CircRNAs and RNA Editing in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is an incurable motor neuron disease caused by upper and lower motor neuron death. As aging is a major risk factor for ALS, age-related molecular changes may provide clues for the development of new therapeutic strategies. Dysregulation of age-dependent RNA metabolism plays a pivotal role in the pathogenesis of ALS. In addition, failure of RNA editing at the glutamine/arginine (Q/R) site of GluA2 mRNA causes excitotoxicity due to excessive Ca^{2+} influx through Ca^{2+}-permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, which is recognized as an underlying mechanism of motor neuron death in ALS. Circular RNAs (circRNAs), a circular form of cognate RNA generated by back-splicing, are abundant in the brain and accumulate with age. Hence, they are assumed to play a role in neurodegeneration. Emerging evidence has demonstrated that age-related dysregulation of RNA editing and changes in circRNA expression are involved in ALS pathogenesis.

amyotrophic lateral sclerosis   brain aging   circular RNA   RNA editing

1. Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by progressive muscle weakness and atrophy due to degeneration of both upper and lower motor neurons, resulting in death from respiratory failure within 2–4 years of diagnosis [1][2]. Since the risk of developing ALS increases drastically with age, the worldwide trend of increased longevity is likely to contribute to the global rise in the incidence of ALS [3]. Although various plausible mechanisms, such as disruption of RNA metabolism, excitotoxicity due to dysregulation of glutamatergic signaling, epigenetic modification, and dysfunction of the endoplasmic reticulum (ER) and mitochondria, have been proposed for the etiology of ALS, the mechanisms underlying motor neuron death in patients with ALS remain elusive [4]. Recent advances in next-generation sequencing have identified at least 40 ALS-linked genes, including transactive response DNA binding protein (*TARDBP*), fused in sarcoma (*FUS*), and chromosome 9 open reading frame 72 (*C9ORF72*) [5]. Most ALS-linked genes encode proteins related to RNA metabolism, suggesting that the disruption of RNA metabolism plays a key role in ALS pathogenesis [6].

Circular RNAs (circRNAs) are single-stranded RNA molecules circularized by the covalent joining of the 3′-end to the 5′-end, known as back-splicing [7][8] and can be divided into three classes: circular intronic RNA (ciRNA), exonic circRNA (ecircRNA), and exon–intron circRNA (EIciRNA) [9]. CiRNAs are produced by canonical splicing and escape from debranching enzyme, whereas ecircRNA and EIciRNAs are generated by back-splicing with the assistance of complementary sequences between flanking intron and RNA-binding proteins (RBPs) [10]. As their

characteristic structure renders them resistant to degradation from the RNA decay machinery, circRNAs are highly stable compared to their cognate RNAs. Notably, expression levels of circRNAs exhibit tissue-, development-, and sex-specific patterns in mammals independent of their cognate RNAs [11][12][13][14][15][16]. CircRNAs play important roles in modulating a variety of biological processes in the nucleus and cytoplasm, and are involved in the regulation of transcription, alternative splicing of pre-mRNA, and chromatin looping in the nucleus [17][18], while acting as sponges of microRNAs (miRNAs) and RBPs in the cytoplasm, thereby regulating translation through the prevention of binding between miRNAs or RBPs and their target RNAs [14][19][20].

Adenosine-to-inosine conversion of RNA (A-to-I RNA editing), a post- or cotranscriptional modification of RNA catalyzed by adenosine deaminase acting on RNA (ADARs), occurs in various classes of RNAs, including miRNAs and circRNAs, and plays an important role in complex CNS functions [21]. RNA editing of intronic regions affects RNA splicing and the biogenesis of circRNAs, whereas editing of exonic regions or miRNAs affects the translation, localization, and stability of RNA [22][23][24][25]. Excitotoxicity resulting from the dysregulation of glutamatergic signaling via excessive Ca^{2+} influx through the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor is a plausible mechanism underlying motor neuron death in patients with ALS [26]. The Ca^{2+} permeability of AMPA receptors depends on the presence or absence of a glutamine/arginine (Q/R) site-edited GluA2 subunit [27], indicating that the dysregulation of RNA editing is involved in the pathogenesis of ALS.

2. Age-Related Changes of circRNAs and RNA Editing

2.1. Age-Related circRNAs in the Brain (Figure 1)

Cellular senescence, a stress-induced state of indefinite growth arrest that increases with age, plays a role in maintaining the survival of healthy cells, facilitates the removal of damaged cells [28][29], and is an antagonistic response to the primary damage of cells and a marker of brain aging [30]. Forkhead box O3 (*FOXO3*), a transcription factor that plays a critical role in brain development and aging, is a longevity gene and is implicated as a causative gene of neurodegenerative diseases [31]. CircFOXO3, the circular form of *FOXO3*, sequesters antistress or antisenescence proteins, thereby arresting the cell cycle and cell proliferation in concert with p21 and cyclin-dependent kinase 2 [20][32]. Increased expression of circFOXO3 is involved in cellular senescence in the CNS, which may lead to neurodegeneration; however, a controversial report has shown that expression levels of circFOXO3 are significantly decreased in the blood of elderly persons and in late passage primary culture cells [33]. CircPVT1, a circular form of an exon of *PVT1*, influences cellular senescence and neurodegeneration by changing the expression levels of let-7 and miR-199-5a: let-7 regulates immune response, autophagy, and apoptosis [34][35][36], whereas miR199-5a regulates the expression levels of sirtuin1 (SIRT1) mRNA, which is associated with brain aging and neurodegeneration resulting from the dysregulation of mitochondrial energy metabolism [37][38][39][40].
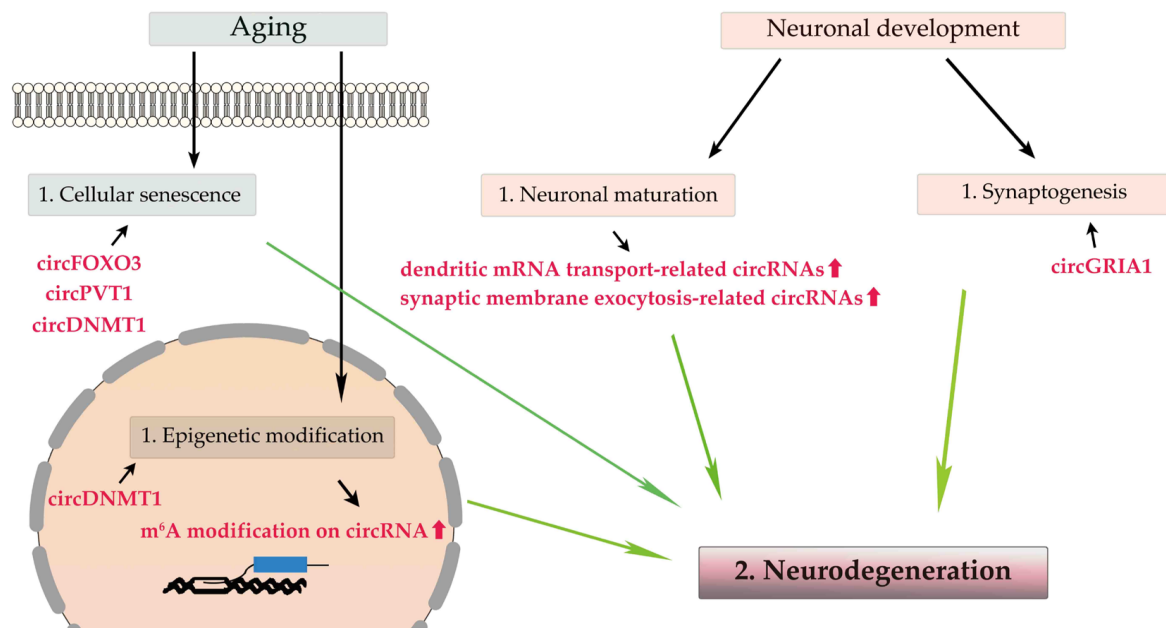
Figure 1. Age-related changes in circRNAs within the brain. Aging causes cellular senescence and epigenetic modification, and neuronal development involves neuronal maturation and synaptogenesis. CircRNAs, including circFOXO3, circPVT1, and circDNMT1, are involved in cellular senescence, and epigenetic m^{6}A modification of circRNAs increases with aging. During neuronal maturation, the expression levels of circRNAs associated with dendric mRNA transport, synaptic membrane exocytosis, and synaptogenesis is increased.

