Chapter 7

MicroRNAs in Amyotrophic Lateral Sclerosis

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Abstract

miRNAs are sequences of 20–22 nucleotides that participate in the development, growth, and cell differentiation by the regulation of the mRNAs.Their possible participation in the development of degenerative diseases has been extensively investigated. Results show quantitative changes in miRNA transcription, to the pathogenesis of various neurodegenerative diseases. In this chapter, the dysregulation of microRNAs reported in the samples taken from amyotrophic lateral sclerosis (ALS) animal model or ALS patients is analyzed. Moreover,their probable participation in the pathogenesis of the disease is also analyzed.

Keywords: ALS, microRNA, miR-206, miR-338-3, miR-9a

1. Introduction

miRNAs are small RNA molecules that do not encode proteins. They are sequences of 20–22 nucleotides that regulate gene expression. miRNAs were identified in 1993 by Lee et al. [1]. Since then numerous studies have been carried out in order to have a better understanding of their functioning as regulators and, in turn, regulating transcription. These molecules are transcribed as a longer RNA between 500 and 3000 nucleotides [2, 3]. Then, a serial enzymatic activity inside the nucleus allows the reduction in the number of nucleotides. These pri-miRNAs are then exposed to an enzymatic process by using Drosha-associated Pasha (also known as DGCR8), resulting in a precursor of 65–75 nucleotides in a loop called pre-miRNA, which is transported to the cytoplasm. Finally, the Dicer enzyme breaks for mature single-stranded fragments comprise 19–25 nucleotides. The last enzymatic activity into cytoplasm provides an miRNA of 20–22 nucleotides with a complementary sequence of seven base pairs that enable an miRNA to bind to the target mRNA [3–6].

The consequence of that complementary interaction could provide the inhibition of translation or the reduction in the stability of the mRNA resulting in the decrease of the target protein expression [7]. The importance of these small molecules in gene expression has led to numerous studies, which aimed at better understanding of its functioning as regulators and, in turn, the regulation of transcription. Another characteristic is its possibility to target several mRNAs given a major potential to regulate gene expression or a specific mRNA that can be regulated by multiple miRNAs [8–10]. Although most authors observed a downregulation by miRNAs, there are examples of upregulation by miRNAs as well. The ability of a single miRNA to act both in repression and activation depends on the number of nucleotides that can mate or phase of the cell cycle in which it is generated [11–16].

In order to homogenize the nomenclature of miRNAs for the pre-miRNA and the pri-miRNA, they are referred to as uncapitalized "mir," for the mature form of the miRNA as miR and MIR for the gene that encodes them [17].

Considering the complexity of the capacity and functions of these small molecules, they have been linked to several diseases such as cancer [18, 19], autoimmune diseases [20, 21], cardiovascular diseases [22–26], and, of particular interest to our group, are those related to neurological diseases.

General reviews on the participation of miRNAs in neurodegenerative diseases have been emerging, and the research on specific neurological diseases confirms a dysregulation biogenesis of these small molecules [27–31]. Impaired concentration of blood miRNAs has been reported in patients with stroke, Alzheimer disease, Huntington disease, Parkinson Disease, and Amyotrophic Lateral Sclerosis (ALS) [30–46]. In this chapter, ALS disease will be analyzed in more detail.

The dysregulation of miRNAs in the samples from ALS patients has been reported by several authors. Until now, it is not clear that which one is the most important dysregulation. This chapter aims at analyzing those reports that shed light on the enrolled miRNAs and their participation in ALS pathology.

2. miR-b2403 and miR-b1336 downregulation

During neuron degeneration in ALS diseases, many alterations on neurofilament have been observed such as the aggregate formation of the perikaryon and proximal axons. In addition, mRNA of low molecular weight neurofilament (NEFL) decreases [47–49]. A number of reports agree that an alteration of NEFL synthesis could contribute to the possible cause of neuron death in ALS patients. Recent reports on the expression analysis of miRNAs, performed on neurons recovered from sporadic ALS patients' spinal cord, confirm the downregulation of miR-b2403 and miR-b1336. These miRNAs modulate NEFL mRNA stability [50]. Consequently, it could be the cause of the decreased mRNA, as previously reported in patients with spinal cord ALS.

3. miR-338-3 upregulation

The overexpression of miR-338-3 was reported in leucocytes of ALS patients. This miRNA regulates gene cytochrome *c* oxidase IV [51]. *In vitro* experiments report that the transfection of miR-338 into the axons of primary sympathetic neurons results in a decrease in mitochondrial COXIV mRNAs and consequently a decrease in enzyme protein levels [52]. This protein belongs to the cytochrome *c* oxidase complex, the ending step in the mitochondrial electron transfer chain. Its downregulation results in a decrease in the ATP level and sensitizes the cells to apoptosis [53, 54]. miR-338 also regulates ATP synthase expression, which is another mitochondrial enzyme. The postmortem samples from the frontal cortex of patients with ALS also report on the upregulation of miR-338-3 [55]. The overexpression of miR-338-3 could induce an axonal respiration functionality and viability damage.

