Aging and Disease
www.aginganddisease.org
Volume 6, Number 5; 80-389, October 2015
http://dx.doi.org/10.14336/AD.2015.0506

Review Article

Mechanisms of Muscle Denervation in Aging: Insights from a Mouse Model of Amyotrophic Lateral Sclerosis

Kevin H.J. Park*

Department of Psychology and Neuroscience Program, Central Michigan University, Mount Pleasant, MI 48859, USA

[Received March 14, 2015; Revised May 5, 2015; Accepted May 6, 2015]

ABSTRACT: Muscle denervation at the neuromuscular junction (NMJ) is thought to be a contributing factor in age-related muscle weakness. Therefore, understanding the mechanisms that modulate NMJ innervation is a key to developing therapies to combat age-related muscle weakness affecting the elderly. Two mouse models, one lacking the Cu/Zn superoxide dismutase (SOD1) gene and another harboring the transgenic mutant human SOD1 gene, display progressive changes at the NMJ, including muscle endplate fragmentation, nerve terminal sprouting, and denervation. These changes at the NMJ share many of the common features observed in the NMJs of aged mice. In this review, research findings demonstrating the effects of PGC-1α, IGF-1, GDNF, MyoD, myogenin, and miR-206 on NMJ innervation patterns in the G93A SOD1 mice will be highlighted in the context of age-related muscle denervation.

Key words: Aging, muscle denervation, amyotrophic lateral sclerosis, $SOD1^{-/-}$ mouse, G93A SOD1 mouse, oxidative stress

Many retrospective and prospective studies have shown that age-related muscle weakness (dynapenia) is associated with decreased muscle function and increased risk for mortality in the elderly [1–4]. Dynapenia is a main cause of muscular instability, contributing to falls and subsequent fractures, ultimately impacting quality of life [5,6]. Both diet and exercise are practical interventions demonstrated to delay many devastating and debilitating age-associated pathologies including type 2 diabetes, cardiovascular disease, cerebrovascular disease, cognitive dysfunction, and even some cancers [7–14]. However, physical activity is the most effective means for increasing the quality of life in the elderly [15,16] and gait speed is a strong predictor of survival rate in elderly subjects [17]. Dynapenia represents a dramatic and inevitable decline in skeletal muscle function, which inevitably poses challenges for implementing a physical activity program to benefit the quality of life in the elderly. It is thought that complex degeneration of the neuromuscular system contributes to dynapenia [18–22].

It has been proposed that age-associated changes occur in both the nervous system and the muscular system, leading to an overall loss in muscular strength [23]. In humans, a significant decrease in the number of motor units and muscle strength is observed with aging [24]. Studies using rodent models of aging show extensive alteration in NMJ morphology. Findings from the Balice-Gordon lab demonstrated significant instability in the NMJ of aged rats using a longitudinal visualization technique for monitoring the NMJ in vivo [25]. Examination of 12- to 20-month-old rats demonstrated a progressive loss of synaptic areas and fragmentation of muscle endplates, leading to significant losses in pre- and post-synaptic structures over time [26]. Subsequent studies in mice have shown similar NMJ denervation with aging [27–29].

***Correspondence should be addressed to:** Kevin H.J. Park, PhD, Department of Psychology and Neuroscience Program, Central Michigan University, Mount Pleasant, MI 48859, USA. Email: park1kh@cmich.edu

ISSN: 2152-5250

Muscle denervation in a mouse model of oxidative stress

One of the leading theories on mechanisms underlying age-related muscle denervation points to oxidative stress [30–32]. Reactive oxygen species (ROS) are natural byproducts of mitochondrial activity involved in respiration and energy production. ROS-mediated oxidative damages to DNAs, proteins, and lipids are normally kept in check by antioxidants. However, excessive ROS production can overwhelm the antioxidant defense, leading to increased oxidative damage of cellular machinery.

Cu/Zn superoxide dismutase (SOD1) is a cytoplasmic antioxidant enzyme involved in the scavenging of superoxide free radicals. Mice lacking SOD1 enzyme (SOD1-/- mice) show increased oxidative damages to proteins, lipids, and DNAs [33]. In addition, these mice display progressive muscle denervation, weakness, and loss; changes seen despite the absence of spinal cord motor neuron and ventral root axon loss [34–38]. NMJ denervation and sprouting are observed in these mice between one and four months of age and precedes muscle loss [35,36], which is observed between three and four months of age [33]. Furthermore, muscle denervation and loss are greater in the gastrocnemius and tiabialis anterior compared to the soleus [33,35,36].

The tibialis anterior and gastrocnemius muscles have higher proportion of fast muscle fibers, whereas the soleus muscle has higher proportion of slow muscle fibers. Therefore, fast muscle seems to be more vulnerable to muscle denervation and loss in these animals. These changes are similar to what has been shown in human aging studies. It has been shown that type II (fast) muscle fibers are more affected than type I (slow) fibers during age-related muscle deterioration and loss in elderly adults [23,39]. A recent study by Chai and colleagues in older mice also showed age-related muscle denervation that was more pronounced in fast muscles [27]. However, findings by Valdez and colleagues did not demonstrate this fiber type-dependent sensitivity to age-related muscle denervation in older mice [28]. It is worth noting that their data indicate that NMJs in the soleus muscle as a whole seem to be less affected than NMJs in gastrocnemius, extensor digitorum longus (EDL), and tibialis anterior muscles [28] .

Mutant SOD1 transgenic mouse model of fALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder affecting the upper and lower motor neurons. One of the first identified gene mutations associated with familial ALS (fALS) are those in the SOD1 gene [40]. This discovery led to the development of the G93A mutant SOD1 transgenic mouse model for fALS (G93A SOD1 mice) [41].

G93A SOD1 mice recapitulate many of the pathological hallmarks of ALS, such as progressive muscle weakness and denervation, motor neuron loss and paralysis [42–44]. It has been demonstrated that muscle denervation is observed as early as 47 days of age in these mice [45–48] and precedes both motor neuron loss [42,43] and muscle atrophy [49,50]. These characteristics are similar to those observed in the rodent models of aging [27,28] as well as in SOD1-/- mice [35,36,51]. In addition, these mice display preferential denervation of fast-twitch muscles [52–55]. It has been suggested that both fast muscle and motor units are selectively vulnerable to the disease process in ALS patients [56,57]. This increased sensitivity to muscle denervation in fast muscles has also been demonstrated in aged mice [27,28] and SOD1-/- mice [35,36].

