNA metabolism, and some overlap may exist among different diseases. For instance, copy number abnormalities of the SMN genes have been reported in sporadic ALS, although decrease of SMN protein in the anterior horn cells of ALS patients may be only a secondary phenomenon [63, 64]. RNA metabolism, however, consists of several intertwined steps, such as pre-mRNA splicing, mRNA transport, translational regulation, or mRNA decay, and the precise RNA pathway that is affected in a single MND remains unknown because virtually every one of the involved RNA-binding proteins has been implicated in more than one of these steps. Thus, it is not clear why motor neurons are so vulnerable to mutations in RNA-binding proteins.

Very recently, familial ALS has been associated with an expansion of a noncoding GGGGCC hexanucleotide repeat in the gene *C9ORF72* [65, 66] that codes for an unknown protein. The transcribed GGGGCC repeat forms intracellular accumulations of RNA fragments in cells in the frontal cortex and the spinal cord from patients carrying the expansion [65]. These RNA *foci* are composed of the expanded nucleotide repeats that may disturb transcription by sequestering RNA-binding proteins involved in transcription regulation as observed for other expanded RNA repeats diseases [67] such as myotonic dystrophy [68]. Interestingly, the GGGGCC sequence also represents a potential binding site of several RNA-binding proteins including hnRNP A2/B1, a TDP-43 interactor [69, 70].

4. Altered Gene Expression, Mitochondrial Damage, and Oxidative Stress in MNDs: Which Are the Links?

Which are the links among altered gene expression, mitochondrial damage, and oxidative stress in MNDs is not clear yet. While oxidative stress and mitochondrial dysfunction are obviously connected into a vicious cycle in which excess in ROS production may influence the functionality of the organelles, that in turn would produce excess ROS, the connection with altered gene expression in MNDs is still somewhat foggy.

A few considerations may help to shed some light on possible, not mutually exclusive, mechanisms.

In analogy to what has been proposed in development [71] and in cancer [72], an interplay among oxidative stress,

thiol redox signaling, and epigenetic modulation by methylation may be critical in motor neurons. The antioxidant capacity of cells is influenced by the production of glutathione (GSH), and increased GSH production influences DNA and histone methylation by limiting the availability of SAM, the cofactor utilized during epigenetic control of gene expression by DNA and histone methyltransferases [71]. The above mentioned forms of methylation, which are relevant in MNDs, are not directly linked, since they involve different enzymes and different targets. However, they all require the same methyl donor, which could be limiting in MNDs.

HDACs themselves seem to be linked to and modulated by oxidative stress. Pan-HDAC inhibition promotes neuronal protection against oxidative stress in a model of glutathione depletion [73], thus suggesting that HDACs are downstream mediator in the mechanisms of toxicity by ROS, while carbonylation of reactive cysteines of some, but not all, class I HDACs causes reduction of histone deacetylase activity and change in histones acetylation and transcription of genes repressed by these HDACs [74]. Thus, oxidative stress may be a modulator of gene expression through the modulation of DNA accessibility.

In turn, the activity of HDACs modulates alternative splicing of human genes when the nascent RNA is still associated with chromatin (in particular the splicing of hundreds of genes is altered upon HDAC inhibition) [75] but also the activity of various TFs. Noticeably, oxidative stress is also a modulator of several TFs and thus ROS and HDACs may concur in the generation of a pathological phenotype through the same mechanism. For instance, as reviewed by Rahman et al. [76], oxidative stress inhibits HDAC activity and activates HAT activity; this leads to NF-κB activation, which, in turn activates proinflammatory mediators. The antioxidant and/or anti-inflammatory effects of thiol molecules (GSH, N-acetyl-L-cysteine and Nacystelyn) and dietary polyphenols (e.g., curcumin and resveratrol) have a role in either the control of NF-κB activation or the modulation of HDAC. Thus, oxidative stress may regulate both TFs and chromatin remodeling which in turn impacts on proinflammatory responses.

Furthermore, SIRTs (class III HDACs) control the expression or the activity of a number of proteins involved in redox regulation (Table 2). Among these proteins, some are mitochondrial and many have been involved in one or more MNDs by transcriptomic/proteomic studies [77–79].

Last, but not the least, we have reported that mitochondrial damage itself is a cause of modification in the abundance of selected splicing variants [80] and that defective RNA metabolism seems to play a role also in SOD1-linked ALS and to descend directly from mitochondrial stress [81].

