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Abstract

Spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) are the two most common motoneuron disorders, which share typical pathological hallmarks while remaining genetically distinct. Indeed, SMA is caused by deletions or mutations in the survival motor neuron 1 (SMN1) gene whilst ALS, albeit being mostly sporadic, can also be caused by mutations within genes, including superoxide dismutase 1 (SOD1), Fused in Sarcoma (FUS), TAR DNA-binding protein 43 (TDP-43) and chromosome 9 open reading frame 72 (C9ORF72). However, it has come to light that these two diseases may be more interlinked than previously thought. Indeed, it has recently been found that FUS directly interacts with an Smn-containing complex, mutant SOD1 perturbs Smn localization, Smn depletion aggravates disease progression of ALS mice, overexpression of SMN in ALS mice significantly improves their phenotype and lifespan, and duplications of SMN1 have been linked to sporadic ALS. Beyond genetic interactions, accumulating evidence further suggests that both diseases share common pathological identities such as intrinsic muscle defects, neuroinflammation, immune organ dysfunction, metabolic perturbations, defects in neuron excitability and selective motoneuron vulnerability. Identifying common molecular effectors that mediate shared pathologies in SMA and ALS would allow for the development of therapeutic strategies and targeted gene therapies that could potentially alleviate symptoms and be equally beneficial in both disorders. In the present review, we will examine our current knowledge of pathogenic commonalities between SMA and ALS, and discuss how furthering this understanding can lead to the establishment of novel therapeutic approaches with wide-reaching impact on multiple motoneuron diseases.

Keywords	amyotrophic lateral sclerosis; spinal muscular atrophy; motoneuron; muscle; therapy
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Dear Pr. Verloes,

We would like to thank you and the reviewers for the positive evaluation of our review entitled "Pathogenic commonalities between spinal muscular atrophy and amyotrophic lateral sclerosis: converging roads to therapeutic development" by Bowerman, M *et al*. We were very pleased to see that the reviewers found our review to be “insightful”, “comprehensive” and “particularly timely”. The reviewers raised some valid comments that we have addressed in the present revised version of the review and in the accompanying rebuttal letter.

We hope you will now find our work suitable for publication in the *European Journal of Medical Genetics*.

I thank you very much for your interest and consideration

Sincerely Yours

Cédric Raoul

We are thankful to the reviewers for their constructive comments on our review. Below, we have summarized each of the reviewers' comment in italic and responded point by point.

Reviewer #1

1. *I suggest extending the part about molecular mechanisms which is in the introduction now (and may be moved into a short extra chapter). For example, there are more studies about the link between FUS and SMN e.g. from the Pasterkamp Groen et al., 2012) and the Cleveland (Sun et al., 2015) groups. I understand that this is not the main focus of this review; however, this would stress the point that there are several commonalities and converging roads to treatments. There are also more common pathways than mentioned, e.g. the role of profilin and its targets in both diseases.*

Response: We thank the reviewer for this comment. We have added a discussion point about Profilin that provides an additional example of common mechanisms between ALS and SMA. We have also further elaborated on the studies from Pasterkamp and Cleveland laboratories that highlight such pathological commonalities. We have chosen to make these changes in the introduction section to not unbalance the distribution between different paragraphs.

2. *The authors may want to mention differential vulnerability between medial and lateral motoneuron pools since the medial neurons show signs of degeneration in SMA first (e.g. work by the Mentis group).*

Response: We agree with reviewer, we should have mentioned this differential vulnerability between motoneuron populations. We have now included a sentence on the early deafferentation that occurs earlier and in a more severe manner in medial compared to lateral motoneuron pools (Mentis G, Neuron, 2011).

3. Minor points:

Title: "A" converging road appears illogical; it should read: converging roads (plural).

p. 7: introduce PIC as abbreviation

Response: We thank the reviewer for having identified these points. The title has been modified as suggested. Abbreviation of "Persistent Inward Current", PIC, is now introduced in the revised version of the manuscript.

Reviewer #2

1. *In this review by Bowerman et al., the authors examine a novel aspect of neurodegeneration: commonalities between SMA and ALS. This is an area that has not been covered recently and it is particularly timely. The review is comprehensive and well written. At times, it is a bit dense and would benefit from the inclusion of an additional figure (perhaps highlighting what an NMJ defect is), and a table (or more) comparing*

commonalities in gene pathways etc. Also, a table highlighting therapeutic development would be nice.

Response: We agree with the reviewer that the manuscript and consequently the readers would benefit from additional figures. We have now included 5 figures in total that illustrate the common cellular and molecular events as well as key features of SMA and ALS gene therapy that we detail throughout the body text.

Reviewer #3

There are major differences between ALS and SMA that be should be critically reviewed and included in this review.

1. *SMA is a monogenic recessive disease compared to the heterogenous causes of ALS. Studies that are focused on the epigenetic role of SMN/SMN2 copy numbers misleading and controversial because they disregard the relevance to full length and truncated SMN gene products. The clinical severity of SMA is clearly a full transcript dosage issue, while ALS is rather determined by toxic gain of function or dominant negative effects of mutated proteins. Transgenic mouse experiments for ALS are difficult to compare to the human disease since mice do not have SMN2 genes. The publication cited for SMN1 duplication as a cause of ALS is problematic. Transgenic animals with SMN over expression have no clinical phenotype.*
2. *The selective vulnerability of various neurons in the two diseases has at least as many similarities as differences. The role of RNA transport in motor axon appears to be the major determinant in neurodegeneration SMA, while this mechanism is considered only in some forms of ALS.*
3. *The pathology of NMJ and muscle is well documented in transgenic animal studies in both conditions, however the differences between ALS and SMA are quite remarkable. Restoration of SMN expression or over expression in muscle does not rescue the phenotype while it does when it is done in motor neurons. There is no evidence that over expression of SMN or any other genes in ALS mice can significantly affect the lifespan of the animals.*
4. *Neuroinflammation has not been a significant pathological factor in clinical SMA, but it has a major ole in pathology of ALS.*
5. *Comparing overall metabolism in ALS and SMA is very speculative to make therapeutic recommendations.*

The review did not come up with a vision how to develop therapeutic interventions for both ALS and SMA, except that for gene therapy similar vectors can be used.

Treatment of SMA has made significant progress, recently because of a clear strategy how to restore the expression of the protein responsible for the disease.

Treating of ALS will not likely happen by manipulating SMN expression.

Response: We fully concur with the reviewer that there are major differences between both diseases, the first being indeed of an etiological concern with their genetic origin. However the aim of this review is to shed light on some intriguing commonalities between pathological mechanisms that cover neuromuscular junction defects, neuroinflammation and metabolic abnormalities. Although these two diseases differ in many aspects, motoneurons remains the primary target and common traits are associated with the selective vulnerability of this population of neurons, of which remain common potential therapeutic targets. We are convinced we still have to learn from each of these diseases and that the different points discussed in our manuscript might stimulate further studies to develop therapeutic interventions. We do not pretend to explain "how to" develop novel therapies; we just intend to propose another angle through which we should consider novel strategies.

Pathogenic commonalities between spinal muscular atrophy and amyotrophic lateral sclerosis: converging roads to therapeutic development

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ABSTRACT

Spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) are the two most common motoneuron disorders, which share typical pathological hallmarks while remaining genetically distinct. Indeed, SMA is caused by deletions or mutations in the *survival motor neuron 1* (*SMN1*) gene whilst ALS, albeit being mostly sporadic, can also be caused by mutations within genes, including *superoxide dismutase 1* (*SOD1*), *Fused in Sarcoma* (*FUS*), *TAR DNA-binding protein 43* (*TDP-43*) and *chromosome 9 open reading frame 72* (*C9ORF72*). However, it has come to light that these two diseases may be more interlinked than previously thought. Indeed, it has recently been found that FUS directly interacts with an Smn-containing complex, mutant SOD1 perturbs Smn localization, *Smn* depletion aggravates disease progression of ALS mice, overexpression of SMN in ALS mice significantly improves their phenotype and lifespan, and duplications of *SMN1* have been linked to sporadic ALS. Beyond genetic interactions, accumulating evidence further suggests that both diseases share common pathological identities such as intrinsic muscle defects, neuroinflammation, immune organ dysfunction, metabolic perturbations, defects in neuron excitability and selective motoneuron vulnerability. Identifying common molecular effectors that mediate shared pathologies in SMA and ALS would allow for the development of therapeutic strategies and targeted gene therapies that could potentially alleviate symptoms and be equally beneficial in both disorders. In the present review, we will examine our current knowledge of pathogenic commonalities between SMA and ALS, and discuss how furthering this understanding can lead to the establishment of novel therapeutic approaches with wide-reaching impact on multiple motoneuron diseases.

INTRODUCTION

Motoneuron diseases (MNDs) encompass a group of devastating neurodegenerative disorders characterized by the progressive and selective degeneration of motoneurons in the spinal cord and/or the brain. Amongst MNDs, spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) are the most common in children and adults, respectively. SMA is a monogenic disease whereby over 95% of cases are due to deletions or mutations within the *survival motor neuron 1* (*SMN1*) gene (Lefebvre et al., 1995). ALS can be sporadic (~80%) or familial (~20%) (Andersen and Al-Chalabi, 2011), and in the latter case can be caused by numerous genetic mutations with the most common being in *chromosome 9 open reading frame 72* (*C9ORF72*) (DeJesus-Hernandez et al., 2011; Renton et al., 2011), *superoxide dismutase 1* (*SOD1*) (Rosen et al., 1993), *Fused in Sarcoma* (*FUS*) (Kwiatkowski et al., 2009; Vance et al., 2009) and *TAR DNA-binding protein 43* (*TDP-43*) (Gitcho et al., 2008; Kabashi et al., 2008; Sreedharan et al., 2008). SMA and ALS are thus genetically distinct (Andersen and Al-Chalabi, 2011; Lefebvre et al., 1995) and have therefore traditionally been considered as separate disorders. However, accumulating evidence suggests that functional interactions between the protein products of causative genes of both of these MNDs may influence each other's pathological traits. Indeed, FUS directly interacts with Smn, whereby ALS-linked FUS mutations stabilize the FUS-SMN interaction and lead to cytosolic redistribution of SMN, reduction of intracellular small nuclear bodies (called Gemini of coiled bodies, Gems), altered levels of small nuclear RNA and axonal defects (Groen et al., 2013; Sun et al., 2015; Yamazaki et al., 2012). Furthermore, mutant SOD1 perturbs Smn localization (Gertz et al., 2012; Kariya et al., 2012), *Smn* depletion aggravates disease progression of SOD1 mutant mice (Turner et al., 2009), overexpression of SMN in SOD1 and TDP-43 mice significantly improves their phenotype and lifespan (Perera et al., 2016; Turner et al., 2014), TDP-43 overexpression enhances correct splicing of the *SMN* gene (Bose et al., 2008) and duplications of *SMN1* have been linked to sporadic ALS (Blauw et al., 2012). Recently, mutations in profilin 1, a monomeric actin binding protein that inhibits the assembly of filamentous actin, have been identified in a subset of ALS patients (Wu et al., 2012). Interestingly, profilin 1 interacts with SMN and is found within the cytoplasm and Gems of motoneurons (Giesemann et al., 1999). While studies have mainly focused on the role of profilin 2 in SMA (Bowerman et al., 2007; Nölle et al., 2011), profilin 1 highlights actin dynamics as a common denominator between ALS and SMA (Hensel and Claus, 2017).

It has thus become obvious that SMA and ALS share more similarities than initially thought and this implication has a direct and significant impact on how we pursue the development of therapeutic strategies that could be

applicable to SMA and ALS as well as other MNDs. Indeed, uncovering of shared pathophysiological events has great potential for large-scale clinical applications. While SMA and ALS are classified as canonical MNDs, several investigations in pre-clinical models and patients have demonstrated the contribution of tissues and cells from both the central nervous system (CNS) and the periphery to disease severity and progression (Hamilton and Gillingwater, 2013; Loeffler et al., 2016). In the present review, we will thus take a whole-body approach to discuss the pathological commonalities between SMA and ALS, focusing on skeletal muscle, neuroinflammation, immune organ dysfunction, metabolic perturbations, defects in neuronal excitability and selective motoneuron vulnerability. In addition, we will expand on how targeted gene therapy approaches could be exploited to treat shared symptoms in both diseases.

SELECTIVE MOTONEURON VULNERABILITY

One of the key commonalities that unite SMA and ALS is the selective vulnerability of motoneurons. Importantly, however, not all populations of motoneurons are equally vulnerable as some are lost very early in disease while others remain relatively intact even at late stages. A good example is the motoneurons that innervate the extraocular muscles, which are typically spared in SMA and ALS patients and animal models (Comley et al., 2016; Gizzi et al., 1992; Kubota et al., 2000; Spataro et al., 2014; Tjust et al., 2012; Valdez et al., 2012). This preserved eye movement is frequently exploited as a means of communication by SMA and ALS patients (Kubota et al., 2000; Spataro et al., 2014). The observation that selective pools of motoneurons are resistant in MNDs is intriguing. Understanding the basis for this selective resistance and vulnerability could provide insight into the molecular effectors that dictate vulnerability, and uncover novel therapeutic approaches. Identifying common patterns or mechanisms of selective vulnerability between SMA and ALS motoneurons would allow for the development of treatment strategies that may have a wide-reaching potential in several MNDs.

A number of studies have profiled the patterns of selective vulnerability in motoneurons of both patients and animal models of SMA and ALS. The pattern of motoneuron loss in SMA is described as extremely stereotyped (Deymeer et al., 2008), whereby motoneurons innervating proximal lower and upper limb muscles are lost before those innervating distal limb muscles, highlighted by the highly consistent pattern of motor unit loss within the muscles of the arm and thigh (Deymeer et al., 2008). There is also a selective vulnerability of motoneurons innervating the core muscles of the abdomen and back while cranial motoneurons, as discussed above, are

spared (Kubota et al., 2000). The differential vulnerability of motoneurons has been much more extensively documented in mouse models of SMA. Indeed, motor units fall somewhere on a spectrum of vulnerability and display a predictable pattern of motoneuron loss in distinct muscles (Ling et al., 2012; Murray et al., 2013; Thomson et al., 2012). For example, synaptic defects occur earlier and are more pronounced in medial motoneurons innervating axial muscles compared to lateral motoneurons innervating distal limb muscles (Mentis et al., 2011). Interestingly, selective vulnerability has even been observed within the same muscle, whereby the caudal band of the *levator auris longus* muscle is consistently more vulnerable than its rostral band in severe SMA mice (Murray et al., 2008).

Conversely, the pattern of motoneuron loss in ALS is somewhat less predictable and is perhaps due to the variety of genetic and sporadic causes of this disease (Andersen and Al-Chalabi, 2011). Furthermore, ALS can manifest as both a bulbar or spinal onset and the location of onset in the spinal forms can equally be highly variable (Shellikeri et al., 2017). Despite this, mouse models of ALS based on a single genetic mutation have revealed a consistent and predictable pattern of motoneuron loss (Valdez et al., 2012).

Predictable patterns of motoneuron loss as well as selective vulnerability and resistance of particular pools of motoneurons therefore seem to be common features between SMA and ALS. Whether there is commonality in the patterns of selective vulnerability between SMA and ALS is somewhat more difficult to address. Indeed, whilst it is easy to find examples of muscles which commonly demonstrate high levels of denervation (e.g. *tibialis anterior*) it is equally simple to identify disparities, such as with the *extensor digitorum longus*, which is seemingly very vulnerable to denervation in ALS, but comparatively resistant in SMA (Boyd et al., 2017; Thomson et al., 2012; Valdez et al., 2012). Interestingly, a recent study has profiled the vulnerability of tongue, extraocular and deep lumbrical muscles in mouse models of SMA and ALS, and identified a remarkable similarity in the relative vulnerability associated with each muscle (Comley et al., 2016), an approach that could be further extended to include additional muscles and models. Ultimately, however, the different patterns of selective vulnerability between SMA and ALS are perhaps not surprising. Multiple factors impact the vulnerability status of an individual motor unit, one of which is age (Murray et al., 2011) as demonstrated by distinct patterns of selective vulnerability in SMA mouse models at differing ages (Murray et al., 2008, 2013).

