Metabolic Dysfunction in ALS Skeletal Muscle

Subjects: Biology

Contributor: Ekene Anakor , William John Duddy , Stephanie Duguez

Defects in mitochondrial structure and function as well as energy metabolism in skeletal muscle contribute to disease pathology and progression, with metabolic dysfunctions appearing long before motor neuron degeneration and death.

motor neurone disease | muscle metabolism | neuromuscular junction | muscle regeneration

1. Mitochondrial Dysfunction

Mitochondria are involved in cellular production of radicals that are implicated in neurodegenerative diseases, and evidence exists for mitochondrial involvement in the skeletal muscle pathogenesis of ALS, exemplified by abnormal mitochondrial aggregates and vacuolations within skeletal muscle in ALS mouse models and human patients/biopsies [1][2] and reviewed by [3]. Furthermore, the excessive presence and accumulation of Reactive Oxygen Species (ROS) as well as ultrastructural mitochondrial abnormalities in the skeletal muscles of mice bearing $SOD1^{G93A}$ mutations and in ALS patients, suggests a disease dependent change in mitochondrial function [4][5]. Excess ROS production in skeletal muscle results in damage to mitochondrial structure and function including mitochondrial DNA deletions and depletions, and decreased activity of respiratory chain mitochondrial enzymes that ultimately leads to decreased generation of ATP [6][7][8]. Interestingly, mitochondrial alterations including a reduction in NADH:CoQ oxidoreductase activity are present in skeletal muscle biopsies obtained from sALS patients, and the severity of mitochondrial dysfunction increased as ALS worsened [4][8][9][10], suggesting that dysfunctional mitochondria are a common trait in ALS skeletal muscles.

2. Dysregulated Skeletal Muscle Energy Metabolism (Hypermetabolism and Dyslipidemia)

Closely linked to mitochondrial dysfunctions, energy dyshomeostasis represents an early and persistent observation during ALS [11]. Abnormalities in skeletal muscle energy metabolism provokes a defect in energy homeostasis exhibited as decreased glycolysis, elevated beta-oxidation in skeletal muscles as well as hypermetabolism [12][13], and may be responsible for the NMJ dismantling seen in a transgenic mouse model ($SOD1^{G86R}$/MCK-UCP1 mice) [14][15]. An ALS-associated protein, TDP-43 regulates body fat composition and skeletal muscle glucose homeostasis in vivo—transgenic mice overexpressing wild type TDP-43 possess myofibers with altered Glut4 translocation and glucose uptake abnormalities [16]. Muscle specific expression of $SOD1^{G93A}$ in MLC/$SOD1^{G93A}$ mice induces fatty acid (FA) recruitment to skeletal muscle that is necessary for sustaining lipid flux into skeletal muscle fibers and ensuring availability of FAs for β-oxidation—these likely precede

muscle denervation and have also been identified in ALS patients and other murine models [6][17]. In addition, hypermetabolism, defined as an abnormally elevated level of resting energy expenditure, has been identified in sALS (25–68% prevalence) and fALS (100% prevalence) patients, with its presence in familial cohorts suggesting a genetic component even though the exact cause(s) remain unknown and is associated with poor prognosis [18]. Clinically, weight loss is a symptom of ALS and body mass index (BMI) has been inversely correlated with ALS risk and progression, with lower BMI values in ALS cohorts associated with malnutrition arising from dysphagia [6].

Overall, mitochondrial dysfunction and energy deficits or hypermetabolism in ALS skeletal muscles are linked, having a capacity to cause NMJ disruption and, consequently, motor neurodegeneration [19][20][21].