Epigenetic modifications, such as DNA and RNA methylation, influence chromatin function, and their age-related changes are associated with brain aging and neurodegeneration [30]. RNA methylation is a major form of epigenetic RNA modification, and the most common site is N^6-methyladenosine (m^{6}A) [41][42]. CircRNAs regulate m^{6}A modification, and conversely, an age-dependent increase in m^{6}A modification affects the biogenesis, stability, translation, and biological function of circRNAs [42]. Significant differences in the m^{6}A modification of several circRNAs in Alzheimer's disease model mice compared with control mice [43] suggest the possible involvement of the m^{6}A modification of circRNAs in neurodegeneration, which still needs to be convincingly demonstrated. DNA methyl-transferase 1 (DNMT1)-mediated DNA hypermethylation regulates age-dependent cell death in the brain [44].

During neuronal maturation, the expression levels of most circRNAs, especially cognate mRNAs that are translated into proteins related to dendritic mRNA transport and synaptic membrane exocytosis, are upregulated without correlation to their cognate RNAs' expression levels [15][45]. Additionally, during synaptogenesis, many circRNAs expressed in the brain are enriched in the synaptic space, and their expression levels are altered regardless of their cognate linear mRNAs' expression levels [15][46]. Therefore, circRNAs play a pivotal role in neuronal maturation and synaptogenesis independent of their cognate mRNAs [12][15], and perturbation of circRNA expression may be a cause of neurodegeneration.

2.2. Age-Related RNA Editing

Among the three ADAR proteins expressed in mammals, ADAR1 and ADAR2 have essential editing activities. ADAR1 is ubiquitously expressed and is primarily responsible for RNA editing in repeat elements in noncoding regions of mRNAs, whereas ADAR2, which is expressed highest in the CNS, is involved in recoding and editing in protein-coding regions [21][47]. ADAR3, which is highly enriched in oligodendrocytes in the brain, lacks editing activity and instead acts as a negative regulator of RNA editing by sequestering the editing substrates of ADAR1 and ADAR2 [21][48][49]. RNA editing within protein-coding sequences alters protein structure and function, leading to alterations in multiple biological processes, including synaptic transmission and immune responses [22][50][51]. RNA editing is increased during development in the mammalian brain [52][53] and, conversely, decreased in age-related diseases [54][55]. These findings suggest a modulatory role for RNA editing in human aging.

3. ALS-Related Changes of circRNAs and Dysregulation of RNA Editing

3.1. ALS-Related circRNA

CircRNAs are associated with brain aging and neurodegeneration, and the presence of disease-specific circRNAs has been reported in the brains of patients with Alzheimer's or Parkinson's disease [56] as well as in the spinal cord and muscles of patients with ALS [57][58].

Several ALS-linked genes encode RBPs, and the aberrant protein aggregation of RBPs is a pathological characteristic of motor neurons in ALS. Therefore, the resulting disruption of RNA metabolism plays a key role in ALS pathogenesis [6]. FUS plays a critical role in splicing regulation, and subcellular mislocalization of FUS leads to cell death-causing aberrant RNA metabolism in ALS motor neurons [59]. The biogenesis of circRNAs is affected by the interaction of FUS with intron-flanking back-splicing junctions without significant effects on the expression of cognate linear RNAs [60]. Additionally, the expression levels of several circRNAs are altered in induced pluripotent stem cell (iPSC)-derived motor neurons of patients with ALS carrying the FUS^{P525L} mutation compared with those carrying FUS^{WT} [61], although the pathogenic significance and effects on motor neuron biology of the circRNA expression changes in ALS patients carrying the FUS mutation remain unknown. The intronic hexanucleotide (GGGGCC) repeat expansion (HRE) of $C9orf72$ is the most common genetic cause of ALS in Europe and America [62][63] in which pathogenic roles of non-AUG translation-mediated production of toxic dipeptide repeat (DPR) proteins and sequestration of RBP in nuclear RNA granules have been hypothesized [64].

Evidence suggests a role for circRNAs in the epigenetic modification of nucleic acids in ALS [65]. Methyl-CpG binding domain protein 2 (MDB2) binds to a fraction of hypomethylated genes and plays a pivotal role in methylation-related transcription regulation [66]. Knockdown of circKCNN2 (has_circ_0127664), a circular form of potassium calcium-activated channel subfamily N member 2 ($KCNN2$), leads to the downregulation of MDB2 [67]. Expression levels of circKCNN2 are considerably reduced in the cortical neurons of patients with frontotemporal dementia, exhibiting mislocalization of the transactive response DNA-binding protein of 43 kDa (TDP-43) from the nucleus to the cytoplasm (TDP-43 pathology) as compared with those in control subjects [68].

A pathogenic role for excitotoxicity resulting from excessive Ca^{2+} influx into motor neurons by GluA2-lacking Ca^{2+}-permeable AMPA receptor ion channels has been proposed in ALS [69][70]. AMPA receptors are homo- or hetero-tetramers of GluA1–GluA4 subunits. Their tightly regulated biogenesis, membrane trafficking, and degradation result in well-regulated physiological CNS activity [71]. The upregulation of GluA1 mRNA, which reduces the proportion of the GluA2 subunit among the four subunits, is associated with excitotoxicity in the spinal cord and iPSC-derived motor neurons of patients with *C9orf72* ALS [72] and *FUS* knockdown mice [73][74][75][76]. CircGRIA1 negatively regulates the expression levels of GluA1 mRNA and protein expression by competitively binding to the promotor region of *GRIA1* [77].