It is therefore perhaps more relevant to look at the properties of motoneurons to determine whether there are common factors that render them more or less vulnerable to disease. Work on mouse models of SMA and ALS have eliminated morphological factors such as body position, motor unit size and fiber type of innervated muscle

(Thomson et al., 2012; Valdez et al., 2012). However, it has been suggested that sprouting competence may play a role in directing relative vulnerability as the analysis of three distinct ALS mouse models revealed that motor units with a relatively increased capacity to sprout were comparatively less vulnerable to degeneration (Frey et al., 2000). Motoneurons thus fall into different developmental categories distinguished in adulthood by their sprouting competence (Pun et al., 2002). Differential sprouting competence also correlates with selective neuronal vulnerability in mouse models of SMA (Murray et al., 2008, 2013). Interestingly, two independent studies aimed at identifying transcriptional differences between differentially vulnerable motoneurons in SMA and ALS reported that the expression of insulin-like growth factor (IGF)-2, a factor that promotes motoneuron sprouting, is a predictive indicator of resistance to disease-induced degeneration (Hedlund et al., 2010; Murray et al., 2015). Furthermore, overexpression of IGF-2 prevents motoneuron loss in mouse models of SMA and ALS, and extends lifespan of ALS mice (Allodi et al., 2016).

The IGF-2 work indicates that shared molecular mechanisms may underlie selective vulnerability in SMA and ALS. In an attempt to identify vulnerability modifiers, recent studies have investigated transcriptional differences between motoneuron populations, whereby differentially susceptible pools of motoneurons were defined in patients or mouse models of SMA or ALS, and the equivalent populations were isolated from neurologically healthy humans, rats or mice (Boyd et al., 2017; Brockington et al., 2013; Hedlund et al., 2010; Kaplan et al., 2014; Murray et al., 2015). Transcriptional analysis of these motoneuron populations revealed a large number of differentially expressed transcripts with previously validated functions in neurodegenerative pathways. We have recently re-analyzed this collection of transcriptional screens to identify commonalities between the data sets (Kline et al., 2017), thus producing a refined list of transcripts commonly altered in differentially vulnerable motoneurons in SMA and ALS. One candidate modifier was alpha-synuclein, which in addition to its well characterized role in Parkinson's disease, also has previously described neuroprotective properties (da Costa et al., 2000; Hashimoto et al., 2002; Manning-Bog et al., 2003). Indeed, overexpression of alpha-synuclein in a mouse model of SMA led to a significant extension in lifespan and a marked preservation of neuromuscular junctions (NMJs) (Kline et al., 2017). Thus, understanding the molecular mechanisms that regulate the differential vulnerability of healthy and diseased motoneurons can lead to the identification of neuroprotective pathways, give insight into the mechanistic similarities between SMA and ALS (Figure 1), and ultimately provide the potential to develop therapeutic strategies beneficial in both diseases.

Please place Figure 1 here

DEFECTS IN NEURONAL EXCITABILITY

An additional shared pathological feature between SMA and ALS is an abnormal excitability of motoneurons due to extrinsic and intrinsic factors. The loss of synapses on spinal motoneurons is one of the key pathological features seen in SMA mice. The primary synapses affected in SMA are formed by glutamatergic VGlut1+ proprioceptive afferent axons on the soma and dendrites of motoneurons, inducing a decrease in monosynaptic excitatory potentials (Mentis et al., 2011; Neve et al., 2016). In addition, an increased frequency of motoneuron postsynaptic events is also observed, which could be attributed to the VGluT2+ afferent terminals (Gogliotti et al., 2012). Interestingly, motoneuron-specific overexpression of Smn in SMA mice abolished the increased frequency of postsynaptic potentials and prevented the loss of VGluT1+ synapses, which supports a motoneuron-dependent effect on the loss of these synaptic contacts (Gogliotti et al., 2012).

SMA motoneurons are also intrinsically hyperexcitable (Gogliotti et al., 2012; Mentis et al., 2011), which has been attributed to a lower voltage threshold for action potential triggering and variable increase in input resistance. SMA motoneurons also display an increased persistent inward current (PIC) amplitude that contributes to firing pattern (Heckman et al., 2009). Specific restoration of Smn in SMA mice allowed for the correction of SMA motoneuron hyperexcitability and decreased the post-synaptic excitatory potentials (Gogliotti et al., 2012). This study strongly supports the proposal that defects in intrinsic motoneuron excitability also contribute to synaptic abnormalities. Induced pluripotent stem cells (iPSCs) from SMA patients also display hyperexcitability due to increased membrane input resistance, hyperpolarized threshold, larger action potential amplitude and increased firing frequency (Liu et al., 2015). The increase in Na^+ current amplitude associated with decreased time for reactivation in SMA iPSCs is expected to participate in the increased propagation of excitability towards the NMJ. Thus, intrinsic defects in SMA neuronal excitability may have a pathological impact both at the soma and at the nerve terminal.

In ALS, excitotoxicity appears to be a major mechanism leading to motoneuron death and contributing significantly to disease pathogenesis (King et al., 2016). Contrary to SMA, the influence of other cell types on altering motoneuron electrical activity in ALS is well established and has lead to the hypothesis of a non-cell-autonomous mechanism as a key contributor to disease progression and presentation. Notably, in ALS patients and animal models, glutamate clearance by astrocytes is defective due to decreased expression of the excitatory amino acid transporter 2 (EAAT2), leading to glutamate-induced excitotoxicity (Van Den Bosch et al., 2006). Moreover, the low expression of the GluR(2) α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)

receptor subunit by vulnerable motoneuron populations may render them unduly susceptible to calcium-mediated toxic events following glutamate receptor activation (Williams et al., 1997). Expression of atypical calcium-permeable AMPA receptors by human motoneurons provides a possible mechanism whereby disturbances of glutamate neurotransmission in ALS may selectively injure this cell group.

Similar to SMA motoneurons, neuronal cells in ALS also demonstrate intrinsic excitability perturbations. Indeed, there is epidemiological evidence showing that increased axonal excitability related to PIC is strongly associated with shorter survival rates in ALS patients (Kanai et al., 2012). Furthermore, the only therapeutic approved for use in ALS, riluzole, is thought to block PIC (Schuster et al., 2012). The increase in PIC is also observed in murine ALS motoneuron primary cultures (Kuo et al., 2005) and iPSCs-derived motoneurons from ALS patients demonstrate hyperexcitability characteristics (Wainger et al., 2014). Several experimental and computational studies point to relationships between motoneuron dendritic morphology and membrane biophysical properties that either reduce or increase membrane resistance and thus excitability (Amendola and Durand, 2008; Elbasiouny et al., 2010; Martin et al., 2013). However, *in vivo* recordings of murine adult ALS motoneurons reveals no changes or hyperexcitability (Delestrée et al., 2014). Thus, while intrinsic hyperexcitability seems to be a hallmark of SMA motoneurons, some controversy still exists for ALS that could be due to differential motoneuron susceptibility, the time course of disease progression and dendritic morphological changes. Having a better understanding of the similarities between the intrinsic electrical activities of SMA and ALS motoneurons (Figure 1) could help in the design of pharmacological treatment approaches that could potentially restore pathologies in both diseases.

INTRINSIC MUSCLE DEFECTS

As a consequence of motoneuron loss, both SMA and ALS muscles display significant NMJ defects in both the pre- and post-synaptic compartments, defined by denervation, neurofilament accumulation, reduced endplate size, immature endplate morphology and aberrant neurotransmission (Mélissa Bowerman et al., 2012; Fischer et al., 2004; Kariya et al., 2008; Kong et al., 2009; Murray et al., 2008; Rizzuto et al., 2015; Sharma et al., 2016). Although muscle pathology in both SMA and ALS has traditionally been considered as a consequence of motoneuron degeneration, accumulating evidence strongly suggests that intrinsic muscle defects exist and contribute to disease progression and presentation.

One of the first indications of the role of muscle in SMA was the report that conditional knockout of *Smn* in skeletal muscle results in a severe muscle dystrophy phenotype (Cifuentes-Diaz et al., 2001). Conversely, Smn restoration specifically in muscle through the use of the myogenic regulator factor (MRF) MyoD promoter improved survival and motor behavior to a similar extent than that obtained with Smn restitution under the motoneuron-specific promoter ChAT (Martinez et al., 2012). Interestingly, complete myofiber size rescue was only observed when using the MyoD promoter, despite no NMJ improvement (Martinez et al., 2012), suggesting a distinct role for SMN in muscle. Histopathological muscle abnormalities have also been highlighted in SMA mice, some of which occur pre-symptomatically, revealing reduced myofiber size, increased number of centrally located nuclei, muscle weakness, increased cell death and fewer myofibers in hind limb muscles (Mélissa Bowerman et al., 2012; Boyer et al., 2013, 2014; Cifuentes-Diaz et al., 2001; Dachs et al., 2011; Hammond et al., 2010; Hsieh-Li et al., 2000; Le et al., 2005; Monani et al., 2000; Nicole et al., 2003). Furthermore, muscle satellite cells, the primary source of progenitors for postnatal muscle growth and regeneration (Wang and Rudnicki, 2011), differentiate abnormally and display a reduced efficiency in myotube formation in severe SMA mice (Hayhurst et al., 2012).

The myogenic developmental program is typically characterized by satellite cells undergoing a sequential repression of *Pax7* and activation of MRFs, including myogenic factor 5 (Myf5), myoblast determination protein (MyoD), myogenin, and muscle-specific regulatory factor 4 (Le Grand and Rudnicki, 2007; Seale et al., 2000). Central nucleation is a common feature of newly generated muscle fibers and the observation of increased centrally nucleated fibers in SMA muscle suggests that Smn deficiency may stimulate myogenesis and/or slow down maturation of newly generated fibers. Indeed, immortalized myoblasts with reduced Smn expression levels display abnormal proliferation, aberrant myoblast fusion and malformed myotubes (Shafey et al., 2005), most likely a consequence of abnormal MyoD, myogenin and Pax7 expression (Bricceno et al., 2014). Combined, these *in vitro* experiments further support a role for Smn in myoblast proliferation and differentiation, independently from the neuronal input. Analysis of SMA patient muscle biopsy cultures shows an aberrant Myf-5 expression (Guettier-Sigrist et al., 2002). We have also demonstrated a pronounced dysregulated expression of *Pax7* and *MRFs* in muscle of SMA mice, even in non-denervated muscles (Boyer et al., 2014). Muscle precursor cells also display defects in SMA, whereby satellite cells with reduced Smn protein levels differentiate abnormally (Hayhurst et al., 2012). Moreover, elevated levels of Smn in satellite cells markedly increase the number of regenerating myofibers following muscle-specific depletion of Smn in mice (Nicole et al., 2003),

strongly indicating a tight association between Smn and the function of satellite cells. Myogenic program abnormalities have also been documented at the level of muscle microRNAs (miRNA), with the reported dysregulation of miR-206, -486, -9 and -132, in Smn-depleted myoblast cells and SMA mouse muscle (Bricceno et al., 2014; Catapano et al., 2016). There is therefore clear evidence that loss of Smn results in intrinsic muscle defects, although it remains to be further defined what are the molecular mechanisms involved and how alterations of the myogenic program affect myofiber maturation, satellite cell formation and muscle homeostasis.

Not surprisingly, emerging evidence also supports an active role for skeletal muscle in ALS pathogenesis. Indeed, the muscle-restricted expression of mutant SOD1 results in skeletal muscle atrophy, reduced muscle strength, activation of anti-oxidant response, mitochondrial dysfunction, motor function deficits, increased cell death, contractile apparatus, NMJ and motoneuron degeneration (Dobrowolny et al., 2008; Wong and Martin, 2010). Similar to SMA mice, aberrant genetic, biochemical and physiological changes in ALS muscle are observed prior to motoneuron loss. Indeed, investigations in pre-symptomatic ALS mice demonstrate an altered electrophysiological activity in diaphragm (Rocha et al., 2013), aberrant expression of proteins involved in cellular metabolism and cytoskeletal processes (Capitanio et al., 2012), differential expression of genes implicated in Wnt, phosphoinositide 3-kinase, and epithelial-mesenchymal transition signaling cascades (de Oliveira et al., 2014) and increased muscle weakness (Derave et al., 2003). The impact of ALS-causing mutations on the myogenic regulatory program has also been addressed. Analysis of skeletal muscle from SOD1 mutant mice reveals aberrant expression of the *Pax7*, *Myf5*, *MyoD* and *Myogenin* transcripts at various stages of disease (Manzano et al., 2011). Furthermore, satellite cells isolated from these mice have a reduced proliferation rate (Manzano et al., 2013), an observation that was also noted in satellite cells from ALS patients (Pradat et al., 2011; Scaramozza et al., 2014). Interestingly, adenoviral-mediated overexpression of myogenin in muscle of SOD1 ALS mice improved motoneuron survival and NMJ innervation while using the same strategy to increase MyoD had a negative influence on the same parameters (Park et al., 2013). Finally, analysis of miRNA profiles of muscle from ALS rodents and patients has identified several candidates such as miR-206, -1, -133a, -133b, -145, -21, -24, -424 and -214 as being significantly differentially expressed compared to healthy control tissue (de Andrade et al., 2016; Sumitha et al., 2014; Toivonen et al., 2014).

Skeletal muscle is a highly plastic tissue, adapting its structure and metabolism in response to diverse physiological and pathological conditions. Accumulating evidence suggests shared intrinsic muscle pathologies between SMA and ALS, such as early muscle weakness and fatigability, dysregulated myogenic program and

altered satellite cell function, all of which contribute to muscle dyshomeostasis (Figure 2). The disrupted interactions between satellite cells, myonuclei, myofibers and NMJs may therefore exacerbate disease pathology in these MNDs. Regardless of whether the muscle defects are intrinsic or not, therapeutic targeting of muscle should be a critical consideration when devising treatment plans for these devastating diseases. Indeed, muscle-targeted therapeutic strategies (*e.g.* myostatin/follistatin pathway, skeletal muscle troponin activator, IGF-1, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, Tweak/Fn14) (Bosch-Marcé et al., 2011; Bowerman et al., 2015; Holzbaur et al., 2006; Morrison et al., 2009; Rose et al., 2009; Shefner et al., 2012; Thau et al., 2012) have already resulted in significant improvements in survival and/or pathological features of SMA and ALS pre-clinical models, some of which are currently in clinical trials.

Please place Figure 2 here

NEUROINFLAMMATION AND IMMUNE ORGAN DYSFUNCTION

More than 30 years ago, the first signs of astrocytic disturbance were observed in the nervous system of SMA and ALS patients (Brock and McIlwain, 1984). Since, a wealth of studies has demonstrated that both astrocyte and microglial cells shift to an activated phenotype, defining a neuroinflammatory context that accompanies the neurodegenerative process. Non-cell-autonomous components that mediate neuro- and peripheral inflammation are thus taking a key role in the selective and progressive loss of motoneurons.

In experimental models of ALS, different strategies have been employed to explore cell-autonomous and non-cell-autonomous pathogenic mechanisms in the context of neuroinflammation (Kanning et al., 2010). Chimeric mice comprising a mixture of wild-type and mutant cells revealed that both non-neuronal and neuronal cells act in concert to provoke disease (Clement et al., 2003). While a toxic action of mutant SOD1 within motoneurons is crucial for onset and early phase of the disease (Boillée et al., 2006; Wang et al., 2009), mutant SOD1 in astrocytes can affect, depending on the mutation, onset and early phase of the disease (Wang et al., 2011), or only disease progression (Yamanaka et al., 2008). In either case, astrocytic SOD1 mutant modulates the extent of the inflammatory response by controlling microglia activation (Wang et al., 2011; Yamanaka et al., 2008). *In vitro* studies with co-cultures of rat, mouse or human stem cell-derived motoneurons on SOD1 mutant expressing astrocytes further demonstrated that astrocytes release soluble factors that are selectively toxic for motoneurons (Aebischer et al., 2011; Di Giorgio et al., 2007, 2008; Marchetto et al., 2008). Several mechanisms

that initiate or sustain the neuroinflammatory environment have been proposed, which puzzlingly encompass both deleterious and protective facets (Bowerman et al., 2013).

While not yet as extensive as in ALS, increasing evidence also underlines the importance of non-cell-autonomous factors in SMA pathogenesis with some striking commonalities between both diseases. Indeed, activated astrocytes, monocytes, macrophages and increased levels of pro-inflammatory cytokines are found in the spinal cord of SMA patients (Kuru et al., 2009; Rindt et al., 2015). Concordantly, an activated astrocyte phenotype is observed in the spinal cord of SMA mice (McGivern et al., 2013), which is similar to ALS, and takes place before motoneuron soma loss in SMA animals (Dachs et al., 2011; McGivern et al., 2013). Microglia activation is *per contra* detected later than astrogliosis in SMA mice (Tarabal et al., 2014), but their contribution to SMA pathogenesis remains largely elusive. Conversely, convincing lines of evidence support the contribution of astrocytes to SMA disease progression. Indeed, overexpression of SMN specifically in astrocytes of SMA mice led to a two- to three-fold increase in lifespan, decreased muscle atrophy, improved motor functions and increased NMJ innervation (Rindt et al., 2015). Interestingly, the loss of glutamatergic excitatory synapses, mainly from proprioceptive afferents, was significantly reduced (Rindt et al., 2015), which could be due to previously discussed contribution of proprioceptive pre-synaptic glutamate transmission on motoneuron excitability and functional integrity (Fletcher et al., 2017).