3. Impaired Muscle Proteostasis

Protein homeostasis is a finely regulated process that is a balance between protein production/synthesis, folding and degradation involving protein quality control, trafficking and clearance, and it is important for preventing cellular dysfunction and propagation of misfolded proteins [22]. Skeletal muscle cells handle protein misfolding more efficiently than MNs, clearing misfolded proteins, including mutant SOD1 and aggregate species of TDP-43, using a combination of an efficient proteasome and autophagic system [23][24]. Protein quality control system includes molecular chaperones and proteolytic mechanisms such autophagy, ubiquitin-proteasome and the unfolded protein response pathways are more efficiently activated in skeletal muscles than the nervous system and appear more relevant in the skeletal muscle [25][26][27], with a significant suppression of autophagic flux in skeletal muscles of $SOD1^{G93A}$ ALS model as the disease progresses [28]. Indeed, TDP-25 (prion-like TDP-43 fragment) mislocalizes to the cytoplasm forming aggregates in myoblasts (although to a lower extent when compared to MNs) and impairs autophagy [24], and pTDP43 inclusions were observed in ALS patient muscles [24][29] especially in axial skeletal muscles [29][30]. Furthermore, proteasome activity in the skeletal muscle of $SOD1^{G93A}$ mice is upregulated in early symptomatic stage with a reduction as the disease progresses towards symptomatic and terminal stages whereas autophagic activation in the skeletal muscle of $SOD1^{G93A}$ mice occurs at presymptomatic and terminal stages [31]. Impairment in proteostasis may be due in part to mutations in ALS-associated proteins including SOD1, p62, valosin-containing protein (VCP), ubiquilin-2 (UBQLN2), optineurin (OPTN), and TANK-binding kinase 1 (TBK1) [32][33].

4. Dysregulated RNA Metabolism in Skeletal Muscle

RNA-binding proteins such as TDP-43 (transactivation response element DNA-binding protein 43), FUS, TAF15 (TATA-binding protein-associated factor 15), EWSR1 (Ewing sarcoma breakpoint region 1), and heterogeneous nuclear ribo-nucleoproteins A1 and A2 (hnRNPA1 and hnRNPA2) are involved in aspects of RNA metabolism including mRNA transcription and stabilization, alternative splicing, RNA transport, and miRNA biogenesis [34][35][36]. They possess RNA recognition motifs and low complexity or prion-like domains that could act as key scaffolds, causing them to accumulate in cytoplasmic stress granules or other membrane-less organelles such as nuclear paraspeckles implicated in ALS [37].

TDP-43 is essential for myoblast differentiation and skeletal muscle regeneration in vitro and in vivo studies, respectively [38]. Cytoplasmic TDP-43 is involved in the formation of temporary structures or amyloid-like assemblies called myo-granules that contain mRNAs encoding for sarcomere associated proteins during normal skeletal muscle formation, and which are increased during regeneration in response to damaged skeletal tissue [38]. Over time, myo-granules from C_2C_{12} myotubes seeded amyloid-like fibrils in vitro, revealing a mechanism by which TDP-43 aggregation could occur [38]. In addition, phosphorylated TDP-43 (pTDP-43) aggregates were observed in the skeletal muscles of sALS and fALS cohorts, highlighting axial skeletal muscles as an additional site of phosphorylated TDP-43 pathology, while suggesting that impaired proteostatic clearance of misfolded proteins might play a role in the pathology [29]. On the other hand, FUS which is involved in aspects of RNA processing and metabolism, was significantly enriched in subsynaptic myonuclei but this enrichment was lost upon denervation and disrupted in the presence of mutant ALS FUS, highlighting mutant FUS toxicity to skeletal muscle in vivo [39]. Furthermore, muscle biopsies from patients with *FUS* mutations revealed muscle atrophy and a loss in FUS subsynaptic enrichment [39]. In addition, mutant FUS toxicity to skeletal muscle was demonstrated in MN-myotube co-cultures and observed toxicity was due to endplate maturation defects arising from inefficient gene expression of acetylcholine receptor subunits in subsynaptic myonuclei as well as impaired myogenic differentiation [39]. Finally, products of the *C9orf72* hexanucleotide repeat expansion (HRE), G4C2 RNA foci and dipeptide repeat (DPR) proteins have been identified in skeletal muscles of animal models of C9-ALS [40][41] and in the skeletal muscles of ALS patients with *C9orf72* mutations [42][43]. Although Swartz and colleagues reported lower levels of *C9orf72* variants in iPSC skeletal muscles compared to iPSC-derived MNs and an absence of TDP-43 mislocalization or ubiquitin/p62-positive inclusions [43], another study showed that C9-ALS myocytes from iPSCs of *C9orf72* ALS patients had increased expression and aggregation of TDP-43 [44], necessitating the need for more studies to investigate contribution of *C9orf72* transcripts to skeletal muscle pathology.