4. miR-29a and miR-29b upregulation

Microarray analysis of miRNAs on samples from three brains of patients with ALS reports the upregulation of miR-29a. This affects the stability and translation of mRNAs of NAV3, a nuclear membrane protein-related neuronal regeneration [55]. Unfortunately, there was a noticeable change in values of the miRNAs for the samples analyzed. In addition, the number of samples was very small so the analysis does not conclude. However, recently Nolan et al. [56] have reported an interesting result. The downregulation of the antiapoptotic Mcl-1 was associated with an upregulation of miR-29a, which enhances the sensitivity of neurons to endoplasmic reticulum stress-induced apoptosis. In previous research, Nolan et al. found a high expression for miR-29a in the brain and spinal cord of a family of ALS mouse model. The intracerebroventricular injection of an miR-29a-specific antagomir does not change disease manifestation, but the change in the life span was observed [57].

5. miR-9a downregulation

TAR DNA-binding protein 43 (TDP-43) is a nuclear protein related to binding the single-stranded DNA, RNA, and proteins [58]. In the nucleus, TDP-43 plays a critical role in regulating RNA splicing as well as modulating microRNA biogenesis. Nevertheless, TDP-43 is a nuclear factor. A mutant form of the TDP-43 protein can be found in the cytoplasm of affected neuron in neurological diseases. TDP-43 is considered a major component of the tau-negative and ubiquitin-positive inclusions in ALS and frontal dementia [59–62]. High levels of TDP-43 are detected in CSF samples from ALS patients [63]. Recently, it was found that miR-9a expression significantly reduced on ALS with the TDP43 A90V mutation [64]. It has been proposed that the genetic interaction studies support the notion that dTDP-43 acts through miR-9a to control the precision of SOP specification [65]. The *in vitro* experiment on mice genetic model tissue, miR-9, demonstrates an upstream regulation of NF mRNAs [66]. In *Drosophila* TDP43 mutants,

the miR-9a expression was significantly inhibited [65]. These findings reveal a novel role for endogenous TDP-43 in neuronal specification and suggest that the functions of the FTD/ALS-associated RNA-binding protein TDP-43 ensure the robustness of control genetic programs [65]. Moreover, there is a possibility that TDP-43 may play an important role in miRNA processing, given an miR-9 downregulation reported on *in vitro* experiments [64].

6. miR-206 downregulation

Though the main feature is the death of motor neurons, other cells contribute to disease like muscle cells. In fact, in ALS animal models it was observed that motor neuron death starts with neuromuscular junction destruction and distal axonal degeneration [67]. The direct partners of the injured motor axons may respectively be the recipients or initiators of the initial damage. The bidirectional signaling between motor neurons and skeletal muscle fibers at neuromuscular synapses has been studied in an animal model. miR-206 is specifically expressed in skeletal muscle and linked to many disorders in skeletal muscle [68]. The expression of miR-206 is regulated by myostatin, TGFβ, and IGF [69, 70]. Moreover, the histone deacetylase 4 and fibroblast growth factor signaling pathways are involved. It was proved that a response to muscle denervation was activated, which promotes skeletal muscle regeneration in response to injury [71–74]. *In vivo* research performed on the ALS model shows the down-regulation of miR-206s. This deficiency was correlated with the acceleration of the disease progression [73]. In patients, miR-206 functions like a key factor for muscle reinnervation and disease progression [75]. However, sera from ALS patients showed an increase in the circulation of miR-206 as well as in SOD1-G93A mouse. Samples from biopsies of Biceps brachii muscle patients with ALS show that miR-206s are overexpressed in the skeletal muscle and plasma of ALS patients [76, 77]. Nevertheless, this miRNA has no enough data about its relation with disease status; it has been proposed as a marker [78].

7. miR-146a downregulation

Quantitative PCR performed on ALS spinal motor neuron samples showed dysregulation of a large number of miRNAs, such as miR-146a and miR-582-3p. An algorithmic program revealed that these miRNAs are able to interact with NFL mRNA 3′UTR and suggested that the main role of these miRNAs is to suppress NFL mRNA [79]. Additional reports on miR-146 function dysregulation are related to the inflammation process by inflammatory factors such as interleukin 1 and tumor necrosis factor-alpha and another process that functions in the innate immune system by regulating Toll-like receptor signaling [80, 81]. On the other hand, *in vitro* experiments performed with mouse neural stem cells showed their relation with proliferation and differentiation, where miR-146 overexpression promoted spontaneous differentiation of neural stem cells by downstream Notch 1 gene [82].

