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Exploiting ncRNA as new therapeutic avenues in ALS

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Progressive degeneration of motor neurons (MNs) is the hallmark of amyotrophic lateral sclerosis (ALS). Limb-innervating lateral motor column MNs (LMC-MNs) seem to be particularly vulnerable and are among the first MNs affected in ALS. Here, we report association of this differential susceptibility with reduced expression of the *mir-17~92* cluster in LMC-MNs prior to disease onset. Reduced *mir-17~92* is accompanied by elevated nuclear PTEN in spinal MNs of presymptomatic $SOD1^{G93A}$ mice. Selective dysregulation of the *mir-17~92*/nuclear PTEN axis in degenerating $SOD1^{G93A}$ LMC-MNs was confirmed in a double-transgenic embryonic stem cell system and recapitulated in human $SOD1^{+/L144F}$-induced pluripotent stem cell (iPSC)-derived MNs. We further show that overexpression of *mir-17~92* significantly rescues human $SOD1^{+/L144F}$ MNs, and intrathecal delivery of adeno-associated virus (AAV)9-*mir-17~92* improves motor deficits and survival in $SOD1^{G93A}$ mice. Thus, *mir-17~92* may have value as a prognostic marker of MN degeneration and is a candidate therapeutic target in *SOD1*-linked ALS.

Selected 5 recent publications:

1. Li CJ, Liau ES, Lee YH, Huang YZ, Liu ZY, Willems A, Garside V, McGlinn E, **Chen JA***, Tian H* (2021) MicroRNA Governs Bistable Cell Differentiation and Lineage Segregation via a Noncanonical Feedback. ***Mol Syst Biol*** *(2021)17:e9945* **(Cover featured article)**.
2. Chang SH, Su YC, Chang M, **Chen JA***. (2021) MicroRNAs mediate precise control of spinal interneuron populations to exert delicate sensory-to-motor outputs. ***eLife*** (DOI: 10.7554/eLife.63768). *This article is selected as a showcase for featured eLife Science Digests.*
3. Tung YT*, Peng KC, Chen, YC, Yen YP, Chang M, Thams S, **Chen JA***. (2019) Mir-17~92 Confers Motor Neuron Subtype Differential Resistance to ALS-Associated Degeneration. ***Cell Stem Cell*** Aug 1;25(2):193-209 **(Cover featured article)**. *This article has been recommended by* ***F1000*** *by Andrew Yoo: 2019. This article is highlighted by Academi a Sinica (English) (Chinese). the Academia Sinica Facebook. It is also featured in a series of newspapers, inc LibertyTimes, UDN, ChinaTimes, etc. Reported by international media: BioArt, Taipei Times, BioCentury, Asia Pacific Biotech News.*
4. Yen YP, Hsieh WF, Tsia YY, Lu YL, Liau ES ,Hsu HC, Chen YC, Liu TC, Chang M, Li J, Lin SP*, Hung JH*, **Chen JA***. (2018) Dlk1-Dio3 Locus-Derived LncRNAs Perpetuate Postmitotic Motor Neuron Cell Fate and Subtype Identity. ***eLife*** (DOI: 10.7554/eLife.38080).*This article is selected as a showcase for featured eLife Science Digests., and the "Biomedical Picture of the Day" by MRC UK.*
5. Li CJ, Hong T, Tung YT, Yen YP, Hsu HC, Lu YL, Chang M, Nie Q*, **Chen JA***. (2017) MicroRNA filters Hox temporal transcription noise to confer boundary formation in the spinal cord. ***Nature Communications*** *8. Article number: 14685 (2017). This article is highlighted by Academia Sinica (English)(Chinese), and on the Academia Sinica Facebook. It has also been featured in Asia Pacific Biotech News.*