Expanding mechanisms and therapeutic targets for ALS

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Abstract

My lab is focusing on the ALS disease protein TDP-43. We have used these yeast models to perform high-throughput genomewide modifier screens to discover suppressors and enhancers of toxicity. We have extended our findings into animal models and even recently into human patients. For example, we discovered mutations in ataxin 2, one of the human homologs of a hit from our yeast TDP-43 modifier screen in ALS patients. We continue to study ataxin 2 function and to identify ways to inhibit its function as a therapeutic strategy for ALS. We are also exploring the normal function of TDP-43 and have recently discovered novel splicing targets that are dysregulated in ALS. One of these is *UNC13A*. SNPs in *UNC13A* are among the strongest hits associated with FTD and ALS in human genome-wide association studies, but how those variants increase risk for disease is unknown. We found that TDP-43 represses a cryptic exon-splicing event in *UNC13A*. Loss of TDP-43 from the nucleus in human brain, neuronal cell lines and motor neurons resulted in the inclusion of a cryptic exon in *UNC13A* mRNA and reduced UNC13A protein expression. The top variants associated with FTD or ALS risk in humans are located in the intron harboring the cryptic exon, and we show that they increase UNC13A cryptic exon splicing in the face of TDP-43 dysfunction. Together, our data provide a direct functional link between one of the strongest genetic risk factors for FTD and ALS (UNC13A genetic variants), and loss of TDP-43 function.

Selected recent publications:

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Alteration of Tau metabolism through FUS in FTLD-spectrum disorders including ALS

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Abstract

The frontotemporal lobar degeneration (FTLD) spectrum includes FTLD, amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and cortico-basal degeneration (CBD). TDP-43 and FUS are causative for ALS and FTLD, which collectively comprise a continuous disease spectrum of multisystem proteinopathies. On the other hand, 4-repeat (4R)-tau predominant aggregations are associated with PSP and CBD, while 3-repeat (3R)-tau accumulates in Pick disease (PiD). Using a mouse model, we reported that FUS regulates alternative splicing of tau proteins in coordination with Splicing factor, proline- and glutamine-rich (SFPQ). Under normal conditions, the two proteins form a high-molecular-weight complex in the nucleus. Disease-associated mutations in FUS gene, however, disrupt formation of the complex resulting in unregulated alternative splicing of tau, a disproportional increase in the 4R-tau/3R-tau ratio, and eventually neurodegeneration. In addition, neuropathological study revealed spatial dissociation of SFPQ and FUS in the neuronal nuclei of ALS/FTLD-FUS, ALS/FTLD-TDP, PSP, and CBD. Furthermore, the ratio of 4R/3R-tau was elevated in cases with ALS/FTLD-TDP and PSP, but was largely unaffected in cases with AD. Thus, impaired interactions between FUS and SFPQ and subsequent imbalanced tau isoform ratio constitute a common pathogenic mechanism across FTLD spectrum disease. Based on these findings, we are developing therapeutics using antisense oligonucleotide to modify conformation of FUS and SFPQ as well as biomarkers which can visualize behavioral alterations in FTLD spectrum including ALS.

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Clinical features and genetic spectrum of ALS in Taiwan

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Abstract

From 2010 to 2020, we recruited a cohort consisting of 494 unrelated Taiwanese patients with ALS, which provided us an opportunity to understand ALS in Taiwan. In this cohort, the mean age of disease onset was 54.9 ± 12.3 years, male to female ratio was 1.4, 10.5% of the patients had familial ALS (FALS), and 19.8% had bulbar-onset disease. Among the 183 patients who received regularly ALS functional rating scale-revised version (ALSFRS-R) evaluation per six months, the mean ALSFRS-R score at first evaluation, six months and 1 year later were 36.1 ± 8.2, 28.5 ± 9.8, and 24.4 ± 11.5, respectively. The mean diagnostic delay was 12.7 ± 7.9 months. The 1st year mean ALSFRS-R score decline rate after evaluation was approximately 1 point per month. Extensive genetic analyses revealed 86 (17.4%) of the 494 patients carried an ALS-related mutation, including 41 (79%; 41/52) with FALS and 45 (10%; 45/442) with apparently sporadic ALS. The most commonly mutated disease genes were *SOD1* (4.5 %; 22/494), followed by *C9ORF72* (4.3%), *TARDBP* (3.2%), and *FUS* (1.8%). Patients with *SOD1* mutations rarely had frontotemporal dementia (FTD) and bulbar-onset disease, patients with the *C9ORF72* mutation more frequently had bulbar-onset disease and FTD. *FUS* mutations are associated with earlier disease onset.

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Exploiting ncRNA as new therapeutic avenues in ALS

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Abstract

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 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.*
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