In addition to similar neuroinflammation histopathology, common molecular components between SMA and ALS neuroinflammatory networks can be identified. SMA iPSC-derived astrocytes show elevated basal calcium (Ca^{2+}) levels and deficits in internal Ca^{2+} signalling that are associated with extracellular signal-regulated kinase (ERK) activation and decreased production of a potent motoneuron survival factor, the glial-derived neurotrophic factor (GDNF)(McGivern et al., 2013). Aberrant Ca^{2+} homeostasis is also detected in astrocytes expressing mutated SOD1 (Almad et al., 2016) and can influence neuronal excitability and synaptic transmission. Indeed, SMA astrocytes display defects in supporting synaptic formation and excitatory transmission *in vitro*, which was associated with decreased levels of the Ephrin ligand, Ephrin B2, known to control synapse formation and plasticity (Zhou et al., 2016). Aberrant expression of EphrinB2 was also found in reactive astrocytes in the spinal cord of SOD1 ALS mice (Urban, et al., 2015). Soluble factors released by SOD1 mutant astrocytes are known to increase motoneuron excitability though persistent sodium inward currents, increase firing rates and frequency of Ca^{2+} transients prior to death of motoneurons (Fritz et al., 2013).

Activation of ERK pathway in astrocytes might also contribute to the inflammatory environment by inducing the production of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-alpha (TNFα, previously reported to be increased in the spinal cord of SMA mice (Rindt et al., 2015). Indeed, AAV-mediated overexpression of SMN in astrocytes resulted in decreased levels of IL-6 and TNFα within the spinal cord of SMA mice (Rindt et al., 2015). Elevated levels of the inflammasome component IL-1β and phosphorylated ERK is also observed in spinal cord astrocytes of ALS mice and patients (Chung et al., 2005; Johann et al., 2015). The secretion of IL-6 by ALS astrocytes can be elicited by the pathogenic pro-inflammatory effector TWEAK (Bowerman et al., 2015), or by the cerebrospinal fluid (CSF) obtained from ALS patients, which in addition to promote TNFα production, leads to decreased astrocytic expression of GDNF by astrocytes (Mishra et al., 2016). The decreased ability of SOD1 mutant astrocytes to support motoneuron survival can be ameliorated by GDNF (Das and Svendsen, 2015). Thus, ERK-dependent neuroinflammation appears to be a shared pathological pathway in SMA and ALS spinal cords (Figure 3).

Additional shared non-cell-autonomous mechanisms have also been recently reported in a microglial cell line. In BV2 cells, SMN was shown to regulate the TRAF6-nuclear factor kappa B (NF-κB) pathway whereby SMN depletion leads to a sustained IL-1β-induced activation of the NF-κB subunit as well as increased production of TNFα and nitric oxide (NO)(Kim and Choi, 2017). In ALS mice, NF-κB activation occurs in microglial cells as disease progresses. SOD1 mutant-expressing microglial cells exert a cytotoxic effect toward motoneurons through an NF-κB-dependent mechanism, which is associated with TNFα and NO production *in vitro*. NO, through activation of the Fas (CD95) death pathway, as well as TNFα were both shown to trigger death of motoneurons (Raoul et al., 2002; Ugolini et al., 2003). In addition, microglial-specific reduction of NF-□B activation significantly reduced astrogliosis and microgliosis as well as delayed progression, but not onset, of the disease (Frakes et al., 2014). Interestingly, TDP-43 interacts with the NF-κB subunit p65 in neurons and glial cells, though predominantly in microglia, in spinal cord of ALS patients. Overexpression of mutant or wild-type TDP-43 enhanced the cytotoxicity of lipopolysaccharide-challenged primary microglial cells and was accompanied by increased production of NO (Swarup et al., 2011). Finally, TRAF6-NF-κB involvement in activated ALS microglia is supported by the observation that its activation is potentiated by the presence of extracellular SOD1 mutant (Kinsella et al., 2016)(Figure 3). The link between neuroinflammatory events in ALS

and SMA is further highlighted by the decreased activation of astrocytes and microglia cells in mutant TDP-43 ALS mice overexpressing Smn (Perera et al., 2016).

Please place Figure 3 here

More systemic factors, including defects in lymphoid organs, can be identified as being common between the two pathologies. Splenic pathology, abnormal architecture and differential size and weight of the spleen has been observed in SMA mice and patients (Deguise et al., 2017; Thomson et al., 2017). These spleen defects are associated with pathologic pulp architecture and abnormal distribution of macrophages, B and T lymphocytes. An increased number of $CD4^+$ and $CD8^+$ T cells, B lymphocytes and altered ratio of F4/80-CD11b macrophage subpopulations was also documented in symptomatic SMA mice (Khairallah et al., 2017). Size reduction of the spleen and its abnormal architecture were also reported in ALS mice (Banerjee et al., 2008; Finkelstein et al., 2011; Seksenyan et al., 2010), accompanied by an increased proportion of T cells and activated natural killer (NK) T cells (a distinct subset of T lymphocytes), a reduced proliferative capacity of T cells, a diminished staining of the B-cell marker CD19, an increased percentage of apoptotic and necrotic T and B cells, a decreased number of $CD4^+$ T cells and an increased proportion of $CD8^+$ T cells. Despite some discrepancies between studies, the overall picture depicts a more systemic damage caused by genetic factors associated with ALS and SMA that should be attentively considered.

In addition to the spleen, abnormal architecture of the thymus is also observed in an SMA mouse model whereby thymic dysplasia is characterized by defective intrathymic T cell development, increased apoptosis as well as increased production of inflammatory cytokines such as IL-6, IL-1β and TNFα (Deguise et al., 2017). In ALS mice, thymic involution with loss of tissue structure is accompanied by a reduction of all thymocyte populations during the course of the disease while a decreased thymic output is strikingly observed in ALS patients (Seksenyan et al., 2010)(Figure 4).

Primary defects in neuroimmunity and in the peripheral immune system or other peripheral defects should be therefore further studied in ALS and SMA to better ascertain shared pathological mechanisms. While in ALS, the findings accumulated over the years have started to reveal some interesting functions that could be therapeutically targeted, in SMA, this field of investigation has just begun and could lead to significant observations.

Please Place Figure 4 here

WHOLE-BODY METABOLIC DYSHOMEOSTASIS

SMA and ALS are both characterized by whole-body metabolic perturbations that if better understood, could lead to the development of therapeutic strategies to restore metabolic homeostasis. The influence of metabolism on SMA and ALS pathogenesis is highlighted by the fact that both dietary and exercise interventions, which are direct modulators of the metabolic state (López-Otín et al., 2016), have been demonstrated to impact disease progression.

In severe SMA mice that die pre-weaning, a maternal diet comprising 9% fat (PicoLab20) significantly increased lifespan and improved neuromuscular phenotype compared to a diet of 5.2% fat (Harlan-Teklad 22/5) (Butchbach et al., 2010). Furthermore, dietary modulation (PicoLab20) combined with an *SMN*-targeted pharmacological intervention (D156844) had a beneficial synergistic effect on survival in SMA mice (Butchbach et al., 2014). Similar observations were obtained in pre-clinical studies combining the histone deacetylase inhibitor trichostatin A (TSA) with a nutritional supplementation cocktail consisting of Vitamin B, infant formula, rodent diet softened with syrup, flavored jelly, whey protein, nutritional shakes and bacon softies (Narver et al., 2008). In patients, while direct effects of specific diet regimens on disease onset and progression have not been performed, it is clear that nutritional management of SMA patients is critical for overall health. There is an urgent need for research endeavours on how nutrient utilization and maintenance of metabolic homeostasis influences disease progression disease (Davis et al., 2014; Mehta et al., 2016).

In ALS, the available pre-clinical and clinical information on the role of diet is more extensive. Recently, a regression analysis of 302 ALS patients revealed an association between a diet high in fruits, vegetables, anti-oxidants and carotenes and functional measurements (Nieves et al., 2016). A smaller prospective randomized double-blind study in 16 ALS patients suggests that a diet enriched with milk whey protein results in weight gain and ameliorated biochemical serum markers (Silva et al., 2010). In *TDP-43*^{A315T} mutant mice, adding a high-fat jelly to their diet significantly increased their lifespan while restoring the bioenergetic balance (Coughlan et al., 2016). In *SOD1*^{G93A} mice, a high-fat diet (21% fat, 0.15% cholesterol) increased weight, survival and spinal cord motoneuron numbers while a calorie-restricted diet (60% of average *ad libitum* food intake) had the opposite effect compared to animals fed on a regular rodent chow (Zhao et al., 2015). Variable extents of improvement on lifespan and/or neuromuscular phenotype have also been reported in *SOD1*^{G93A} and *SOD1*^{G86R} mice on specific

dietary regimens such as the Deanna protocol (Ari et al., 2014), a ketogenic diet (Zhao et al., 2006), extra virgin olive oil (Oliván et al., 2014), vitamin D3 (Gianforcaro and Hamadeh, 2012), a high calorie diet (Dupuis et al., 2004) and vitamin E (Gurney et al., 1996). Finally, similar to SMA studies, a combinatorial approach of dietary (21% fat and 0.15% cholesterol Calorie Energy supplemented Diet) and drug (M30) interventions has a synergistic benefit on survival and motor function (Golko-Perez et al., 2016).

As mentioned above, activating metabolic pathways via exercise also impacts SMA and ALS disease pathogenesis. In SMA mice, daily wheel running from post-natal day 10 prolongs survival, prevents motoneuron loss and improves both motor function and cardiac defects (Biondi et al., 2012; Grondard et al., 2005). A follow-up study further showed that Smn-depleted animals subjected to a 10-month running or swimming program had improved neuromuscular pathology, energetic metabolism, motor function and muscle fatigue compared to sedentary animals (Chali et al., 2016). In ALS patients, various exercise regimens demonstrate similar benefits on muscle strength (Bohannon, 1983), spasticity (Drory et al., 2001), ALS functional rating scale (Bello-Haas et al., 2007; Drory et al., 2001; Lunetta et al., 2016), and quality of life defined by Short Form-36 (Bello-Haas et al., 2007). In *SOD1*^{G93A} mice, a 10-week treadmill program significantly increased lifespan compared to sedentary animal (Kirkinezos et al., 2003). Similarly, swimming-based training improves motor function, delays motoneuron death and also increases survival (Deforges et al., 2009). It is important to note that the positive effects of exercise on survival and neuromuscular phenotype appear to be dependent on training intensity and type of activity (Deforges et al., 2009; Mahoney et al., 2004). There are presently several clinical trials for SMA and ALS patients to determine the therapeutic benefits of exercise and their results will most likely provide added enlightenment to the discussed pre-clinical and small-scale clinical studies.

While it remains unclear whether intrinsic metabolic defects in specific cells and tissues such as motoneurons, skeletal muscle, glial cells and lymphoid organs or a systemic metabolic dysregulation are the source of dyshomeostasis in SMA and ALS, patients nevertheless present syndromes that have well-documented severe functional consequences. Indeed, instances of hyperinsulinemia (Bowerman et al., 2014; Davis et al., 2015), insulin resistance (Davis et al., 2015; Reyes et al., 1984), hyperlipidemia (Dahl and Peters, 1975; Dedic et al., 2012), hyperglycemia (Melissa Bowerman et al., 2012; Shimizu et al., 2011), hyperleptinemia (Kölbel et al., 2017), aberrant fatty acid metabolism (Pradat et al., 2010; Zolkipli et al., 2012), hypoglycemia (Bruce et al., 1995), hyperglucagonemia (Melissa Bowerman et al., 2012; Hubbard et al., 1992), glucose intolerance (Davis et al., 2015; Pradat et al., 2010) and development of diabetes (Borkowska et al., 2015; Hamasaki et al., 2015) have

all been reported in SMA and ALS patients and animal models. As we move along therapeutic progress for both diseases, it will be interesting to see if the gene-targeted therapies correct the metabolic abnormalities described herein or if they will have to be complemented with interventions aimed at restoring metabolic homeostasis.

TARGETED GENE THERAPIES

Because of the lack of effective pharmacological treatments, the possibility of gene therapy has attracted particular attention in the context of fatal MNDs. In particular, the possibility to restore SMN in SMA patients by delivering a transgene encoding a fully functional SMN protein has appeared as a rational approach for this monogenic disease. Identifying a vector-based system to deliver the transgene specifically in motoneurons has long remained a major hurdle to successful gene therapy. Indeed, targeting motoneurons along the entire spinal cord as well as other neurons involved in spinal and supraspinal motor circuits, represents a major challenge. In addition, although motoneurons display a selective vulnerability in both SMA and ALS, it is evident, as discussed above, that other CNS and non-CNS cell types also have important pathological contributions and optimally should be targeted by gene therapy approaches (Hamilton and Gillingwater, 2013; Imlach et al., 2012; Lalancette-Hebert et al., 2016; Lobsiger and Cleveland, 2007; Simone et al., 2016).

The development of vectors derived from the adeno-associated virus (AAV) was a major step towards effective gene therapy against MNDs. AAVs are small-sized viral particles that have the capability to efficiently transduce post-mitotic cells within the rodent and primate CNS. To achieve widespread transduction of the CNS, the vector can be delivered either directly into the CSF or systemically via the bloodstream, an approach that is also applicable to non-human primates (Bevan et al., 2011). In particular, AAV9 vectors have a remarkable ability to cross the blood-brain barrier (BBB), a feature which has been further evolved by modifying the AAV9 capsid to generate the PHP.B variant (Deverman et al., 2016; Duque et al., 2009; Foust et al., 2010). Importantly, when delivered to the bloodstream or to the CSF, AAV vectors also transduce peripheral organs such as the liver, which may have implications for the treatment of SMA (Bevan et al., 2011; Dirren et al., 2014). Intravenous injection of a self-complementary AAV9-SMN vector has shown therapeutic efficacy in mouse models of SMA (Dominguez et al., 2011; Foust et al., 2010; Valori et al., 2010). These proof-of-principle experiments have prompted a phase I clinical trial in 1-8 months old severe SMA Type I patients with a high-dose administration of the vector (clinicaltrials.gov: NCT02122952). Although the long-term outcome of this treatment is still unknown,

clear therapeutic efficacy has already been reported. Some of the treated children are now able to sit unassisted and all of them have reached month 13.6 without any adverse event, an age at which only 25% would have been predicted to survive the disease. If the dramatic effect of the treatment is confirmed over longer term, this trial will be a milestone achievement, opening the path for further gene therapy approaches for MNDs.

It is however unclear if a similar gene therapy can be applied to ALS patients. While AAV-SMN gene therapy can provide some therapeutic benefits in a mouse model of TDP-43-mediated ALS (Perera et al., 2016), gene therapy for ALS faces additional challenges. As the treatment will be administered to patients near the time of disease onset, vector systems need to be adapted for delivery to the adult CNS. It is unlikely that intravenous injections can be considered as the dose of AAV9 particles needed to target the adult CNS via this route of delivery will be too high, unless more efficient vectors can be developed. Instead, AAV vectors can be injected directly into the CSF of adult mice and non-human primates to target either motoneurons or astrocytes (Dirren et al., 2014; Meyer et al., 2015; Samaranch et al., 2012). Alternatively, injection of AAV vectors into skeletal muscle can target the innervating motoneurons. This approach can be used to treat individual muscles that are critically affected by the disease, such as the diaphragm, but cannot be envisaged for large portions of the skeletal musculature, which consists of more than 300 bilateral muscles in the human body (Towne et al., 2010, 2011).

The genes directly associated with ALS such as *SOD1*, *TARDBP*, *FUS* and *C9ORF72*, are the most evident targets for gene therapy. AAV-based therapeutic vectors for RNA interference against SOD1 mutants are under development for the treatment of this familial form of ALS (van Zundert and Brown, 2017). However, when it comes to treating sporadic ALS, which represents 90% of the cases, other effectors should be considered. It is therefore critical to identify gene targets that may support the survival and function of diseased motoneurons. As discussed above, a rational approach to identify key factors is to explore cell- and non-cell-autonomous pathways similarly affected across MNDs such as SMA and ALS. It is therefore likely that treatments will need to be designed to manipulate these molecular targets in a cell type-specific manner. By combining expression systems that are preferential for a given cell type with AAV capsids with adequate tropism, it is possible to engineer vectors that selectively induce transgene expression either in certain types of neurons or glial cells, or in the skeletal muscles (Colin et al., 2009; Dirren et al., 2014; Kügler, 2016; Wang et al., 2008)(Figure 5). These vector systems could be used in both ALS and SMA to rescue the activity of glial cells that support motoneurons or at the level of skeletal muscle to protect NMJs. Overall, gene therapy increasingly appears as a promising approach to tackle degenerative MNDs. As we move forward, it will be critical to identify the key molecular

targets that control motoneuron dysfunction and death, and devise precise and effective vector systems to rescue the cell types that are therapeutically relevant.