The dysfunction of the ER and mitochondria due to the alteration of ER–mitochondrial signaling is another hypothesis for ALS pathogenesis [78]. The ER physically contacts the mitochondria through specialized lesions called mitochondria-associated membranes (MAMs), and studies have reported an association between MAM disruption and the pathogenesis of various neurodegenerative diseases, including ALS [79][80][81]. Mutations in sigma nonopioid intracellular receptor 1 (*SIGMAR1*), which encodes the sigma-1 receptor (Sig1R), cause juvenile ALS (ALS16), and mutant Sig1R loses its MAM-specific chaperone protein function [82]. Overexpression of $Sig1R^{E102Q}$ mutant proteins induces neuronal cell death [83], and loss of wild-type Sig1R proteins induces the collapse of MAMs in the motor neurons of $Sig1R^{-/-}$ mice [79]. The significance of changes in the expression levels of SigR1 in ALS has been inconsistently reported; expression levels of mutant Sig1R proteins (c672*51G > T) are either elevated in leukocytes and the frontal cortex [84] or not different in primary lymphoblastoid cells derived from patients with ALS carrying mutant $Sig1R^{E102Q}$ [85].

3.2. Dysregulation of RNA Editing in ALS Motor Neurons

Evidence that elevated glutamate levels in the postmortem tissue and CSF of patients with ALS [86][87][88][89], the loss of high-affinity glutamate uptake [90], and riluzole, an inhibitor of glutamate release, improve one-year survival rates, especially in the late stages of ALS [91][92][93][94] has implicated excitotoxicity as a cause of ALS pathogenesis. Among the subtypes of glutamate receptors, Ca^{2+}-permeable AMPA receptors specifically mediate the slow death of motor neurons, and the increase in their Ca^{2+} permeability results from the incorporation of the Q/R site-unedited GluA2 subunit into their assembly.In the spinal motor neurons of patients with sporadic ALS, Q/R site-unedited GluA2 is expressed because of the downregulation of ADAR2 [95][96]. Motor neuron-specific conditional ADAR2 knockout mice (ADAR2$^{flox/flox}$/VAChT. Cre; AR2 mice) exhibit progressive motor dysfunction with degeneration of motor neurons, resulting from excessive Ca^{2+} influx into motor neurons through Ca^{2+}-permeable AMPA receptors that have Q/R site-unedited GluA2 subunits [97][98][99]. The death cascade initiated by ADAR2 downregulation is specific to the motor neurons of patients with ALS and is not observed in other neurons of patients with ALS or in the motor neurons of normal control subjects or patients with other neurological diseases [95][96][100].

3.3. Aging, circRNAs, and RNA Editing in ALS

Aging is a major risk factor for neurodegenerative diseases, and dysregulation of circRNAs and RNA editing with aging are associated with neurodegenerative diseases, including ALS. Although evidence has demonstrated age-associated changes in RNA editing activity and circRNA processing as described above, only some evidence has demonstrated RNA editing of the exonic region of circRNAs or the role of RNA editing in the biogenesis of circRNAs.

A-to-I RNA editing influences the biogenesis of circRNAs, and the complementary sequence across flanking introns, which contains many Alu repeats, facilitates the formation of circRNAs. Editing sites in Alu repeats are the main targets of ADARs [101][102][103]. The expression levels of circRNAs correlate negatively with those of ADAR1 during neuronal differentiation without modulation of cognate RNAs [15][25][104][105][106].

Although a large fraction of brain circRNA is derived from the exonic coding region [15], whether the A-to-I sites in circRNAs are edited by ADARs, similarly to those in their cognate RNAs, is unclear. It confirmed that the editing efficiency at the Q/R site of circGRIA2 (has_circ_0125620), a circular form of *GRIA2*, changed in parallel with that of the cognate GluA2 mRNA in cultured cells [107]. Therefore, RNA editing of the exonic region of circRNAs may be reduced as RNA editing of their cognate mRNA is dysregulated in motor neurons in sporadic ALS.

4. CircRNAs and the Dysregulation of RNA Editing as Potential Biomarkers and Therapeutic Targets in ALS

4.1. Potential Biomarker Candidates for ALS

CircRNAs are most abundant in the brain and are stable after secretion into body fluids because of their distinctive structure [16][45][108]. As dysregulation of RNA editing increases the formation of circRNAs and extracellular total circRNA levels [107][109], changes in the expression levels of circRNAs could be biomarker candidates for ALS. Several studies have reported comprehensive changes in circRNA expression levels in tissues and sera derived from patients with ALS [57][58][110]. A study has reported reduced expression levels of circPICALM (hsa_circ_0023919) and increased expression levels of circSETD3 (hsa_circ_0000567), circFAM120A (hsa_circ_0005218), circHERC1 (hsa_circ_0035796), circTAF15 (hsa_circ_0043138), circ TNRC6B (hsa_circ_0063411), and circSUSD1 (hsa_circ_0088036) in leukocytes from patients with ALS as compared with healthy control subjects [110]. Among these, hsa_circ_0000567 and hsa_circ_0063411 contain binding sites for miR-9 and miR-641, respectively, the expression levels of which are shown to change in ALS patients [111][112], and hsa_circ_0023919, hsa_circ_0063411, and hsa_circ_0088036 are potential diagnostic biomarkers because of their high sensitivity and specificity to ALS [110][113].

4.2. Therapeutic Targets for ALS

A potential role for circRNAs in neurodegeneration has been proposed [114], and a circRNA-based therapeutic strategy, such as the delivery or knockdown of circRNAs, has been put forward for ALS. Based on the hypothesis that accumulated TDP-43 is toxic to neurons, intron-derived circRNAs resulting from the inhibition of the intron

debranching enzyme (DBR1), which catalyzes the debranching of lariat introns, were tested, and inhibition of DBR1 was found to suppress the toxicity of TDP-43 in yeast [115]. Moreover, DNA methyl-transferases (DNMTs) inhibitor improves motor function and extends the lifespan of superoxide dismutase 1 (*SOD-1*) mutant ALS model mice [116], in which expression levels of DNMT1 are increased in the spinal cord. Recently, improved expression levels of circRNAs via the extracellular vesicle-mediated delivery of circRNAs were demonstrated [117][118]; therefore, the delivery of circRNAs or siRNA-mediated knockdown to improve the expression levels of circRNAs has been developed as a potential future therapeutic strategy.

The dysregulation of RNA editing due to ADAR2 downregulation can also be a potential therapeutic target for ALS. As the downregulation of ADAR2 explains many aspects of disease-specific pathological changes in sporadic ALS, the restoration of ADAR2 activity and the reduction of excessive Ca^{2+} influx through abnormal AMPA are promising therapeutic strategies for ALS. The delivery of ADAR2 cDNA using a neuron-specific promoter to motor neurons with adeno-associated virus serotype 9 (AAV-9) in AR2 mice, a mouse model of sporadic ALS, markedly suppressed progressive motor dysfunction without adverse effects [119].

References

1. Rowland, L.P.; Shneider, N.A. Amyotrophic Lateral Sclerosis. N. Engl. J. Med. 2001, 344, 1688–1700.

2. Feldman, E.L.; Goutman, S.A.; Petri, S.; Mazzini, L.; Savelieff, M.G.; Shaw, P.J.; Sobue, G. Amyotrophic Lateral Sclerosis. Lancet 2022, 400, 1363–1380.

3. Arthur, K.C.; Calvo, A.; Price, T.R.; Geiger, J.T.; Chiò, A.; Traynor, B.J. Projected Increase in Amyotrophic Lateral Sclerosis from 2015 to 2040. Nat. Commun. 2016, 7, 12408.