5. A Unifying Mechanism for MNDs?

From what summarized above, it is tempting to speculate that indeed all MNDs are mainly forms of RNA dysmetabolisms. Motor neurons seem to be exceedingly susceptible to defects in RNA transcription or processing; one appealing explanation is that they require that RNA is not only correctly

TABLE 2: Effects of class II HDACs (Sirtuins) on redox-related proteins.

Sirtuin	Target	Effect	Reference
SIRT1 (nucleus and mitochondria)	FOXO3a	↑ Transcriptional activity	[82]
	PGC-1α	↑ Transcriptional coactivation	[83, 84]
	HIF1α	↓ Transcriptional activity	[85]
	HIF2α	↑ Transcriptional activity	[86]
	eNOS	↑ Enzyme activity	[87]
	p53	Mediates transcriptional activity, depending on SIRT1 expression level	[88, 89]
SIRT2 (cytoplasm)	FOXO3a	↑ Transcriptional activity	[90]
	HIF1α	↓ Transcriptional activity	[91]
SIRT3 (mitochondria)	SOD2	↑ Enzyme activity	[92, 93]
	OTC	↑ Enzyme activity	[94]
	NDUFA9	↑ Enzyme activity	[95]
	GDH	↑ Enzyme activity	[96]
	IDH2	↑ Enzyme activity	[97]
SIRT4 (mitochondria)	GDH	↓ Enzyme activity	[98]
SIRT5 (mitochondria)	CPS1	↑ Enzyme activity	[99]
SIRT6 (mitochondria)	HIF1α	↓ Transcriptional activity	[100]
SIRT7 (nucleoli)	p53	Mediates transcriptional activity, depending on SIRT7 expression level	[101]

CPS1: carbamoyl phosphate synthetase 1; eNOS: endothelial nitric oxide synthase; FOXO3a: Forkhead box O3 a; GDH: glutamate dehydrogenase; HIF1α: hypoxia-inducible factor 1, alpha subunit; HIF2α: hypoxia-inducible factor 2, alpha subunit; IDH2: isocitrate dehydrogenase 2; NDUFA9: NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9; OTC: ornithine transcarbamylase; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SOD2: superoxide dismutase 2.

transcribed and spliced, but also correctly transported along axons to neuromuscular junctions (NMJ). While there is no clear demonstration of the presence of mRNAs at the NMJs yet, this process (at least in ALS) might resent from the known alterations in axonal transport that precedes onset of symptoms [102].

However, one form or the other of alteration of RNA expression may have different weight in different MNDs and, most importantly, RNA dysmetabolisms may be a primary event (for instance in SMA or in TDP43- and FUS/TLS-linked ALS) or dysregulation of components of the genetic machinery (the HATs/HDACs system, transcription factors, the splicing complex) may be secondary to oxidative stress or energy failure. In turn, which step is the primary site of damage may dictate the severity of disease (age of onset, progression), and which cell type beside motor neurons is primarily affected may dictate the form of MND. This field surely deserves further investigation aimed to the individuation of novel therapeutic approaches for MNDs.

Abbreviations

ALS:	Amyotrophic lateral sclerosis
ALS2:	Alsin
ANG:	Angiogenin
AR:	Androgen receptor
CHMP2B:	Charged multivesicular protein 2B
COXVb:	Cytochrome c oxidase subunit Vb
DAO:	D-amino acid oxidase
DNMT:	DNA methyltransferase
ER:	Endoplasmic reticulum
FIG4:	PI(3,5)P(2)5-phosphatase
FUS/TLS:	Fused in sarcoma/translocated in liposarcoma
GLE1:	Nucleoporin GLE1
GSH:	Glutathione
HAT:	Histone acetyl transferase
HDAC:	Histone deacetylase
HMT:	Histone methyltransferase
LCCS:	Lethal congenital contracture syndrome
MND:	Motor neuron disease
nAChR:	Neuronal nicotinic acetylcholine receptor
OPTN:	Optineurin;
PBP:	Progressive bulbar palsy
PLS:	Primary lateral sclerosis
PMA:	Progressive muscular atrophy
PRMT5:	Protein arginine methyltransferase 5
PRMT7:	Protein arginine methyltransferase 7
ROS:	Reactive oxygen species
SAHA:	Suberoylanilide hydroxamic acid
SAM:	S-adenosylmethionine
SBMA:	Spinal and bulbar muscular atrophy
SETX:	Senataxin
Sig-1R Sigma:	1 receptor

SIRT: Sirtuin
SMA: Spinal muscular atrophy
SMN: Survival motor neuron
SOD1:   Cu, Zn superoxide dismutase
SPG11:   Spataxin
TDP-43:   TAR DNA-binding protein 43
TF: Transcription factor
UBQLN2:   Ubiquilin 2
UPR: Unfolded protein response
VAPB: VAMP-associated protein
VCP: Valosin-containing protein.