Epigenetic regulation, especially that mediated by microRNAS (miRNAs) and histone deacetylases or HDACs, are affected in ALS skeletal muscle [45]. At neuromuscular synapses, miR-206 and HDAC4 control the denervation-innervation process and both are proposed to be involved in ALS progression as their expression levels are altered in the skeletal muscles of animal models and ALS patients [46][47][48][49]. Upregulation of HDAC4 mRNA in muscle biopsies of ALS patients correlates with disease severity, with its expression being higher in patients with faster disease progression [48]. Furthermore, HDAC links neuronal activity and muscle transcription during denervation since HDAC4 is normally concentrated at the neuromuscular junction with low levels in skeletal muscles [50]. HDAC4 may have a role in muscle pathology, with its expression increasing during skeletal muscle denervation, activating the muscle atrophy [50]. On the other hand, miR-206 is a negative regulator of skeletal muscle HDAC4 [51] and may have a role in NMJ maintenance [52]. In muscle biopsies from patients with genetic forms of ALS (*SOD1* and *C9orf72* mutations), miR-206 level is strongly increased while the HDAC4 protein expression is decreased [47]. This elevated expression of miR-206 at the onset of neurological symptoms is suggested to be a compensatory mechanism aimed at re-establishing the connection between the muscle and nerve via reinnervation [47].