A potential mechanism mediating muscle denervation in the G93A SOD1 mice may be increased oxidative stress resulting from transgenic expression of mutant SOD1 gene. Examination of the gastrocnemius muscle showed increases in malondialdehyde and protein carbonyl levels which are indicative of oxidative damage to lipids and proteins, respectively [58]. In a related study, Muller and colleagues compared ROS production in response to sciatic nerve transection in muscles of three different models of mice that show muscle denervation: SOD1-/-, G93A SOD1, and aged mice [59]. Examination of gastrocnemius and tibialis anterior muscles following nerve injury showed varying levels of increase in ROS. The authors reported three-fold increase in ROS in 28- to 32-month-old wildtype mice compared to 10-month-old wildtype mice (aged vs. young wildtype mice) [59]. In SOD1-/- mice, ROS production is increased by 30% and 100% in 5-month-old and 20-month-old mice, respectively, compared with age-matched wildtype mice [59]. Lastly, G93A SOD1 mice showed 10-fold increase in ROS generation compared to age-matched wildtype mice [59].

These findings suggest that many features of the muscle denervation observed in the G93A SOD1 mice are similar to features of muscle denervation observed in aged mice and SOD1-/- mice, and may be mediated by oxidative stress. Since G93A SOD1 mice represent the most frequently studied fALS mouse model, there have been a large number of studies examining the physiological mechanisms modulating the disease progression in these mice. In the following sections, research findings demonstrating the effects of PGC-1α, IGF-1, GDNF, MyoD, myogenin, and miR-206 on NMJ innervation patterns in the G93A SOD1 mice will be highlighted in the context of age-related muscle denervation.

Role of PGC-1α as a mediator of exercise and caloric restriction effects in NMJ maintenance

The effect of voluntary exercise and caloric restriction (CR) on age-related muscle denervation has been directly examined by Valdez and colleagues [29]. In their study, they examined mice that were either subjected to 20 months of caloric restriction (from 4 to 24 months of age) or 1 month of voluntary wheel running (from 21 to 22 months of age) [29]. Their findings show that many of the age-related changes (e.g., fragmentation, denervation, and sprouting) in NMJs are reduced in response to the exercise and diet regimen used in the study [29].

Although the effects of exercise and CR on the disease progression in G93A SOD1 have been examined, the effects on muscle denervation phenotype have not been directly examined to date. A number of studies in G93A SOD1 mice have examined the role of physical activity on the survival rate and neuroprotection of spinal cord motor neurons. Kaspar and colleagues showed that wheel running exercise increases spinal cord motor neuron survival and improves Rota-rod performance [60]. Treadmill running in these mice have also shown benefits on motor neuron survival and Rota-rod performance [61]. However, additional studies seem to suggest that the intensity of the exercise may be an important factor in moderating the disease progression; moderate exercise may impart benefit while high intensity exercise hastens disease progression in G93A SOD1 mice [61,62]. On the other hand, caloric restriction studies to date in G93A SOD1 mice have only shown a detrimental effect on disease progression and motor function [63–65].

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcription co-activator involved in both mitochondrial biogenesis and oxidative metabolism in skeletal muscle [66]. PGC1-α overexpression in muscle increases mitochondrial biogenesis and enhancement of muscle oxidative phenotype [67]. Research findings suggest that the effects of caloric restriction may be in part mediated by PGC-1α [68] and AMP-activated protein kinase α (AMPK) [69]. The critical role of AMPK and PGC-1α in mediating exercise effects has also been demonstrated by Narkar and colleagues, where they showed that pharmacological activation of AMPK and PGC-1α imparts an endurance phenotype in sedentary mice [70].

Two of the currently approved antidiabetic drugs, metoformin and pioglitzone, have been shown to activate AMPK and PGC-1α, respectively [71–74]. Studies examining the effect of metformin demonstrated that the treatment using multiple doses in drinking water (0.5mg/ml, 2mg/ml, and 5mg/ml) did not improve the survival rate or disease progresssion in G93A SOD1 mice, but did show a moderate increase in the motor unit number in EDL of male mice [75]. On the other hand, G93A SOD1 mice treated with pioglitzone, a PPAR- agonist, showed improved motor function, muscle fiber integrity, and motor neuron survival [76]. This finding has been confirmed using a genetic approach; transgenic overexpression of PGC-1α improved Rota-rod performance and increased motor neuron survival in G93A SOD1 mice [77,78]. Interestingly, despite the motor function improvement in these mice, Liang and colleagues did not observe an increase in AChRα subunit expression [78].

This result is surprising since regulation of NMJ genes and AChR clustering by PGC-1α has been demonstrated using muscle-specific PGC-1α transgenic and knockout mice [79]. Furthermore, findings suggest that muscle activity or state of innervation may be a better predictor of the PGC-1α level. Active older adults (70 ±5 years) who maintained greater muscle strength than sedentary older individuals (63 ±10 years) displayed much higher PGC-1α levels in their muscle, comparable to levels observed in the muscle of young individuals (22 ±2 years) [80]. In rats, chronic unilateral sciatic or peroneal nerve denervation reduces the level of PGC-1α by 70% in ipsilateral muscles [81]. Experimental findings showing decreased PGC-1α in the muscles of both elderly humans and aged rats may reflect age-related muscle denervation [82,83].

Despite these findings, studies targeting the transgenic PGC-1α expression to skeletal muscle in the G93A SOD1 mice suggest that PGC-1α is not sufficient for halting muscle denervation in these mice. A study by Da Cruz and colleagues demonstrated that transgenic overexpression of PGC-1α in the muscle of G37R mutant SOD1 mice did not modulate NMJ denervation in these mice, even though PGC-1α overexpression in the muscle increased mitochondrial biogenesis, AChR clustering, and improved muscle endurance [84]. A similar study in G93A SOD1 mice resulted in enhanced oxidative phenotype in the skeletal muscle, but did not improve Rota-rod performance or muscle strength [85].