8. miR-524-5p downregulation

Nevertheless, miR-524-5p was inversely associated with the activity of the MAPK/ERK pathway by suppressing the expression of BRAF and ERK2 proteins on melanoma [83], as a tumor suppressor in glioblastoma by Jagged-1 and Hes-1 downregulation [84] and in gastric cancer cells [85]. The results obtained by the application of miRNA recognition element program, on samples obtained from spinal cord neurons of sporadic ALS patients, showed that this miRNA is able to directly regulate the NFL by downregulating its synthesis in neuron cells. However, in ALS patients, it is decreasing and by consequence there is an overproduction of NFL which is a deleterious effect. On the other hand, the overexpression of miR-524-5p inhibits the MAPK/ERK pathway; apparently these cells could demonstrate a high activity on the MAPK/ERK pathway and cytoplasm NS accumulation.

9. miR-124 downregulation

miR-124 has been found to be the most abundant microRNA expressed in neuronal cells. Its targets are laminin $\gamma 1$ and integrin $\beta 1$. Nevertheless, experiments to alter expression of miR-124 in neural cells did not appear to affect differentiation [86]. However, later research reports described the role of miR-124 during neuronal differentiation by the overexpression of miR-9* and miR-124 in neural progenitors [87]. In a recent work, it was demonstrated that exosomes containing miR-124a releasing from neurons that can be directly internalized into astrocytes, with a concomitant increase in miR-124a, induce an increase in the levels of GLT1 protein [88]. miR-124a was found downregulated in the spinal cord of mutant SOD1 mouse models. *In vivo* injection of miR-124a into oligonucleotides in the spinal cord of ALS mice significantly prevents further pathological loss of GLT1 protein.

10. Other dysregulate miR

De Felice et al. [51] analyzed 911 mRNA expression by microarray in leukocytes of 14 patients with sporadic ALS. In addition to miR-338-3p, they identified eight miRNAs with changes in expression, e.g., hsa-miR-451, hsa-miR-1275, hsa-miR-328, hsamiR-638, has-miR-149, and the expression decreased for miR583 and miR-665 [51]. Campos-Melo et al. [79] also reported a decrease in most miRNAs, such as miR-146a, miR-524-5, and miR-582-3, from neurons of the spinal cord in the lower back. In addition, miR-b2403 and miR-b1336 are underregulated in the spinal cord samples; both are related to the stabilization of mRNA NEFL as well as miR-338-3 as previously reported [50, 51]. The consequence of the accumulation effects on the NEFL mRNA could be the cause for the decrease in mRNA previously reported in patients with spinal cord ELA [47]. Reports of miRNAs expression analysis performed on the samples of neurons recovered from the brain or spinal cord of ALS patients have been able to confirm a reduction in miRNAs that modulate gene NEFL stability (for the synthesis of light neurofi-

lament), the cytochrome *c* oxidase gene, and protein of the nuclear membrane NAV3 and related neuronal regeneration.

Other cells that contribute to the disease are microglia cells, lymphocytes, and Schwann cells [89–91]. A recent hypothesis is that Schwann and muscle cells are also direct partners of the injured motor axons and may respectively be the recipients or initiators of the initial damage [67, 92].

In a mice ALS model, it has been proved that miR-365 and miR-125b suppress the IL-6/STAT3 pathway in microglia cells with an increase in the levels of TNFα mRNA [93]. This agrees with the fact that TNFα is upregulated in G93A mice and ALS patients [94, 95], which indicates that miR-365 and miR-125b dysregulations might develop the pathological cytokine profile on ALS.

11. Conclusion

Until now, there is no consensus on which miRNA could be the best target for therapy. To alter the cell homeostasis of miRNAs, more than one change is needed for their biogenesis. Similar to previous reports, miRNA can have several target mRNAs and one mRNA can be regulated by different microRNAs. ALS research provides an example of NEFL synthesis alteration, which can be regulated by miR-b2403, miR-b1336, miR-146a, miR-524-5p, and miR-582-3p. Probably, for the development of diseases, the coincidence of more than one dysregulation is necessary, or the accumulative alteration of various changes in the transcriptome, to induce neuron cell death. On the other hand, the dysregulation of miRNAs on neighbor cells participates in ALS pathology, where microglia cells, lymphocytes, Schwann cells, and muscle cells show a dysregulation in the miRNA transcript. Further, miRNAs also participate in neuron death. Nevertheless, research on miRNAs involves looking at miRNAs from the perspective of biomarkers. Moreover, the systematic comparative analysis of their profile between healthy people and ALS patients provides information on which pathways can be suggested as possible targets for directed therapy. In addition, the analysis also provides an opportunity to know more about the development of this disease, metabolic pathways altered, and cells involved in ALS pathology.

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References

[1] Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843–854.

[2] Lee RC, Ambros V. An extensive class of small RNAs in *Caenorhabditis elegans*. Science. 2001;294(5543):862–964.

[3] Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S, Kim VN. The nuclear RNase III Drosha initiates microRNA processing. Nature. 2003;425(6956):415–419.

[4] Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN. MicroRNA genes are transcribed by RNA polymerase II. EMBO J. 2004;23:4051–4605.