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CONCLUSION

In the present review, we have discussed the cellular and mechanistic pathological similarities between SMA and ALS, two common and devastating MNDs. From the primary motoneuron target to peripheral tissues and systems, understanding the commonalities between both diseases will be of utmost benefit for the development of wide-reaching therapeutic strategies. It is also important to consider that the similarities between the two MNDs do not lie in specific molecular effectors but in general dysfunctional pathways, which are easier to modulate with one single treatment approach. In addition, identifying key dysregulated pathways may elucidate regulatory networks between cells and tissues, potentially further uncovering primary and secondary causes of disease etiology. Using non-genetic injury-induced models of neurodegeneration, muscle atrophy and neuroinflammation will also provide insight into general vs disease-specific mechanisms. Nevertheless, an integrated combinatorial approach encompassing targeted gene therapy as well as pharmacological, dietary and exercise interventions at various stages during disease progression, will most likely become the optimal strategy to alleviate the CNS and non-CNS defects that arise during the lifetime of SMA and ALS patients.

REFERENCES

Aebischer, J., Cassina, P., Otsmane, B., Moumen, A., Seilhean, D., Meininger, V., Barbeito, L., Pettmann, B., Raoul, C., 2011. IFNγ triggers a LIGHT-dependent selective death of motoneurons contributing to the non-cell-autonomous effects of mutant SOD1. Cell Death Differ. 18, 754–768. doi:10.1038/cdd.2010.143

Allodi, I., Comley, L., Nichterwitz, S., Nizzardo, M., Simone, C., Benitez, J.A., Cao, M., Corti, S., Hedlund, E., 2016. Differential neuronal vulnerability identifies IGF-2 as a protective factor in ALS. Sci. Rep. 6, 25960. doi:10.1038/srep25960

Almad, A.A., Doreswamy, A., Gross, S.K., Richard, J.-P., Huo, Y., Haughey, N., Maragakis, N.J., 2016. Connexin 43 in astrocytes contributes to motor neuron toxicity in amyotrophic lateral sclerosis. Glia 64, 1154–1169. doi:10.1002/glia.22989

Amendola, J., Durand, J., 2008. Morphological differences between wild-type and transgenic superoxide dismutase 1 lumbar motoneurons in postnatal mice. J. Comp. Neurol. 511, 329–341. doi:10.1002/cne.21818

Andersen, P.M., Al-Chalabi, A., 2011. Clinical genetics of amyotrophic lateral sclerosis: what do we really know? Nat. Rev. Neurol. 7, 603–615. doi:10.1038/nrneurol.2011.150

Ari, C., Poff, A.M., Held, H.E., Landon, C.S., Goldhagen, C.R., Mavromates, N., D'Agostino, D.P., 2014. Metabolic therapy with Deanna Protocol supplementation delays disease progression and extends survival in amyotrophic lateral sclerosis (ALS) mouse model. PloS One 9, e103526. doi:10.1371/journal.pone.0103526

Banerjee, R., Mosley, R.L., Reynolds, A.D., Dhar, A., Jackson-Lewis, V., Gordon, P.H., Przedborski, S., Gendelman, H.E., 2008. Adaptive immune neuroprotection in G93A-SOD1 amyotrophic lateral sclerosis mice. PloS One 3, e2740. doi:10.1371/journal.pone.0002740

Bello-Haas, V.D., Florence, J.M., Kloos, A.D., Scheirbecker, J., Lopate, G., Hayes, S.M., Pioro, E.P., Mitsumoto, H., 2007. A randomized controlled trial of resistance exercise in individuals with ALS. Neurology 68, 2003–2007. doi:10.1212/01.wnl.0000264418.92308.a4

Bevan, A.K., Duque, S., Foust, K.D., Morales, P.R., Braun, L., Schmelzer, L., Chan, C.M., McCrate, M., Chicoine, L.G., Coley, B.D., Porensky, P.N., Kolb, S.J., Mendell, J.R., Burghes, A.H.M., Kaspar, B.K., 2011. Systemic gene delivery in large species for targeting spinal cord, brain, and peripheral tissues for pediatric disorders. Mol. Ther. J. Am. Soc. Gene Ther. 19, 1971–1980. doi:10.1038/mt.2011.157

Biondi, O., Lopes, P., Desseille, C., Branchu, J., Chali, F., Ben Salah, A., Pariset, C., Chanoine, C., Charbonnier, F., 2012. Physical exercise reduces cardiac defects in type 2 spinal muscular atrophy-like mice. J. Physiol. 590, 5907–5925. doi:10.1113/jphysiol.2012.238196

Blauw, H.M., Barnes, C.P., van Vught, P.W.J., van Rheenen, W., Verheul, M., Cuppen, E., Veldink, J.H., van den Berg, L.H., 2012. SMN1 gene duplications are associated with sporadic ALS. Neurology 78, 776–780. doi:10.1212/WNL.0b013e318249f697

Bohannon, R.W., 1983. Results of resistance exercise on a patient with amyotrophic lateral sclerosis. A case report. Phys. Ther. 63, 965–968.

Boillée, S., Yamanaka, K., Lobsiger, C.S., Copeland, N.G., Jenkins, N.A., Kassiotis, G., Kollias, G., Cleveland, D.W., 2006. Onset and progression in inherited ALS determined by motor neurons and microglia. Science 312, 1389–1392. doi:10.1126/science.1123511

Borkowska, A., Jankowska, A., Szlagatys-Sidorkiewicz, A., Sztangierska, B., Liberek, A., Plata-Nazar, K., Kamińska, B., 2015. Coexistence of type 1 diabetes mellitus and spinal muscular atrophy in an 8-year-old girl: a case report. Acta Biochim. Pol. 62, 167–168.

Bosch-Marcé, M., Wee, C.D., Martinez, T.L., Lipkes, C.E., Choe, D.W., Kong, L., Van Meerbeke, J.P., Musarò, A., Sumner, C.J., 2011. Increased IGF-1 in muscle modulates the phenotype of severe SMA mice. Hum. Mol. Genet. 20, 1844–1853. doi:10.1093/hmg/ddr067

Bose, J.K., Wang, I.-F., Hung, L., Tarn, W.-Y., Shen, C.-K.J., 2008. TDP-43 overexpression enhances exon 7 inclusion during the survival of motor neuron pre-mRNA splicing. J. Biol. Chem. 283, 28852–28859. doi:10.1074/jbc.M805376200

Bowerman, M., Michalski, J.-P., Beauvais, A., Murray, L.M., DeRepentigny, Y., Kothary, R., 2014. Defects in pancreatic development and glucose metabolism in SMN-depleted mice independent of canonical spinal muscular atrophy neuromuscular pathology. Hum. Mol. Genet. 23, 3432–3444. doi:10.1093/hmg/ddu052

Bowerman, M., Murray, L.M., Beauvais, A., Pinheiro, B., Kothary, R., 2012. A critical smn threshold in mice dictates onset of an intermediate spinal muscular atrophy phenotype associated with a distinct neuromuscular junction pathology. Neuromuscul. Disord. NMD 22, 263–276. doi:10.1016/j.nmd.2011.09.007

Bowerman, M., Salsac, C., Coque, E., Eiselt, É., Deschaumes, R.G., Brodovitch, A., Burkly, L.C., Scamps, F., Raoul, C., 2015. Tweak regulates astrogliosis, microgliosis and skeletal muscle atrophy in a mouse model of amyotrophic lateral sclerosis. Hum. Mol. Genet. 24, 3440–3456. doi:10.1093/hmg/ddv094

Bowerman, M., Shafey, D., Kothary, R., 2007. Smn depletion alters profilin II expression and leads to upregulation of the RhoA/ROCK pathway and defects in neuronal integrity. J. Mol. Neurosci. MN 32, 120–131.

Bowerman, M., Swoboda, K.J., Michalski, J.-P., Wang, G.-S., Reeks, C., Beauvais, A., Murphy, K., Woulfe, J., Screaton, R.A., Scott, F.W., Kothary, R., 2012. Glucose metabolism and pancreatic defects in spinal muscular atrophy. Ann. Neurol. 72, 256–268. doi:10.1002/ana.23582

Bowerman, M., Vincent, T., Scamps, F., Perrin, F.E., Camu, W., Raoul, C., 2013. Neuroimmunity dynamics and the development of therapeutic strategies for amyotrophic lateral sclerosis. Front. Cell. Neurosci. 7, 214. doi:10.3389/fncel.2013.00214

Boyd, P.J., Tu, W.-Y., Shorrock, H.K., Groen, E.J.N., Carter, R.N., Powis, R.A., Thomson, S.R., Thomson, D., Graham, L.C., Motyl, A.A.L., Wishart, T.M., Highley, J.R., Morton, N.M., Becker, T., Becker, C.G., Heath, P.R., Gillingwater, T.H., 2017. Bioenergetic status modulates motor neuron vulnerability and pathogenesis in a zebrafish model of spinal muscular atrophy. PLoS Genet. 13, e1006744. doi:10.1371/journal.pgen.1006744

Boyer, J.G., Deguise, M.-O., Murray, L.M., Yazdani, A., De Repentigny, Y., Boudreau-Larivière, C., Kothary, R., 2014. Myogenic program dysregulation is contributory to disease pathogenesis in spinal muscular atrophy. Hum. Mol. Genet. 23, 4249–4259. doi:10.1093/hmg/ddu142

Boyer, J.G., Murray, L.M., Scott, K., De Repentigny, Y., Renaud, J.-M., Kothary, R., 2013. Early onset muscle weakness and disruption of muscle proteins in mouse models of spinal muscular atrophy. Skelet. Muscle 3, 24. doi:10.1186/2044-5040-3-24

Bricceno, K.V., Martinez, T., Leikina, E., Duguez, S., Partridge, T.A., Chernomordik, L.V., Fischbeck, K.H., Sumner, C.J., Burnett, B.G., 2014. Survival motor neuron protein deficiency impairs myotube formation by altering myogenic gene expression and focal adhesion dynamics. Hum. Mol. Genet. 23, 4745–4757. doi:10.1093/hmg/ddu189

Brock, T.O., McIlwain, D.L., 1984. Astrocytic proteins in the dorsal and ventral roots in amyotrophic lateral sclerosis and Werdnig-Hoffmann disease. J. Neuropathol. Exp. Neurol. 43, 609–619.

Brockington, A., Ning, K., Heath, P.R., Wood, E., Kirby, J., Fusi, N., Lawrence, N., Wharton, S.B., Ince, P.G., Shaw, P.J., 2013. Unravelling the enigma of selective vulnerability in neurodegeneration: motor neurons resistant to degeneration in ALS show distinct gene expression characteristics and decreased susceptibility to excitotoxicity. Acta Neuropathol. (Berl.) 125, 95–109. doi:10.1007/s00401-012-1058-5

Bruce, A.K., Jacobsen, E., Dossing, H., Kondrup, J., 1995. Hypoglycaemia in spinal muscular atrophy. Lancet Lond. Engl. 346, 609–610.

Butchbach, M.E.R., Rose, F.F., Rhoades, S., Marston, J., McCrone, J.T., Sinnott, R., Lorson, C.L., 2010. Effect of diet on the survival and phenotype of a mouse model for spinal muscular atrophy. Biochem. Biophys. Res. Commun. 391, 835–840. doi:10.1016/j.bbrc.2009.11.148

Butchbach, M.E.R., Singh, J., Gurney, M.E., Burghes, A.H.M., 2014. The effect of diet on the protective action of D156844 observed in spinal muscular atrophy mice. Exp. Neurol. 256, 1–6. doi:10.1016/j.expneurol.2014.03.005

Capitanio, D., Vasso, M., Ratti, A., Grignaschi, G., Volta, M., Moriggi, M., Daleno, C., Bendotti, C., Silani, V., Gelfi, C., 2012. Molecular signatures of amyotrophic lateral sclerosis disease progression in hind and forelimb muscles of an SOD1(G93A) mouse model. Antioxid. Redox Signal. 17, 1333–1350. doi:10.1089/ars.2012.4524

Catapano, F., Zaharieva, I., Scoto, M., Marrosu, E., Morgan, J., Muntoni, F., Zhou, H., 2016. Altered Levels of MicroRNA-9, -206, and -132 in Spinal Muscular Atrophy and Their Response to Antisense Oligonucleotide Therapy. Mol. Ther. Nucleic Acids 5, e331. doi:10.1038/mtna.2016.47

Chali, F., Desseille, C., Houdebine, L., Benoit, E., Rouquet, T., Bariohay, B., Lopes, P., Branchu, J., Della Gaspera, B., Pariset, C., Chanoine, C., Charbonnier, F., Biondi, O., 2016. Long-term exercise-specific neuroprotection in spinal muscular atrophy-like mice. J. Physiol. 594, 1931–1952. doi:10.1113/JP271361

Chung, Y.H., Joo, K.M., Lim, H.C., Cho, M.H., Kim, D., Lee, W.B., Cha, C.I., 2005. Immunohistochemical study on the distribution of phosphorylated extracellular signal-regulated kinase (ERK) in the central nervous system of SOD1G93A transgenic mice. Brain Res. 1050, 203–209. doi:10.1016/j.brainres.2005.05.060

Cifuentes-Diaz, C., Frugier, T., Tiziano, F.D., Lacène, E., Roblot, N., Joshi, V., Moreau, M.H., Melki, J., 2001. Deletion of murine SMN exon 7 directed to skeletal muscle leads to severe muscular dystrophy. J. Cell Biol. 152, 1107–1114.

Clement, A.M., Nguyen, M.D., Roberts, E.A., Garcia, M.L., Boillée, S., Rule, M., McMahon, A.P., Doucette, W., Siwek, D., Ferrante, R.J., Brown, R.H., Julien, J.-P., Goldstein, L.S.B., Cleveland, D.W., 2003. Wild-type nonneuronal cells extend survival of SOD1 mutant motor neurons in ALS mice. Science 302, 113–117. doi:10.1126/science.1086071

Colin, A., Faideau, M., Dufour, N., Auregan, G., Hassig, R., Andrieu, T., Brouillet, E., Hantraye, P., Bonvento, G., Déglon, N., 2009. Engineered lentiviral vector targeting astrocytes in vivo. Glia 57, 667–679. doi:10.1002/glia.20795

Comley, L.H., Nijssen, J., Frost-Nylen, J., Hedlund, E., 2016. Cross-disease comparison of amyotrophic lateral sclerosis and spinal muscular atrophy reveals conservation of selective vulnerability but differential neuromuscular junction pathology. J. Comp. Neurol. 524, 1424–1442. doi:10.1002/cne.23917

Coughlan, K.S., Halang, L., Woods, I., Prehn, J.H.M., 2016. A high-fat jelly diet restores bioenergetic balance and extends lifespan in the presence of motor dysfunction and lumbar spinal cord motor neuron loss in TDP-43A315T mutant C57BL6/J mice. Dis. Model. Mech. 9, 1029–1037. doi:10.1242/dmm.024786

da Costa, C.A., Ancolio, K., Checler, F., 2000. Wild-type but not Parkinson's disease-related ala-53 --> Thr mutant alpha -synuclein protects neuronal cells from apoptotic stimuli. J. Biol. Chem. 275, 24065–24069. doi:10.1074/jbc.M002413200

Dachs, E., Hereu, M., Piedrafita, L., Casanovas, A., Calderó, J., Esquerda, J.E., 2011. Defective neuromuscular junction organization and postnatal myogenesis in mice with severe spinal muscular atrophy. J. Neuropathol. Exp. Neurol. 70, 444–461. doi:10.1097/NEN.0b013e31821cbd8b

Dahl, D.S., Peters, H.A., 1975. Lipid disturbances associated with spiral muscular atrophy. Clinical, electromyographic, histochemical, and lipid studies. Arch. Neurol. 32, 195–203.

