GMR
The Original by FUNPEC-RP

New insights of miRNAs dysregulation in the molecular pathological basis of neurodegenerative sclerosis: A systematic review

J.C. Pereira[1], J.O. Costa[1], C.C.P. Costa[1], N.S. Lima[1], J.B.S. Barros[1], D.C.P. Bento[1], A.A.S. Reis[1,2*] and R.S. Santos[1,2*]

[1] Laboratório de Patologia Molecular, Instituto de Ciências Biológicas (ICBII), Universidade Federal de Goiás (UFG), Goiânia, GO, Brasil
[2] Departamento de Bioquímica e Biologia Molecular, Instituto de Ciências Biológicas (ICBII), Universidade Federal de Goiás (UFG), Goiânia, GO, Brasil

*These authors contributed equally to this study

Corresponding author: A.A.S. Reis; R.S. Santos
E-mail: angela@ufg.br; rdssantos@ufg.br

Genet. Mol. Res. 20 (3): gmr18843
Received March 27, 2021
Accepted June 23, 2021
Published July 29, 2021
DOI http://dx.doi.org/10.4238/gmr18843

ABSTRACT. Neurodegenerative diseases affect nerve cells, causing impairment in mobility and cognitive abilities, characteristics present in two highly relevant neuropathologies, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). The pathogenesis of these diseases, although distinct, share common neurodegenerative mechanisms. Several studies suggest that miRNAs, small molecules of endogenous non-coding RNA, may assume an important regulatory role in neurodegeneration where their differential expression enables the elucidation of the molecular basis of this process, in addition to offering possible therapeutic targets. We performed a systematic review of the literature through a search in Web of Science, Pubmed/NCBI, and virtual health library (BVS) databases, applying terms indexed in MeSH and DeCS, such as "microRNA", "amyotrophic lateral sclerosis" and "multiple sclerosis". We included studies in English, Portuguese, or Spanish, published in the last five years, relating miRNAs associated with

pathophysiological pathways of ALS and MS. We excluded studies on non-humans or with polymorphisms in pre-miR genes, duplicated data, or with unavailable data, resulting in a final number of 70 studies included. According to systematic review findings, the families miR-9, miR-23, miR-26, miR-125, miR-133, miR-146, miR-181, miR-206, miR-320, and miR-326 are frequently dysregulated in ALS and MS. The miR-155 and let-7 families are commonly associated with both diseases, regulating genes involved in mechanisms such as neuroinflammation, neurogenesis, and cell differentiation. The elucidation of the newest miRNAs and their main pathways may assist in the characterization of the molecular basis of these diseases, mainly involving those associated with pro-inflammatory processes, microglia activation, and neuronal death, mechanisms associated with ALS. They also can involve myelin breakdown mechanisms, astrocyte damage, and neuronal death, which are related to MS. These molecular markers may help determine biomarkers for amyotrophic lateral sclerosis and multiple sclerosis.

Key words: Neurodegeneration; Post-transcriptional regulation; Neuroinflammation; Amyotrophic lateral sclerosis; Multiple sclerosis

INTRODUCTION

Neurodegenerative diseases (ND) are characterized by progressive neuronal loss and dysfunction in the central nervous system (CNS), affecting approximately 30 million people worldwide (Sheikh et al., 2013). Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) are rare degenerative diseases with common symptoms, such as weakness and muscle tone alterations (Sand, 2015; Hardiman et al., 2017).

ALS compromises motor neurons, resulting in progressive muscle weakness and paralysis, affecting 2.0/100,000 persons/year worldwide (Chiò et al., 2013). In Brazil, the incidence is estimated to be 0.9-1.5 cases per 100,000 inhabitants. However, it is complex to define a profile of these ALS patients due to the few studies and the high degree of miscegenation of the Brazilian population (Prado et al., 2016). Most ALS cases are classified as sporadic, while ~5-10% have a family history with a genetic background (Hardiman et al., 2017). The disease is more common in men between 55 and 65 years (Van Es et al., 2017).

On the other hand, MS is an autoimmune disorder characterized by inflammatory demyelination, where symptoms may involve sensory, motor, visual, and brainstem pathways, which vary according to the disease' stage (Garg and Smith., 2015). MS is commonly associated with women between 20 and 40 years, where the incidence rate ranges in ~3.6/100,000 persons/year, while in men the number of cases is about 2.0/100,000 persons/year (Garg and Smith., 2015; Hunter, 2016).