[5] Landthaler M, Yalcin A, Tuschl T. The human DiGeorge syndrome critical region gene 8 and its *D. melanogaster* homolog are required for miRNA biogenesis. Curr. Biol. 2004;14:2162–2167.

[6] Schwarz DS, Hutvágner G, Du T, Xu Z, Aronin N, Zamore PD. Asymmetry in the assembly of the RNAi enzyme complex. Cell. 2003;115:199–208.

[7] Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136;215–233. DOI: 10.1016/j.cell.2009.01.002.

[8] Lagos-Quintana M, Rauhut R, Meyer J, Borkhardt A, Tuschl T. New microRNAs from mouse and human. RNA. 2003;9:175–179.

[9] Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature. 2005;433(7027):769–773.

[10] Kamanu TK, Radovanovic A, Archer JA, Bajic VB. Exploration of miRNA families for hypotheses generation. Sci. Rep. 2013;3:2940. DOI: 10.1038/srep02940.

[11] Ørom UA, Nielsen FC, Lund AH. Microrna-10a binds the 5'UTR of ribosomal protein mRNAs and enhances their translation. Mol. Cell. 2008;30:460–471. DOI: 10.1016/j.molcel.2008.05.001.

[12] Buchan JR, Parker R. Molecular biology. The two faces of miRNA. Science. 2007;318:1877–1878.

[13] Ghosh T, Soni K, Scaria V, Halimani M, Bhattacharjee C, Pillai B. MicroRNA-mediated up-regulation of an alternatively polyadenylated variant of the mouse cytoplasmic {beta}-actin gene. Nucl. Acids Res. 2008;36:6318–6332. DOI: 10.1093/nar/gkn624.

[14] Iwasaki S, Tomari Y. Argonaute-mediated translational repression (and activation). Fly (Austin). 2009;3:204–206.

[15] Saraiya AA, Li W, Wang CC. Transition of a microRNA from repressing to activating translation depending on the extent of base pairing with the target. PLoS One. 2013;8(2):e55672. DOI:10.1371/annotation/cb23f7bd-0d8c-4fa2-8ce8-1d641c03f561.

[16] Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can upregulate translation. Science. 2007;318(5858):1931–1934.

[17] Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A, Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. Nucl. Acids Res. 2006;34(Database issue):D140–D144.

[18] Fang Z, Tang J, Bai Y, Lin H, You H, Jin H, Lin L, You P, Li J, Dai Z, Liang X, Su Y, Hu Q, Wang F, Zhang ZY. Plasma levels of microRNA-24, microRNA-320a, and microRNA-423-5p are potential biomarkers for colorectal carcinoma. J. Exp. Clin. Cancer Res. 2015;34:86. DOI: 10.1186/s13046-015-0198-6.

[19] Zhu MY, Zhang W, Yang T. Diverse microRNAs with convergent functions regulate tumorigenesis. Oncol. Lett. 2016;11:915–920.

[20] Singh RP, Massachi I, Manickavel S, Singh S, Rao NP, Hasan S, Mc Curdy DK, Sharma S, Wong D, Hahn BH, Rehimi H. The role of miRNA in inflammation and autoimmunity. Autoimmun. Rev. 2013;12:1160–1165. DOI: 10.1016/j.autrev.2013.07.003.

[21] Jimenez SA, Piera-Velazquez S. Potential role of human-specific genes, human-specific microRNAs and human-specific non-coding regulatory RNAs in the pathogenesis of systemic sclerosis and Sjogren's syndrome[J]. Autoimmun. Rev. 2013;12:1046–1051. DOI: 10.1016/j.autrev.2013.04.004.

[22] Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. Nat. Med. 2007;13:486–491.

[23] Luo X, Lin H, Pan Z, Xiao J, Zhang Y, Lu Y, Yang B, Wang Z. Down-regulation of miR-1/miR-133 contributes to re-expression of pacemaker channel genes HCN2 and HCN4 in hypertrophic heart. J. Biol. Chem. 2008;283:20045–20052. DOI: 10.1074/jbc.M801035200.

[24] Callis TE, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, Chen JF, Deng Z, Gunn B, Shumate J, Willis MS, Selzman CH, Wang DZ. MicroRNA-208a is a regulator of cardiachypertrophy and conduction in mice. J. Clin. Invest. 2009;119:2772–2786. DOI: 10.1172/JCI36154.

[25] Shan H, Zhang Y, Lu Y, Pan Z, Cai B, Wang N, Li X, Feng T, Hong Y, Yang B. Down-regulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodelling in canines. Cardiovasc. Res. 2009;83:465–472. DOI: 10.1093/cvr/cvp130.

[26] Matkovich SJ, Wang W, Tu Y, Eschenbacher WH, Dorn LE, Condorelli G, Diwan A, Nerbonne JM, Dorn GW II. MicroRNA-133a protects against myocardial fibrosis and modulates electrical repolarization without affecting hypertrophy in pressure-over-

loaded adult hearts. Circ. Res. 2010;106:166–175. DOI: 10.1161/CIRCRESAHA.109.202176.