Das, M.M., Svendsen, C.N., 2015. Astrocytes show reduced support of motor neurons with aging that is accelerated in a rodent model of ALS. Neurobiol. Aging 36, 1130–1139. doi:10.1016/j.neurobiolaging.2014.09.020

Davis, R.H., Godshall, B.J., Seffrood, E., Marcus, M., LaSalle, B.A., Wong, B., Schroth, M.K., Swoboda, K.J., 2014. Nutritional practices at a glance: spinal muscular atrophy type I nutrition survey findings. J. Child Neurol. 29, 1467–1472. doi:10.1177/0883073813503988

Davis, R.H., Miller, E.A., Zhang, R.Z., Swoboda, K.J., 2015. Responses to Fasting and Glucose Loading in a Cohort of Well Children with Spinal Muscular Atrophy Type II. J. Pediatr. 167, 1362–1368.e1. doi:10.1016/j.jpeds.2015.09.023

de Andrade, H.M.T., de Albuquerque, M., Avansini, S.H., de S Rocha, C., Dogini, D.B., Nucci, A., Carvalho, B., Lopes-Cendes, I., França, M.C., 2016. MicroRNAs-424 and 206 are potential prognostic markers in spinal onset amyotrophic lateral sclerosis. J. Neurol. Sci. 368, 19–24. doi:10.1016/j.jns.2016.06.046

de Oliveira, G.P., Maximino, J.R., Maschietto, M., Zanoteli, E., Puga, R.D., Lima, L., Carraro, D.M., Chadi, G., 2014. Early gene expression changes in skeletal muscle from SOD1(G93A) amyotrophic lateral sclerosis animal model. Cell. Mol. Neurobiol. 34, 451–462. doi:10.1007/s10571-014-0029-x

Dedic, S.I.K., Stevic, Z., Dedic, V., Stojanovic, V.R., Milicev, M., Lavrnic, D., 2012. Is hyperlipidemia correlated with longer survival in patients with amyotrophic lateral sclerosis? Neurol. Res. 34, 576–580. doi:10.1179/1743132812Y.0000000049

Deforges, S., Branchu, J., Biondi, O., Grondard, C., Pariset, C., Lécolle, S., Lopes, P., Vidal, P.-P., Chanoine, C., Charbonnier, F., 2009. Motoneuron survival is promoted by specific exercise in a mouse model of amyotrophic lateral sclerosis. J. Physiol. 587, 3561–3572. doi:10.1113/jphysiol.2009.169748

Deguise, M.-O., De Repentigny, Y., McFall, E., Auclair, N., Sad, S., Kothary, R., 2017. Immune dysregulation may contribute to disease pathogenesis in spinal muscular atrophy mice. Hum. Mol. Genet. doi:10.1093/hmg/ddw434

DeJesus-Hernandez, M., Mackenzie, I.R., Boeve, B.F., Boxer, A.L., Baker, M., Rutherford, N.J., Nicholson, A.M., Finch, N.A., Flynn, H., Adamson, J., Kouri, N., Wojtas, A., Sengdy, P., Hsiung, G.-Y.R., Karydas, A., Seeley, W.W., Josephs, K.A., Coppola, G., Geschwind, D.H., Wszolek, Z.K., Feldman, H., Knopman, D.S., Petersen, R.C., Miller, B.L., Dickson, D.W., Boylan, K.B., Graff-Radford, N.R., Rademakers, R., 2011. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 72, 245–256. doi:10.1016/j.neuron.2011.09.011

Delestrée, N., Manuel, M., Iglesias, C., Elbasiouny, S.M., Heckman, C.J., Zytnicki, D., 2014. Adult spinal motoneurones are not hyperexcitable in a mouse model of inherited amyotrophic lateral sclerosis. J. Physiol. 592, 1687–1703. doi:10.1113/jphysiol.2013.265843

Derave, W., Van Den Bosch, L., Lemmens, G., Eijnde, B.O., Robberecht, W., Hespel, P., 2003. Skeletal muscle properties in a transgenic mouse model for amyotrophic lateral sclerosis: effects of creatine treatment. Neurobiol. Dis. 13, 264–272.

Deverman, B.E., Pravdo, P.L., Simpson, B.P., Kumar, S.R., Chan, K.Y., Banerjee, A., Wu, W.-L., Yang, B., Huber, N., Pasca, S.P., Gradinaru, V., 2016. Cre-dependent selection yields AAV variants for widespread gene transfer to the adult brain. Nat. Biotechnol. 34, 204–209. doi:10.1038/nbt.3440

Deymeer, F., Serdaroglu, P., Parman, Y., Poda, M., 2008. Natural history of SMA IIIb: muscle strength decreases in a predictable sequence and magnitude. Neurology 71, 644–649. doi:10.1212/01.wnl.0000324623.89105.c4

Di Giorgio, F.P., Boulting, G.L., Bobrowicz, S., Eggan, K.C., 2008. Human embryonic stem cell-derived motor neurons are sensitive to the toxic effect of glial cells carrying an ALS-causing mutation. Cell Stem Cell 3, 637–648. doi:10.1016/j.stem.2008.09.017

Di Giorgio, F.P., Carrasco, M.A., Siao, M.C., Maniatis, T., Eggan, K., 2007. Non-cell autonomous effect of glia on motor neurons in an embryonic stem cell-based ALS model. Nat. Neurosci. 10, 608–614. doi:10.1038/nn1885

Dirren, E., Towne, C.L., Setola, V., Redmond, D.E., Schneider, B.L., Aebischer, P., 2014. Intracerebroventricular injection of adeno-associated virus 6 and 9 vectors for cell type-specific transgene expression in the spinal cord. Hum. Gene Ther. 25, 109–120. doi:10.1089/hum.2013.021

Dobrowolny, G., Aucello, M., Rizzuto, E., Beccafico, S., Mammucari, C., Boncompagni, S., Bonconpagni, S., Belia, S., Wannenes, F., Nicoletti, C., Del Prete, Z., Rosenthal, N., Molinaro, M., Protasi, F., Fanò, G., Sandri, M., Musarò, A., 2008. Skeletal muscle is a primary target of SOD1G93A-mediated toxicity. Cell Metab. 8, 425–436. doi:10.1016/j.cmet.2008.09.002

Dominguez, E., Marais, T., Chatauret, N., Benkhelifa-Ziyyat, S., Duque, S., Ravassard, P., Carcenac, R., Astord, S., Pereira de Moura, A., Voit, T., Barkats, M., 2011. Intravenous scAAV9 delivery of a codon-optimized SMN1 sequence rescues SMA mice. Hum. Mol. Genet. 20, 681–693. doi:10.1093/hmg/ddq514

Drory, V.E., Goltsman, E., Reznik, J.G., Mosek, A., Korczyn, A.D., 2001. The value of muscle exercise in patients with amyotrophic lateral sclerosis. J. Neurol. Sci. 191, 133–137.

Dupuis, L., Oudart, H., René, F., Gonzalez de Aguilar, J.-L., Loeffler, J.-P., 2004. Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: benefit of a high-energy diet in a transgenic mouse model. Proc. Natl. Acad. Sci. U. S. A. 101, 11159–11164. doi:10.1073/pnas.0402026101

Duque, S., Joussemet, B., Riviere, C., Marais, T., Dubreil, L., Douar, A.-M., Fyfe, J., Moullier, P., Colle, M.-A., Barkats, M., 2009. Intravenous administration of self-complementary AAV9 enables transgene delivery to adult motor neurons. Mol. Ther. J. Am. Soc. Gene Ther. 17, 1187–1196. doi:10.1038/mt.2009.71

Elbasiouny, S.M., Amendola, J., Durand, J., Heckman, C.J., 2010. Evidence from computer simulations for alterations in the membrane biophysical properties and dendritic processing of synaptic inputs in mutant superoxide dismutase-1 motoneurons. J. Neurosci. Off. J. Soc. Neurosci. 30, 5544–5558. doi:10.1523/JNEUROSCI.0434-10.2010

Finkelstein, A., Kunis, G., Seksenyan, A., Ronen, A., Berkutzki, T., Azoulay, D., Koronyo-Hamaoui, M., Schwartz, M., 2011. Abnormal changes in NKT cells, the IGF-1 axis, and liver pathology in an animal model of ALS. PloS One 6, e22374. doi:10.1371/journal.pone.0022374

Fischer, L.R., Culver, D.G., Tennant, P., Davis, A.A., Wang, M., Castellano-Sanchez, A., Khan, J., Polak, M.A., Glass, J.D., 2004. Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. Exp. Neurol. 185, 232–240.

Fletcher, E.V., Simon, C.M., Pagiazitis, J.G., Chalif, J.I., Vukojicic, A., Drobac, E., Wang, X., Mentis, G.Z., 2017. Reduced sensory synaptic excitation impairs motor neuron function via Kv2.1 in spinal muscular atrophy. Nat. Neurosci. doi:10.1038/nn.4561

Foust, K.D., Wang, X., McGovern, V.L., Braun, L., Bevan, A.K., Haidet, A.M., Le, T.T., Morales, P.R., Rich, M.M., Burghes, A.H.M., Kaspar, B.K., 2010. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nat. Biotechnol. 28, 271–274. doi:10.1038/nbt.1610

Frakes, A.E., Ferraiuolo, L., Haidet-Phillips, A.M., Schmelzer, L., Braun, L., Miranda, C.J., Ladner, K.J., Bevan, A.K., Foust, K.D., Godbout, J.P., Popovich, P.G., Guttridge, D.C., Kaspar, B.K., 2014. Microglia induce motor neuron death via the classical NF-κB pathway in amyotrophic lateral sclerosis. Neuron 81, 1009–1023. doi:10.1016/j.neuron.2014.01.013

Frey, D., Schneider, C., Xu, L., Borg, J., Spooren, W., Caroni, P., 2000. Early and selective loss of neuromuscular synapse subtypes with low sprouting competence in motoneuron diseases. J. Neurosci. Off. J. Soc. Neurosci. 20, 2534–2542.

Fritz, E., Izaurieta, P., Weiss, A., Mir, F.R., Rojas, P., Gonzalez, D., Rojas, F., Brown, R.H., Madrid, R., van Zundert, B., 2013. Mutant SOD1-expressing astrocytes release toxic factors that trigger motoneuron death by inducing hyperexcitability. J. Neurophysiol. 109, 2803–2814. doi:10.1152/jn.00500.2012

Gertz, B., Wong, M., Martin, L.J., 2012. Nuclear localization of human SOD1 and mutant SOD1-specific disruption of survival motor neuron protein complex in transgenic amyotrophic lateral sclerosis mice. J. Neuropathol. Exp. Neurol. 71, 162–177. doi:10.1097/NEN.0b013e318244b635

Gianforcaro, A., Hamadeh, M.J., 2012. Dietary vitamin D3 supplementation at 10× the adequate intake improves functional capacity in the G93A transgenic mouse model of ALS, a pilot study. CNS Neurosci. Ther. 18, 547–557. doi:10.1111/j.1755-5949.2012.00316.x

Giesemann, T., Rathke-Hartlieb, S., Rothkegel, M., Bartsch, J.W., Buchmeier, S., Jockusch, B.M., Jockusch, H., 1999. A role for polyproline motifs in the spinal muscular atrophy protein SMN. Profilins bind to and colocalize with smn in nuclear gems. J. Biol. Chem. 274, 37908–37914.

Gitcho, M.A., Baloh, R.H., Chakraverty, S., Mayo, K., Norton, J.B., Levitch, D., Hatanpaa, K.J., White, C.L., Bigio, E.H., Caselli, R., Baker, M., Al-Lozi, M.T., Morris, J.C., Pestronk, A., Rademakers, R., Goate, A.M., Cairns, N.J., 2008. TDP-43 A315T mutation in familial motor neuron disease. Ann. Neurol. 63, 535–538. doi:10.1002/ana.21344

Gizzi, M., DiRocco, A., Sivak, M., Cohen, B., 1992. Ocular motor function in motor neuron disease. Neurology 42, 1037–1046.

Gogliotti, R.G., Quinlan, K.A., Barlow, C.B., Heier, C.R., Heckman, C.J., Didonato, C.J., 2012. Motor neuron rescue in spinal muscular atrophy mice demonstrates that sensory-motor defects are a consequence, not a cause, of motor neuron dysfunction. J. Neurosci. Off. J. Soc. Neurosci. 32, 3818–3829. doi:10.1523/JNEUROSCI.5775-11.2012

Golko-Perez, S., Mandel, S., Amit, T., Kupershmidt, L., Youdim, M.B.H., Weinreb, O., 2016. Additive Neuroprotective Effects of the Multifunctional Iron Chelator M30 with Enriched Diet in a Mouse Model of Amyotrophic Lateral Sclerosis. Neurotox. Res. 29, 208–217. doi:10.1007/s12640-015-9574-4

Groen, E.J.N., Fumoto, K., Blokhuis, A.M., Engelen-Lee, J., Zhou, Y., van den Heuvel, D.M.A., Koppers, M., van Diggelen, F., van Heest, J., Demmers, J.A.A., Kirby, J., Shaw, P.J., Aronica, E., Spliet, W.G.M., Veldink, J.H., van den Berg, L.H., Pasterkamp, R.J., 2013. ALS-associated mutations in FUS disrupt the axonal distribution and function of SMN. Hum. Mol. Genet. 22, 3690–3704. doi:10.1093/hmg/ddt222

Grondard, C., Biondi, O., Armand, A.-S., Lécolle, S., Della Gaspera, B., Pariset, C., Li, H., Gallien, C.-L., Vidal, P.-P., Chanoine, C., Charbonnier, F., 2005. Regular exercise prolongs survival in a type 2 spinal muscular atrophy model mouse. J. Neurosci. Off. J. Soc. Neurosci. 25, 7615–7622. doi:10.1523/JNEUROSCI.1245-05.2005

Guettier-Sigrist, S., Hugel, B., Coupin, G., Freyssinet, J.-M., Poindron, P., Warter, J.-M., 2002. Possible pathogenic role of muscle cell dysfunction in motor neuron death in spinal muscular atrophy. Muscle Nerve 25, 700–708. doi:10.1002/mus.10081

Gurney, M.E., Cutting, F.B., Zhai, P., Doble, A., Taylor, C.P., Andrus, P.K., Hall, E.D., 1996. Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis. Ann. Neurol. 39, 147–157. doi:10.1002/ana.410390203

Hamasaki, H., Takeuchi, Y., Masui, Y., Ohta, Y., Abe, K., Yoshino, H., Yanai, H., 2015. Development of diabetes in a familial amyotrophic lateral sclerosis patient carrying the I113T SOD1 mutation. Case Report. Neuro Endocrinol. Lett. 36, 414–416.

Hamilton, G., Gillingwater, T.H., 2013. Spinal muscular atrophy: going beyond the motor neuron. Trends Mol. Med. 19, 40–50. doi:10.1016/j.molmed.2012.11.002

Hammond, S.M., Gogliotti, R.G., Rao, V., Beauvais, A., Kothary, R., DiDonato, C.J., 2010. Mouse survival motor neuron alleles that mimic SMN2 splicing and are inducible rescue embryonic lethality early in development but not late. PloS One 5, e15887. doi:10.1371/journal.pone.0015887

Hashimoto, M., Hsu, L.J., Rockenstein, E., Takenouchi, T., Mallory, M., Masliah, E., 2002. alpha-Synuclein protects against oxidative stress via inactivation of the c-Jun N-terminal kinase stress-signaling pathway in neuronal cells. J. Biol. Chem. 277, 11465–11472. doi:10.1074/jbc.M111428200

Hayhurst, M., Wagner, A.K., Cerletti, M., Wagers, A.J., Rubin, L.L., 2012. A cell-autonomous defect in skeletal muscle satellite cells expressing low levels of survival of motor neuron protein. Dev. Biol. 368, 323–334. doi:10.1016/j.ydbio.2012.05.037

Heckman, C.J., Mottram, C., Quinlan, K., Theiss, R., Schuster, J., 2009. Motoneuron excitability: the importance of neuromodulatory inputs. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 120, 2040–2054. doi:10.1016/j.clinph.2009.08.009

Hedlund, E., Karlsson, M., Osborn, T., Ludwig, W., Isacson, O., 2010. Global gene expression profiling of somatic motor neuron populations with different vulnerability identify molecules and pathways of degeneration and protection. Brain J. Neurol. 133, 2313–2330. doi:10.1093/brain/awq167

Hensel, N., Claus, P., 2017. The Actin Cytoskeleton in SMA and ALS: How Does It Contribute to Motoneuron Degeneration? Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry 1073858417705059. doi:10.1177/1073858417705059

Holzbaur, E.L.F., Howland, D.S., Weber, N., Wallace, K., She, Y., Kwak, S., Tchistiakova, L.A., Murphy, E., Hinson, J., Karim, R., Tan, X.Y., Kelley, P., McGill, K.C., Williams, G., Hobbs, C., Doherty, P., Zaleska,

M.M., Pangalos, M.N., Walsh, F.S., 2006. Myostatin inhibition slows muscle atrophy in rodent models of amyotrophic lateral sclerosis. Neurobiol. Dis. 23, 697–707. doi:10.1016/j.nbd.2006.05.009

Hsieh-Li, H.M., Chang, J.G., Jong, Y.J., Wu, M.H., Wang, N.M., Tsai, C.H., Li, H., 2000. A mouse model for spinal muscular atrophy. Nat. Genet. 24, 66–70. doi:10.1038/71709

Hubbard, R.W., Will, A.D., Peterson, G.W., Sanchez, A., Gillan, W.W., Tan, S.A., 1992. Elevated plasma glucagon in amyotrophic lateral sclerosis. Neurology 42, 1532–1534.