The pathogenesis of ALS and MS is still unclear, however, both environmental exposure and genetic factors may be involved in the diseases' etiology (Garg and Smith., 2015; Hardiman et al., 2017). Considering the genetic background, microRNAs (miRNAs)

are molecules responsible for regulating gene expression, being suggested by several studies their role in the ND pathogenesis (Nelson et al., 2008; Tan et al., 2015; Sharma and Lu, 2018). The miRNAs are small non-coding RNA molecules with 19 to 25 nucleotides able to bind to complementary sequences to specific regions of the messenger RNAs (mRNA), resulting in post-transcriptional regulation of the gene expression (Lu and Rothenberg, 2018).

Previously associated with pathologies such as cancer, cardiovascular, liver, and ND, such as Alzheimer's disease, ALS, and MS, miRNAs may assist in diagnosis, classification, prognosis, and treatments of several pathologies (Sharma and Lu, 2018). In this study, we searched for, through a systematic review, the most dysregulated miRNAs in ALS and MS, focusing on the latest insights into pathophysiological pathways of miRNAs associated with these diseases, which may evidence their mechanisms in neurological function regulation.

MATERIAL AND METHODS

Register and search strategy

This systematic review is registered in the international Prospective Register of Ongoing Systematic Reviews (PROSPERO) under the number CRD42020164537. For a better report, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) (Table S1).

The search was conducted between October 2019 and May 2020 in Web of Science, PubMed/NCBI, and Virtual Health Library (BVS) databases. Were used the indexed terms in medical subject headings (MeSH) and health sciences descriptors (DeCS) for “microRNA”, “amyotrophic lateral sclerosis”, and “multiple sclerosis”. The boolean operators “AND” and “OR” were used to separate the terms (Table S2).

Studies selection, quality evaluation, and data extraction

To be eligible, the studies should be full-available, published in the last five years, and written in English, Portuguese, or Spanish, describing miRNAs involved in pathological mechanisms, disease progression, and response to ALS and MS treatment. We excluded duplicate data, studies in non-humans or with polymorphisms in pre-miR genes, and studies with unavailable data.

In all stages, two independent reviewers assessed the eligibility of the studies. Discrepancies were resolved by consensus. The studies were selected first by titles and abstracts according to inclusion criteria. Posteriorly, the reading of the full text was done, where articles that did not show an association between miRNAs and the respective diseases were excluded (Table S3). For methodological quality assessment, we applied the critical appraisal tools from the Joanna Briggs Institute (JBI) (Institute TJB). Only studies that answered at least 70% of the questions evaluated in the protocols were included since the JBI allows researchers to define the criteria for articles inclusion. After evaluating the methodological quality, data were extracted manually in a model form (Table S4).

RESULTS

Through the search strategy, 364,824 studies were found in all databases, which were reduced to 18,888 after filter application. A total of 177 articles were chosen by titles and 122 after abstract reading, resulting in 55 articles excluded for not answering the inclusion criteria. The main exclusion reasons were: (1) published outside of the last five years, (2) non-human studies, and (3) duplicated data. After full-text reading, 70 publications were included in this systematic review (Figure 1).