Role of IGF-1 in NMJ maintenance

Insulin-like growth factor-1 (IGF-1) is a neuroprotective hormone that has also shown to mediate exercise effect on neurogenesis and neural activity [86–88]. Kaspar and colleagues examined the effect of IGF-1's neurotrophic property in ALS using the G93A SOD1 mice. They utilized retrograde uptake property of adeno-associated virus (AAV) at presynaptic terminals to deliver IGF-1 to the motor neurons via intramuscular injections of AAV-IGF-1 [89]. Intramuscular injections of AAV-IGF-1 in adult G93A SOD1 improved both the muscle function and motor neuron survival [89]. These identical changes were also observed in exercised G93A SOD1 mice [60].

Intramuscular injections of AAV-IGF-1 increased IGF-1 expression in both the muscle and spinal cord motor neurons [89]. When IGF-1 expression was restricted to the muscle using a lentiviral vector that was not retrogradely transported to the spinal cord, Kaspar and colleagues observed in these mice a moderate but statistically significant increase in survival that was less than that for AAV-IGF-1 treatment [89].

A number of studies have addressed the question of central versus local action of IGF-1 on the survival of G93A SOD1 mice. It has been shown that continuous intrathecal infusion of IGF-1 into the spinal cord is neuroprotective and improves survival rate [90]. However, in another study where the IGF-1 level in the spinal cord was elevated via intrathecal delivery of IGF-1:tetanus toxin fragment C fusion protein, there was no effect on the survival rate [91]. Similarly, spinal cord-targeted transgenic expression of IGF-1 in G93A SOD1 mice did not improve motor neuron degeneration and muscle function decline [92].

It has been demonstrated that muscle-targeted expression of IGF-1 improves muscle function and reduces age-related muscle atrophy [93], and enhances nerve branching at NMJ and increases muscle endplate size in older mice (22-24 month old), resulting in measures that are similar to those observed in young mice (2-6 month old) [94]. Muscle expression of IGF-1 also enhances nerve regeneration following nerve injury in mice, as demonstrated by increased markers of muscle repair and nerve regeneration as well as accelerated recovery of nerve conduction in the damaged nerve [95].

Dobrowolny and colleagues directly examined the effect of muscle-directed expression of muscle isoform of IGF-1 (mIGF-1) on NMJ changes in G93A mutant SOD1 mice [96]. The findings demonstrate that skeletal muscle expression of mIGF-1 extends survival and protects motor neurons in G93A SOD1 mice [96]. In addition, mIGF-1 expression increased agrin expression and preserved AChR clustering [96]. However, in another study, muscle-directed expression of IGF-1 in G93A SOD1 mice did not improve motor neuron survival or motor function [92].

These equivocal findings are surprising given the fact that positive effects of localized IGF-1 on nerve injury-mediated muscle denervation have been demonstrated. Caroni and colleagues showed that intramuscular injections of IGF-1 increased GAP-43, which suggests axon growth, but did not affect acetylcholine receptor (AChR) clustering [97]. In a follow-up study, the authors blocked the IGF-1 activity in the muscle using IGF-1 binding proteins [98]. In this study, they induced paralysis using Botulinum toxin A to induce nerve sprouting. Interference with IGF-1 action through subcutaneous delivery of IGF-BP4 to the paralyzed muscle using osmotic minipump prevents nerve sprouting, suggesting that IGF-1 mediates nerve sprouting at the NMJ [98]. However, a double-blind placebo-controlled phase III randomized clinical trial has proven that a two-year treatment of twice-daily subcutaneous injections of IGF-1 is clinically ineffective in ALS patients [99].

Role of GDNF in NMJ maintenance

Glial cell line-derived neurotrophic factor (GDNF) is also a neurotrophic factor found to have a strong pro-survival effect on motor neurons [100]. GDNF mRNA is detectable in the central nervous system as well as in the peripheral organs, including skeletal muscle [101–103]. The role of GDNF in NMJ innervation was demonstrated by studies showing that skeletal muscle-targeted expression of GDNF in transgenic mice increases the number of muscle of endplates and multiply-innervated NMJs [104,105]. However, when subcutaneously injected the exogenous GDNF's ability to maintain synaptic remodeling in mice is observed only if chronic exposure is initiated within the developmentally-critical postnatal time window between postnatal day zero and eight [106].

It has been shown that the GDNF level in the postnatal muscle decreases with age. In rats, the GDNF mRNA level in the skeletal muscle is reduced three months after birth; however, constant high levels of GDNF protein are detected in postnatal muscle [107]. Examination of muscle samples from human adults 20-43 years of age also demonstrated the presence of GDNF in the skeletal muscle, and its expression in the vicinity of neuromuscular junctions as indicated by co-localization of GDNF and α-bungarotoxin staining [103]. Research evidence from adult rats suggests that GDNF activity in muscle may modulate NMJ morphology. It has been shown that when rats are subjected to two weeks of involuntary exercise, the GDNF level is increased in soleus but decreased in EDL [108]. Examination of muscle endplates revealed a decrease in the total area per endplate in EDL while an increase was observed in the soleus [108]. This correlation between GDNF levels and muscle endplate sizes has been further documented in subsequent studies [109,110].

In G93A SOD1 mice, intramuscular injections of AAV expressing GDNF in adult mice improved Rota-rod performance and spinal cord motor neuron survival [111]. The effect observed in this study is likely mediated by both central and local mechanisms, since GDNF levels were upregulated in both the muscle and spinal cord [111]. Although immunoreactivity for transgene-derived GDNF was shown to be highly co-localized with α-bungarotoxin staining, the effect on muscle denervation was not directly assessed in this study [111].

In order to directly test the role of central versus local effect of GDNF on the neuropathology, Li and colleagues transgenically targeted GDNF expression to either neurons or myofibers in G93A SOD1 mice [112]. Direct measures of muscle denervation demonstrated that transgenic GDNF expression targeted to the muscle increased the number of innervated NMJs, whereas neuronally targeted transgenic GDNF expression did not produce such an effect [112]. Therefore, muscle-directed transgenic expression of GDNF is important for NMJ maintenance in these mice.