4. Brown, R.H.; Al-Chalabi, A. Amyotrophic Lateral Sclerosis. N. Engl. J. Med. 2017, 377, 162–172.

5. Goutman, S.A.; Hardiman, O.; Al-Chalabi, A.; Chió, A.; Savelieff, M.G.; Kiernan, M.C.; Feldman, E.L. Emerging Insights into the Complex Genetics and Pathophysiology of Amyotrophic Lateral Sclerosis. Lancet Neurol. 2022, 21, 465–479.

6. Butti, Z.; Patten, S.A. RNA Dysregulation in Amyotrophic Lateral Sclerosis. Front. Genet. 2018, 9, 712.

7. Braun, S.; Domdey, H.; Wiebauer, K. Inverse Splicing of a Discontinuous Pre-mRNA Intron Generates a Circular Exon in a HeLa Cell Nuclear Extract. Nucleic Acids Res. 1996, 24, 4152–4157.

8. Ashwal-Fluss, R.; Meyer, M.; Pamudurti, N.R.; Ivanov, A.; Bartok, O.; Hanan, M.; Evantal, N.; Memczak, S.; Rajewsky, N.; Kadener, S. circRNA Biogenesis Competes with Pre-mRNA Splicing. Mol. Cell 2014, 56, 55–66.

9. Meng, S.; Zhou, H.; Feng, Z.; Xu, Z.; Tang, Y.; Li, P.; Wu, M. CircRNA: Functions and Properties of a Novel Potential Biomarker for Cancer. Mol. Cancer 2017, 16, 94.

10. Ren, S.; Lin, P.; Wang, J.; Yu, H.; Lv, T.; Sun, L.; Du, G. Circular RNAs: Promising Molecular Biomarkers of Human Aging-Related Diseases via Functioning as An miRNA Sponge. Mol. Ther. Methods Clin. Dev. 2020, 18, 215–229.

11. Chen, Y.; Yao, L.; Tang, Y.; Jhong, J.H.; Wan, J.; Chang, J.; Cui, S.; Luo, Y.; Cai, X.; Li, W.; et al. CircNet 2.0: An Updated Database for Exploring Circular RNA Regulatory Networks in Cancers. Nucleic Acids Res. 2022, 50, D93–D101.

12. Mahmoudi, E.; Cairns, M.J. Circular RNAs Are Temporospatially Regulated Throughout Development and Ageing in the Rat. Sci. Rep. 2019, 9, 2564.

13. Jeck, W.R.; Sorrentino, J.A.; Wang, K.; Slevin, M.K.; Burd, C.E.; Liu, J.; Marzluff, W.F.; Sharpless, N.E. Circular RNAs Are Abundant, Conserved, and Associated with ALU Repeats. RNA 2013, 19, 141–157.

14. Holdt, L.M.; Stahringer, A.; Sass, K.; Pichler, G.; Kulak, N.A.; Wilfert, W.; Kohlmaier, A.; Herbst, A.; Northoff, B.H.; Nicolaou, A.; et al. Circular Non-coding RNA ANRIL Modulates Ribosomal RNA Maturation and Atherosclerosis in Humans. Nat. Commun. 2016, 7, 12429.

15. Rybak-Wolf, A.; Stottmeister, C.; Glažar, P.; Jens, M.; Pino, N.; Giusti, S.; Hanan, M.; Behm, M.; Bartok, O.; Ashwal-Fluss, R.; et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. Mol. Cell 2015, 58, 870–885.

16. Vo, J.N.; Cieslik, M.; Zhang, Y.; Shukla, S.; Xiao, L.; Zhang, Y.; Wu, Y.M.; Dhanasekaran, S.M.; Engelke, C.G.; Cao, X.; et al. The Landscape of Circular RNA in Cancer. Cell 2019, 176, 869–881.e13.

17. Li, Z.; Huang, C.; Bao, C.; Chen, L.; Lin, M.; Wang, X.; Zhong, G.; Yu, B.; Hu, W.; Dai, L.; et al. Exon-Intron Circular RNAs Regulate Transcription in the Nucleus. Nat. Struct. Mol. Biol. 2015, 22, 256–264.

18. Liu, Y.; Su, H.; Zhang, J.; Liu, Y.; Feng, C.; Han, F. Back-Spliced RNA from Retrotransposon Binds to Centromere and Regulates Centromeric Chromatin Loops in Maize. PLoS Biol. 2020, 18, e3000582.

19. Hansen, T.B.; Jensen, T.I.; Clausen, B.H.; Bramsen, J.B.; Finsen, B.; Damgaard, C.K.; Kjems, J. Natural RNA Circles Function as Efficient microRNA Sponges. Nature 2013, 495, 384–388.

20. Du, W.W.; Yang, W.; Liu, E.; Yang, Z.; Dhaliwal, P.; Yang, B.B. Foxo3 Circular RNA Retards Cell Cycle Progression via Forming Ternary Complexes with p21 and CDK2. Nucleic Acids Res. 2016, 44, 2846–2858.

21. Nishikura, K. A-to-I Editing of Coding and Non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016, 17, 83–96.

22. Rueter, S.M.; Dawson, T.R.; Emeson, R.B. Regulation of Alternative Splicing by RNA Editing. Nature 1999, 399, 75–80.

23. Heraud-Farlow, J.E.; Walkley, C.R. What Do Editors Do? Understanding the Physiological Functions of A-to-I RNA Editing by Adenosine Deaminase Acting on RNAs. Open Biol. 2020, 10, 200085.

24. Yang, W.; Chendrimada, T.P.; Wang, Q.; Higuchi, M.; Seeburg, P.H.; Shiekhattar, R.; Nishikura, K. Modulation of microRNA Processing and Expression Through RNA Editing by ADAR Deaminases. Nat. Struct. Mol. Biol. 2006, 13, 13–21.

25. Ivanov, A.; Memczak, S.; Wyler, E.; Torti, F.; Porath, H.T.; Orejuela, M.R.; Piechotta, M.; Levanon, E.Y.; Landthaler, M.; Dieterich, C.; et al. Analysis of Intron Sequences Reveals Hallmarks of Circular RNA Biogenesis in Animals. Cell Rep. 2015, 10, 170–177.

26. Guo, C.; Ma, Y.Y. Calcium Permeable-AMPA Receptors and Excitotoxicity in Neurological Disorders. Front. Neural Circuits 2021, 15, 711564.

27. Greger, I.H.; Khatri, L.; Ziff, E.B. RNA Editing at arg607 Controls AMPA Receptor Exit from the Endoplasmic Reticulum. Neuron 2002, 34, 759–772.

28. Baker, D.J.; Petersen, R.C. Cellular Senescence in Brain Aging and Neurodegenerative Diseases: Evidence and Perspectives. J. Clin. Investig. 2018, 128, 1208–1216.

29. Azam, S.; Haque, M.E.; Balakrishnan, R.; Kim, I.S.; Choi, D.K. The Ageing Brain: Molecular and Cellular Basis of Neurodegeneration. Front. Cell Dev. Biol. 2021, 9, 683459.