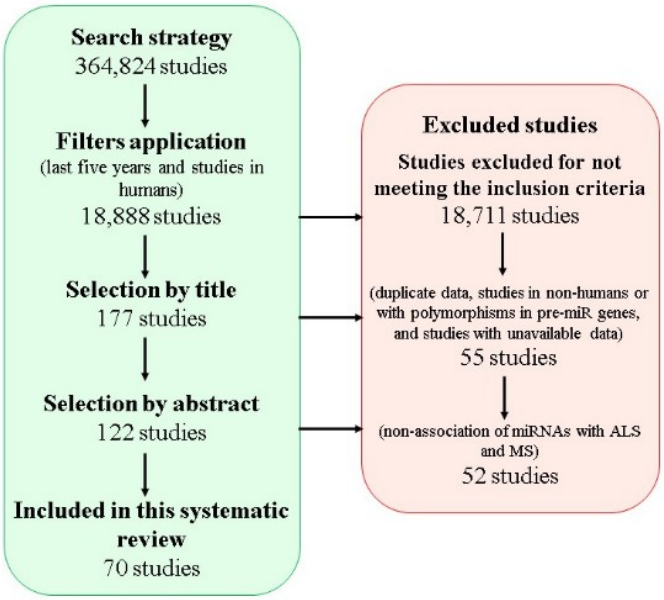

Figure 1. Study selection. Through the search strategy using the medical subject headings (MeSH) and health sciences descriptors (DeCS) terms 364,824 studies were found, and 18,888 after applying the filters. In this stage, 18,711 did not achieve the inclusion criteria. A total of 177 studies were selected based on the title, and 122 based on the abstract. Based on the exclusion criteria we removed 55 duplicated data, non-human studies, or data published outside of the stipulated years of publication. We excluded 52 studies, mostly for non-association of miRNAs with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), resulting in a final number of 70 studies that composed this study.

For data synthesis, we considered the mechanisms associated with the diseases, the regulation (up or down-regulated), and in which tissue they were found (Table S4). Were identified 77 families of miRNAs related to ALS, and 99 families with MS (Demuth and Hahn, 2009). The miRNAs families are groups that have similar sequences, often with similar functions, and descended from a common ancestor (e.g., family miR-1: miR-1a, miR-1b). We highlighted the 7 main dysregulated families (up or downregulated), in each disease, according to the most frequent families related in the included studies. We also identified miRNAs common to both pathologies and evaluated the biochemical and/or biological similarities shared by them, aiming to understand their main pathophysiological mechanisms in these ND.

According to systematic review findings, were identified miRNAs down-regulated, up-regulated, and mixed regulated in both diseases. The most frequent miRNAs found in

ALS were the let-7 family (let-7a-5p, let-7d-5p, let-7e, let-7f-5p, let-7i-5p), while as up-regulated miRNAs were miR-155, miR-9 family (miR-9, miR-9-5p) and miR- 206. Among the most found with mixed regulation were miR-133 (miR-133b, miR-133a, miR-133a/b), miR-146 (miRNA-146, miRNA-146a, miRNA-146a*) and miR-23 families (miR-23, miR-23a, miR-23b, miR-23a-3p).

These miRNAs dysregulation is directly associated with neuronal death mechanisms and muscle proliferation, repair, and regeneration. In addition, they promote pro-inflammatory pathways through immune responses associated with microglia activation. They are also related to the maintenance of neuromuscular synapses, neuronal development, and muscle mass degeneration through the regulation of several genes (*NEFM, NEFH, NFKB1, FAS, CD4, EIF2C4, AGO4, CCL2*, and *AQP1*). Figure 2 summarizes the results of the studies for miRNA dysregulation in ALS.