To determine the therapeutic potential of GDNF treatment, Suzuki and colleagues have used human stem cells to examine the effect of chronic GDNF delivered to either muscle or spinal cord on the muscle denervation phenotype in the adult rat model of fALS (G93 SOD1 rats) [113,114]. In one study, GDNF-secreting human neural progenitor cells were intrathecally transplanted into the spinal cord at 70 days of age. Although the transplantation imparted local protection on spinal cord motor neurons, there was no change in the number of innervated NMJs [114]. In another study, the group implanted human mesenchymal stem cells engineered to express GDNF (hMSC-GDNF) intramuscularly at 80 days age, with a goal of delivering GDNF to NMJs locally. Although their findings showed that transplantations of either hMSC-GDNF or hMSC expressing GFP increased the number of innervated NMJs, only the hMSC-GDNF transplant showed statistically significant increase when compared to non-transplanted G93A SOD1 rats [113]. These results suggest that in addition to the GDNF effect, the transplanted hMSCs themselves are able to modulate muscle denervation by providing additional trophic support to the muscle and NMJs.

Role of MyoD, myogenin, and miR-206 in NMJ maintenance

The findings from various growth factor studies using the G93A SOD1 mice and G93A SOD1 rats suggest that muscle may indeed play a role in mediating muscle denervation process. MyoD and its related basic helix-loop-helix (Myf5, myogenin, and MRF4) are muscle specific regulatory factors. During development, these myogenic regulatory factors have critical roles in skeletal muscle development [115–117]; For example, MyoD is involved in determining skeletal muscle lineage [118], whereas myogenin is important for muscle differentiation [119,120]. In adult muscle, myogenin is expressed preferentially in slow muscle (composed of predominantly type I muscle fibers) [121–123] and MyoD is enriched in fast muscle (composed of predominantly type II muscle fibers) [121,123].

A number of studies suggest that fast muscle is more sensitive to age-related muscle denervation process as compared to slow muscle [27,39]. Similarly, it has also been suggested that the fast muscles and motor units in both ALS patients and mouse models are preferentially denervated [52,54–57]. It has been shown that expression of either exogenous MyoD or myogenin in skeletal muscle can shift the muscle phenotype. MyoD expression has been shown to impart type IIx muscle fiber phenotype under denervation condition [124], while myogenin expression has been shown to enhance the oxidative phenotype in muscle fibers [122,123].

Recently, my colleagues and I used adenovirus constructs to express either human MyoD or myogenin in muscles of adult G93A SOD1 mice to evaluate their effects on disease progression [85]. Adenovirus expressing either human MyoD, human myogenin, or GFP was injected into hind limb muscles bilaterally at 30 days of age. Treatment effects on the NMJ innervation patterns were examined using stereology on gastrocnemius samples taken at 100 days of age. Our findings show that postnatal muscle expression of MyoD exacerbates both muscle denervation and Rota-rod performance decline, while postnatal muscle expression of myogenin attenuates muscle denervation and improves Rota-rod performance when compared to the virus control G93A SOD1 group [85]. Therefore, MyoD and myogenin differentially modulate muscle denervation in these mice.

It has been shown that myogenic transcription factors can regulate the expression of microRNAs (miRs) in muscle [125,126]. miRs are short non-coding mRNAs that are post-transcriptional regulators of gene expression. Of the many miRs that have been identified in the muscle, it has been shown that miR-206 can be regulated by both MyoD and myogenin [125,127–129]. miR-206 shows skeletal muscle-specific expression and is thought to regulate many aspects of skeletal muscle function, including NMJ formation [126]. Although its expression has been reported to be enriched in slow muscle [127,130], its upregulation following muscle denervation is enhanced in fast muscles [127]. Although NMJ development and innervation is unaffected in miR-206 knockout mice, NMJ reinnervation is delayed following nerve transection or injury [127]. In the absence of miR-206, muscle denervation is exacerbated in the skeletal muscle of G93A SOD1 mice [127]. Upon further investigation, the authors determined that the effect in their study is in part mediated via repression of histone deacetylase 4 (HDAC4) translation by miR-206. The HDAC4 protein level was increased in miR-206 knockout mice, and when HDAC4 is selectively knocked out in the skeletal muscle of wildtype mice, NMJ reinnervation following nerve injury is enhanced [127]. However, the

effect of HDAC4 knockout on muscle denervation in G93A SOD1 mice was not directly investigated.

Conclusion

The similarities in muscle denervation profiles between SOD1-/-, G93A SOD1, and aged mice suggest that both SOD1-/- and G93A SOD1 mice represent an accelerated muscle-aging model for oxidative stress-mediated muscle denervation. Much of the past studies in G93A SOD1 mice have focused on neuroprotective effects on spinal cord motor neurons. However, investigation of effects on muscle denervation in G93A SOD1 increasingly provides valuable insight into potential mechanisms of progressive muscle denervation. Recent findings have highlighted muscle-specific factors such as MyoD, myogenin, and miR-206 as mediators of muscle denervation. Furthermore, evidence of muscle-targeted genetic manipulations demonstrating greater impact on muscle denervation highlights the importance of the muscle in NMJ innervation regulation.

References

[1] Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R (2004). Skeletal Muscle Cutpoints Associated with Elevated Physical Disability Risk in Older Men and Women. Am J Epidemiol, 159:413–21.

[2] Visser M, Schaap LA (2011). Consequences of sarcopenia. Clin Geriatr Med, 27:387–99.

[3] Metter EJ, Talbot LA, Schrager M, Conwit R (2002). Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci, 57:B359–65.

[4] Clark BC, Manini TM (2008). Sarcopenia =/= dynapenia. J Gerontol A Biol Sci Med Sci, 63:829–34.

[5] Evans WJ (2010). Skeletal muscle loss: Cachexia, sarcopenia, and inactivity. Am J Clin Nutr, 91:1123S–7S.

[6] Walston JD (2012). Sarcopenia in older adults. Curr. Opin Rheumatol, 24:623–7.

[7] Bales CW, Kraus WE (2013). Caloric restriction: implications for human cardiometabolic health. J Cardiopulm Rehabil Prev, 33:201–8.

[8] Robertson LT, Mitchell JR (2013). Benefits of short-term dietary restriction in mammals. Exp Gerontol, 48:1043–8.

[9] Weiss EP, Fontana L (2011). Caloric restriction: powerful protection for the aging heart and vasculature. AJP Hear Circ Physiol, 301:H1205–19.

[10] Dolinsky VW, Dyck JRB (2011). Calorie restriction and resveratrol in cardiovascular health and disease. Biochim Biophys Acta, 1812:1477–89.