30. Hou, Y.; Dan, X.; Babbar, M.; Wei, Y.; Hasselbalch, S.G.; Croteau, D.L.; Bohr, V.A. Ageing as a Risk Factor for Neurodegenerative Disease. Nat. Rev. Neurol. 2019, 15, 565–581.

31. Du, S.; Zheng, H. Role of FoxO Transcription Factors in Aging and Age-Related Metabolic and Neurodegenerative Diseases. Cell Biosci. 2021, 11, 188.

32. Du, W.W.; Yang, W.; Chen, Y.; Wu, Z.K.; Foster, F.S.; Yang, Z.; Li, X.; Yang, B.B. Foxo3 Circular RNA Promotes Cardiac Senescence by Modulating Multiple Factors Associated with Stress and Senescence Responses. Eur. Heart J. 2017, 38, 1402–1412.

33. Haque, S.; Ames, R.M.; Moore, K.; Pilling, L.C.; Peters, L.L.; Bandinelli, S.; Ferrucci, L.; Harries, L.W. circRNAs Expressed in Human Peripheral Blood Are Associated with Human Aging Phenotypes, Cellular Senescence and Mouse Lifespan. GeroScience 2020, 42, 183–199.

34. Roush, S.; Slack, F.J. The Let-7 Family of microRNAs. Trends Cell Biol. 2008, 18, 505–516.

35. Lehmann, S.M.; Krüger, C.; Park, B.; Derkow, K.; Rosenberger, K.; Baumgart, J.; Trimbuch, T.; Eom, G.; Hinz, M.; Kaul, D.; et al. An Unconventional Role for miRNA: Let-7 Activates Toll-Like Receptor 7 and Causes Neurodegeneration. Nat. Neurosci. 2012, 15, 827–835.

36. Pang, Y.; Lin, W.; Zhan, L.; Zhang, J.; Zhang, S.; Jin, H.; Zhang, H.; Wang, X.; Li, X. Inhibiting Autophagy Pathway of PI3K/AKT/mTOR Promotes Apoptosis in SK-N-SH Cell Model of Alzheimer's Disease. J. Healthc. Eng. 2022, 2022, 6069682.

37. Panda, A.C.; Grammatikakis, I.; Kim, K.M.; De, S.; Martindale, J.L.; Munk, R.; Yang, X.; Abdelmohsen, K.; Gorospe, M. Identification of Senescence-Associated Circular RNAs (SAC-RNAs) Reveals Senescence Suppressor CircPVT1. Nucleic Acids Res. 2017, 45, 4021–4035.

38. Han, W.; Tao, X.; Weng, T.; Chen, L. Circular RNA PVT1 Inhibits Tendon Stem/Progenitor Cell Senescence by Sponging microRNA-199a-5p. Toxicol. Vitr. 2022, 79, 105297.

39. Jęśko, H.; Wencel, P.; Strosznajder, R.P.; Strosznajder, J.B. Sirtuins and Their Roles in Brain Aging and Neurodegenerative Disorders. Neurochem. Res. 2017, 42, 876–890.

40. Sousa, C.; Mendes, A.F. Monoterpenes as Sirtuin-1 Activators: Therapeutic Potential in Aging and Related Diseases. Biomolecules 2022, 12, 921.

41. Boulias, K.; Greer, E.L. Biological Roles of Adenine Methylation in RNA. Nat. Rev. Genet. 2023, 24, 143–160.

42. Xu, T.; He, B.; Sun, H.; Xiong, M.; Nie, J.; Wang, S.; Pan, Y. Novel Insights into the Interaction Between N6-Methyladenosine Modification and Circular RNA. Mol. Ther. Nucleic Acids 2022, 27, 824–837.

43. Zhang, X.; Yang, S.; Han, S.; Sun, Y.; Han, M.; Zheng, X.; Li, F.; Wei, Y.; Wang, Y.; Bi, J. Differential Methylation of circRNA m6A in an APP/PS1 Alzheimer's Disease Mouse Model. Mol. Med. Rep. 2023, 27, 1–8.

44. Bayer, C.; Pitschelatow, G.; Hannemann, N.; Linde, J.; Reichard, J.; Pensold, D.; Zimmer-Bensch, G. DNA Methyltransferase 1 (DNMT1) Acts on Neurodegeneration by Modulating Proteostasis-Relevant Intracellular Processes. Int. J. Mol. Sci. 2020, 21, 5420.

45. D'Anca, M.; Buccellato, F.R.; Fenoglio, C.; Galimberti, D. Circular RNAs: Emblematic Players of Neurogenesis and Neurodegeneration. Int. J. Mol. Sci. 2022, 23, 4134.

46. You, X.; Vlatkovic, I.; Babic, A.; Will, T.; Epstein, I.; Tushev, G.; Akbalik, G.; Wang, M.; Glock, C.; Quedenau, C.; et al. Neural Circular RNAs Are Derived from Synaptic Genes and Regulated by Development and Plasticity. Nat. Neurosci. 2015, 18, 603–610.

47. Yang, Y.; Okada, S.; Sakurai, M. Adenosine-to-Inosine RNA Editing in Neurological Development and Disease. RNA Biol. 2021, 18, 999–1013.

48. Eisenberg, E.; Levanon, E.Y. A-to-I RNA Editing—Immune Protector and Transcriptome Diversifier. Nat. Rev. Genet. 2018, 19, 473–490.

49. Lorenzini, I.; Moore, S.; Sattler, R. RNA Editing Deficiency in Neurodegeneration. Adv. Neurobiol. 2018, 20, 63–83.

50. Solomon, O.; Di Segni, A.; Cesarkas, K.; Porath, H.T.; Marcu-Malina, V.; Mizrahi, O.; Stern-Ginossar, N.; Kol, N.; Farage-Barhom, S.; Glick-Saar, E.; et al. RNA Editing by ADAR1 Leads to Context-Dependent Transcriptome-Wide Changes in RNA Secondary Structure. Nat. Commun. 2017, 8, 1440.

51. Montano, M.; Long, K. RNA Surveillance-an Emerging Role for RNA Regulatory Networks in Aging. Ageing Res. Rev. 2011, 10, 216–224.

52. Wahlstedt, H.; Daniel, C.; Ensterö, M.; Ohman, M. Large-Scale mRNA Sequencing Determines Global Regulation of RNA Editing During Brain Development. Genome Res. 2009, 19, 978–986.

53. Shtrichman, R.; Germanguz, I.; Mandel, R.; Ziskind, A.; Nahor, I.; Safran, M.; Osenberg, S.; Sherf, O.; Rechavi, G.; Itskovitz-Eldor, J. Altered A-to-I RNA Editing in Human Embryogenesis. PLoS ONE 2012, 7, e41576.

54. Hosaka, T.; Tsuji, H.; Kwak, S. RNA Editing: A New Therapeutic Target in Amyotrophic Lateral Sclerosis and Other Neurological Diseases. Int. J. Mol. Sci. 2021, 22, 10958.