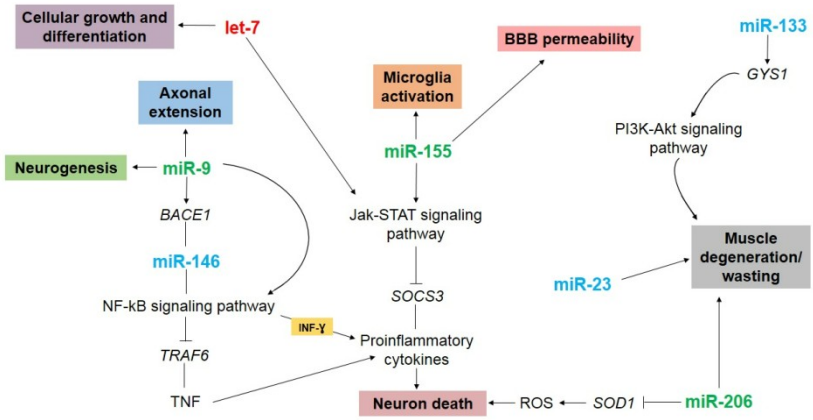

Figure 2. miRNAs in amyotrophic lateral sclerosis (ALS) and their implications in the disease pathophysiological mechanisms. MiR-155, one of the most common in our study, is involved in inflammatory mechanisms, through the direct microglia activation, interference in the permeability of the blood-brain barrier (BBB), and secretion of pro-inflammatory cytokines, an action in common with the let-7 family, which results in neuronal death. Furthermore, the miRNAs are frequently related to mechanisms associated with amyotrophic lateral sclerosis (ALS) pathogenesis, such as deficit in neurogenesis, axonal lesions, and increased of reactive oxygen species (ROS), which is associated with oxidative stress. Genes: *Beta-Secretase 1 (BACE1), Glycogen synthase 1 (GYS1), Tumor Necrosis Factor (TNF), Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF6), Suppressor of cytokine signaling 3 (SOCS3), Superoxide dismutase 1 (SOD1).* Pathways: Janus Kinases / Signal Transducers and Activators of Transcription (Jak-STAT), Nuclear Factor Kappa Beta (NF-κB), Phosphatidylinositol 3‑Kinase/Protein Kinase B (PI3K/Akt). Proinflammatory molecules: Interferon *gamma* (IFN-Ɣ).

Regarding MS, we found miRNAs predominantly with positive regulation, which were: miR-155 (miR-155 and miR-155-5p), miR-125 (miR-125, miR-125a-3p, miR-125a-5p and miR-125b), miR-326 and let-7 families (let-7a-5p, let-7b-5p, let-7c and let-7e). However, a mixed regulation was frequently observed in miR-26 (miR-26a, miR-26a-5p, miR-26b, miR-26b-5p), miR-320 (miR-320, miR -320a) and miR-181 families (miR-181a, miR-181a-5p, miR-181c, miR-181c-3p).

These miRNAs are involved with inflammation induced by the activation of pro-inflammatory cytokines, changes in the blood-brain barrier (BBB) homeostasis and permeability, and demyelination. They are also fundamental in Th1 and Th17 cell development, a subpopulation of T lymphocytes with pro-inflammatory characteristics due

to the secretion of several cytokines. In neurodegeneration, they are also important in regulating phagocytic processes and immune pathways. Figure 3 summarizes the results of the studies for miRNA dysregulation in MS.

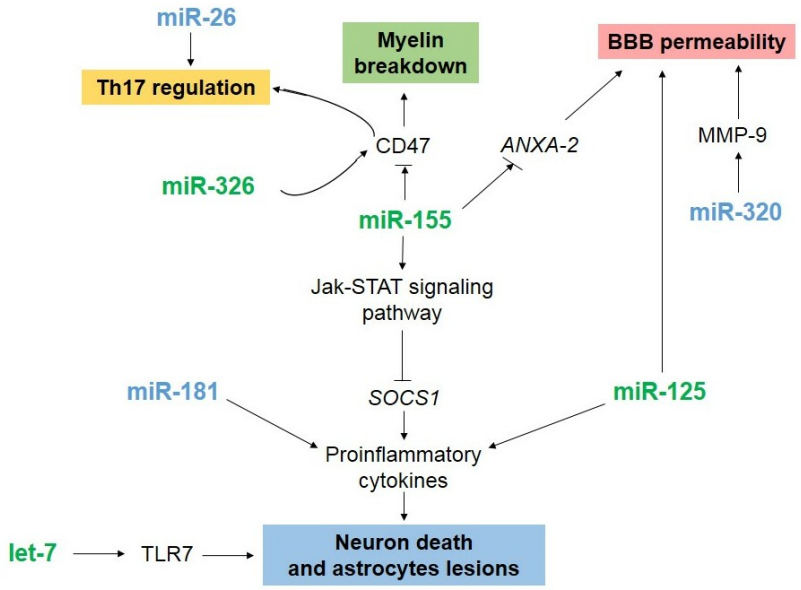

Figure 3 - MiRNAs in MS and their implications in the disease pathophysiological mechanisms. In multiple sclerosis (MS), miR-155 is also involved in inflammatory mechanisms common to amyotrophic lateral sclerosis (ALS), such as the activation of proinflammatory cytokines and dysregulation of the blood-brain barrier (BBB) permeability, which induces demyelination and neuronal death. Genes: *Annexin A2 (ANXA-2), Suppressor of cytokine signaling 1 (SOCS3)*. Cells: T helper 17 (Th17). Receptors: Toll-Like Receptor 7 (TLR7). Enzyme: Matrix Metallopeptidase 9 (MMP-9). Proteins: Cluster of Differentiation 47 (CD47). Pathways: Janus Kinases / Signal Transducers and Activators of Transcription (Jak-STAT).