Imlach, W.L., Beck, E.S., Choi, B.J., Lotti, F., Pellizzoni, L., McCabe, B.D., 2012. SMN is required for sensory-motor circuit function in Drosophila. Cell 151, 427–439. doi:10.1016/j.cell.2012.09.011

Johann, S., Heitzer, M., Kanagaratnam, M., Goswami, A., Rizo, T., Weis, J., Troost, D., Beyer, C., 2015. NLRP3 inflammasome is expressed by astrocytes in the SOD1 mouse model of ALS and in human sporadic ALS patients. Glia 63, 2260–2273. doi:10.1002/glia.22891

Kabashi, E., Valdmanis, P.N., Dion, P., Spiegelman, D., McConkey, B.J., Vande Velde, C., Bouchard, J.-P., Lacomblez, L., Pochigaeva, K., Salachas, F., Pradat, P.-F., Camu, W., Meininger, V., Dupre, N., Rouleau, G.A., 2008. TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. Nat. Genet. 40, 572–574. doi:10.1038/ng.132

Kanai, K., Shibuya, K., Sato, Y., Misawa, S., Nasu, S., Sekiguchi, Y., Mitsuma, S., Isose, S., Fujimaki, Y., Ohmori, S., Koga, S., Kuwabara, S., 2012. Motor axonal excitability properties are strong predictors for survival in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 83, 734–738. doi:10.1136/jnnp-2011-301782

Kanning, K.C., Kaplan, A., Henderson, C.E., 2010. Motor neuron diversity in development and disease. Annu. Rev. Neurosci. 33, 409–440. doi:10.1146/annurev.neuro.051508.135722

Kaplan, A., Spiller, K.J., Towne, C., Kanning, K.C., Choe, G.T., Geber, A., Akay, T., Aebischer, P., Henderson, C.E., 2014. Neuronal matrix metalloproteinase-9 is a determinant of selective neurodegeneration. Neuron 81, 333–348. doi:10.1016/j.neuron.2013.12.009

Kariya, S., Park, G.-H., Maeno-Hikichi, Y., Leykekhman, O., Lutz, C., Arkovitz, M.S., Landmesser, L.T., Monani, U.R., 2008. Reduced SMN protein impairs maturation of the neuromuscular junctions in mouse models of spinal muscular atrophy. Hum. Mol. Genet. 17, 2552–2569. doi:10.1093/hmg/ddn156

Kariya, S., Re, D.B., Jacquier, A., Nelson, K., Przedborski, S., Monani, U.R., 2012. Mutant superoxide dismutase 1 (SOD1), a cause of amyotrophic lateral sclerosis, disrupts the recruitment of SMN, the spinal muscular atrophy protein to nuclear Cajal bodies. Hum. Mol. Genet. 21, 3421–3434. doi:10.1093/hmg/dds174

Khairallah, M.-T., Astroski, J., Custer, S.K., Androphy, E.J., Franklin, C.L., Lorson, C.L., 2017. SMN deficiency negatively impacts red pulp macrophages and spleen development in mouse models of spinal muscular atrophy. Hum. Mol. Genet. 26, 932–941. doi:10.1093/hmg/ddx008

Kim, E.K., Choi, E.-J., 2017. SMN1 functions as a novel inhibitor for TRAF6-mediated NF-κB signaling. Biochim. Biophys. Acta 1864, 760–770. doi:10.1016/j.bbamcr.2017.02.011

King, A.E., Woodhouse, A., Kirkcaldie, M.T.K., Vickers, J.C., 2016. Excitotoxicity in ALS: Overstimulation, or overreaction? Exp. Neurol. 275 Pt 1, 162–171. doi:10.1016/j.expneurol.2015.09.019

Kinsella, S., König, H.-G., Prehn, J.H.M., 2016. Bid Promotes K63-Linked Polyubiquitination of Tumor Necrosis Factor Receptor Associated Factor 6 (TRAF6) and Sensitizes to Mutant SOD1-Induced Proinflammatory Signaling in Microglia. eNeuro 3. doi:10.1523/ENEURO.0099-15.2016

Kirkinezos, I.G., Hernandez, D., Bradley, W.G., Moraes, C.T., 2003. Regular exercise is beneficial to a mouse model of amyotrophic lateral sclerosis. Ann. Neurol. 53, 804–807. doi:10.1002/ana.10597

Kline, R.A., Kaifer, K.A., Osman, E.Y., Carella, F., Tiberi, A., Ross, J., Pennetta, G., Lorson, C.L., Murray, L.M., 2017. Comparison of independent screens on differentially vulnerable motor neurons reveals alpha-synuclein as a common modifier in motor neuron diseases. PLoS Genet. 13, e1006680. doi:10.1371/journal.pgen.1006680

Kölbel, H., Hauffa, B.P., Wudy, S.A., Bouikidis, A., Della Marina, A., Schara, U., 2017. Hyperleptinemia in children with autosomal recessive spinal muscular atrophy type I-III. PloS One 12, e0173144. doi:10.1371/journal.pone.0173144

Kong, L., Wang, X., Choe, D.W., Polley, M., Burnett, B.G., Bosch-Marcé, M., Griffin, J.W., Rich, M.M., Sumner, C.J., 2009. Impaired synaptic vesicle release and immaturity of neuromuscular junctions in spinal muscular atrophy mice. J. Neurosci. Off. J. Soc. Neurosci. 29, 842–851. doi:10.1523/JNEUROSCI.4434-08.2009

Kubota, M., Sakakihara, Y., Uchiyama, Y., Nara, A., Nagata, T., Nitta, H., Ishimoto, K., Oka, A., Horio, K., Yanagisawa, M., 2000. New ocular movement detector system as a communication tool in ventilator-assisted Werdnig-Hoffmann disease. Dev. Med. Child Neurol. 42, 61–64.

Kügler, S., 2016. Tissue-Specific Promoters in the CNS. Methods Mol. Biol. Clifton NJ 1382, 81–91. doi:10.1007/978-1-4939-3271-9_6

Kuo, J.J., Siddique, T., Fu, R., Heckman, C.J., 2005. Increased persistent Na(+) current and its effect on excitability in motoneurones cultured from mutant SOD1 mice. J. Physiol. 563, 843–854. doi:10.1113/jphysiol.2004.074138

Kuru, S., Sakai, M., Konagaya, M., Yoshida, M., Hashizume, Y., Saito, K., 2009. An autopsy case of spinal muscular atrophy type III (Kugelberg-Welander disease). Neuropathol. Off. J. Jpn. Soc. Neuropathol. 29, 63–67. doi:10.1111/j.1440-1789.2008.00910.x

Kwiatkowski, T.J., Bosco, D.A., Leclerc, A.L., Tamrazian, E., Vanderburg, C.R., Russ, C., Davis, A., Gilchrist, J., Kasarskis, E.J., Munsat, T., Valdmanis, P., Rouleau, G.A., Hosler, B.A., Cortelli, P., de Jong, P.J., Yoshinaga, Y., Haines, J.L., Pericak-Vance, M.A., Yan, J., Ticozzi, N., Siddique, T., McKenna-Yasek, D., Sapp, P.C., Horvitz, H.R., Landers, J.E., Brown, R.H., 2009. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. Science 323, 1205–1208. doi:10.1126/science.1166066

Lalancette-Hebert, M., Sharma, A., Lyashchenko, A.K., Shneider, N.A., 2016. Gamma motor neurons survive and exacerbate alpha motor neuron degeneration in ALS. Proc. Natl. Acad. Sci. U. S. A. 113, E8316–E8325. doi:10.1073/pnas.1605210113

Le Grand, F., Rudnicki, M.A., 2007. Skeletal muscle satellite cells and adult myogenesis. Curr. Opin. Cell Biol. 19, 628–633. doi:10.1016/j.ceb.2007.09.012

Le, T.T., Pham, L.T., Butchbach, M.E.R., Zhang, H.L., Monani, U.R., Coovert, D.D., Gavrilina, T.O., Xing, L., Bassell, G.J., Burghes, A.H.M., 2005. SMNDelta7, the major product of the centromeric survival motor neuron (SMN2) gene, extends survival in mice with spinal muscular atrophy and associates with full-length SMN. Hum. Mol. Genet. 14, 845–857. doi:10.1093/hmg/ddi078

Lefebvre, S., Bürglen, L., Reboullet, S., Clermont, O., Burlet, P., Viollet, L., Benichou, B., Cruaud, C., Millasseau, P., Zeviani, M., 1995. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 80, 155–165.

Ling, K.K.Y., Gibbs, R.M., Feng, Z., Ko, C.-P., 2012. Severe neuromuscular denervation of clinically relevant muscles in a mouse model of spinal muscular atrophy. Hum. Mol. Genet. 21, 185–195. doi:10.1093/hmg/ddr453

Liu, H., Lu, J., Chen, H., Du, Z., Li, X.-J., Zhang, S.-C., 2015. Spinal muscular atrophy patient-derived motor neurons exhibit hyperexcitability. Sci. Rep. 5, 12189. doi:10.1038/srep12189

Lobsiger, C.S., Cleveland, D.W., 2007. Glial cells as intrinsic components of non-cell-autonomous neurodegenerative disease. Nat. Neurosci. 10, 1355–1360. doi:10.1038/nn1988

Loeffler, J.-P., Picchiarelli, G., Dupuis, L., Gonzalez De Aguilar, J.-L., 2016. The Role of Skeletal Muscle in Amyotrophic Lateral Sclerosis. Brain Pathol. Zurich Switz. 26, 227–236. doi:10.1111/bpa.12350

López-Otín, C., Galluzzi, L., Freije, J.M.P., Madeo, F., Kroemer, G., 2016. Metabolic Control of Longevity. Cell 166, 802–821. doi:10.1016/j.cell.2016.07.031

Lunetta, C., Lizio, A., Sansone, V.A., Cellotto, N.M., Maestri, E., Bettinelli, M., Gatti, V., Melazzini, M.G., Meola, G., Corbo, M., 2016. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. J. Neurol. 263, 52–60. doi:10.1007/s00415-015-7924-z

Mahoney, D.J., Rodriguez, C., Devries, M., Yasuda, N., Tarnopolsky, M.A., 2004. Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. Muscle Nerve 29, 656–662. doi:10.1002/mus.20004

Manning-Bog, A.B., McCormack, A.L., Purisai, M.G., Bolin, L.M., Di Monte, D.A., 2003. Alpha-synuclein overexpression protects against paraquat-induced neurodegeneration. J. Neurosci. Off. J. Soc. Neurosci. 23, 3095–3099.

Manzano, R., Toivonen, J.M., Calvo, A.C., Oliván, S., Zaragoza, P., Rodellar, C., Montarras, D., Osta, R., 2013. Altered in vitro proliferation of mouse SOD1-G93A skeletal muscle satellite cells. Neurodegener. Dis. 11, 153–164. doi:10.1159/000338061

Manzano, R., Toivonen, J.M., Oliván, S., Calvo, A.C., Moreno-Igoa, M., Muñoz, M.J., Zaragoza, P., García-Redondo, A., Osta, R., 2011. Altered expression of myogenic regulatory factors in the mouse model of amyotrophic lateral sclerosis. Neurodegener. Dis. 8, 386–396. doi:10.1159/000324159

Marchetto, M.C.N., Muotri, A.R., Mu, Y., Smith, A.M., Cezar, G.G., Gage, F.H., 2008. Non-cell-autonomous effect of human SOD1 G37R astrocytes on motor neurons derived from human embryonic stem cells. Cell Stem Cell 3, 649–657. doi:10.1016/j.stem.2008.10.001

Martin, E., Cazenave, W., Cattaert, D., Branchereau, P., 2013. Embryonic alteration of motoneuronal morphology induces hyperexcitability in the mouse model of amyotrophic lateral sclerosis. Neurobiol. Dis. 54, 116–126. doi:10.1016/j.nbd.2013.02.011

Martinez, T.L., Kong, L., Wang, X., Osborne, M.A., Crowder, M.E., Van Meerbeke, J.P., Xu, X., Davis, C., Wooley, J., Goldhamer, D.J., Lutz, C.M., Rich, M.M., Sumner, C.J., 2012. Survival motor neuron protein in motor neurons determines synaptic integrity in spinal muscular atrophy. J. Neurosci. Off. J. Soc. Neurosci. 32, 8703–8715. doi:10.1523/JNEUROSCI.0204-12.2012

McGivern, J.V., Patitucci, T.N., Nord, J.A., Barabas, M.-E.A., Stucky, C.L., Ebert, A.D., 2013. Spinal muscular atrophy astrocytes exhibit abnormal calcium regulation and reduced growth factor production. Glia 61, 1418–1428. doi:10.1002/glia.22522

Mehta, N.M., Newman, H., Tarrant, S., Graham, R.J., 2016. Nutritional Status and Nutrient Intake Challenges in Children With Spinal Muscular Atrophy. Pediatr. Neurol. 57, 80–83. doi:10.1016/j.pediatrneurol.2015.12.015

Mentis, G.Z., Blivis, D., Liu, W., Drobac, E., Crowder, M.E., Kong, L., Alvarez, F.J., Sumner, C.J., O'Donovan, M.J., 2011. Early functional impairment of sensory-motor connectivity in a mouse model of spinal muscular atrophy. Neuron 69, 453–467. doi:10.1016/j.neuron.2010.12.032

Meyer, K., Ferraiuolo, L., Schmelzer, L., Braun, L., McGovern, V., Likhite, S., Michels, O., Govoni, A., Fitzgerald, J., Morales, P., Foust, K.D., Mendell, J.R., Burghes, A.H.M., Kaspar, B.K., 2015. Improving single injection CSF delivery of AAV9-mediated gene therapy for SMA: a dose-response study in mice and nonhuman primates. Mol. Ther. J. Am. Soc. Gene Ther. 23, 477–487. doi:10.1038/mt.2014.210

Mishra, P.-S., Dhull, D.K., Nalini, A., Vijayalakshmi, K., Sathyaprabha, T.N., Alladi, P.A., Raju, T.R., 2016. Astroglia acquires a toxic neuroinflammatory role in response to the cerebrospinal fluid from amyotrophic lateral sclerosis patients. J. Neuroinflammation 13, 212. doi:10.1186/s12974-016-0698-0

Monani, U.R., Sendtner, M., Coovert, D.D., Parsons, D.W., Andreassi, C., Le, T.T., Jablonka, S., Schrank, B., Rossoll, W., Rossol, W., Prior, T.W., Morris, G.E., Burghes, A.H., 2000. The human centromeric survival motor neuron gene (SMN2) rescues embryonic lethality in Smn(-/-) mice and results in a mouse with spinal muscular atrophy. Hum. Mol. Genet. 9, 333–339.