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References

[1] S. Saxena and P. Caroni, "Selective neuronal vulnerability in neurodegenerative diseases: from stressor thresholds to degeneration," *Neuron*, vol. 71, no. 1, pp. 35–48, 2011.

[2] M. J. Strong and P. H. Gordon, "Primary lateral sclerosis, hereditary spastic paraplegia and amyotrophic lateral sclerosis: discrete entities or spectrum?" *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, vol. 6, no. 1, pp. 8–16, 2005.

[3] H. O. Nousiainen, M. Kestilä, N. Pakkasjärvi et al., "Mutations in mRNA export mediator *GLE1* result in a fetal motoneuron disease," *Nature Genetics*, vol. 40, no. 2, pp. 155–157, 2008.

[4] M. R. Lunn and C. H. Wang, "Spinal muscular atrophy," *The Lancet*, vol. 371, no. 9630, pp. 2120–2133, 2008.

[5] G. Sobue, Y. Hashizume, E. Mukai, M. Hirayama, T. Mitsuma, and A. Takahashi, "X-linked recessive bulbospinal neuronopathy. A clinicopathological study," *Brain*, vol. 112, part 1, pp. 209–232, 1989.

[6] A. R. La Spada, E. M. Wilson, D. B. Lubahn, A. E. Harding, and K. H. Fischbeck, "Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy," *Nature*, vol. 352, no. 6330, pp. 77–79, 1991.

[7] A. D. Sperfeld, J. Karitzky, D. Brummer et al., "X-linked bulbospinal neuronopathy: Kennedy disease," *Archives of Neurology*, vol. 59, no. 12, pp. 1921–1926, 2002.

[8] B. Udd, V. Juvonen, L. Hakamies et al., "High prevalence of Kennedy's disease Western Finland—is the syndrome underdiagnosed?" *Acta Neurologica Scandinavica*, vol. 98, no. 2, pp. 128–133, 1998.

[9] P. N. Valdmanis, H. Daoud, P. A. Dion, and G. A. Rouleau, "Recent advances in the genetics of amyotrophic lateral sclerosis," *Current Neurology and Neuroscience Reports*, vol. 9, no. 3, pp. 198–205, 2009.

[10] P. A. Cox and O. W. Sacks, "Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam," *Neurology*, vol. 58, no. 6, pp. 956–959, 2002.

[11] B. A. Golomb, E. K. Kwon, S. Koperski, and M. A. Evans, "Amyotrophic lateral sclerosis-like conditions in possible association with cholesterol-lowering drugs: an analysis of patient reports to the University of California, San Diego (UCSD) statin effects study," *Drug Safety*, vol. 32, no. 8, pp. 649–661, 2009.

[12] C. A. Harwood, C. J. McDermott, and P. J. Shaw, "Physical activity as an exogenous risk factor in motor neuron disease (MND): a review of the evidence," *Amyotrophic Lateral Sclerosis*, vol. 10, no. 4, pp. 191–204, 2009.

[13] A. Chiò, G. Benzi, M. Dossena, R. Mutani, and G. Mora, "Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players," *Brain*, vol. 128, part 3, pp. 472–476, 2005.

[14] P. Wicks, J. Ganesalingham, C. Collin, M. Prevett, N. P. Leigh, and A. Al-Chalabi, "Three soccer playing friends with simultaneous amyotrophic lateral sclerosis," *Amyotrophic Lateral Sclerosis*, vol. 8, no. 3, pp. 177–179, 2007.

[15] E. J. Kasarskis, J. H. Lindquist, C. J. Coffman et al., "Clinical aspects of ALS in Gulf War Veterans," *Amyotrophic Lateral Sclerosis*, vol. 10, no. 1, pp. 35–41, 2009.

[16] N. Vanacore, P. Cocco, D. Fadda, and M. Dosemeci, "Job strain, hypoxia and risk of amyotrophic lateral sclerosis: results from a death certificate study," *Amyotrophic Lateral Sclerosis*, vol. 11, no. 5, pp. 430–434, 2010.