Some miRNAs, such as miR-155, (upregulated in both diseases) and let-7 family (downregulated in ALS and upregulated in MS), were frequently related in both diseases. MiR-155 is associated with these diseases due to inflammation, demyelination, active immune responses mediated by Th1 and Th17 cells, and positive regulation of phagocytosis in microglia. However, the dysregulation of the let-7 family is implicated in protein folding, mitosis, cell adhesion, and activation of immunological pathways related to innate responses through regulating genes like *FAS, CD4, EIF2C4, AGO4, CCL2,* and *AQP1*. Thus, all miRNAs reported in this systematic review could play an important role as ND biomarkers.

DISCUSSION

This systematic review aimed to point the newest miRNAs associated with pathophysiological pathways of ALS and MS. The role of miRNAs in ND has been widely discussed, considering the complexity of etiology, progression, and complications involved in neurodegenerative disorders. These diseases show similar manifestations, with a clinical

diagnostic that may be difficult and confusing (Slota and Booth, 2019). MiRNAs are expressed in different body fluids such as blood, cerebrospinal fluid (CSF), urine, sweat, and in different tissues, such as the brain or muscle, which facilitates their application as ND biomarkers (Rajgor, 2018).

Several miRNAs are considered tissue-specific, which may help in the specificity of the ND diagnosis. MiR-206, miR-133a, and miR-133b, named as myo-miRNAs, are widely expressed in the striated muscle. On the other hand, the let-7 and miR-155 families are associated with inflammatory pathways through microglial activation and pro-inflammatory cytokines release (McCoy, 2017).

The miR-206 and the miR-133 family, frequently reported in ALS, were associated with degeneration and muscle mass loss. Furthermore, the miR-206 increased expression is related to the early development of the disease (<55 years), due to the role in neuromuscular junctions' formation and reinnervation (Dardiotis et al., 2018). Dardiotis et al. (2018) define this miRNA as one of the most promising biomarkers for ALS, enabling the diagnosis of the disease in the early stages, after the loss of the first muscle innervation.

The miR-133 family is associated with myogenesis and muscle regeneration processes (Nie et al., 2015) and demonstrated a mixed regulation in articles selected in our review. Negative regulation of the miR-133a is frequently related to the late ALS development, while positive regulation is associated with the early onset (<55 years) (Jensen et al., 2016; Pegoraro et al., 2017). These findings allow us to infer that miR-133a and miR-206 may be used together as predictors of ALS development in young patients, as well as in the disease progression.

In ALS, miR-23 had a heterogeneous expression. Is mostly abundant in oligodendrocytes, acting in the myelin formation and maintenance, preventing muscle atrophy, a process resulting from the demyelination mechanism. The miR-23 downregulation was associated with the late stages of ALS, while the upregulation had been associated with the initial stages of muscle atrophy, acting in regulatory pathways of the skeletal muscle proteolysis (Simion et al., 2017).

Considering the inflammatory process in ALS, the miR-146 family also showed a mixed regulation. This miRNA can act as a key regulator through the regulation of NF-κB expression, which activates the transcription of several pro-inflammatory cytokines (Gaudet et al., 2017). MiR-146 also proves to be one of the most inducible and regulating miRNAs of neuronal functions, when compared to other miRNAs highly expressed in the brain, such as miR-9 and miR-125b. It is one of the most inducible regulators of brain functions (Lukiw, 2011).

MiR-9 acts in neurogenesis and axonal extension pathways and demonstrated high expression in samples of ALS patients. This miRNA is also important in cell differentiation and proliferation, neuronal cell apoptosis control, and in the regulation of several transcription factors, such as Foxg1, Nr2e1, and Pax6 (Shibata et al., 2011). In ALS, miR-9 shows a significant increase in early disease onset, making it a potential biomarker in the initial ALS stages (Ricci et al., 2018).