[11] Huffman DM (2010). Exercise as a calorie restriction mimetic: Implications for improving healthy aging and longevity. Interdiscip Top Gerontol, 37:157–74.

[12] Vina J, Borras C, Sanchis-Gomar F, Martinez-Bello VE, Olaso-Gonzalez G, Gambini J, et al (2014). Pharmacological properties of physical exercise in the elderly. Curr Pharm Des, 20:3019–29.

[13] Mercken EM, Carboneau BA, Krzysik-Walker SM, De CaboR (2012). Of mice and men: The benefits of caloric restriction, exercise, and mimetics. Ageing Res Rev, 11:390–8.

[14] Allen J, Morelli V (2011). Aging and exercise. Clin Geriatr Med, 27:661–71.

[15] Chodzko-Zajko W, Schwingel A, Park CH (2008). Successful Aging: The Role of Physical Activity, Am J Lifestyle Med, 3:20–8.

[16] Stewart KJ (2005). Physical activity and aging. Ann N Y Acad Sci, 1055 :193–206.

[17] Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al (2011). Gait speed and survival in older adults. JAMA, 305:50–58.

[18] Rosenberg IH (2011). Sarcopenia: origins and clinical relevance. Clin Geriatr Med, 27:337–9.

[19] Ryall JG, Schertzer JD, Lynch GS (2008). Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness. Biogerontology, 9:213–28.

[20] Thompson LV (2009). Age-related muscle dysfunction. Exp Gerontol, 44:106–11.

[21] Janssen I (2010). Evolution of sarcopenia research. Appl Physiol Nutr Metab, 35:707–12.

[22] Delbono O (2003). Neural control of aging skeletal muscle. Aging Cell, 2:21–9.

[23] Lexell J (1997). Evidence for nervous system degeneration with advancing age. J Nutr, 127:1011S–3S.

[24] Vandervoort AA (2002). Aging of the human neuromuscular system. Muscle and Nerve, 25:17–25.

[25] Lichtman JW, Magrassi L, Purves D (1987). Visualization of neuromuscular junctions over periods of several months in living mice. J Neurosci, 7:1215–22.

[26] Balice-Gordon RJ (1997). Age-related changes in neuromuscular innervation. Muscle Nerve Suppl, 5:S83–7.

[27] Chai RJ, Vukovic J, Dunlop S, Grounds MD, Shavlakadze T (2011). Striking denervation of neuromuscular junctions without lumbar motoneuron loss in geriatric mouse muscle. PLoS One, 6:e28090.

[28] Valdez G, Tapia JC, Lichtman JW, Fox MA, Sanes JR (2012). Shared resistance to aging and als in neuromuscular junctions of specific muscles. PLoS One, 7:e34640.

[29] Valdez G, Tapia JC, Kang H, Clemenson GD, Gage FH, Lichtman JW, et al (2010) Attenuation of age-related changes in mouse neuromuscular synapses by caloric restriction and exercise. Proc Natl Acad Sci USA., 107:14863–8.

[30] Salmon AB, Richardson A, Pérez VI (2010). Update on the oxidative stress theory of aging: Does oxidative stress play a role in aging or healthy aging? Free Radic Biol Med, 48:642–55.

[31] Fulle S, Protasi F, Di Tano G, Pietrangelo T, Beltramin A, Boncompagni S, et al (2004). The contribution of reactive oxygen species to sarcopenia and muscle ageing. Exp Gerontol, 39:17–24.

[32] Sastre J (2003). The role of mitochondrial oxidative stress in aging. Free Radic Biol Med, 35:1–8.

[33] Muller FL, Song W, Liu Y, Chaudhuri A, Pieke-Dahl S, Strong R, et al (2006). Absence of CuZn superoxide dismutase leads to elevated oxidative stress and acceleration of age-dependent skeletal muscle atrophy. Free Radic Biol Med, 40:1993–2004.

[34] Jang YC, Lustgarten MS, Liu Y, Muller FL, Bhattacharya A, Liang H, et al (2010). Increased superoxide in vivo accelerates age-associated muscle atrophy through mitochondrial dysfunction and neuromuscular junction degeneration. FASEB J, 24:1376–90.

[35] Fischer LR, Li Y, Asress SA, Jones DP, Glass JD (2012). Absence of SOD1 leads to oxidative stress in peripheral nerve and causes a progressive distal motor axonopathy. Exp Neurol, 233:163–71.

[36] Fischer LR, Igoudjil A, Magrané J, Li Y, Hansen JM, Manfredi G, Glass JD (2011). SOD1 targeted to the mitochondrial intermembrane space prevents motor neuropathy in the Sod1 knockout mouse. Brain, 134:196–209.

[37] Shefner JM, Reaume AG, Flood DG, Scott RW, Kowall NW, Ferrante RJ, et al (1999). Mice lacking cytosolic copper/zinc superoxide dismutase display a distinctive motor axonopathy. Neurology, 53:1239–46.

[38] Flood DG, Reaume AG, Gruner JA, Hoffman EK, Hirsch JD, Lin YG, et al (1999). Hindlimb motor neurons require Cu/Zn superoxide dismutase for maintenance of neuromuscular junctions. Am J Pathol, 155:663–72.

[39] Lexell J (1995). Human aging, muscle mass, and fiber type composition. J Gerontol A Biol Sci Med Sci, 50:11–16.

[40] Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature, 362:59–62.

[41] Gurney ME (1994). Transgenic-mouse model of amyotrophic lateral sclerosis. N Engl J Med, 331:1721–2.

[42] Chiu AY, Zhai P, Dal Canto MC, Peters TM, Kwon YW, Prattis SM, et al (1995). Age-dependent penetrance of disease in a transgenic mouse model of familial amyotrophic lateral sclerosis. Mol Cell Neurosci, 6:349–62.

[43] Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, et al (1994). Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science, 264:1772–5.

[44] Tu PH, Raju P, Robinson KA, Gurney ME, Trojanowski JQ, Lee VM (1996). Transgenic mice carrying a human mutant superoxide dismutase transgene develop neuronal cytoskeletal pathology resembling human amyotrophic lateral sclerosis lesions. Proc Natl Acad Sci USA, 93:3155–60.

[45] Fischer LR, Culver DG, Tennant P, Davis AA, Wang M, Castellano-Sanchez A, et al (2004). Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. Exp Neurol, 185:232–40.