55. Slotkin, W.; Nishikura, K. Adenosine-to-Inosine RNA Editing and Human Disease. Genome Med. 2013, 5, 105.

56. Dube, U.; Del-Aguila, J.L.; Li, Z.; Budde, J.P.; Jiang, S.; Hsu, S.; Ibanez, L.; Fernandez, M.V.; Farias, F.; Norton, J.; et al. An Atlas of Cortical Circular RNA Expression in Alzheimer Disease Brains Demonstrates Clinical and Pathological Associations. Nat. Neurosci. 2019, 22, 1903–1912.

57. Aquilina-Reid, C.; Brennan, S.; Curry-Hyde, A.; Teunisse, G.M.; The Nygc Als Consortium; Janitz, M. Circular RNA Expression and Interaction Patterns Are Perturbed in Amyotrophic Lateral Sclerosis. Int. J. Mol. Sci. 2022, 23, 14665.

58. Tsitsipatis, D.; Mazan-Mamczarz, K.; Si, Y.; Herman, A.B.; Yang, J.H.; Guha, A.; Piao, Y.; Fan, J.; Martindale, J.L.; Munk, R.; et al. Transcriptomic Analysis of Human ALS Skeletal Muscle Reveals a Disease-Specific Pattern of Dysregulated circRNAs. Aging 2022, 14, 9832–9859.

59. Assoni, A.F.; Foijer, F.; Zatz, M. Amyotrophic Lateral Sclerosis, FUS and Protein Synthesis Defects. Stem Cell Rev. Rep. 2023, 19, 625–638.

60. Errichelli, L.; Dini Modigliani, S.; Laneve, P.; Colantoni, A.; Legnini, I.; Capauto, D.; Rosa, A.; De Santis, R.; Scarfò, R.; Peruzzi, G.; et al. FUS Affects Circular RNA Expression in Murine Embryonic Stem Cell-Derived Motor Neurons. Nat. Commun. 2017, 8, 14741.

61. Colantoni, A.; Capauto, D.; Alfano, V.; D'Ambra, E.; D'Uva, S.; Tartaglia, G.G.; Morlando, M. FUS Alters circRNA Metabolism in Human Motor Neurons Carrying the ALS-Linked P525L Mutation. Int. J. Mol. Sci. 2023, 24, 3181.

62. DeJesus-Hernandez, M.; Mackenzie, I.R.; Boeve, B.F.; Boxer, A.L.; Baker, M.; Rutherford, N.J.; Nicholson, A.M.; Finch, N.A.; Flynn, H.; Adamson, J.; et al. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. Neuron 2011, 72, 245–256.

63. Renton, A.E.; Majounie, E.; Waite, A.; Simón-Sánchez, J.; Rollinson, S.; Gibbs, J.R.; Schymick, J.C.; Laaksovirta, H.; van Swieten, J.C.; Myllykangas, L.; et al. A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. Neuron 2011, 72, 257–268.

64. Rohrer, J.D.; Isaacs, A.M.; Mizielinska, S.; Mead, S.; Lashley, T.; Wray, S.; Sidle, K.; Fratta, P.; Orrell, R.W.; Hardy, J.; et al. C9orf72 Expansions in Frontotemporal Dementia and Amyotrophic Lateral Sclerosis. Lancet Neurol. 2015, 14, 291–301.

65. Belzil, V.V.; Katzman, R.B.; Petrucelli, L. ALS and FTD: An Epigenetic Perspective. Acta Neuropathol. 2016, 132, 487–502.

66. Leighton, G.O.; Irvin, E.M.; Kaur, P.; Liu, M.; You, C.; Bhattaram, D.; Piehler, J.; Riehn, R.; Wang, H.; Pan, H.; et al. Densely Methylated DNA Traps Methyl-CpG-Binding Domain Protein 2 but Permits Free Diffusion by Methyl-CpG-Binding Domain Protein 3. J. Biol. Chem. 2022, 298, 102428.

67. Liu, D.; Liu, W.; Chen, X.; Yin, J.; Ma, L.; Liu, M.; Zhou, X.; Xian, L.; Li, P.; Tan, X.; et al. circKCNN2 Suppresses the Recurrence of Hepatocellular Carcinoma at Least Partially via Regulating miR-520c-3p/methyl-DNA-binding Domain Protein 2 Axis. Clin. Transl. Med. 2022, 12, e662.

68. Cervera-Carles, L.; Dols-Icardo, O.; Molina-Porcel, L.; Alcolea, D.; Cervantes-Gonzalez, A.; Muñoz-Llahuna, L.; Clarimon, J. Assessing Circular RNAs in Alzheimer's Disease and Frontotemporal Lobar Degeneration. Neurobiol. Aging 2020, 92, 7–11.

69. Van Damme, P.; Dewil, M.; Robberecht, W.; Van Den Bosch, L. Excitotoxicity and Amyotrophic Lateral Sclerosis. Neurodegener. Dis. 2005, 2, 147–159.

70. King, A.E.; Woodhouse, A.; Kirkcaldie, M.T.; Vickers, J.C. Excitotoxicity in ALS: Overstimulation, or Overreaction? Exp. Neurol. 2016, 275, 162–171.

71. Diering, G.H.; Huganir, R.L. The AMPA Receptor Code of Synaptic Plasticity. Neuron 2018, 100, 314–329.

72. Gregory, J.M.; Livesey, M.R.; McDade, K.; Selvaraj, B.T.; Barton, S.K.; Chandran, S.; Smith, C. Dysregulation of AMPA Receptor Subunit Expression in Sporadic ALS Post-Mortem Brain. J.

Pathol. 2020, 250, 67–78.

73. Udagawa, T.; Fujioka, Y.; Tanaka, M.; Honda, D.; Yokoi, S.; Riku, Y.; Ibi, D.; Nagai, T.; Yamada, K.; Watanabe, H.; et al. FUS Regulates AMPA Receptor Function and FTLD/ALS-Associated Behaviour via GluA1 mRNA Stabilization. Nat. Commun. 2015, 6, 7098.

74. Capauto, D.; Colantoni, A.; Lu, L.; Santini, T.; Peruzzi, G.; Biscarini, S.; Morlando, M.; Shneider, N.A.; Caffarelli, E.; Laneve, P.; et al. A Regulatory Circuitry Between Gria2, miR-409, and miR-495 Is Affected by ALS FUS Mutation in ESC-Derived Motor Neurons. Mol. Neurobiol. 2018, 55, 7635–7651.

75. Selvaraj, B.T.; Livesey, M.R.; Zhao, C.; Gregory, J.M.; James, O.T.; Cleary, E.M.; Chouhan, A.K.; Gane, A.B.; Perkins, E.M.; Dando, O.; et al. C9ORF72 Repeat Expansion Causes Vulnerability of Motor Neurons to Ca2+-Permeable AMPA Receptor-Mediated Excitotoxicity. Nat. Commun. 2018, 9, 347.

76. Dafinca, R.; Barbagallo, P.; Farrimond, L.; Candalija, A.; Scaber, J.; Ababneh, N.A.; Sathyaprakash, C.; Vowles, J.; Cowley, S.A.; Talbot, K. Impairment of Mitochondrial Calcium Buffering Links Mutations in C9ORF72 and TARDBP in iPS-Derived Motor Neurons from Patients with ALS/FTD. Stem Cell Rep. 2020, 14, 892–908.