In MS, the miR-320 family had a mixed regulation being associated with the BBB permeability, along with miR-155 and miR-125 families. The literature also describes an abundant presence of the miR-320 family in B cells and demonstrates that their downregulation induces the inhibition of the matrix metalloproteinase-9 protein (MMP-9),

increasing BBB permeability, which contributes to the MS development through the intensification of the demyelination process (Dolati et al., 2018).

MiR-125 and miR-181 families can regulate the expression of pro-inflammatory cytokines. In our study, the miR-125 family showed a positive regulation. The positive regulation of miR-125a-5p is associated with BBB maintenance, through junction formation and regulation of cerebral vascular networks, while miR-125a-3p is associated with blocking oligodendrocyte maturation, which inhibits consequently the myelination (Lecca et al., 2016; Wu et al., 2016). For miR-181 families, MS patients showed mixed regulation. However, the miR-181 family is highly expressed in the brain, playing a role in the suppression of cytokines (Ma et al., 2016).

The high expression of miR-26 and miR-326 families in MS patients' brains was related to the regulation of the development of B and T cells and monocytes. MiR-326, frequently overexpressed in MS injuries, is associated with the upregulation of Th17 cells and the stimulation of CD4+ T cells, increasing inflammation and demyelination processes (Jagot and Davoust, 2016). On the other hand, the negative regulation of miR-26a was reported in regulation of Th1 and Th17 cells, as well as miR-326 (Jagot and Davoust, 2016, Mameli et al., 2016). MiR-26a-5p downregulation can stimulate morphogenesis, neuronal development, and axon regeneration (Potenza et al., 2018).

Among the seven main families of miRNAs dysregulated in ALS and MS, highlighted in this study, we observed that the miR-155 and let-7 families were frequently dysregulated in both diseases. These miRNAs families can regulate microglia activation, demyelination, BBB permeability, apoptosis, cell growth, and development (McCoy, 2017). Thus, understand the pathophysiological mechanisms involved in the performance of these miRNAs, as well as the common and divergent pathological pathways, could contribute to the consolidation of specific and precise alternatives in molecular methods of diagnosis.

Neuroinflammation is a common pathological mechanism to ALS and MS, accelerating neurodegeneration. The MiR-155 family showed a positive regulation in both diseases (McCoy, 2017). Considered a pro-inflammatory miRNA, it can mediate immune response, increase BBB permeability, and activate several inflammatory pathways through targeting the NF-κB gene. The miR-155 downregulation reduces the activation and secretion of pro-inflammatory cytokines, minimizing neuronal death (Dolati et al., 2018).

Let-7 miRNA families were mostly downregulated in ALS and showed mixed expression in MS. Some studies demonstrate protective roles for this miRNAs family, and others relate contribution to the development of some pathologies (Gaudet et al., 2017; Liguori et al., 2018). The let-7 family is an important regulator of inflammatory pathways in the CNS. However, extracellular action may worsen the neuroinflammatory condition (Gaudet et al., 2017).

For ALS, the let-7 family was the main miRNAs down-regulated, while the up-regulated were miR-155, miR-9 family, and miR-206. In mixed regulation (up and downregulated), miR-133, miR-146, and miR-23 families were highlighted. Moreover, for MS, miR-155, miR-125, miR-326, and let-7 families were up-regulated and the miR-26, miR-320, and miR-181 families showed mixed regulation. In common to ALS and MS were miR-155, which demonstrated positive regulation in both diseases, and the let-7 family, being negatively regulated in ALS and positively in MS.

These new insights for miRNAs regulation in both diseases allow us to clarify the molecular mechanisms related to the two diseases and provide bases for understanding

pathological pathways involved in ALS and MS, once the miRNAs are crucial in gene expression. However, several miRNAs have not yet been identified or are still poorly elucidated.

Furthermore, most miRNAs identified have a remarkable role in immune and neurodegenerative pathways, showing the importance of understanding different pathophysiology mechanisms of ALS and MS. These miRNAs may assist in the early diagnosis of these ND, enabling treatment in the first stages of the disease, which may improve patients' quality of life. However, future studies are necessary to identify shared miRNAs and/or specific miRNAs that have not yet been studied in ND.

ACKNOWLEDGMENTS

Research supported by personal resources from the coordinators (Rodrigo da Silva Santos, Ph.D. and Angela Adamski da Silva Reis, Ph.D.).