[46] 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, 20:2534–42.

[47] Gould TW, Buss RR, Vinsant S, Prevette D, Sun W, Knudson CM, et al (2006). Complete dissociation of motor neuron death from motor dysfunction by Bax deletion in a mouse model of ALS. J Neurosci, 26:8774–86.

[48] Kennel PF, Finiels F, Revah F, Mallet J (1996). Neuromuscular function impairment is not caused by motor neurone loss in FALS mice: an electromyographic study. Neuroreport, 7:1427–31.

[49] Brooks KJ, Hill MDW, Hockings PD, Reid DG (2004). MRI detects early hindlimb muscle atrophy in Gly93Ala superoxide dismutase-1 (G93A SOD1) transgenic mice, an animal model of familial amyotrophic lateral sclerosis. NMR Biomed, 17:28–32.

[50] Marcuzzo S, Zucca I, Mastropietro A, de Rosbo NK, Cavalcante P, Tartari S, et al (2011). Hind limb muscle atrophy precedes cerebral neuronal degeneration in G93A-SOD1 mouse model of amyotrophic lateral sclerosis: A longitudinal MRI study. Exp Neurol, 231:30–7.

[51] Shi Y, Ivannikov MV, Walsh ME, Liu Y, Zhang Y, Jaramillo CA, et al (2014). The Lack of CuZnSOD leads to impaired neurotransmitter release, neuromuscular junction destabilization and reduced muscle strength in mice. PLoS One, 9:1–11.

[52] Gordon T, Putman CT, Hegedus J (2007). Amyotrophic lateral sclerosis - evidence of early denervation of fast-twitch muscles. Basic Appl Myol, 17:141–5.

[53] Hegedus J, Putman CT, Tyreman N, Gordon T (2008). Preferential motor unit loss in the SOD1 G93A transgenic mouse model of amyotrophic lateral sclerosis. J Physiol, 586:3337–51.

[54] Hegedus J, Putman CT, Gordon T (2007). Time course of preferential motor unit loss in the SOD1G93A mouse model of amyotrophic lateral sclerosis. Neurobiol Dis, 28:154–64.

[55] Atkin JD, Scott RL, West JM, Lopes E, Quah AKJ, Cheema SS (2005). Properties of slow- and fast-twitch muscle fibres in a mouse model of amyotrophic lateral sclerosis. Neuromuscul Disord, 15:377–88.

[56] Sanjak M, Brinkmann J, Belden DS, Roelke K, Waclawik A, Neville HE, et al (2001). Quantitative assessment of motor fatigue in amyotrophic lateral sclerosis. J Neurol Sci, 191:55–9.

[57] Dengler R, Konstanzer A, Kuther G, Hesse S, Wolf W, Struppler A (1990). Amyotrophic lateral sclerosis: macro-EMG and twitch forces of single motor units. Muscle Nerve, 13:545–50.

[58] Mahoney DJ, Kaczor JJ, Bourgeois J, Yasuda N, Tarnopolsky MA (2006). Oxidative stress and antioxidant enzyme upregulation in SOD1-G93A mouse skeletal muscle. Muscle Nerve, 33:809–16.

[59] Muller FL, Song W, Jang YC, Liu Y, Sabia M, Richardson A, et al (2007). Denervation-induced skeletal muscle atrophy is associated with increased mitochondrial ROS production. Am J Physiol Regul Integr Comp Physiol, 293:R1159–68.

[60] Kaspar BK, Frost LM, Christian L, Umapathi P, Gage FH (2005). Synergy of insulin-like growth factor-1 and exercise in amyotrophic lateral sclerosis. Ann Neurol, 57:649–55.

[61] Carreras I, Yuruker S, Aytan N, Hossain L, Choi JK, Jenkins BG, et al (2009). Moderate exercise delays the motor performance decline in a transgenic model of ALS. Brain Res, 1313:192–201.

[62] Mahoney DJ, Rodriguez C, Devries M, Yasuda N, Tarnopolsky MA (2004). Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. Muscle Nerve, 29:656–62.

[63] Patel BP, Safdar A, Raha S, Tarnopolsky MA, Hamadeh MJ (2010). Caloric restriction shortens lifespan through an increase in lipid peroxidation, inflammation and apoptosis in the G93A mouse, an animal model of ALS. PLoS One, 5:e9386.

[64] Hamadeh MJ, Rodriguez MC, Kaczor JJ, Tarnopolsky MA (2005). Caloric restriction transiently improves motor performance but hastens clinical onset of disease in the Cu/Zn-superoxide dismutase mutant G93A mouse. Muscle and Nerve, 31:214–20.

[65] Hamadeh MJ, Tarnopolsky MA (2006). Transient caloric restriction in early adulthood hastens disease endpoint in male, but not female, Cu/Zn-SOD mutant G93A mice. Muscle and Nerve, 34:709–19.

[66] Handschin C, Spiegelman BM (2008). The role of exercise and PGC1alpha in inflammation and chronic disease. Nature, 454:463–9.

[67] Lin J, Wu H, Tarr PT, Zhang C-Y, Wu Z, Boss O, et al (2002). Transcriptional co-activator PGC-1a drives the formation of slow-twitch muscle fibres. Nature, 418:797–801.

[68] Anderson RM, Shanmuganayagam D, Weindruch R (2009). Caloric restriction and aging: studies in mice and monkeys. Toxicol Pathol, 37:47–51.

[69] Cantó C, Auwerx J (2011). Calorie Restriction: Is AMPK a Key Sensor and Effector? Physiology (Bethesda), 26:214–24.

[70] Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, et al (2008). AMPK and PPARδ Agonists Are Exercise Mimetics. Cell, 134:405–15.

[71] Hawley SA, Gadalla AE, Olsen GS, Hardie DG (2002). The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. Diabetes, 51:2420–5.

[72] Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al (2001). Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest, 108:1167–74.

[73] Rangwala SM, Lazar MA (2004). Peroxisome proliferator-activated receptor gamma in diabetes and metabolism. Trends Pharmacol Sci, 25:331–6.

[74] Spiegelman BM (1998). PPAR-γ: Adipogenic regulator and thiazolidinedione receptor. Diabetes, 47:507–14.