References

1. Shaw, P.J. Molecular and Cellular Pathways of Neurodegeneration in Motor Neurone Disease. J. Neurol. Neurosurg. Psychiatry 2005, 76, 1046–1057.
2. Xu, Z.; Jung, C.; Higgins, C.; Levine, J.; Kong, J. Mitochondrial Degeneration in Amyotrophic Lateral Sclerosis. J. Bioenerg. Biomembr. 2004, 36, 395–399.
3. Loeffler, J.P.; Picchiarelli, G.; Dupuis, L.; Gonzalez De Aguilar, J.L. The Role of Skeletal Muscle in Amyotrophic Lateral Sclerosis. Brain Pathol. 2016, 26, 227–236.
4. Echaniz-Laguna, A.; Zoll, J.; Ponsot, E.; N'Guessan, B.; Tranchant, C.; Loeffler, J.P.; Lampert, E. Muscular Mitochondrial Function in Amyotrophic Lateral Sclerosis Is Progressively Altered as the Disease Develops: A Temporal Study in Man. Exp. Neurol. 2006, 198, 25–30.
5. Xiao, Y.; Karam, C.; Yi, J.; Zhang, L.; Li, X.; Yoon, D.; Wang, H.; Dhakal, K.; Ramlow, P.; Yu, T.; et al. ROS-Related Mitochondrial Dysfunction in Skeletal Muscle of an ALS Mouse Model during the Disease Progression. Pharm. Res. 2018, 138, 25–36.
6. Quessada, C.; Bouscary, A.; René, F.; Valle, C.; Ferri, A.; Ngo, S.T.; Loeffler, J.P. Skeletal Muscle Metabolism: Origin or Prognostic Factor for Amyotrophic Lateral Sclerosis (Als) Development? Cells 2021, 10, 1449.
7. Leclerc, N.; Ribera, F.; Zoll, J.; Warter, J.M.; Poindron, P.; Lampert, E.; Borg, J. Selective Changes in Mitochondria Respiratory Properties in Oxidative or Glycolytic Muscle Fibers Isolated from G93AhumanSOD1 Transgenic Mice. Neuromuscul. Disord. 2001, 11, 722–727.
8. Wiedemann, F.R.; Winkler, K.; Kuznetsov, A.V.; Bartels, C.; Vielhaber, S.; Feistner, H.; Kunz, W.S. Impairment of Mitochondrial Function in Skeletal Muscle of Patients with Amyotrophic Lateral Sclerosis. J. Neurol. Sci. 1998, 156, 65–72.
9. Al-Sarraj, S.; King, A.; Cleveland, M.; Pradat, P.F.; Corse, A.; Rothstein, J.D.; Leigh, P.N.; Abila, B.; Bates, S.; Wurthner, J.; et al. Mitochondrial Abnormalities and Low Grade Inflammation Are Present in the Skeletal Muscle of a Minority of Patients with Amyotrophic Lateral Sclerosis; An Observational Myopathology Study. Acta Neuropathol Commun. 2014, 2, 165.
10. Krasnianski, A.; Deschauer, M.; Neudecker, S.; Gellerich, F.N.; Müller, T.; Schoser, B.G.; Krasnianski, M.; Zierz, S. Mitochondrial Changes in Skeletal Muscle in Amyotrophic Lateral Sclerosis and Other Neurogenic Atrophies. Brain 2005, 128, 1870–1876.
11. Vandoorne, T.; De Bock, K.; Van Den Bosch, L. Energy Metabolism in ALS: An Underappreciated Opportunity? Acta Neuropathol. 2018, 135, 489–509.
12. Palamiuc, L.; Schlagowski, A.; Ngo, S.T.; Vernay, A.; Dirrig-Grosch, S.; Henriques, A.; Boutillier, A.-L.; Zoll, J.; Echaniz-Laguna, A.; Loeffler, J.-P.; et al. A Metabolic Switch toward Lipid Use in

Glycolytic Muscle Is an Early Pathologic Event in a Mouse Model of Amyotrophic Lateral Sclerosis. EMBO Mol. Med. 2015, 7, 526–546.