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Chiò A, Logroscino G, Traynor BJ, Collins J, et al. (2013). Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology*. 41: 118-130. https://doi.org/10.1159/000351153.

Dardiotis E, Aloizou A, Siokas V, Patrinos GP, et al. (2018). The role of MicroRNAs in patients with amyotrophic lateral sclerosis. *J. Mol. Neurosci*. 66: 617-628. https://doi.org/10.1007/s12031-018-1204-1.

Demuth JP, Hahn MW (2009). The life and death of gene families. *Bioessays*. 31: 29-39. https://doi.org/10.1002/bies.080085.

Dolati S, Marofi F, Babaloo Z, Aghebati-Maleki L, et al. (2018). Dysregulated network of miRNAs involved in the pathogenesis of multiple sclerosis. *Biomed. Pharmacother*. 104: 280-290. https://doi.org/10.1016/j.biopha.2018.05.050.

Garg N and Smith TW (2015). An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. *Brain Behav*.5: e00362. https://doi.org/10.1002/brb3.362.

Gaudet AD, Fonken LK, Watkins LR, Nelson RJ, et al. (2017). MicroRNAs: roles in regulating neuroinflammation. *Neuroscientist*. 24: 221-245. https://doi.org/10.1177/1073858417721150.

Hardiman O, Al-Chalabi A, Chiò A, Corr EM, et al. (2017). Amyotrophic lateral sclerosis. *Nat. Rev. Dis. Primers*. 3: 17071. https://doi.org/10.1038/nrdp.2017.71.

Hunter SF (2016). Overview and diagnosis of multiple sclerosis. *Am. J. Manag. Care*. 22: s141-150. PMID: 27356023.

Institute TJB. Critical Appraisal Tools. Available at: [https://jbi.global/critical-appraisal-tools]. Accessed June 25, 2021.

Jagot F and Davoust N (2016). Is it worth considering circulating microRNAs in multiple sclerosis?. *Front. Immunol.*7: 129. https://doi.org/10.3389/fimmu.2016.00129.

Jensen L, Jørgensen LH, Bech RD, Frandsen U, et al. (2016). Skeletal muscle remodeling as a function of disease progression in amyotrophic lateral sclerosis. *Biomed Res. Int.* 2016: 5930621. https://doi.org/10.1155/2016/5930621.

Lecca D, Marangon D, Coppolino GT, Méndez AM, et al. (2016). MiR-125a-3p timely inhibits oligodendroglial maturation and is pathologically up-regulated in human multiple sclerosis. *Sci. Rep.* 6: 34503. https://doi.org/10.1038/srep34503.

Liguori M, Nuzziello N, Introna A, Consiglio A, et al. (2018). Dysregulation of microRNAs and target genes networks in peripheral blood of patients with sporadic amyotrophic lateral sclerosis. *Front. Mol. Neurosci*. 11: 288. https://doi.org/10.3389/fnmol.2018.00288.

Lu TX and Rothenberg ME (2018). MicroRNA. *J. Allergy Clin. Immunol*. 141: 1202-1207. https://doi.org/10.1016/j.jaci.2017.08.034.

Lukiw WJ (2011). NF-κB-regulated micro RNAs (miRNAs) in primary human brain cells. *Exp. Neurol*. 235: 484-490. https://doi.org/10.1016/j.expneurol.2011.11.022.

Ma Q, Zhao H, Tao Z, Wang R, et al. (2016). MicroRNA-181c exacerbates brain injury in acute ischemic stroke. *Aging Dis*. 7: 705-714. https://doi.org/10.14336/AD.2016.0320.

Mameli G, Arru G, Caggiu E, Niegowska M, et al. (2016). Natalizumab therapy modulates miR-155, miR-26a, and proinflammatory cytokine expression in MS patients. *PLoS One*. 11: e0157153. https://doi.org/10.1371/journal.pone.0157153.

McCoy CE (2017). miR-155 dysregulation and therapeutic intervention in multiple sclerosis. *Adv. Exp. Med. Biol.* 1024: 111-131. https://doi.org/10.1007/978-981-10-5987-2_5.

Moher D, Liberati A, Tetzlaff J, Altman DG, et al. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 6: e1000097. https://doi.org/10.1371/journal.pmed.1000097.