[27] Nelson PT, Wang WX, Rajeev BW. MicroRNAs (miRNAs) in neurodegenerative diseases. Brain Pathol. 2008;18:130–138. DOI: 10.1111/j.1750-3639.2007.00120.x.

[28] Abe M, Bonini NM. MicroRNAs and neurodegeneration: role and impact. Trends Cell Biol. 2013;23:30–36. DOI: 10.1016/j.tcb.2012.08.013.

[29] Maciotta S, Meregalli M, Torrente Y. The involvement of microRNAs in neurodegenerative diseases. Front. Cell Neurosci. 2013;7:265. DOI: 10.3389/fncel.2013.00265.

[30] Gascon E, Gao F-B. The emerging roles of microRNAs in the pathogenesis of frontotemporal dementia–amyotrophic lateral sclerosis (FTD-ALS) spectrum disorders. J. Neurogenet. 2014;28:30–40. DOI: 10.3109/01677063.2013.876021.

[31] Volonte C, Apolloni S, Parisi C. MicroRNAs: newcomers into the ALS picture. CNS Neurol. Disord. Drug Targets. 2015;14:194–207.

[32] Zeng L, Liu J, Wang Y, Wang L, Weng S, Tang Y, Zheng C, Cheng Q, Chen S, Yang GY. MicroRNA-210 as a novel blood biomarker in acute cerebral ischemia. Front. Biosci. (Elite Ed.). 2011;3:1265–1272.

[33] Gan CS, Wang CW, Tan KS. Circulatory microRNA-145 expression is increased in cerebral ischemia. Genet. Mol. Res. 2012;11:147–152. DOI: 10.4238/2012.January.27.1.

[34] Ouyang YB, Stary CM, Yang GY, Giffard R. microRNAs: innovative targets for cerebral ischemia and stroke. Curr. Drug. Targets. 2013;14:90–101.

[35] Sepramaniam S, Tan JR, Tan KS, DeSilva DA, Tavintharan S, Woon FP, Wang CW, Yong FL, Karolina DS, Kaur P, Liu FJ, Lim KY, Armugam A, Jeyaseelan K. Circulating microRNAs as biomarkers of acute stroke. Int. J. Mol. Sci. 2014;15:1418–1432. DOI: 10.3390/ijms15011418.

[36] Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, Kauppinen S, Delacourte A, De Strooper B. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. Proc. Natl. Acad. Sci. U. S. A. 2008;105:6415–6420. DOI: 10.1073/pnas.0710263105.

[37] Smith P, Al Hashimi A, Girard J, Delay C, Hébert SS. In vivo regulation of amyloid precursor protein neuronal splicing by microRNAs. J. Neurochem. 2011;116:240–247. DOI: 10.1111/j.1471-4159.2010.07097.x.

[38] Absalon S, Kochanek DM, Raghavan V, Krichevsky AM. MiR-26b, upregulated in Alzheimer's disease, activates cell cycle entry, tau-phosphorylation, and apoptosis in postmitotic neurons. J. Neurosci. 2013;33:14645–14659. DOI: 10.1523/JNEUROSCI.1327-13.2013.

[39] Banzhaf-Strathmann J, Benito E, May S, Arzberger T, Tahirovic S, Kretzschmar H, Fischer A, Edbauer D. MicroRNA-125b induces tau hyperphosphorylation and

cognitive deficits in Alzheimer's disease. EMBO J. 2014;33:1667–1680. DOI: 10.15252/embj.201387576.

[40] Gaughwin PM, Ciesla M, Lahiri N, Tabrizi SJ, Brundin P, Björkqvist M. Hsa-miR-34b is a plasma-stable microRNA that is elevated in pre-manifest Huntington's disease. Hum. Mol. Genet. 2011;20:2225–2237. DOI: 10.1093/hmg/ddr111.

[41] Hoss AG, Labadorf A, Latourelle JC, Kartha VK, Hadzi TC, Gusella JF, MacDonald ME, Chen JF, Akbarian S, Weng Z, Vonsattel JP, Myers RH. miR-10b-5p expression in Huntington's disease brain relates to age of onset and the extent of striatal involvement. BMC Med. Genom. 2015;8:10. DOI: 10.1186/s12920-015-0083-3.

[42] Müller S. In silico analysis of regulatory networks underlines the role of miR-10b-5p and its target BDNF in Huntington's disease. Transl. Neurodegener. 2014;3:17. DOI: 10.1186/2047-9158-3-17. eCollection 2014.

[43] Junn E, Lee KW, Jeong BS, Chan TW, Im JY, Mouradian MM. Repression of alpha-synuclein expression and toxicity by microRNA-7. Proc. Natl. Acad. Sci. U. S. A. 2009;106:13052–13057. DOI: 10.1073/pnas.0906277106.