[17] H. Chen, M. Richard, D. P. Sandler, D. M. Umbach, and F. Kamel, "Head injury and amyotrophic lateral sclerosis," *American Journal of Epidemiology*, vol. 166, no. 7, pp. 810–816, 2007.

[18] S. Schmidt, L. C. Kwee, K. D. Allen, and E. Z. Oddone, "Association of ALS with head injury, cigarette smoking and APOE genotypes," *Journal of the Neurological Sciences*, vol. 291, no. 1-2, pp. 22–29, 2010.

[19] A. C. McKee et al., "TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy," *Journal of Neuropathology and Experimental Neurology*, vol. 69, no. 9, pp. 918–929, 2010.

[20] V. Gallo, H. B. Bueno-De-Mesquita, R. Vermeulen et al., "Smoking and risk for amyotrophic lateral sclerosis: analysis of the EPIC cohort," *Annals of Neurology*, vol. 65, no. 4, pp. 378–385, 2009.

[21] F. Kamel, D. M. Umbach, H. Hu et al., "Lead exposure as a risk factor for amyotrophic lateral sclerosis," *Neurodegenerative Diseases*, vol. 2, no. 3-4, pp. 195–201, 2005.

[22] B. R. Brooks, "Risk factors in the early diagnosis of ALS: North American epidemiological studies," *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, vol. 1, supplement 1, pp. S19–S26, 2000.

[23] C. J. Burns, K. K. Beard, and J. B. Cartmill, "Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update," *Occupational and Environmental Medicine*, vol. 58, no. 1, pp. 24–30, 2001.

[24] N. A. Sutedja, J. H. Veldink, K. Fischer et al., "Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: a systematic review," *Amyotrophic Lateral Sclerosis*, vol. 10, no. 5-6, pp. 302–309, 2009.

[25] M. Cozzolino and M. T. Carri, "Mitochondrial dysfunction in ALS," *Progress in Neurobiology*, vol. 97, no. 2, pp. 54–66, 2012.

[26] M. Hayashi, S. Araki, N. Arai et al., "Oxidative stress and disturbed glutamate transport in spinal muscular atrophy," *Brain and Development*, vol. 24, no. 8, pp. 770–775, 2002.

[27] L. Wan, E. Ottinger, S. Cho, and G. Dreyfuss, "Inactivation of the SMN complex by oxidative stress," *Molecular Cell*, vol. 31, no. 2, pp. 244–254, 2008.

[28] E. A. Schon and S. Przedborski, "Mitochondria: the next (Neurode) generation," *Neuron*, vol. 70, no. 6, pp. 1033–1053, 2011.

[29] A. Berger, J. A. Mayr, D. Meierhofer et al., "Severe depletion of mitochondrial DNA in spinal muscular atrophy," *Acta Neuropathologica*, vol. 105, no. 3, pp. 245–251, 2003.

[30] S. Jongpiputvanich, T. Sueblinvong, and T. Norapucsunton, "Mitochondrial respiratory chain dysfunction in various neuromuscular diseases," *Journal of Clinical Neuroscience*, vol. 12, no. 4, pp. 426–428, 2005.

[31] G. Acsadi, I. Lee, X. Li et al., "Mitochondrial dysfunction in a neural cell model of spinal muscular atrophy," *Journal of Neuroscience Research*, vol. 87, no. 12, pp. 2748–2756, 2009.

[32] T. Voigt, K. Meyer, O. Baum, and D. Schümperli, "Ultrastructural changes in diaphragm neuromuscular junctions in a severe mouse model for Spinal Muscular Atrophy and their prevention by bifunctional U7 snRNA correcting SMN2 splicing," *Neuromuscular Disorders*, vol. 20, no. 11, pp. 744–752, 2010.

[33] S. Ranganathan, G. G. Harmison, K. Meyertholen, M. Pennuto, B. G. Burnett, and K. H. Fischbeck, "Mitochondrial abnormalities in spinal and bulbar muscular atrophy," *Human Molecular Genetics*, vol. 18, no. 1, pp. 27–42, 2009.

[34] A. M. J. Beauchemin, B. Gottlieb, L. K. Beitel, Y. A. Elhaji, L. Pinsky, and M. A. Trifiro, "Cytochrome *c* oxidase subunit Vb interacts with human androgen receptor: a potential mechanism for neurotoxicity in spinobulbar muscular atrophy," *Brain Research Bulletin*, vol. 56, no. 3-4, pp. 285–297, 2001.