Nelson PT, Wang WX and Rajeev BW (2008). MicroRNAs (miRNAs) in neurodegenerative diseases. *Brain Pathol.* 18: 130-138. https://doi.org/10.1111/j.1750-3639.2007.00120.x.

Nie M, Deng Z, Liu J and Wang D (2015). Noncoding RNAs, emerging regulators of skeletal muscle development and diseases. *Biomed Res. Int.* 2015: 676575. https://doi.org/10.1155/2015/676575.

Pegoraro V, Merico A and Angeline C (2017). Micro-RNAs in ALS muscle: differences in gender, age at onset and disease duration. *J. Neurol. Sci.* 380: 58-63. https://doi.org/10.1016/j.jns.2017.07.008.

Potenza N, Mosca N, Mondola P, Damiano S, et al. (2018). Human miR-26a-5p regulates the glutamate transporter SLC1A1 (EAAT3) expression. Relevance in multiple sclerosis. *Biochim. Biophys. Acta. Mol. Basis Dis.* 1864: 317-323. https://doi.org/10.1016/j.bbadis.2017.09.024.

Prado LGR, Bicalho ICS, Vidigal-Lopes M, Ferreira CJA, et al. (2016). Amyotrophic lateral sclerosis in Brazil: case series and review of the Brazilian literature. *Amyotroph. Lateral Scler. Frontotemporal Degener.* 17: 282-288. https://doi.org/10.3109/21678421.2016.1143011.

Rajgor D (2018). Macro roles for microRNAs in neurodegenerative diseases. *Noncoding RNA Res*. 3: 154-159. https://doi.org/10.1016/j.ncrna.2018.07.001.

Ricci C, Marzocchi C and Battistini S (2018). MicroRNAs as biomarkers in Amyotrophic Lateral Sclerosis. *Cells*. 7: 219. https://doi.org/10.3390/cells7110219.

Sand IK (2015). Classification, diagnosis, and differential diagnosis of multiple sclerosis. *Curr. Opin. Neurol*. 28: 193-205. https://doi.org/10.1097/wco.0000000000000206.

Sharma S and Lu HC (2018). MicroRNAs in neurodegeneration: current findings and potential impacts. *J. Alzheimers Dis. Parkinsonism*. 8: 420. https://doi.org/10.4172/2161-0460.1000420.

Sheikh S, Safia, Haque E and Mir SS (2013). Neurodegenerative diseases: multifactorial conformational diseases and their therapeutic interventions. *J. Neurodegener. Dis*. 2013: 563481. https://doi.org/10.1155/2013/563481.

Shibata M, Nakao H, Kiyonari H, Abe T, et al. (2011). MicroRNA-9 regulates neurogenesis in mouse telencephalon by targeting multiple transcription factors. *J. Neurosci.* 31: 3407-3422. https://doi.org/10.1523/jneurosci.5085-10.2011.

Simion V, Sobilo J, Cleomoncon R, Natkunarajah S, et al. (2017). Positive radionuclide imaging of miRNA expression using RILES and the human sodium iodide symporter as reporter gene is feasible and supports a protective role of miRNA-23a in response to muscular atrophy. *PLoS One*. 12: e0177492. https://doi.org/10.1371/journal.pone.0177492.

Slota JA and Booth SA (2019). MicroRNAs in neuroinflammation: implications in disease pathogenesis, biomarker discovery and therapeutic applications. *Noncoding RNA.* 5: 35. https://doi.org/10.3390/ncrna5020035.

Tan L, Yu JT and Tan L (2015). Causes and consequences of microRNA dysregulation in neurodegenerative diseases. *Mol. Neurobiol.* 51: 1249-1262. https://doi.org/10.1007/s12035-014-8803-9.

Van Es MA, Hardiman O, Chiò A, Al-Chalabi A, et al. (2017). Amyotrophic lateral sclerosis. *Lancet*. 390: 2084-2098. https://doi.org/10.1016/S0140-6736(17)31287-4.

Wu T and Chen G (2016). miRNAs Participate in MS Pathological Processes and Its Therapeutic Response. *Mediators Inflamm*. 2016: 4578230. https://doi.org/10.1155/2016/4578230.