Morrison, B.M., Lachey, J.L., Warsing, L.C., Ting, B.L., Pullen, A.E., Underwood, K.W., Kumar, R., Sako, D., Grinberg, A., Wong, V., Colantuoni, E., Seehra, J.S., Wagner, K.R., 2009. A soluble activin type IIB

receptor improves function in a mouse model of amyotrophic lateral sclerosis. Exp. Neurol. 217, 258–268. doi:10.1016/j.expneurol.2009.02.017

Murray, L.M., Beauvais, A., Bhanot, K., Kothary, R., 2013. Defects in neuromuscular junction remodelling in the Smn(2B/-) mouse model of spinal muscular atrophy. Neurobiol. Dis. 49, 57–67. doi:10.1016/j.nbd.2012.08.019

Murray, L.M., Beauvais, A., Gibeault, S., Courtney, N.L., Kothary, R., 2015. Transcriptional profiling of differentially vulnerable motor neurons at pre-symptomatic stage in the Smn (2b/-) mouse model of spinal muscular atrophy. Acta Neuropathol. Commun. 3, 55. doi:10.1186/s40478-015-0231-1

Murray, L.M., Comley, L.H., Gillingwater, T.H., Parson, S.H., 2011. The response of neuromuscular junctions to injury is developmentally regulated. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 25, 1306–1313. doi:10.1096/fj.10-171934

Murray, L.M., Comley, L.H., Thomson, D., Parkinson, N., Talbot, K., Gillingwater, T.H., 2008. Selective vulnerability of motor neurons and dissociation of pre- and post-synaptic pathology at the neuromuscular junction in mouse models of spinal muscular atrophy. Hum. Mol. Genet. 17, 949–962. doi:10.1093/hmg/ddm367

Narver, H.L., Kong, L., Burnett, B.G., Choe, D.W., Bosch-Marcé, M., Taye, A.A., Eckhaus, M.A., Sumner, C.J., 2008. Sustained improvement of spinal muscular atrophy mice treated with trichostatin A plus nutrition. Ann. Neurol. 64, 465–470. doi:10.1002/ana.21449

Neve, A., Trüb, J., Saxena, S., Schümperli, D., 2016. Central and peripheral defects in motor units of the diaphragm of spinal muscular atrophy mice. Mol. Cell. Neurosci. 70, 30–41. doi:10.1016/j.mcn.2015.11.007

Nicole, S., Desforges, B., Millet, G., Lesbordes, J., Cifuentes-Diaz, C., Vertes, D., Cao, M.L., De Backer, F., Languille, L., Roblot, N., Joshi, V., Gillis, J.-M., Melki, J., 2003. Intact satellite cells lead to remarkable protection against Smn gene defect in differentiated skeletal muscle. J. Cell Biol. 161, 571–582. doi:10.1083/jcb.200210117

Nieves, J.W., Gennings, C., Factor-Litvak, P., Hupf, J., Singleton, J., Sharf, V., Oskarsson, B., Fernandes Filho, J.A.M., Sorenson, E.J., D'Amico, E., Goetz, R., Mitsumoto, H., Amyotrophic Lateral Sclerosis Multicenter Cohort Study of Oxidative Stress (ALS COSMOS) Study Group, 2016. Association Between Dietary Intake and Function in Amyotrophic Lateral Sclerosis. JAMA Neurol. 73, 1425–1432. doi:10.1001/jamaneurol.2016.3401

Nölle, A., Zeug, A., van Bergeijk, J., Tönges, L., Gerhard, R., Brinkmann, H., Al Rayes, S., Hensel, N., Schill, Y., Apkhazava, D., Jablonka, S., O'mer, J., Srivastav, R.K., Baasner, A., Lingor, P., Wirth, B., Ponimaskin, E., Niedenthal, R., Grothe, C., Claus, P., 2011. The spinal muscular atrophy disease protein SMN is linked to the Rho-kinase pathway via profilin. Hum. Mol. Genet. 20, 4865–4878. doi:10.1093/hmg/ddr425

Oliván, S., Martínez-Beamonte, R., Calvo, A.C., Surra, J.C., Manzano, R., Arnal, C., Osta, R., Osada, J., 2014. Extra virgin olive oil intake delays the development of amyotrophic lateral sclerosis associated with

reduced reticulum stress and autophagy in muscle of SOD1G93A mice. J. Nutr. Biochem. 25, 885–892. doi:10.1016/j.jnutbio.2014.04.005

Park, K.H.J., Franciosi, S., Leavitt, B.R., 2013. Postnatal muscle modification by myogenic factors modulates neuropathology and survival in an ALS mouse model. Nat. Commun. 4, 2906. doi:10.1038/ncomms3906

Perera, N.D., Sheean, R.K., Crouch, P.J., White, A.R., Horne, M.K., Turner, B.J., 2016. Enhancing survival motor neuron expression extends lifespan and attenuates neurodegeneration in mutant TDP-43 mice. Hum. Mol. Genet. 25, 4080–4093. doi:10.1093/hmg/ddw247

Pradat, P.-F., Barani, A., Wanschitz, J., Dubourg, O., Lombès, A., Bigot, A., Mouly, V., Bruneteau, G., Salachas, F., Lenglet, T., Meininger, V., Butler-Browne, G., 2011. Abnormalities of satellite cells function in amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Off. Publ. World Fed. Neurol. Res. Group Mot. Neuron Dis. 12, 264–271. doi:10.3109/17482968.2011.566618

Pradat, P.-F., Bruneteau, G., Gordon, P.H., Dupuis, L., Bonnefont-Rousselot, D., Simon, D., Salachas, F., Corcia, P., Frochot, V., Lacorte, J.-M., Jardel, C., Coussieu, C., Le Forestier, N., Lacomblez, L., Loeffler, J.-P., Meininger, V., 2010. Impaired glucose tolerance in patients with amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Off. Publ. World Fed. Neurol. Res. Group Mot. Neuron Dis. 11, 166–171. doi:10.3109/17482960902822960

Pun, S., Sigrist, M., Santos, A.F., Ruegg, M.A., Sanes, J.R., Jessell, T.M., Arber, S., Caroni, P., 2002. An intrinsic distinction in neuromuscular junction assembly and maintenance in different skeletal muscles. Neuron 34, 357–370.

Raoul, C., Estévez, A.G., Nishimune, H., Cleveland, D.W., deLapeyrière, O., Henderson, C.E., Haase, G., Pettmann, B., 2002. Motoneuron death triggered by a specific pathway downstream of Fas. potentiation by ALS-linked SOD1 mutations. Neuron 35, 1067–1083.

Renton, A.E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J.R., Schymick, J.C., Laaksovirta, H., van Swieten, J.C., Myllykangas, L., Kalimo, H., Paetau, A., Abramzon, Y., Remes, A.M., Kaganovich, A., Scholz, S.W., Duckworth, J., Ding, J., Harmer, D.W., Hernandez, D.G., Johnson, J.O., Mok, K., Ryten, M., Trabzuni, D., Guerreiro, R.J., Orrell, R.W., Neal, J., Murray, A., Pearson, J., Jansen, I.E., Sondervan, D., Seelaar, H., Blake, D., Young, K., Halliwell, N., Callister, J.B., Toulson, G., Richardson, A., Gerhard, A., Snowden, J., Mann, D., Neary, D., Nalls, M.A., Peuralinna, T., Jansson, L., Isoviita, V.-M., Kaivorinne, A.-L., Hölttä-Vuori, M., Ikonen, E., Sulkava, R., Benatar, M., Wuu, J., Chiò, A., Restagno, G., Borghero, G., Sabatelli, M., ITALSGEN Consortium, Heckerman, D., Rogaeva, E., Zinman, L., Rothstein, J.D., Sendtner, M., Drepper, C., Eichler, E.E., Alkan, C., Abdullaev, Z., Pack, S.D., Dutra, A., Pak, E., Hardy, J., Singleton, A., Williams, N.M., Heutink, P., Pickering-Brown, S., Morris, H.R., Tienari, P.J., Traynor, B.J., 2011. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 72, 257–268. doi:10.1016/j.neuron.2011.09.010

Reyes, E.T., Perurena, O.H., Festoff, B.W., Jorgensen, R., Moore, W.V., 1984. Insulin resistance in amyotrophic lateral sclerosis. J. Neurol. Sci. 63, 317–324.

Rindt, H., Feng, Z., Mazzasette, C., Glascock, J.J., Valdivia, D., Pyles, N., Crawford, T.O., Swoboda, K.J., Patitucci, T.N., Ebert, A.D., Sumner, C.J., Ko, C.-P., Lorson, C.L., 2015. Astrocytes influence the severity of spinal muscular atrophy. Hum. Mol. Genet. 24, 4094–4102. doi:10.1093/hmg/ddv148

Rizzuto, E., Pisu, S., Musarò, A., Del Prete, Z., 2015. Measuring Neuromuscular Junction Functionality in the SOD1(G93A) Animal Model of Amyotrophic Lateral Sclerosis. Ann. Biomed. Eng. 43, 2196–2206. doi:10.1007/s10439-015-1259-x

Rocha, M.C., Pousinha, P.A., Correia, A.M., Sebastião, A.M., Ribeiro, J.A., 2013. Early changes of neuromuscular transmission in the SOD1(G93A) mice model of ALS start long before motor symptoms onset. PloS One 8, e73846. doi:10.1371/journal.pone.0073846

Rose, F.F., Mattis, V.B., Rindt, H., Lorson, C.L., 2009. Delivery of recombinant follistatin lessens disease severity in a mouse model of spinal muscular atrophy. Hum. Mol. Genet. 18, 997–1005. doi:10.1093/hmg/ddn426

Rosen, D.R., Siddique, T., Patterson, D., Figlewicz, D.A., Sapp, P., Hentati, A., Donaldson, D., Goto, J., O'Regan, J.P., Deng, H.X., 1993. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362, 59–62. doi:10.1038/362059a0

Samaranch, L., Salegio, E.A., San Sebastian, W., Kells, A.P., Foust, K.D., Bringas, J.R., Lamarre, C., Forsayeth, J., Kaspar, B.K., Bankiewicz, K.S., 2012. Adeno-associated virus serotype 9 transduction in the central nervous system of nonhuman primates. Hum. Gene Ther. 23, 382–389. doi:10.1089/hum.2011.200

Scaramozza, A., Marchese, V., Papa, V., Salaroli, R., Sorarù, G., Angelini, C., Cenacchi, G., 2014. Skeletal muscle satellite cells in amyotrophic lateral sclerosis. Ultrastruct. Pathol. 38, 295–302. doi:10.3109/01913123.2014.937842

Schuster, J.E., Fu, R., Siddique, T., Heckman, C.J., 2012. Effect of prolonged riluzole exposure on cultured motoneurons in a mouse model of ALS. J. Neurophysiol. 107, 484–492. doi:10.1152/jn.00714.2011

Seale, P., Sabourin, L.A., Girgis-Gabardo, A., Mansouri, A., Gruss, P., Rudnicki, M.A., 2000. Pax7 is required for the specification of myogenic satellite cells. Cell 102, 777–786.

Seksenyan, A., Ron-Harel, N., Azoulay, D., Cahalon, L., Cardon, M., Rogeri, P., Ko, M.K., Weil, M., Bulvik, S., Rechavi, G., Amariglio, N., Konen, E., Koronyo-Hamaoui, M., Somech, R., Schwartz, M., 2010. Thymic involution, a co-morbidity factor in amyotrophic lateral sclerosis. J. Cell. Mol. Med. 14, 2470–2482. doi:10.1111/j.1582-4934.2009.00863.x

Shafey, D., Côté, P.D., Kothary, R., 2005. Hypomorphic Smn knockdown C2C12 myoblasts reveal intrinsic defects in myoblast fusion and myotube morphology. Exp. Cell Res. 311, 49–61. doi:10.1016/j.yexcr.2005.08.019

Sharma, A., Lyashchenko, A.K., Lu, L., Nasrabady, S.E., Elmaleh, M., Mendelsohn, M., Nemes, A., Tapia, J.C., Mentis, G.Z., Shneider, N.A., 2016. ALS-associated mutant FUS induces selective motor neuron degeneration through toxic gain of function. Nat. Commun. 7, 10465. doi:10.1038/ncomms10465

Shefner, J., Cedarbaum, J.M., Cudkowicz, M.E., Maragakis, N., Lee, J., Jones, D., Watson, M.L., Mahoney, K., Chen, M., Saikali, K., Mao, J., Russell, A.J., Hansen, R.L., Malik, F., Wolff, A.A., Neals/Cytokinetics Study Team, 2012. Safety, tolerability and pharmacodynamics of a skeletal muscle activator in amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Off. Publ. World Fed. Neurol. Res. Group Mot. Neuron Dis. 13, 430–438. doi:10.3109/17482968.2012.684214

Shellikeri, S., Karthikeyan, V., Martino, R., Black, S.E., Zinman, L., Keith, J., Yunusova, Y., 2017. The neuropathological signature of bulbar-onset ALS: A systematic review. Neurosci. Biobehav. Rev. 75, 378–392. doi:10.1016/j.neubiorev.2017.01.045

Shimizu, T., Honda, M., Ohashi, T., Tsujino, M., Nagaoka, U., Kawata, A., Watabe, K., Matsubara, S., Hayashi, H., 2011. Hyperosmolar hyperglycemic state in advanced amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Off. Publ. World Fed. Neurol. Res. Group Mot. Neuron Dis. 12, 379–381. doi:10.3109/17482968.2010.539234

Silva, L.B. de C., Mourão, L.F., Silva, A.A., Lima, N.M.F.V., Almeida, S.R., Franca Jr, M.C., Nucci, A., Amaya-Farfán, J., 2010. Effect of nutritional supplementation with milk whey proteins in amyotrophic lateral sclerosis patients. Arq. Neuropsiquiatr. 68, 263–268.

Simone, C., Ramirez, A., Bucchia, M., Rinchetti, P., Rideout, H., Papadimitriou, D., Re, D.B., Corti, S., 2016. Is spinal muscular atrophy a disease of the motor neurons only: pathogenesis and therapeutic implications? Cell. Mol. Life Sci. CMLS 73, 1003–1020. doi:10.1007/s00018-015-2106-9

Spataro, R., Ciriacono, M., Manno, C., La Bella, V., 2014. The eye-tracking computer device for communication in amyotrophic lateral sclerosis. Acta Neurol. Scand. 130, 40–45. doi:10.1111/ane.12214

Sreedharan, J., Blair, I.P., Tripathi, V.B., Hu, X., Vance, C., Rogelj, B., Ackerley, S., Durnall, J.C., Williams, K.L., Buratti, E., Baralle, F., de Belleroche, J., Mitchell, J.D., Leigh, P.N., Al-Chalabi, A., Miller, C.C., Nicholson, G., Shaw, C.E., 2008. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. Science 319, 1668–1672. doi:10.1126/science.1154584

Sumitha, R., Sidhu, R.J.S., Sathyaprabha, T.N., Nalini, A., Raju, T.R., Alladi, P.A., 2014. Differential expression of microRNA-206 in the gastrocnemius and biceps brachii in response to CSF from sporadic amyotrophic lateral sclerosis patients. J. Neurol. Sci. 345, 254–256. doi:10.1016/j.jns.2014.07.005

Sun, S., Ling, S.-C., Qiu, J., Albuquerque, C.P., Zhou, Y., Tokunaga, S., Li, H., Qiu, H., Bui, A., Yeo, G.W., Huang, E.J., Eggan, K., Zhou, H., Fu, X.-D., Lagier-Tourenne, C., Cleveland, D.W., 2015. ALS-causative mutations in FUS/TLS confer gain and loss of function by altered association with SMN and U1-snRNP. Nat. Commun. 6, 6171. doi:10.1038/ncomms7171

Swarup, V., Phaneuf, D., Dupré, N., Petri, S., Strong, M., Kriz, J., Julien, J.-P., 2011. Deregulation of TDP-43 in amyotrophic lateral sclerosis triggers nuclear factor κB-mediated pathogenic pathways. J. Exp. Med. 208, 2429–2447. doi:10.1084/jem.20111313

Tarabal, O., Caraballo-Miralles, V., Cardona-Rossinyol, A., Correa, F.J., Olmos, G., Lladó, J., Esquerda, J.E., Calderó, J., 2014. Mechanisms involved in spinal cord central synapse loss in a mouse model of spinal muscular atrophy. J. Neuropathol. Exp. Neurol. 73, 519–535. doi:10.1097/NEN.0000000000000074

Thau, N., Knippenberg, S., Körner, S., Rath, K.J., Dengler, R., Petri, S., 2012. Decreased mRNA expression of PGC-1α and PGC-1α-regulated factors in the SOD1G93A ALS mouse model and in human sporadic ALS. J. Neuropathol. Exp. Neurol. 71, 1064–1074. doi:10.1097/NEN.0b013e318275df4b

Thomson, A.K., Somers, E., Powis, R.A., Shorrock, H.K., Murphy, K., Swoboda, K.J., Gillingwater, T.H., Parson, S.H., 2017. Survival of motor neurone protein is required for normal postnatal development of the spleen. J. Anat. 230, 337–346. doi:10.1111/joa.12546

Thomson, S.R., Nahon, J.E., Mutsaers, C.A., Thomson, D., Hamilton, G., Parson, S.H., Gillingwater, T.H., 2012. Morphological characteristics of motor neurons do not determine their relative susceptibility to degeneration in a mouse model of severe spinal muscular atrophy. PloS One 7, e52605. doi:10.1371/journal.pone.0052605

Tjust, A.E., Brannstrom, T., Pedrosa Domellof, F., 2012. Unaffected motor endplate occupancy in eye muscles of ALS G93A mouse model. Front. Biosci. Sch. Ed. 4, 1547–1555.