[35] A. Malaspina, N. Kaushik, and J. de Belleroche, "Differential expression of 14 genes in amyotrophic lateral sclerosis spinal cord detected using gridded cDNA arrays," *Journal of Neurochemistry*, vol. 77, no. 1, pp. 132–145, 2001.

[36] C. W. Lederer, A. Torrisi, M. Pantelidou, N. Santama, and S. Cavallaro, "Pathways and genes differentially expressed in the motor cortex of patients with sporadic amyotrophic lateral sclerosis," *BMC Genomics*, vol. 8, article 26, 2007.

[37] F. Tanaka et al., "Neuropathology and omics in motor neuron diseases," *Neuropathology*. In press.

[38] M. R. Vargas, M. Pehar, P. J. Díaz-Amarilla, J. S. Beckman, and L. Barbeito, "Transcriptional profile of primary astrocytes expressing ALS-linked mutant SOD1," *Journal of Neuroscience Research*, vol. 86, no. 16, pp. 3515–3525, 2008.

[39] J. L. Gonzalez de Aguilar, C. Niederhauser-Wiederkehr, B. Halter et al., "Gene profiling of skeletal muscle in an amyotrophic lateral sclerosis mouse model," *Physiological Genomics*, vol. 32, no. 2, pp. 207–218, 2008.

[40] P. F. Pradat et al., "Muscle gene expression is a marker of amyotrophic lateral sclerosis severity," *Neuro-Degenerative Diseases*, vol. 9, no. 1, pp. 38–52, 2012.

[41] C. Y. Wu, D. Whye, L. Glazewski et al., "Proteomic assessment of a cell model of spinal muscular atrophy," *BMC Neuroscience*, vol. 12, article 25, 2011.

[42] R. N. Saha and K. Pahan, "HATs and HDACs in neurodegeneration: A tale of disconcerted acetylation homeostasis," *Cell Death and Differentiation*, vol. 13, no. 4, pp. 539–550, 2006.

[43] S. Petri, M. Kiaei, K. Kipiani et al., "Additive neuroprotective effects of a histone deacetylase inhibitor and a catalytic antioxidant in a transgenic mouse model of amyotrophic lateral sclerosis," *Neurobiology of Disease*, vol. 22, no. 1, pp. 40–49, 2006.

[44] M. E. Cudkowicz, P. L. Andres, S. A. Macdonald et al., "Phase 2 study of sodium phenylbutyrate in ALS," *Amyotrophic Lateral Sclerosis*, vol. 10, no. 2, pp. 99–106, 2009.

[45] F. Sugai, Y. Yamamoto, K. Miyaguchi et al., "Benefit of valproic acid in suppressing disease progression of ALS model mice," *European Journal of Neuroscience*, vol. 20, no. 11, pp. 3179–3183, 2004.

[46] H. L. Feng, Y. Leng, C. H. Ma, J. Zhang, M. Ren, and D. M. Chuang, "Combined lithium and valproate treatment delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model," *Neuroscience*, vol. 155, no. 3, pp. 567–572, 2008.

[47] Y. E. Yoo and C. P. Ko, "Treatment with trichostatin A initiated after disease onset delays disease progression and increases survival in a mouse model of amyotrophic lateral sclerosis," *Experimental Neurology*, vol. 231, no. 1, pp. 147–159, 2011.

[48] S. H. Kim, N. P. Shanware, M. J. Bowler, and R. S. Tibbetts, "Amyotrophic lateral sclerosis-associated proteins TDP-43 and FUS/TLS function in a common biochemical complex to co-regulate HDAC6 mRNA," *The Journal of Biological Chemistry*, vol. 285, no. 44, pp. 34097–34105, 2010.

[49] L. E. Kernochan, M. L. Russo, N. S. Woodling et al., "The role of histone acetylation in SMN gene expression," *Human Molecular Genetics*, vol. 14, no. 9, pp. 1171–1182, 2005.

[50] E. Hahnen, I. Y. Eyüpoglu, L. Brichta et al., "In vitro and ex vivo evaluation of second-generation histone deacetylase inhibitors for the treatment of spinal muscular atrophy," *Journal of Neurochemistry*, vol. 98, no. 1, pp. 193–202, 2006.