13. Dupuis, L.; Oudart, H.; René, F.; Gonzalez de Aguilar, J.-L.; Loeffler, J.-P. Evidence for Defective Energy Homeostasis in Amyotrophic Lateral Sclerosis: Benefit of a High-Energy Diet in a Transgenic Mouse Model. Proc. Natl. Acad. Sci. USA 2004, 101, 11159–11164.
14. Dupuis, L.; Echaniz-Laguna, A. Skeletal Muscle in Motor Neuron Diseases: Therapeutic Target and Delivery Route for Potential Treatments. Curr. Drug Targets 2012, 11, 1250–1261.
15. Dupuis, L.; Gonzalez de Aguilar, J.L.; Echaniz-Laguna, A.; Eschbach, J.; Rene, F.; Oudart, H.; Halter, B.; Huze, C.; Schaeffer, L.; Bouillaud, F.; et al. Muscle Mitochondrial Uncoupling Dismantles Neuromuscular Junction and Triggers Distal Degeneration of Motor Neurons. PLoS ONE 2009, 4, e5390.
16. Stallings, N.R.; Puttaparthi, K.; Dowling, K.J.; Luther, C.M.; Burns, D.K.; Davis, K.; Elliott, J.L. TDP-43, an ALS Linked Protein, Regulates Fat Deposition and Glucose Homeostasis. PLoS ONE 2013, 8, e71793.
17. Dobrowolny, G.; Lepore, E.; Martini, M.; Barberi, L.; Nunn, A.; Scicchitano, B.M.; Musarò, A. Metabolic Changes Associated with Muscle Expression of SOD1G93A. Front. Physiol. 2018, 9, 831.
18. Steyn, F.J.; Ioannides, Z.A.; van Eijk, R.P.A.; Heggie, S.; Thorpe, K.A.; Ceslis, A.; Heshmat, S.; Henders, A.K.; Wray, N.R.; van den Berg, L.H.; et al. Hypermetabolism in ALS Is Associated with Greater Functional Decline and Shorter Survival. J. Neurol. Neurosurg. Psychiatry 2018, 89, 1016–1023.
19. Luo, G.; Yi, J.; Ma, C.; Xiao, Y.; Yi, F.; Yu, T.; Zhou, J. Defective Mitochondrial Dynamics Is an Early Event in Skeletal Muscle of an Amyotrophic Lateral Sclerosis Mouse Model. PLoS ONE 2013, 8, e82112.
20. So, E.; Mitchell, J.C.; Memmi, C.; Chennell, G.; Vizcay-Barrena, G.; Allison, L.; Shaw, C.E.; Vance, C. Mitochondrial Abnormalities and Disruption of the Neuromuscular Junction Precede the Clinical Phenotype and Motor Neuron Loss in HFUSWT Transgenic Mice. Hum. Mol. Genet. 2018, 27, 463–474.
21. Pharaoh, G.; Sataranatarajan, K.; Street, K.; Hill, S.; Gregston, J.; Ahn, B.; Kinter, C.; Kinter, M.; van Remmen, H. Metabolic and Stress Response Changes Precede Disease Onset in the Spinal Cord of Mutant SOD1 ALS Mice. Front. Neurosci. 2019, 13, 487.
22. Pfirrmann, T.; Chondrogianni, N.; Olzscha, H.; Vasilaki, A. Editorial: Dysregulated Protein Homeostasis in the Aging Organism. Front. Mol. Biosci. 2021, 8, 1011.
23. Galbiati, M.; Crippa, V.; Rusmini, P.; Cristofani, R.; Cicardi, M.E.; Giorgetti, E.; Onesto, E.; Messi, E.; Poletti, A. ALS-Related Misfolded Protein Management in Motor Neurons and Muscle Cells.

Neurochem. Int. 2014, 79, 70–78.