[44] Doxakis E. Post-transcriptional regulation of alpha-synuclein expression by mir-7 and mir-153. J. Biol. Chem. 2010;285:12726–12734. DOI: 10.1074/jbc.M109.086827.

[45] Margis R, Margis R, Rieder CR. Identification of blood microRNAs associated to Parkinsonĭs disease. J. Biotechnol. 2011;152(3):96–101. DOI: 10.1016/j.jbiotec.2011.01.023.

[46] Bergeron C, Beric-Maskarel K, Muntasser S, Weyer L, Somerville MJ, Percy ME. Neurofilament light and polyadenylated mRNA levels are decreased in amyotrophic lateral sclerosis motor neurons. J. Neuropathol. Exp. Neurol. 1994;53:221–230.

[47] Wong NK, He BP, Strong MJ. Characterization of neuronal intermediate filament protein expression in cervical spinal motor neurons in sporadic amyotrophic lateral sclerosis (ALS). J. Neuropathol. Exp. Neurol. 2000;59:972–982.

[48] Ge WW, Leystra-Lantz C, Wen W, Strong MJ. Selective loss of trans-acting instability determinants of neurofilament mRNA in amyotrophic lateral sclerosis spinal cord. J. Biol. Chem. 2003;278:26558–26563.

[49] Ishtiaq M, Campos-Melo D, Volkening K, Strong MJ. Analysis of novel NEFL mRNA targeting microRNAs in amyotrophic lateral sclerosis. PLoS One. 2014;9(1):e85653. DOI: 10.1371/journal.pone.0085653. eCollection 2014

[50] De Felice B, Guida M, Coppola C, De Mieri G, Cotrufo R. A miRNA signature in leukocytes from sporadic amyotrophic lateral sclerosis. Gene. 2012;508:35–40. DOI: 10.1016/j.gene.2012.07.058.

[51] Aschraf A, Schwechter AD, Mameza, MG, Natera-Naranjo O, Gioio AE, Kaplan BB. MicroRNA-338 regulates local cytochrome oxidase IV mRNA levels and oxidative

phosphorylation in the axons of sympathetic neurons. J. Neurosci. 2008;28:12581–12590, DOI: 10.1523/JNEUROSCI.3338-08.2008.

[52] Li Y, Park JS, Deng JH, Bai Y. Cytochrome c oxidase subunit IV is essential for assembly and respiratory function of the enzyme complex. J. Bioenerg. Biomembr. 2006;38:283–291.

[53] Kar AN, Sun CY, Reichard K, Gervasi NM, Pickel J, Nakazawa K, Gioio AE, Kaplan BB. Dysregulation of the axonal trafficking of nuclear-encoded mitochondrial mRNA alters neuronal mitochondrial activity and mouse behavior. Dev. Neurobiol. 2014;74:333–350. DOI: 10.1002/dneu.22141.

[54] Shioya M, Obayashi S, Tabunoki H, Arima K, Saito Y, Ishida T, Satoh J. Aberrant microRNA expression in the brains of neurodegenerative diseases: miR-29a decreased in Alzheimer disease brains targets neurone navigator 3. Neuropathol. Appl. Neurobiol. 2010;36:320–330. DOI: 10.1111/j.1365-2990.2010.01076.x.

[55] Nolan K, Walter F, Tuffy LP, Poeschel S, Gallagher R, Haunsberger S, Bray I, Stallings RL, Concannon CG, Prehn JH. ER stress-mediated upregulation of miR-29a enhances sensitivity to neuronal apoptosis. Eur. J. Neurosci. 2016;43(5):640–652. doi:10.1111/ejn.13160.

[56] Nolan K, Mitchem MR, Jimenez-Mateos EM, Henshall DC, Concannon CG, Prehn JH. Increased expression of microRNA-29a in ALS mice: functional analysis of its inhibition. J. Mol. Neurosci. 2014;53:231–241. DOI: 10.1007/s12031-014-0290-y.

[57] Buratti E. Functional significance of TDP-43 mutations in disease. Adv. Genet. 2015;91:1–53. DOI: 10.1016/bs.adgen.2015.07.001.

[58] Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem. Biophys. Res. Commun. 2006;351(3):602–611.

[59] Arai T, Hasegawa M, Nonoka T, Kametani F, Yamashita M, Hosokawa M, Niizato K, Tsuchiya K, Kobayashi Z, Ikeda K, Yoshida M, Onaya M, Fujishiro H, Akiyama H. Phosphorylated and cleaved TDP-43 in ALS, FTLD and other neurodegenerative disorders and in cellular models of TDP-43 proteinopathy. Neuropathology. 2010;30(2):170–181.

[60] Hasegawa M, Nonaka T, Tsuji H, Tamaoka A, Yamashita M, Kametani F, Yoshida M, Arai T, Akiyama H. Molecular dissection of TDP-43 proteinopathies. J. Mol. Neurosci. 2011;45(3):480–485.