[51] A. M. Avila, B. G. Burnett, A. A. Taye et al., "Trichostatin A increases SMN expression and survival in a mouse model of spinal muscular atrophy," *Journal of Clinical Investigation*, vol. 117, no. 3, pp. 659–671, 2007.

[52] M. Riessland, L. Brichta, E. Hahnen, and B. Wirth, "The benzamide M344, a novel histone deacetylase inhibitor, significantly increases SMN2 RNA/protein levels in spinal muscular atrophy cells," *Human Genetics*, vol. 120, no. 1, pp. 101–110, 2006.

[53] K. Rak, B. D. Lechner, C. Schneider, H. Drexl, M. Sendtner, and S. Jablonka, "Valproic acid blocks excitability in SMA type I mouse motor neurons," *Neurobiology of Disease*, vol. 36, no. 3, pp. 477–487, 2009.

[54] H. R. Fuller, N. T. Man, L. T. Lam, V. A. Shamanin, E. J. Androphy, and G. E. Morris, "Valproate and bone loss: iTRAQ proteomics show that valproate reduces collagens and osteonectin in SMA cells," *Journal of Proteome Research*, vol. 9, no. 8, pp. 4228–4233, 2010.

[55] M. C. Evans, J. J. Cherry, E. J. Androphy et al., "Differential regulation of the SMN2 gene by individual HDAC proteins," *Biochemical and Biophysical Research Communications*, vol. 414, no. 1, pp. 25–30, 2011.

[56] M. Minamiyama, M. Katsuno, H. Adachi et al., "Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy," *Human Molecular Genetics*, vol. 13, no. 11, pp. 1183–1192, 2004.

[57] S. L. Berger, "The complex language of chromatin regulation during transcription," *Nature*, vol. 447, no. 7143, pp. 407–412, 2007.

[58] O. Tapia, R. Bengoechea, M. T. Berciano, and M. Lafarga, "Nucleolar targeting of coilin is regulated by its hypomethylation state," *Chromosoma*, vol. 119, no. 5, pp. 527–540, 2010.

[59] K. Tripsianes, "Structural basis for dimethylarginine recognition by the Tudor domains of human SMN and SPF30 proteins," *Nature Structural & Molecular Biology*, vol. 18, no. 12, pp. 1414–1420, 2011.

[60] G. B. Gonsalvez, L. Tian, J. K. Ospina, F. M. Boisvert, A. I. Lamond, and A. G. Matera, "Two distinct arginine methyltransferases are required for biogenesis of Sm-class ribonucleoproteins," *Journal of Cell Biology*, vol. 178, no. 5, pp. 733–740, 2007.

[61] J. Hauke, M. Riessland, S. Lunke et al., "Survival motor neuron gene 2 silencing by DNA methylation correlates with spinal muscular atrophy disease severity and can be bypassed by histone deacetylase inhibition," *Human Molecular Genetics*, vol. 18, no. 2, pp. 304–317, 2009.

[62] D. Bäumer, O. Ansorge, M. Almeida, and K. Talbot, "The role of RNA processing in the pathogenesis of motor neuron degeneration," *Expert Reviews in Molecular Medicine*, vol. 12, p. e21, 2010.

[63] P. Corcia, W. Camu, J. Praline, P. H. Gordon, P. Vourch, and C. Andres, "The importance of the SMN genes in the genetics of sporadic ALS," *Amyotrophic Lateral Sclerosis*, vol. 10, no. 5-6, pp. 436–440, 2009.

[64] Y. Piao, T. Hashimoto, S. Takahama et al., "Survival motor neuron (SMN) protein in the spinal anterior horn cells of patients with sporadic amyotrophic lateral sclerosis," *Brain Research*, vol. 1372, pp. 152–159, 2011.

[65] M. Dejesus-Hernandez et al., "Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS," *Neuron*, vol. 72, no. 2, pp. 245–256, 2011.

[66] A. E. Renton et al., "A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD," *Neuron*, vol. 72, no. 2, pp. 257–268, 2011.

[67] M. Wojciechowska and W. J. Krzyzosiak, "Cellular toxicity of expanded RNA repeats: focus on RNA foci," *Human Molecular Genetics*, vol. 20, no. 19, pp. 3811–3821, 2011.

[68] G. Sicot, G. Gourdon, and M. Gomes-Pereira, "Myotonic dystrophy, when simple repeats reveal complex pathogenic entities: new findings and future challenges," *Human Molecular Genetics*, vol. 20, no. 2, pp. R116–R123, 2011.