[75] Kaneb HM, Sharp PS, Rahmani-Kondori N, Wells DJ (2011). Metformin treatment has no beneficial effect in a dose-response survival study in the SOD1 G93A mouse model of ALS and is harmful in female mice. PLoS One, 6:e24189.

[76] Schutz B, Reimann J, Dumitrescu-Ozimek L, Kappes-Horn K, Landreth GE, Schurmann B, et al (2005). The oral antidiabetic pioglitazone protects from neurodegeneration and amyotrophic lateral sclerosis-like symptoms in superoxide dismutase-G93A transgenic mice. J Neurosci, 25:7805–12.

[77] Zhao W, Vargese M, Yemul S, Pan Y, Cheng A, Marano P, et al (2011). Peroxisome proliferator activator receptor gamma coactivator-1 alpha (PGC-1a) improves motor performance and survival in a mouse model of amyotrophic lateral sclerosis. Mol Neurodegener, 6:51–8.

[78] Liang H, Ward WF, Jang YC, Bhattacharya A, Bokov AF, Li Y, et al (2011). PGC-1alpha protects neurons and alters disease progression in an amyotrophic lateral sclerosis mouse model. Muscle Nerve, 44:947–56.

[79] Handschin C, Kobayashi YM, Chin S, Seale P, Campbell KP, Spiegelman BM (2007). PGC-1alpha regulates the neuromuscular junction program and ameliorates Duchenne muscular dystrophy. Genes Dev, 21:770–83.

[80] Safdar A, Hamadeh MJ, Kaczor JJ, Raha S, deBeer J, Tarnopolsky MA (2001). Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. PLoS One, 5:e10778.

[81] Adhihetty PJ, O'Leary MFN, Chabi B, Wicks KL, Hood DA (2007). Effect of denervation on mitochondrially mediated apoptosis in skeletal muscle. J Appl Physiol, 102:1143–51.

[82] Joseph AM, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LMD, et al (2012). The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell, 11:801–9.

[83] Chabi B, Ljubicic V, Menzies KJ, Huang JH, Saleem A, Hood DA (2008). Mitochondrial function and apoptotic susceptibility in aging skeletal muscle. Aging Cell, 7:2–12.

[84] Da Cruz S, Parone PA, Lopes VS, Lillo C, McAlonis-Downes M, Lee SK, et al (2012). Elevated PGC-1α activity sustains mitochondrial biogenesis and muscle function without extending survival in a mouse model of inherited ALS. Cell Metab, 15:778–86.

[85] Park KHJ, Franciosi S, Leavitt BR (2013). Postnatal muscle modification by myogenic factors modulates neuropathology and survival in an ALS mouse model. Nat Commun, 4:2906.

[86] Carro E, Trejo JL, Busiguina S, Torres-Aleman I (2001). Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci, 21:5678–84.

[87] Trejo L, Carro E, Torres-Aleman I (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci, 21:1628–34.

[88] Carro E, Nuñez A, Busiguina S, Torres-Aleman I (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. J Neurosci, 20:2926–33.

[89] Kaspar BK, Llado J, Sherkat N, Rothstein JD, Gage FH (2003). Retrograde viral delivery of IGF-1 prolongs survival in a mouse ALS model. Science, 301:839–42.

[90] Nagano I, Ilieva H, Shiote M, Murakami T, Yokoyama M, Shoji M, et al (2005). Therapeutic benefit of intrathecal injection of insulin-like growth factor-1 in a mouse model of Amyotrophic Lateral Sclerosis. J Neurol Sci, 235:61–8.

[91] Chian R-J, Li J, Ay I, Celia SA, Kashi BB, Tamrazian E, et al (2009). IGF-1:tetanus toxin fragment C fusion protein improves delivery of IGF-1 to spinal cord but fails to prolong survival of ALS mice. Brain Res, 1287:1–19.

[92] Messi ML, Clark HM, Prevette DM, Oppenheim RW, Delbono O (2007). The lack of effect of specific overexpression of IGF-1 in the central nervous system or skeletal muscle on the pathophysiology in the G93A SOD-1 mouse model of ALS. Exp Neurol, 207:52–63.

[93] Musarò A, McCullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M, et al (2001). Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. Nat Genet, 27:195–200.

[94] Messi ML, Delbono O (2003). Target-derived trophic effect on skeletal muscle innervation in senescent mice. J Neurosci, 23:1351–9.

[95] Rabinovsky ED, Gelir E, Gelir S, Lui HUI, Kattash M, DeMayo FJ, et al (2003). Targeted expression of IGF-1 transgene to skeletal muscle accelerates muscle and motor neuron regeneration. FASEB J, 17:53–5.

[96] Dobrowolny G, Giacinti C, Pelosi L, Nicoletti C, Winn N, Barberi L, et al (2005). Muscle expression of a local Igf-1 isoform protects motor neurons in an ALS mouse model. J Cell Biol, 168:193–9.

[97] Caroni P, Grandes P (1990). Nerve sprouting in innervated adult skeletal muscle induced by exposure to elevated levels of insulin-like growth factors. J Cell Biol, 110:1307–17.

[98] Caroni P, Schneider C, Kiefer MC, Zapf J (1994). Role of muscle insulin-like growth factors in nerve sprouting: Suppression of terminal sprouting in paralyzed muscle by IGF-binding protein 4. J Cell Biol, 125:893–902.

[99] Sorenson EJ, Windbank AJ, Mandrekar JN, Bamlet WR, Appel SH, Armon C, et al (2008). Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. Neurology, 71:1770–5.

[100] Henderson CE, Phillips HS, Pollock RA, Davies AM, Lemeulle C, Armanini M, et al (1994). GDNF: a potent survival factor for motoneurons present in peripheral nerve and muscle. Science, 266:1062–4.

[101] Trupp M, Rydén M, Jörnvall H, Funakoshi H, Timmusk T, Arenas E, et al (1995). Peripheral expression and biological activities of GDNF, a new neurotrophic factor for avian and mammalian peripheral neurons. J Cell Biol, 130:137–48.

[102] Nosrat CA, Tomac A, Lindqvist E, Lindskog S, Humpel C, Strömberg I, et al (1996). Cellular expression of GDNF mRNA suggests multiple functions inside and outside the nervous system. Cell Tissue Res, 286:191–207.