[61] Neumann M, Kwong LK, Sampathu DM, Trojanowski JQ, Lee VM. TDP-43 proteinopathy in frontotemporal lobar degeneration and amyotrophic lateral sclerosis: protein misfolding diseases without amyloidosis. Arch. Neurol. 2007;64(10):1388–1394

[62] Kasai T, Tokuda T, Ishigami N, Sasayama H, Foulds P, Mitchell DJ, Mann DM, Allsop D, Nakagawa M. Increased TDP-43 protein in cerebrospinal fluid of patients with amyotrophic lateral sclerosis. Acta Neuropathol. 2009;117(1):55–62.

[63] Zhang Z, Almeida S, Lu Y, Nishimura AL, Peng L, Sun D, Wu B, Karydas AM, Tartaglia MC, Fong JC, Miller BL, Farese RV Jr, Moore MJ, Shaw CE, Gao FB. Downregulation of microRNA-9 in iPSC-derived neurons of FTD/ALS patients with TDP-43 mutations. PLoS One. 2013;8(10):e76055.

[64] Li Z, Lu Y, Xu XL, Gao FB. The FTD/ALS-associated RNA-binding protein TDP-43 regulates the robustness of neuronal specification through microRNA-9a in *Drosophila*. Hum. Mol. Genet. 2013;22(2):218–225.

[65] Haramati S, Chapnik E, Sztainberg Y, Eilam R, Zwang R, Gershoni N, McGlinn E, Heiser PW, Wills AM, Wirguin I, Rubin LL, Misawa H, Tabin CJ, Brown R Jr, Chen A, Hornstein E. miRNA malfunction causes spinal motor neuron disease. Proc. Natl. Acad. Sci. U. S. A. 2010;107(29):13111–13116.

[66] Dupuis L, Loeffler JP. Neuromuscular junction destruction during amyotrophic lateral sclerosis: insights from transgenic models. Curr. Opin. Pharmacol. 2009;9(3):341–346.

[67] Ma G, Wang Y, Li Y, Cui L, Zhao Y, Zhao B, Li K. MiR-206, a key modulator of skeletal muscle development and disease. Int. J. Biol. Sci. 2015;11(3):345–352.

[68] Rachagani S, Cheng Y, Reecy JM. Myostatin genotype regulates muscle-specific miRNA expression in mouse pectoralis muscle. BMC Res. Notes. 2010;3:297.

[69] Winbanks CE, Wang B, Beyer C, Koh P, White L, Kantharidis P, Gregorevic P. TGF-beta regulates miR-206 and miR-29 to control myogenic differentiation through regulation of HDAC4. J. Biol. Chem. 2011;286(16):13805–13814.

[70] van Rooij E, Liu N, Olson EN. MicroRNAs flex their muscles. Trends Genet. 2008;24(4): 159–166.

[71] Williams AH, Liu N, van Rooij E, Olson EN. MicroRNA control of muscle development and disease. Curr. Opin. Cell Biol. 2009;21(3):461–469

[72] Williams AH, Valdez G, Moresi V, Qi X, McAnally J, Elliott JL, Bassel-Duby R, Sanes JR, Olson EN. MicroRNA-206 delays ALS progression and promotes regeneration of neuromuscular synapses in mice. Science. 2009;326(5959):1549–1554.

[73] Liu N, Williams AH, Maxeiner JM, Bezprozvannaya S, Shelton JM, Richardson JA, Bassel-Duby R, Olson EN. microRNA-206 promotes skeletal muscle regeneration and delays progression of Duchenne muscular dystrophy in mice. J. Clin. Invest. 2012;122(6):2054–2065.

[74] Bruneteau G, Simonet T, Bauché S, Mandjee N, Malfatti E, Girard E, Tanguy ML, Behin A, Khiami F, Sariali E, Hell-Remy C, Salachas F, Pradat PF, Fournier E, Lacomblez L, Koenig J, Romero NB, Fontaine B, Meininger V, Schaeffer L, Hantaï D. Muscle histone

deacetylase 4 upregulation in amyotrophic lateral sclerosis: potential role in reinnervation ability and disease progression. Brain. 2013;136(Pt 8):2359–2368.

[75] Russell AP, Wada S, Vergani L, Hock MB, Lamon S, Léger B, et al. Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis. Neurobiol Dis. 2012;49C:107–117.

[76] Andrade H, Albuquerque M, Peluzzo T, Dogni D, Nucci A, Lopes-Cendes I, Franca M, Avansini S. Hsa-miR-424 and has-miR-206 are overexpressed in the skeletal muscle and plasma of patients with amyotrophic lateral sclerosis (ALS). Neurology. 2015;84(14 Suppl):P2.054

[77] Toivonen JM, Manzano R, Oliván S, Zaragoza P, García-Redondo A, Osta R. MicroRNA-206: a potential circulating biomarker candidate for amyotrophic lateral sclerosis. PLoS One. 2014;9(2):e89065.