[69] E. Buratti, A. Brindisi, M. Giombi, S. Tisminetzky, Y. M. Ayala, and F. E. Baralle, "TDP-43 binds heterogeneous nuclear ribonucleoprotein A/B through its C-terminal tail: an important region for the inhibition of cystic fibrosis transmembrane conductance regulator exon 9 splicing," *The Journal of Biological Chemistry*, vol. 280, no. 45, pp. 37572–37584, 2005.

[70] O. A. Sofola, P. Jin, Y. Qin et al., "RNA-binding proteins hnRNP A2/B1 and CUGBP1 suppress fragile X CGG premutation repeat-induced neurodegeneration in a drosophila model of FXTAS," *Neuron*, vol. 55, no. 4, pp. 565–571, 2007.

[71] M. J. Hitchler and F. E. Domann, "An epigenetic perspective on the free radical theory of development," *Free Radical Biology and Medicine*, vol. 43, no. 7, pp. 1023–1036, 2007.

[72] M. J. Hitchler and F. E. Domann, "Metabolic defects provide a spark for the epigenetic switch in cancer," *Free Radical Biology and Medicine*, vol. 47, no. 2, pp. 115–127, 2009.

[73] B. Langley, M. A. D'Annibale, K. Suh et al., "Pulse inhibition of histone deacetylases induces complete resistance to oxidative death in cortical neurons without toxicity and reveals a role for cytoplasmic p21$^{waf1/cip1}$ in cell cycle-independent neuroprotection," *Journal of Neuroscience*, vol. 28, no. 1, pp. 163–176, 2008.

[74] K. Doyle and F. A. Fitzpatrick, "Redox signaling, alkylation (carbonylation) of conserved cysteines inactivates class I histone deacetylases 1, 2 and 3 and antagonizes their transcriptional repressor function," *The Journal of Biological Chemistry*, vol. 285, no. 23, pp. 17417–17424, 2010.

[75] J. Hnilicová, S. Hozeifi, E. Dušková, J. Icha, T. Tománková, and D. Staněk, "Histone deacetylase activity modulates alternative splicing," *PLoS ONE*, vol. 6, no. 2, 2011.

[76] I. Rahman, J. Marwick, and P. Kirkham, "Redox modulation of chromatin remodeling: Impact on histone acetylation and deacetylation, NF-κB and pro-inflammatory gene expression," *Biochemical Pharmacology*, vol. 68, no. 6, pp. 1255–1267, 2004.

[77] Q. Li, C. V. Velde, A. Israelson et al., "ALS-linked mutant superoxide dismutase 1 (SOD1) alters mitochondrial protein composition and decreases protein import," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 49, pp. 21146–21151, 2010.

[78] D. Bergemalm, K. Forsberg, P. Andreas Jonsson et al., "Changes in the spinal cord proteome of an amyotrophic lateral sclerosis murine model determined by differential in-gel electrophoresis," *Molecular and Cellular Proteomics*, vol. 8, no. 6, pp. 1306–1317, 2009.

[79] T. Massignan, F. Casoni, M. Basso et al., "Proteomic analysis of spinal cord of presymptomatic amyotrophic lateral sclerosis G93A SOD1 mouse," *Biochemical and Biophysical Research Communications*, vol. 353, no. 3, pp. 719–725, 2007.

[80] A. Maracchioni, A. Totaro, D. F. Angelini et al., "Mitochondrial damage modulates alternative splicing in neuronal cells: Implications for neurodegeneration," *Journal of Neurochemistry*, vol. 100, no. 1, pp. 142–153, 2007.

[81] S. C. Lenzken, V. Romeo, F. Zolezzi et al., "Mutant SOD1 and mitochondrial damage alter expression and splicing of genes controlling neuritogenesis in models of neurodegeneration," *Human Mutation*, vol. 32, no. 2, pp. 168–182, 2011.

[82] A. Brunet, L. B. Sweeney, J. F. Sturgill et al., "Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase," *Science*, vol. 303, no. 5666, pp. 2011–2015, 2004.

[83] Z. Lu, X. Xu, X. Hu et al., "PGC-1α regulates expression of myocardial mitochondrial antioxidants and myocardial oxidative stress after chronic systolic overload," *Antioxidants and Redox Signaling*, vol. 13, no. 7, pp. 1011–1022, 2010.