24. Cicardi, M.E.; Cristofani, R.; Rusmini, P.; Meroni, M.; Ferrari, V.; Vezzoli, G.; Tedesco, B.; Piccolella, M.; Messi, E.; Galbiati, M.; et al. Tdp-25 Routing to Autophagy and Proteasome Ameliorates Its Aggregation in Amyotrophic Lateral Sclerosis Target Cells. Sci. Rep. 2018, 8, 12390.
25. Nassif, M.; Matus, S.; Castillo, K.; Hetz, C. Amyotrophic Lateral Sclerosis Pathogenesis: A Journey through the Secretory Pathway. Antioxid. Redox Signal. 2010, 13, 1955–1989.
26. Sandri, M. Protein Breakdown in Muscle Wasting: Role of Autophagy-Lysosome and Ubiquitin-Proteasome. Int. J. Biochem. Cell Biol. 2013, 45, 2121–2129.
27. Crippa, V.; Boncoraglio, A.; Galbiati, M.; Aggarwal, T.; Rusmini, P.; Giorgetti, E.; Cristofani, R.; Carra, S.; Pennuto, M.; Poletti, A. Differential Autophagy Power in the Spinal Cord and Muscle of Transgenic ALS Mice. Front. Cell Neurosci. 2013, 7, 234.
28. Xiao, Y.; Ma, C.; Yi, J.; Wu, S.; Luo, G.; Xu, X.; Lin, P.H.; Sun, J.; Zhou, J. Suppressed Autophagy Flux in Skeletal Muscle of an Amyotrophic Lateral Sclerosis Mouse Model during Disease Progression. Physiol Rep. 2015, 3, e12271.
29. Cykowski, M.D.; Powell, S.Z.; Appel, J.W.; Arumanayagam, A.S.; Rivera, A.L.; Appel, S.H. Phosphorylated TDP-43 (PTDP-43) Aggregates in the Axial Skeletal Muscle of Patients with Sporadic and Familial Amyotrophic Lateral Sclerosis. Acta Neuropathol. Commun. 2018, 6, 28.
30. Mori, F.; Tada, M.; Kon, T.; Miki, Y.; Tanji, K.; Kurotaki, H.; Tomiyama, M.; Ishihara, T.; Onodera, O.; Kakita, A.; et al. Phosphorylated TDP-43 Aggregates in Skeletal and Cardiac Muscle Are a Marker of Myogenic Degeneration in Amyotrophic Lateral Sclerosis and Various Conditions. Acta Neuropathol. Commun. 2019, 7, 165.
31. Oliván, S.; Calvo, A.C.; Gasco, S.; Muñoz, M.J.; Zaragoza, P.; Osta, R. Time-Point Dependent Activation of Autophagy and the UPS in SOD1G93A Mice Skeletal Muscle. PLoS ONE 2015, 10, e0134830.
32. Fernando, R.; Drescher, C.; Nowotny, K.; Grune, T.; Castro, J.P. Impaired Proteostasis during Skeletal Muscle Aging. Free Radic. Biol. Med 2019, 132, 58–66.
33. Cicardi, M.E.; Marrone, L.; Azzouz, M.; Trotti, D. Proteostatic Imbalance and Protein Spreading in Amyotrophic Lateral Sclerosis. EMBO J. 2021, 40, e106389.
34. Le Gall, L.; Anakor, E.; Connolly, O.; Vijayakumar, U.; Duddy, W.; Duguez, S. Molecular and Cellular Mechanisms Affected in ALS. J. Pers. Med. 2020, 10, 101.
35. Butti, Z.; Patten, S.A. RNA Dysregulation in Amyotrophic Lateral Sclerosis. Front. Genet. 2019, 9, 712.