77. Xu, K.; Zhang, Y.; Xiong, W.; Zhang, Z.; Wang, Z.; Lv, L.; Liu, C.; Hu, Z.; Zheng, Y.T.; Lu, L.; et al. CircGRIA1 Shows an Age-Related Increase in Male Macaque Brain and Regulates Synaptic Plasticity and Synaptogenesis. Nat. Commun. 2020, 11, 3594.

78. Markovinovic, A.; Greig, J.; Martín-Guerrero, S.M.; Salam, S.; Paillusson, S. Endoplasmic Reticulum-Mitochondria Signaling in Neurons and Neurodegenerative Diseases. J. Cell Sci. 2022, 135, jcs248534.

79. Watanabe, S.; Ilieva, H.; Tamada, H.; Nomura, H.; Komine, O.; Endo, F.; Jin, S.; Mancias, P.; Kiyama, H.; Yamanaka, K. Mitochondria-Associated Membrane Collapse Is a Common Pathomechanism in SIGMAR1- and SOD1-Linked ALS. EMBO Mol. Med. 2016, 8, 1421–1437.

80. Lau, D.H.W.; Hartopp, N.; Welsh, N.J.; Mueller, S.; Glennon, E.B.; Mórotz, G.M.; Annibali, A.; Gomez-Suaga, P.; Stoica, R.; Paillusson, S.; et al. Disruption of ER-Mitochondria Signalling in Fronto-temporal Dementia and Related Amyotrophic Lateral Sclerosis. Cell Death Dis. 2018, 9, 327.

81. Sakai, S.; Watanabe, S.; Komine, O.; Sobue, A.; Yamanaka, K. Novel Reporters of Mitochondria-Associated Membranes (MAM), MAMtrackers, Demonstrate MAM Disruption as a Common Pathological Feature in Amyotrophic Lateral Sclerosis. FASEB J. 2021, 35, e21688.

82. Al-Saif, A.; Al-Mohanna, F.; Bohlega, S. A Mutation in Sigma-1 Receptor Causes Juvenile Amyotrophic Lateral Sclerosis. Ann. Neurol. 2011, 70, 913–919.

83. Tagashira, H.; Shinoda, Y.; Shioda, N.; Fukunaga, K. Methyl Pyruvate Rescues Mitochondrial Damage Caused by SIGMAR1 Mutation Related to Amyotrophic Lateral Sclerosis. Biochim. Biophys. Acta 2014, 1840, 3320–3334.

84. Luty, A.A.; Kwok, J.B.; Dobson-Stone, C.; Loy, C.T.; Coupland, K.G.; Karlström, H.; Sobow, T.; Tchorzewska, J.; Maruszak, A.; Barcikowska, M.; et al. Sigma Nonopioid Intracellular Receptor 1 Mutations Cause Frontotemporal Lobar Degeneration-Motor Neuron Disease. Ann. Neurol. 2010, 68, 639–649.

85. Dreser, A.; Vollrath, J.T.; Sechi, A.; Johann, S.; Roos, A.; Yamoah, A.; Katona, I.; Bohlega, S.; Wiemuth, D.; Tian, Y.; et al. The ALS-Linked E102Q Mutation in Sigma Receptor-1 Leads to ER Stress-Mediated Defects in Protein Homeostasis and Dysregulation of RNA-Binding Proteins. Cell Death Differ. 2017, 24, 1655–1671.

86. Plaitakis, A.; Constantakakis, E.; Smith, J. The Neuroexcitotoxic Amino Acids Glutamate and Aspartate Are Altered in the Spinal Cord and Brain in Amyotrophic Lateral Sclerosis. Ann. Neurol. 1988, 24, 446–449.

87. Rothstein, J.D.; Tsai, G.; Kuncl, R.W.; Clawson, L.; Cornblath, D.R.; Drachman, D.B.; Pestronk, A.; Stauch, B.L.; Coyle, J.T. Abnormal Excitatory Amino Acid Metabolism in Amyotrophic Lateral Sclerosis. Ann. Neurol. 1990, 28, 18–25.

88. Shaw, P.J.; Forrest, V.; Ince, P.G.; Richardson, J.P.; Wastell, H.J. CSF and Plasma Amino Acid Levels in Motor Neuron Disease: Elevation of CSF Glutamate in a Subset of Patients. Neurodegeneration 1995, 4, 209–216.

89. Spreux-Varoquaux, O.; Bensimon, G.; Lacomblez, L.; Salachas, F.; Pradat, P.F.; Le Forestier, N.; Marouan, A.; Dib, M.; Meininger, V. Glutamate Levels in Cerebrospinal Fluid in Amyotrophic Lateral Sclerosis: A Reappraisal Using a New HPLC Method with Coulometric Detection in a Large Cohort of Patients. J. Neurol. Sci. 2002, 193, 73–78.

90. Rothstein, J.D.; Martin, L.J.; Kuncl, R.W. Decreased Glutamate Transport by the Brain and Spinal Cord in Amyotrophic Lateral Sclerosis. N. Engl. J. Med. 1992, 326, 1464–1468.

91. Lacomblez, L.; Bensimon, G.; Leigh, P.N.; Guillet, P.; Meininger, V. Dose-Ranging Study of Riluzole in Amyotrophic Lateral Sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Lancet 1996, 347, 1425–1431.

92. Martin, D.; Thompson, M.A.; Nadler, J.V. The Neuroprotective Agent Riluzole Inhibits Release of Glutamate and Aspartate from Slices of Hippocampal Area CA1. Eur. J. Pharmacol. 1993, 250, 473–476.

93. Bensimon, G.; Lacomblez, L.; Meininger, V. A Controlled Trial of Riluzole in Amyotrophic Lateral Sclerosis. ALS/Riluzole Study Group. N. Engl. J. Med. 1994, 330, 585–591.

94. Fang, T.; Al Khleifat, A.; Meurgey, J.H.; Jones, A.; Leigh, P.N.; Bensimon, G.; Al-Chalabi, A. Stage at Which Riluzole Treatment Prolongs Survival in Patients with Amyotrophic Lateral Sclerosis: A Retrospective Analysis of Data from a Dose-Ranging Study. Lancet Neurol. 2018, 17, 416–422.

95. Kawahara, Y.; Ito, K.; Sun, H.; Aizawa, H.; Kanazawa, I.; Kwak, S. Glutamate Receptors: RNA Editing and Death of Motor Neurons. Nature 2004, 427, 801.

96. Hideyama, T.; Yamashita, T.; Aizawa, H.; Tsuji, S.; Kakita, A.; Takahashi, H.; Kwak, S. Profound Downregulation of the RNA Editing Enzyme ADAR2 in ALS Spinal Motor Neurons. Neurobiol. Dis. 2012, 45, 1121–1128.

97. Hideyama, T.; Yamashita, T.; Suzuki, T.; Tsuji, S.; Higuchi, M.; Seeburg, P.H.; Takahashi, R.; Misawa, H.; Kwak, S. Induced Loss of ADAR2 Engenders Slow Death of Motor Neurons from Q/R Site-Unedited GluR2. J. Neurosci. 2010, 30, 11917–11925.