[84] K. Aquilano, P. Vigilanza, S. Baldelli, B. Pagliei, G. Rotilio, and M. R. Ciriolo, "Peroxisome proliferator-activated receptor γ co-activator 1 α (PGC-1α) and sirtuin 1 (SIRT1) reside in mitochondria: possible direct function in mitochondrial biogenesis," *The Journal of Biological Chemistry*, vol. 285, no. 28, pp. 21590–21599, 2010.

[85] J. H. Lim, Y. M. Lee, Y. S. Chun, J. Chen, J. E. Kim, and J. W. Park, "Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1alpha." *Molecular cell*, vol. 38, no. 6, pp. 864–878, 2010.

[86] E. M. Dioum, R. Chen, M. S. Alexander et al., "Regulation of hypoxia-inducible factor 2α signaling by the stress responsive deacetylase sirtuin 1," *Science*, vol. 324, no. 5932, pp. 1289–1293, 2009.

[87] I. Mattagajasingh, C. S. Kim, A. Naqvi et al., "SIRT1 promotes endothelium-dependent vascular relaxation by activating endothelial nitric oxide synthase," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 37, pp. 14855–14860, 2007.

[88] Y. Yang, W. Fu, J. Chen et al., "SIRT1 sumoylation regulates its deacetylase activity and cellular response to genotoxic stress," *Nature Cell Biology*, vol. 9, no. 11, pp. 1253–1262, 2007.

[89] M. K. Han, E. K. Song, Y. Guo, X. Ou, C. Mantel, and H. E. Broxmeyer, "SIRT1 regulates apoptosis and *Nanog* expression in mouse embryonic stem cells by controlling p53 subcellular localization," *Cell Stem Cell*, vol. 2, no. 3, pp. 241–251, 2008.

[90] F. Wang, M. Nguyen, F. X. F. Qin, and Q. Tong, "SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction," *Aging Cell*, vol. 6, no. 4, pp. 505–514, 2007.

[91] E. L. Bell, B. M. Emerling, S. J. H. Ricoult, and L. Guarente, "SirT3 suppresses hypoxia inducible factor 1α and tumor growth by inhibiting mitochondrial ROS production," *Oncogene*, vol. 30, no. 26, pp. 2986–2996, 2011.

[92] R. Tao, M. C. Coleman, J. D. Pennington et al., "Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress," *Molecular Cell*, vol. 40, no. 6, pp. 893–904, 2010.

[93] Y. Chen, J. Zhang, Y. Lin et al., "Tumour suppressor SIRT3 deacetylates and activates manganese superoxide dismutase to scavenge ROS," *EMBO Reports*, vol. 12, no. 6, pp. 534–541, 2011.

[94] W. C. Hallows, W. Yu, B. C. Smith et al., "Sirt3 promotes the urea cycle and fatty acid oxidation during dietary restriction," *Molecular Cell*, vol. 41, no. 2, pp. 139–149, 2011.

[95] B. H. Ahn, H. S. Kim, S. Song et al., "A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 38, pp. 14447–14452, 2008.

[96] D. B. Lombard, F. W. Alt, H. L. Cheng et al., "Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation," *Molecular and Cellular Biology*, vol. 27, no. 24, pp. 8807–8814, 2007.

[97] S. Someya, W. Yu, W. C. Hallows et al., "Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction," *Cell*, vol. 143, no. 5, pp. 802–812, 2010.

[98] M. C. Haigis, R. Mostoslavsky, K. M. Haigis et al., "SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic β cells," *Cell*, vol. 126, no. 5, pp. 941–954, 2006.

[99] T. Nakagawa, D. J. Lomb, M. C. Haigis, and L. Guarente, "SIRT5 deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle," *Cell*, vol. 137, no. 3, pp. 560–570, 2009.

[100] L. Zhong, A. D'Urso, D. Toiber et al., "The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1α," *Cell*, vol. 140, no. 2, pp. 280–293, 2010.

[101] O. Vakhrusheva, C. Smolka, P. Gajawada et al., "Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice," *Circulation Research*, vol. 102, no. 6, pp. 703–710, 2008.

[102] L. G. Bilsland, E. Sahai, G. Kelly, M. Golding, L. Greensmith, and G. Schiavo, "Deficits in axonal transport precede ALS symptoms in vivo," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 47, pp. 20523–20528, 2010.