36. Xue, Y.C.; Ng, C.S.; Xiang, P.; Liu, H.; Zhang, K.; Mohamud, Y.; Luo, H. Dysregulation of RNA-Binding Proteins in Amyotrophic Lateral Sclerosis. Front. Mol. Neurosci. 2020, 13, 78.
37. Harrison, A.F.; Shorter, J. RNA-Binding Proteins with Prion-like Domains in Health and Disease. Biochem. J. 2017, 474, 1417–1438.
38. Vogler, T.O.; Wheeler, J.R.; Nguyen, E.D.; Hughes, M.P.; Britson, K.A.; Lester, E.; Rao, B.; Betta, N.D.; Whitney, O.N.; Ewachiw, T.E.; et al. TDP-43 and RNA Form Amyloid-like Myo-Granules in Regenerating Muscle. Nature 2018, 563, 508–513.
39. Picchiarelli, G.; Demestre, M.; Zuko, A.; Been, M.; Higelin, J.; Dieterlé, S.; Goy, M.-A.; Mallik, M.; Sellier, C.; Scekic-Zahirovic, J.; et al. FUS-Mediated Regulation of Acetylcholine Receptor Transcription at Neuromuscular Junctions Is Compromised in Amyotrophic Lateral Sclerosis. Nat. Neurosci. 2019, 22, 1793–1805.
40. Shaw, M.P.; Higginbottom, A.; McGown, A.; Castelli, L.M.; James, E.; Hautbergue, G.M.; Shaw, P.J.; Ramesh, T.M. Stable Transgenic C9orf72 Zebrafish Model Key Aspects of the ALS/FTD Phenotype and Reveal Novel Pathological Features. Acta Neuropathol. Commun. 2018, 6, 125.
41. Freibaum, B.D.; Lu, Y.; Lopez-Gonzalez, R.; Kim, N.C.; Almeida, S.; Lee, K.H.; Badders, N.; Valentine, M.; Miller, B.L.; Wong, P.C.; et al. GGGGCC Repeat Expansion in C9orf72 Compromises Nucleocytoplasmic Transport. Nature 2015, 525, 129–133.
42. Cykowski, M.D.; Dickson, D.W.; Powell, S.Z.; Arumanayagam, A.S.; Rivera, A.L.; Appel, S.H. Dipeptide Repeat (DPR) Pathology in the Skeletal Muscle of ALS Patients with C9ORF72 Repeat Expansion. Acta Neuropathol. 2019, 138, 667–670.
43. Swartz, E.W.; Baek, J.; Pribadi, M.; Wojta, K.J.; Almeida, S.; Karydas, A.; Gao, F.-B.; Miller, B.L.; Coppola, G. A Novel Protocol for Directed Differentiation of C9orf72-Associated Human Induced Pluripotent Stem Cells Into Contractile Skeletal Myotubes. Stem Cells Transl. Med. 2016, 5, 1461–1472.
44. Lynch, E.; Semrad, T.; Belsito, V.S.; FitzGibbons, C.; Reilly, M.; Hayakawa, K.; Suzuki, M. C9ORF72-Related Cellular Pathology in Skeletal Myocytes Derived from ALS-Patient Induced Pluripotent Stem Cells. DMM Dis. Model. Mech. 2019, 12, dmm039552.
45. Lazo-Gómez, R.; Ramírez-Jarquín, U.N.; Tovar-y-Romo, L.B.; Tapia, R. Histone Deacetylases and Their Role in Motor Neuron Degeneration. Front. Cell Neurosci. 2013, 7, 243.
46. Williams, A.H.; Valdez, G.; Moresi, V.; Qi, X.; McAnally, J.; Elliott, J.L.; Bassel-Duby, R.; Sanes, J.R.; Olson, E.N. MicroRNA-206 Delays ALS Progression and Promotes Regeneration of Neuromuscular Synapses in Mice. Science 2009, 326, 1549–1554.
47. Pegoraro, V.; Marozzo, R.; Angelini, C. MicroRNAs and HDAC4 Protein Expression in the Skeletal Muscle of ALS Patients. Clin. Neuropathol. 2020, 39, 105–114.

48. Bruneteau, G.; Simonet, T.; Bauché, S.; Mandjee, N.; Malfatti, E.; Girard, E.; Tanguy, M.L.; Behin, A.; Khiami, F.; Sariali, E.; et al. Muscle Histone Deacetylase 4 Upregulation in Amyotrophic Lateral Sclerosis: Potential Role in Reinnervation Ability and Disease Progression. Brain 2013, 136, 2359–2368.
49. di Pietro, L.; Baranzini, M.; Berardinelli, M.G.; Lattanzi, W.; Monforte, M.; Tasca, G.; Conte, A.; Logroscino, G.; Michetti, F.; Ricci, E.; et al. Potential Therapeutic Targets for ALS: MIR206, MIR208b and MIR499 Are Modulated during Disease Progression in the Skeletal Muscle of Patients. Sci. Rep. 2017, 7, 9538.
50. Cohen, T.J.; Waddell, D.S.; Barrientos, T.; Lu, Z.; Feng, G.; Cox, G.A.; Bodine, S.C.; Yao, T.P. The Histone Deacetylase HDAC4 Connects Neural Activity to Muscle Transcriptional Reprogramming. J. Biol. Chem. 2007, 282, 33752–33759.
51. Simon, L.; Ford, S.M.; Song, K.; Berner, P.; Vande Stouwe, C.; Nelson, S.; Bagby, G.J.; Molina, P.E. Decreased Myoblast Differentiation in Chronic Binge Alcohol-Administered Simian Immunodeficiency Virus-Infected Male Macaques: Role of Decreased MiR-206. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2017, 313, R240–R250.
52. Valdez, G.; Heyer, M.P.; Feng, G.; Sanes, J.R. The Role of Muscle MicroRNAs in Repairing the Neuromuscular Junction. PLoS ONE 2014, 9, e93140.