98. Yamashita, T.; Hideyama, T.; Hachiga, K.; Teramoto, S.; Takano, J.; Iwata, N.; Saido, T.C.; Kwak, S. A Role for Calpain-Dependent Cleavage of TDP-43 in Amyotrophic Lateral Sclerosis Pathology. Nat. Commun. 2012, 3, 1307.

99. Yamashita, T.; Kwak, S. The Molecular Link Between Inefficient GluA2 Q/R Site-RNA Editing and TDP-43 Pathology in Motor Neurons of Sporadic Amyotrophic Lateral Sclerosis Patients. Brain Res. 2014, 1584, 28–38.

100. Kawahara, Y.; Sun, H.; Ito, K.; Hideyama, T.; Aoki, M.; Sobue, G.; Tsuji, S.; Kwak, S. Underediting of GluR2 mRNA, a Neuronal Death Inducing Molecular Change in Sporadic ALS, Does Not Occur in Motor Neurons in ALS1 or SBMA. Neurosci. Res. 2006, 54, 11–14.

101. Zhang, Y.; Xue, W.; Li, X.; Zhang, J.; Chen, S.; Zhang, J.L.; Yang, L.; Chen, L.L. The Biogenesis of Nascent Circular RNAs. Cell Rep. 2016, 15, 611–624.

102. Zhang, X.O.; Wang, H.B.; Zhang, Y.; Lu, X.; Chen, L.L.; Yang, L. Complementary Sequence-Mediated Exon Circularization. Cell 2014, 159, 134–147.

103. Chung, H.; Calis, J.J.A.; Wu, X.; Sun, T.; Yu, Y.; Sarbanes, S.L.; Dao Thi, V.L.; Shilvock, A.R.; Hoffmann, H.H.; Rosenberg, B.R.; et al. Human ADAR1 Prevents Endogenous RNA from Triggering Translational Shutdown. Cell 2018, 172, 811–824.e14.

104. Aktaş, T.; Avşar Ilık, İ.; Maticzka, D.; Bhardwaj, V.; Pessoa Rodrigues, C.; Mittler, G.; Manke, T.; Backofen, R.; Akhtar, A. DHX9 Suppresses RNA Processing Defects Originating from the Alu Invasion of the Human Genome. Nature 2017, 544, 115–119.

105. Ma, C.; Wang, X.; Yang, F.; Zang, Y.; Liu, J.; Wang, X.; Xu, X.; Li, W.; Jia, J.; Liu, Z. Circular RNA hsa_circ_0004872 Inhibits Gastric Cancer Progression via the miR-224/Smad4/ADAR1 Successive Regulatory Circuit. Mol. Cancer 2020, 19, 157.

106. Omata, Y.; Okawa, M.; Haraguchi, M.; Tsuruta, A.; Matsunaga, N.; Koyanagi, S.; Ohdo, S. RNA Editing Enzyme ADAR1 Controls miR-381-3p-mediated Expression of Multidrug Resistance Protein MRP4 via Regulation of circRNA in Human Renal Cells. J. Biol. Chem. 2022, 298, 102184.

107. Hosaka, T.; Yamashita, T.; Teramoto, S.; Hirose, N.; Tamaoka, A.; Kwak, S. ADAR2-Dependent A-to-I RNA Editing in the Extracellular Linear and Circular RNAs. Neurosci. Res. 2019, 147, 48–57.

108. Kim, E.; Kim, Y.K.; Lee, S.V. Emerging Functions of Circular RNA in Aging. Trends Genet. 2021, 37, 819–829.

109. Kokot, K.E.; Kneuer, J.M.; John, D.; Rebs, S.; Möbius-Winkler, M.N.; Erbe, S.; Müller, M.; Andritschke, M.; Gaul, S.; Sheikh, B.N.; et al. Reduction of A-to-I RNA Editing in the Failing Human Heart Regulates Formation of Circular RNAs. Basic Res. Cardiol. 2022, 117, 32.

110. Dolinar, A.; Koritnik, B.; Glavač, D.; Ravnik-Glavač, M. Circular RNAs as Potential Blood Biomarkers in Amyotrophic Lateral Sclerosis. Mol. Neurobiol. 2019, 56, 8052–8062.

111. Campos-Melo, D.; Droppelmann, C.A.; He, Z.; Volkening, K.; Strong, M.J. Altered microRNA Expression Profile in Amyotrophic Lateral Sclerosis: A Role in the Regulation of NFL mRNA Levels. Mol. Brain 2013, 6, 26.

112. Vrabec, K.; Boštjančič, E.; Koritnik, B.; Leonardis, L.; Dolenc Grošelj, L.; Zidar, J.; Rogelj, B.; Glavač, D.; Ravnik-Glavač, M. Differential Expression of Several miRNAs and the Host Genes AATK and DNM2 in Leukocytes of Sporadic ALS Patients. Front. Mol. Neurosci. 2018, 11, 106.

113. Ravnik-Glavač, M.; Glavač, D. Circulating RNAs as Potential Biomarkers in Amyotrophic Lateral Sclerosis. Int. J. Mol. Sci. 2020, 21, 1714.

114. Wu, D.P.; Zhao, Y.D.; Yan, Q.Q.; Liu, L.L.; Wei, Y.S.; Huang, J.L. Circular RNAs: Emerging Players in Brain Aging and Neurodegenerative Diseases. J. Pathol. 2023, 259, 1–9.

115. Armakola, M.; Higgins, M.J.; Figley, M.D.; Barmada, S.J.; Scarborough, E.A.; Diaz, Z.; Fang, X.; Shorter, J.; Krogan, N.J.; Finkbeiner, S.; et al. Inhibition of RNA Lariat Debranching Enzyme Suppresses TDP-43 Toxicity in ALS Disease Models. Nat. Genet. 2012, 44, 1302–1309.

116. Martin, L.J.; Adams, D.A.; Niedzwiecki, M.V.; Wong, M. Aberrant DNA and RNA Methylation Occur in Spinal Cord and Skeletal Muscle of Human SOD1 Mouse Models of ALS and in Human ALS: Targeting DNA Methylation Is Therapeutic. Cells 2022, 11, 3448.

117. Yang, L.; Han, B.; Zhang, Z.; Wang, S.; Bai, Y.; Zhang, Y.; Tang, Y.; Du, L.; Xu, L.; Wu, F.; et al. Extracellular Vesicle-Mediated Delivery of Circular RNA SCMH1 Promotes Functional Recovery in Rodent and Nonhuman Primate Ischemic Stroke Models. Circulation 2020, 142, 556–574.

118. Yu, X.; Bai, Y.; Han, B.; Ju, M.; Tang, T.; Shen, L.; Li, M.; Yang, L.; Zhang, Z.; Hu, G.; et al. Extracellular Vesicle-Mediated Delivery of circDYM Alleviates CUS-Induced Depressive-Like

Behaviours. J. Extracell. Vesicles 2022, 11, e12185.

119. Yamashita, T.; Chai, H.L.; Teramoto, S.; Tsuji, S.; Shimazaki, K.; Muramatsu, S.; Kwak, S. Rescue of Amyotrophic Lateral Sclerosis Phenotype in a Mouse Model by Intravenous AAV9-ADAR2 Delivery to Motor Neurons. EMBO Mol. Med. 2013, 5, 1710–1719.

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