Toivonen, J.M., Manzano, R., Oliván, S., Zaragoza, P., García-Redondo, A., Osta, R., 2014. MicroRNA-206: a potential circulating biomarker candidate for amyotrophic lateral sclerosis. PloS One 9, e89065. doi:10.1371/journal.pone.0089065

Towne, C., Schneider, B.L., Kieran, D., Redmond, D.E., Aebischer, P., 2010. Efficient transduction of non-human primate motor neurons after intramuscular delivery of recombinant AAV serotype 6. Gene Ther. 17, 141–146. doi:10.1038/gt.2009.119

Towne, C., Setola, V., Schneider, B.L., Aebischer, P., 2011. Neuroprotection by gene therapy targeting mutant SOD1 in individual pools of motor neurons does not translate into therapeutic benefit in fALS mice. Mol. Ther. J. Am. Soc. Gene Ther. 19, 274–283. doi:10.1038/mt.2010.260

Turner, B.J., Alfazema, N., Sheean, R.K., Sleigh, J.N., Davies, K.E., Horne, M.K., Talbot, K., 2014. Overexpression of survival motor neuron improves neuromuscular function and motor neuron survival in mutant SOD1 mice. Neurobiol. Aging 35, 906–915. doi:10.1016/j.neurobiolaging.2013.09.030

Turner, B.J., Parkinson, N.J., Davies, K.E., Talbot, K., 2009. Survival motor neuron deficiency enhances progression in an amyotrophic lateral sclerosis mouse model. Neurobiol. Dis. 34, 511–517. doi:10.1016/j.nbd.2009.03.005

Ugolini, G., Raoul, C., Ferri, A., Haenggeli, C., Yamamoto, Y., Salaün, D., Henderson, C.E., Kato, A.C., Pettmann, B., Hueber, A.-O., 2003. Fas/tumor necrosis factor receptor death signaling is required for axotomy-induced death of motoneurons in vivo. J. Neurosci. Off. J. Soc. Neurosci. 23, 8526–8531.

Urban, M.W., Scura, D., Li, K., Zhou, W., Rothstein, J.D., Dalva, M.B., Lepore, A.C., 2015. Pathological upregulation of EphrinB2 in ALS spinal cord astrocytes. Presented at the International Symposium on Neural Regeneration.

Valdez, G., Tapia, J.C., Lichtman, J.W., Fox, M.A., Sanes, J.R., 2012. Shared resistance to aging and ALS in neuromuscular junctions of specific muscles. PloS One 7, e34640. doi:10.1371/journal.pone.0034640

Valori, C.F., Ning, K., Wyles, M., Mead, R.J., Grierson, A.J., Shaw, P.J., Azzouz, M., 2010. Systemic delivery of scAAV9 expressing SMN prolongs survival in a model of spinal muscular atrophy. Sci. Transl. Med. 2, 35ra42. doi:10.1126/scitranslmed.3000830

Van Den Bosch, L., Van Damme, P., Bogaert, E., Robberecht, W., 2006. The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis. Biochim. Biophys. Acta 1762, 1068–1082. doi:10.1016/j.bbadis.2006.05.002

van Zundert, B., Brown, R.H., 2017. Silencing strategies for therapy of SOD1-mediated ALS. Neurosci. Lett. 636, 32–39. doi:10.1016/j.neulet.2016.07.059

Vance, C., Rogelj, B., Hortobágyi, T., De Vos, K.J., Nishimura, A.L., Sreedharan, J., Hu, X., Smith, B., Ruddy, D., Wright, P., Ganesalingam, J., Williams, K.L., Tripathi, V., Al-Saraj, S., Al-Chalabi, A., Leigh, P.N., Blair, I.P., Nicholson, G., de Belleroche, J., Gallo, J.-M., Miller, C.C., Shaw, C.E., 2009. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science 323, 1208–1211. doi:10.1126/science.1165942

Wainger, B.J., Kiskinis, E., Mellin, C., Wiskow, O., Han, S.S.W., Sandoe, J., Perez, N.P., Williams, L.A., Lee, S., Boulting, G., Berry, J.D., Brown, R.H., Cudkowicz, M.E., Bean, B.P., Eggan, K., Woolf, C.J., 2014. Intrinsic membrane hyperexcitability of amyotrophic lateral sclerosis patient-derived motor neurons. Cell Rep. 7, 1–11. doi:10.1016/j.celrep.2014.03.019

Wang, B., Li, J., Fu, F.H., Chen, C., Zhu, X., Zhou, L., Jiang, X., Xiao, X., 2008. Construction and analysis of compact muscle-specific promoters for AAV vectors. Gene Ther. 15, 1489–1499. doi:10.1038/gt.2008.104

Wang, L., Gutmann, D.H., Roos, R.P., 2011. Astrocyte loss of mutant SOD1 delays ALS disease onset and progression in G85R transgenic mice. Hum. Mol. Genet. 20, 286–293. doi:10.1093/hmg/ddq463

Wang, L., Sharma, K., Grisotti, G., Roos, R.P., 2009. The effect of mutant SOD1 dismutase activity on non-cell autonomous degeneration in familial amyotrophic lateral sclerosis. Neurobiol. Dis. 35, 234–240. doi:10.1016/j.nbd.2009.05.002

Wang, Y.X., Rudnicki, M.A., 2011. Satellite cells, the engines of muscle repair. Nat. Rev. Mol. Cell Biol. 13, 127–133. doi:10.1038/nrm3265

Williams, T.L., Day, N.C., Ince, P.G., Kamboj, R.K., Shaw, P.J., 1997. Calcium-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors: a molecular determinant of selective vulnerability in amyotrophic lateral sclerosis. Ann. Neurol. 42, 200–207. doi:10.1002/ana.410420211

Wong, M., Martin, L.J., 2010. Skeletal muscle-restricted expression of human SOD1 causes motor neuron degeneration in transgenic mice. Hum. Mol. Genet. 19, 2284–2302. doi:10.1093/hmg/ddq106

Wu, C.-H., Fallini, C., Ticozzi, N., Keagle, P.J., Sapp, P.C., Piotrowska, K., Lowe, P., Koppers, M., McKenna-Yasek, D., Baron, D.M., Kost, J.E., Gonzalez-Perez, P., Fox, A.D., Adams, J., Taroni, F., Tiloca, C., Leclerc, A.L., Chafe, S.C., Mangroo, D., Moore, M.J., Zitzewitz, J.A., Xu, Z.-S., van den Berg, L.H., Glass, J.D., Siciliano, G., Cirulli, E.T., Goldstein, D.B., Salachas, F., Meininger, V., Rossoll, W., Ratti, A., Gellera, C., Bosco, D.A., Bassell, G.J., Silani, V., Drory, V.E., Brown, R.H., Landers, J.E., 2012. Mutations in the profilin 1 gene cause familial amyotrophic lateral sclerosis. Nature 488, 499–503. doi:10.1038/nature11280

Yamanaka, K., Chun, S.J., Boillee, S., Fujimori-Tonou, N., Yamashita, H., Gutmann, D.H., Takahashi, R., Misawa, H., Cleveland, D.W., 2008. Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis. Nat. Neurosci. 11, 251–253. doi:10.1038/nn2047

Yamazaki, T., Chen, S., Yu, Y., Yan, B., Haertlein, T.C., Carrasco, M.A., Tapia, J.C., Zhai, B., Das, R., Lalancette-Hebert, M., Sharma, A., Chandran, S., Sullivan, G., Nishimura, A.L., Shaw, C.E., Gygi, S.P., Shneider, N.A., Maniatis, T., Reed, R., 2012. FUS-SMN protein interactions link the motor neuron diseases ALS and SMA. Cell Rep. 2, 799–806. doi:10.1016/j.celrep.2012.08.025

Zhao, Z., Lange, D.J., Voustianiouk, A., MacGrogan, D., Ho, L., Suh, J., Humala, N., Thiyagarajan, M., Wang, J., Pasinetti, G.M., 2006. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. BMC Neurosci. 7, 29. doi:10.1186/1471-2202-7-29

Zhao, Z., Sui, Y., Gao, W., Cai, B., Fan, D., 2015. Effects of diet on adenosine monophosphate-activated protein kinase activity and disease progression in an amyotrophic lateral sclerosis model. J. Int. Med. Res. 43, 67–79. doi:10.1177/0300060514554725

Zhou, C., Feng, Z., Ko, C.-P., 2016. Defects in Motoneuron-Astrocyte Interactions in Spinal Muscular Atrophy. J. Neurosci. Off. J. Soc. Neurosci. 36, 2543–2553. doi:10.1523/JNEUROSCI.3534-15.2016

Zolkipli, Z., Sherlock, M., Biggar, W.D., Taylor, G., Hutchison, J.S., Peliowski, A., Alman, B.A., Ling, S.C., Tein, I., 2012. Abnormal fatty acid metabolism in spinal muscular atrophy may predispose to perioperative risks. Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc. 16, 549–553. doi:10.1016/j.ejpn.2012.01.004

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FIGURE LEGENDS

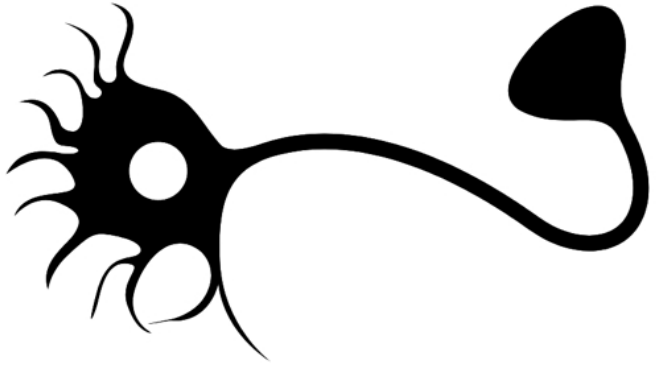
Figure 1. Similarities between SMA and ALS motoneurons

Figure 2. Similarities between SMA and ALS skeletal muscles

Figure 3. Schematic illustrating the common cellular and molecular events that can influence motoneuron integrity. Astrocytic- or microglia-derived signals include IL-6, IL-1β, TNFα and NO. NO can perpetuate inflammatory status and, similar to TNFα directly act on motoneurons to trigger death signaling. Reduced levels of the astrocyte-derived GDNF, a potent neurotrophic factor, can influence motoneuron survival while reduced levels of astrocytic EphrinB2 can influence motoneuron synaptic plasticity. Intracellular and extracellular mechanisms converge in both SMA and ALS to NF-κB signaling, which plays an important function in governing microglia reactivity.

Figure 4. Tissues and cells that share common functional, physiological and molecular pathologies in SMA and ALS.

Figure 5. Key AAV characteristics for optimal SMA and ALS gene therapy



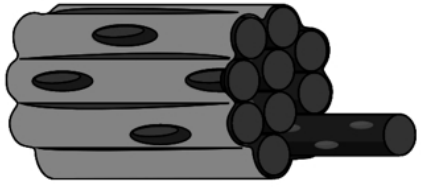
Selective vulnerability of
tongue, extraocular and deep lumbrical motoneurons

Correlation between vulnerability
and sprouting competence

IGF-2 as a marker
of differentially vulnerable motoneurons

α-synuclein as a marker
of differentially vulnerable motoneurons

Abnormal electrophysiological properties

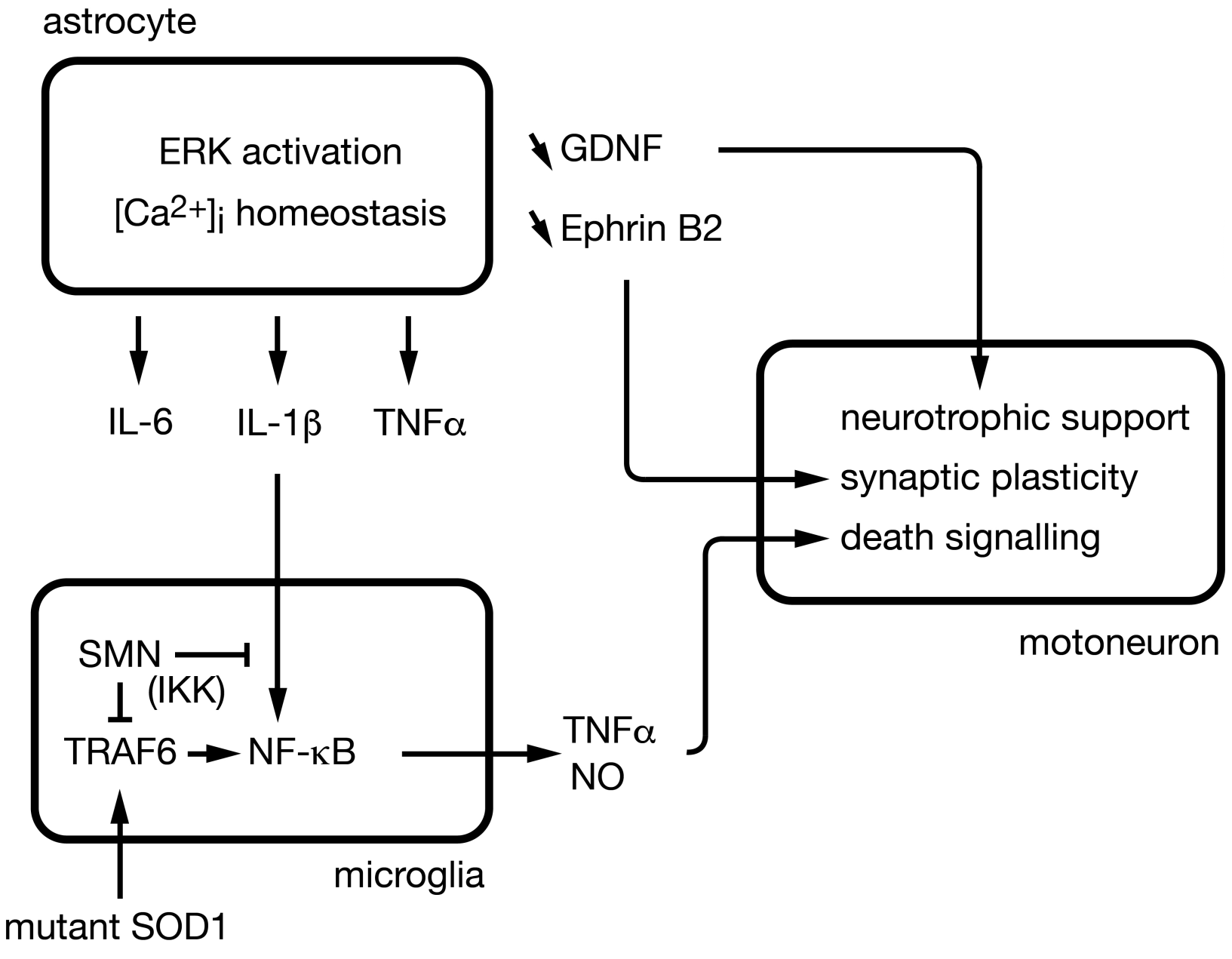


Pre-symptomatic functional, histological and molecular intrinsic defects

Aberrant expression of the myogenic regulatory program

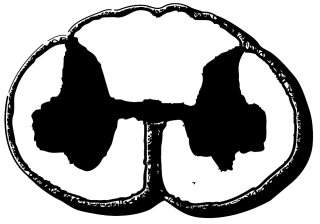
Satellite cell dysregulation

Differential expression of miRNAs


astrocyte
ERK activation
[Ca2+]i homeostasis
GDNF
Ephrin B2
IL-6
IL-1β
TNFα
neurotrophic support
synaptic plasticity
death signalling
motoneuron
SMN
(IKK)
TRAF6
NF-κB
TNFα
NO
microglia
mutant SOD1

SMA and ALS pathogenic commonalities

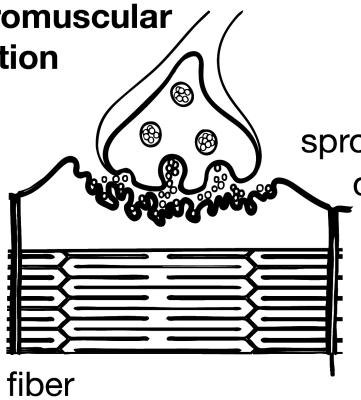
spinal cord



motoneuron intrinsic excitability

neuroinflammation

neuromuscular junction



sprouting competence

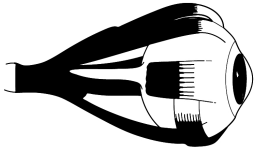
denervation

endplate morphology

muscle fiber

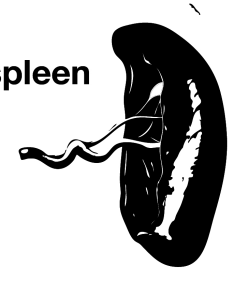
myogenic regulatory program

metabolism



resistance of extraocular muscles

spleen



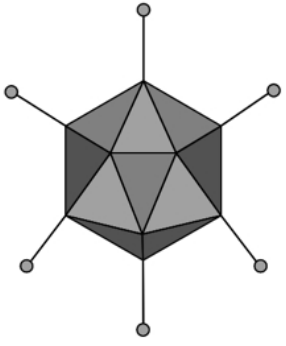
size and architecture

distribution of lymphocytes

thymus

architecture

thymic output

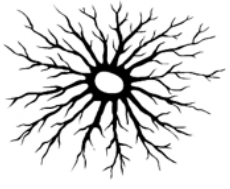


Tissue/cell specificity

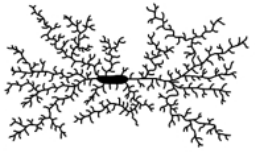
Systemic delivery

Motoneuron

Astrocyte



Microglia



Skeletal muscle