[103] Suzuki H, Hase A, Miyata Y, Arahata K, Akazawa C (1998). Prominent expression of glial cell line-derived neurotrophic factor in human skeletal muscle. J Comp Neurol, 402:303–12.

[104] Nguyen QT, Parsadanian AS, Snider WD, Lichtman JW (1998). Hyperinnervation of neuromuscular junctions caused by GDNF overexpression in muscle. Science, 279:1725–9.

[105] Zwick M, Teng L, Mu X, Springer JE, Davis BM (2001). Overexpression of GDNF induces and maintains hyperinnervation of muscle fibers and multiple end-plate formation. Exp Neurol, 171:342–50.

[106] Keller-Peck CR, Feng G, Sanes JR, Yan Q, Lichtman JW, Snider WD (2001). Glial cell line-derived neurotrophic factor administration in postnatal life results in motor unit enlargement and continuous synaptic remodeling at the neuromuscular junction. J Neurosci, 21:6136–46.

[107] Nagano M, Suzuki H (2003). Quantitative analyses of expression of GDNF and neurotrophins during postnatal development in rat skeletal muscles. Neurosci Res, 45:391–9.

[108] McCullough MJ, Peplinski NG, Kinnell KR, Spitsbergen JM (2011). Glial cell line-derived neurotrophic factor protein content in rat skeletal muscle is altered by increased physical activity in vivo and in vitro. Neuroscience, 174:234–44.

[109] Gyorkos AM, McCullough MJ, Spitsbergen JM (2014). Glial cell line-derived neurotrophic factor (GDNF) expression and NMJ plasticity in skeletal muscle following endurance exercise. Neuroscience, 257:111–8.

[110] Gyorkos AM, Spitsbergen JM (2014). GDNF content and NMJ morphology are altered in recruited muscles following high-speed and resistance wheel training. Physiol Rep, 2:e00235.

[111] Wang LJ, Lu YY, Muramatsu S, Ikeguchi K, Fujimoto K, Okada T, et al (2002). Neuroprotective effects of glial cell line-derived neurotrophic factor mediated by an adeno-associated virus vector in a transgenic animal model of amyotrophic lateral sclerosis. J Neurosci, 22:6920–8.

[112] Li W, Brakefield D, Pan Y, Hunter D, Myckatyn TM, Parsadanian A (2007). Muscle-derived but not centrally derived transgene GDNF is neuroprotective in G93A-SOD1 mouse model of ALS. Exp Neurol, 203:457–71.

[113] Suzuki M, McHugh J, Tork C, Shelley B, Hayes A, Bellantuono I, et al (2008). Direct muscle delivery of GDNF with human mesenchymal stem cells improves

motor neuron survival and function in a rat model of familial ALS. Mol Ther, 16:2002–10.

[114] Suzuki M, McHugh J, Tork C, Shelley B, Klein SM, Aebischer P, et al (2007). GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS. PLoS One, 2:e689.

[115] Megeney LA, Rudnicki MA (1995). Determination versus differentation and the MyoD family of transcription factors. Biochem Cell Biol, 73:723–32.

[116] Perry RLS, Rudnicki MA (2000). Molecular mechanisms regulating myogenic determination and differentiation. Front Biosci, 5:D570–D767.

[117] Berkes CA, Tapscott SJ (2005). MyoD and the transcriptional control of myogenesis. Semin Cell Dev Biol, 16:585–95.

[118] Rudnicki MA, Schnegelsberg PN, Stead RH, Braun T, Arnold HH, Jaenisch R (1993). MyoD or Myf-5 is required for the formation of skeletal muscle. Cell, 75:1351–9.

[119] Hasty P, Bradley A, Morris JH, Edmondson DG, Venuti JM, Olson EN (1993). Muscle deficiency and neonatal death in mice with a targeted mutation in the myogenin gene. Nature, 364:501–6.

[120] Nabeshima YK, Hanaoka M, Hayasaka M, Esumi E, Li S, Nonaka I (1993). Myogenin gene disruption results in perinatal lethality beacause of severe muscle defect. Nature, 364:532-5.

[121] Hughes SM, Taylor JM, Tapscott SJ, Gurley CM, Carter WJ, Peterson CA (1993). Selective accumulation of myoD and myogenin mRNAs in fast and slow adult skeletal muscle is controlled by innervation and hormones. Dev, 118:1137–47.

[122] Ekmark M, Grønevik E, Schjerling P, Gundersen K (2003). Myogenin induces higher oxidative capacity in pre-existing mouse muscle fibres after somatic DNA transfer. J Physiol, 548:259–69.

[123] Hughes SM, Chi MM-Y, Lowry OH, Gundersen K (1999). Myogenin induces a shift of enzyme activity from glycolytic to oxidative metabolism in muscles of transgenic mice. J Cell Biol, 145:633–42.

[124] Ekmark M, Rana ZA, Stewart G, Hardie DG, Gundersen K (2007). De-phosphorylation of MyoD is linking nerve-evoked activity to fast myosin heavy chain expression in rodent adult skeletal muscle. J Physiol, 584:637–50.

[125] Rao PK, Kumar RM, Farkhondeh M, Baskerville S, Lodish HF (2006). Myogenic factors that regulate expression of muscle-specific microRNAs. Proc Natl Acad Sci USA, 103:8721–6.

[126] McCarthy J (2008). MicroRNA-206: the skeletal muscle-specific myomiR. Biochim Biophys Acta, 1779:682–91.

[127] Williams AH, Valdez G, Moresi V, Qi X, Mcanally J, Elliott JL, et al (2009). MicroRNA-206 delays ALS progression and promotes regeneration of neuromuscular synapses in mice. Science, 326:1549–54.

[128] Moresi V, Williams AH, Meadows E, Flynn JM, Potthoff MJ, McAnally J, et al (2010). Myogenin and class II HDACs control neurogenic muscle atrophy by inducing E3 ubiquitin ligases. Cell, 143:35–45.

[129] Rosenberg MI, Georges SA, Asawachaicharn A, Analau E, Tapscott SJ (2006). MyoD inhibits Fstl1 and Utrn expression by inducing transcription of miR-206. J Cell Biol, 175:77–85.

[130] McCarthy JJ, Esser KA (2007). MicroRNA-1 and microRNA-133a expression are decreased during skeletal muscle hypertrophy. J Appl Physiol, 102:306–13.