[78] Campos-Melo D, Droppelmann CA, He Z, Volkening K, Strong MJ. Altered microRNA expression profile in amyotrophic lateral sclerosis: a role in the regulation of NFL mRNA levels. Mol. Brain. 2013;6:26.

[79] Sonkoly E, Ståhle M, Pivarcsi A. MicroRNAs and immunity: novel players in the regulation of normal immune function and inflammation. Semin. Cancer Biol. 2008;18(2):131–140.

[80] Sheedy FJ, O'Neill LA. Adding fuel to fire: microRNAs as a new class of mediators of inflammation. Ann. Rheum. Dis. 2008;67(Suppl 3):iii50–iii55.

[81] Xiao WZ, Lu AQ, Liu XW, Li Z, Zi Y, Wang ZW. Role of miRNA-146 in proliferation and differentiation of mouse neural stem cells. Biosci. Rep. 2015;35(5):e00245.

[82] Liu SM, Lu J, Lee HC, Chung FH, Ma N. miR-524-5p suppresses the growth of oncogenic BRAF melanoma by targeting BRAF and ERK2. Oncotarget. 2014;5(19):9444–9459.

[83] Chen L, Zhang W, Yan W, Han L, Zhang K, Shi Z, Zhang J, Wang Y, Li Y, Yu S, Pu P, Jiang C, Jiang T, Kang C. The putative tumor suppressor miR-524-5p directly targets Jagged-1 and Hes-1 in glioma. Carcinogenesis. 2012;33(11):2276–2282.

[84] Li FQ, Xu B, Wu YJ, Yang ZL, Qian JJ. Differential microRNA expression in signet-ring cell carcinoma compared with tubular adenocarcinoma of human gastric cancer. Genet. Mol. Res. 2015;14(1):739–747.

[85] Cao X, Pfaff SL, Gage FH. A functional study of miR-124 in the developing neural tube. Genes Dev. 2007;21(5):531–536.

[86] Yoo AS, Staahl BT, Chen L, Crabtree GR. MicroRNA-mediated switching of chromatin-remodelling complexes in neural development. Nature. 2009;460(7255):642–646.

[87] Morel L, Regan M, Higashimori H, Ng SK, Esau C, Vidensky S, Rothstein J, Yang Y. Neuronal exosomal miRNA-dependent translational regulation of astroglial glutamate transporter GLT1. J. Biol. Chem. 2013;288(10):7105–7116.

[88] Ilieva H, Polymenidou M, Cleveland DW. Non-cell autonomous toxicity in neurodegenerative disorders: ALS and beyond. J. Cell Biol. 2009;187(6):761–772

[89] Boillee S, Vande Velde C, Cleveland DW. ALS: a disease of motor neurons and their nonneuronal neighbors. Neuron. 2006;52(1):39–59.

[90] Lobsiger CS, Boillee S, McAlonis-Downes M, Khan AM, Feltri ML, Yamanaka K, Cleveland DW. Schwann cells expressing dismutase active mutant SOD1 unexpectedly slow disease progression in ALS mice. Proc. Natl. Acad. Sci. U. S. A. 2009;106(11):4465–4470.

[91] Chen K, Northington FJ, Martin LJ. Inducible nitric oxide synthase is present in motor neuron mitochondria and Schwann cells and contributes to disease mechanisms in ALS mice. Brain Struct. Funct. 2010;214(2–3):219–234.

[92] Parisi C, Arisi I, D'Ambrosi N, Storti AE, Brandi R, D'Onofrio M, Volonté C. Dysregulated microRNAs in amyotrophic lateral sclerosis microglia modulate genes linked to neuroinflammation. Cell Death Dis. 2013;4:e959.

[93] Poloni M, Facchetti D, Mai R, Micheli A, Agnoletti L, Francolini G, Mora G, Camana C, Mazzini L, Bachetti T. Circulating levels of tumour necrosis factor-alpha and its soluble receptors are increased in the blood of patients with amyotrophic lateral sclerosis. Neurosci. Lett. 2000;287(3):211–214.

[94] Hensley K, Fedynyshyn J, Ferrell S, Floyd RA, Gordon B, Grammas P, Hamdheydari L, Mhatre M, Mou S, Pye QN, Stewart C, West M, West S, Williamson KS. Message and protein-level elevation of tumor necrosis factor alpha (TNF alpha) and TNF alpha-modulating cytokines in spinal cords of the G93A-SOD1 mouse model for amyotrophic lateral sclerosis. Neurobiol. Dis. 2003;14(1):74–80.

[95] D'Ambrosi N, Finocchi P, Apolloni S, Cozzolino M, Ferri A, Padovano V, Pietrini G, Carrì MT, Volonté C. The proinflammatory action of microglial P2 receptors is enhanced in SOD1 models for amyotrophic lateral sclerosis. J. Immunol. 2009;183(7):4648–4656.