THE ALS RESEARCH FORUM
Discovering a Common Goal, Discovering a Cure
PRIZE4LIFE ALS ASSOCIATION

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Research News

ALS Patient-derived Oligodendrocytes Are Toxic to Motor Neurons Via Multiple Mechanisms

A paper in the October 18 PNAS adds to the evidence implicating oligodendrocytes in motor neuron death in ALS. Using stem cell-derived oligodendrocytes from ALS patients, researchers demonstrate that ALS oligodendrocytes harm motor neurons through cell-to-cell contact and by secreting toxic substances. In this model, motor neuron damage could be reduced by shutting down SOD1 production even in oligodendrocytes derived from sporadic ALS patients, but not in those derived from C9ORF72-ALS patients. However, SOD1 shutdown needs to happen early to alleviate toxicity; by the time the oligodendrocytes are mature, it's too late.

ALS-FTD Mouse Model Develops Motor Neuron Disease

Scientists have developed two new mouse models of ALS and frontotemporal dementia that exhibit not only motor neuron degeneration, but also a TDP-43 pathology reminiscent of human disease. The mice overexpress ALS-causing mutations in UBQLN2 under the control of a Thy1.2 promoter, and display cognitive impairments, motor neuron death and an early demise. In postmortem analysis, they exhibit pathological ubiquitinated inclusions in the brain and spinal cord, TDP-43 aggregates in motor neurons of the spinal cord, and astrocytosis. These mice may provide a valuable tool to investigate how mutations in a protein that helps rid the cell of misfolded proteins can lead to ALS and FTD. The findings were reported in the November 9 Proceedings of the National Academy of Sciences.

MAM Disruption Impairs Mitochondrial Function in Both SOD1 and SIGMAR1-ALS

Transient contact sites between mitochondrial and ER membranes, called mitochondria-associated ER membranes (MAMs), play an important role in cellular homeostasis, calcium signaling, and mitochondrial function. The ALS-linked proteins VAPB and TDP-43 can perturb these structures and lead to mitochondrial dysfunction (see July 2014 news). Results published November 7 online in EMBO Molecular Medicine link two more ALS-linked proteins to MAM disruption: mutant SOD1 (mSOD1) and the sigma 1 receptor (Sig1R). These proteins were enriched at the MAM, and in both Sig1R null and SOD1-ALS mice the MAMs collapsed. This resulted in dispersion of the inositol triphosphate receptor type-3 (IP_3R3), which is normally concentrated at motor neuron MAMs and interacts with wild-type Sig1R to regulate calcium signaling. These findings suggest that loss of MAM integrity may be a convergent mechanism underlying multiple forms of ALS.

New Spectroscopy Method Detects Myelin Changes in Early ALS

Using a spectroscopic method to image myelin in live mice, scientists have observed

myelin degeneration in ALS mice prior to axonal degeneration and immune dysfunction. The new approach, called stimulated Raman scattering (SRS) microscopy, is a label-free imaging technique that uses two laser beams to visualize specific molecules based on their unique absorption and emission properties. The researchers tailored the SRS microscopy to visualize myelin and changes it undergoes in different diseases. Strikingly, morphological changes associated with myelin degeneration could be detected in live mutant SOD1-ALS mice at the earliest stages of muscle denervation, and similar changes were visible in ALS patient autopsy tissue. This technique, described in the October 31 Nature Communications, provides a useful tool to track early disease progression in peripheral nerves and the effect of therapeutic interventions.

Novel Minipeptides Correct Mitochondrial Abnormalities Associated with CMT
Mutations in the mitochondrial membrane protein mitofusin 2 (MFN2) cause the neurodegenerative disorder Charcot-Marie Tooth disease type 2A. MFN2 is a GTPase that participates in the dynamic process of mitochondrial tethering and fusion, but a complete understanding its mechanism of action has been lacking. A paper published October 24 in Nature online provides the first description of structural changes MFN2 undergoes as it transitions between conformations that either promote or restrict mitochondrial fusion. The researchers designed minipeptides to stabilize the active state of MFN2, and successfully enhanced mitochondrial fusion in cellular models of CMT2A. These findings open the doors to novel therapeutic approaches to repair mitochondrial abnormalities in CMT patients and potentially in other diseases associated with mitochondrial dysfunction.

Drug News

Positive Trials of Spinal Muscular Atrophy Bode Well for Antisense Approach
Following positive interim results in two Phase III clinical trials, Biogen and Ionis Pharmaceuticals are advancing toward regulatory approval of a new antisense oligonucleotide (ASO) therapy, called nusinersen, for treating spinal muscular atrophy (SMA). In both trials, which targeted different forms of the disease, all participants began receiving the drug in an open label study after interim analysis revealed striking improvements in motor function in the treatment arm (see Aug 2016 news). The success of this ASO therapy is a dramatic step for families affected by SMA, but also is a promising indicator that ASO therapies that modify splicing or silence genetic targets could be effective in other neurodegenerative diseases.

Kadimastem Partners with Hadassah Medical Center for ALS Clinical Trial
Israeli biotechnology company Kadimastem has finalized an agreement with Hadassah Ein-Kerem Medical Center in Israel to conduct its first clinical trial of a human stem cell therapy for the treatment of ALS. The therapy, called AstroRx, uses stem-cell-derived astrocytes, which are delivered intrathecally, to provide trophic support to degenerating motor neurons. Preclinical studies in ALS rat models have shown that the treatment prolongs survival in these models. Following consultation with the US FDA, the company will be conducting a Phase I/IIA safety and efficacy trial on 21 patients, to begin mid-2017.

Partners in ALS ONE Join Forces to Advance Therapies for ALS
The ALS ONE partnership, founded in January 2016 by the late ALS patient Kevin Gosnell (see Jan 2016 news), has received a $2M funding commitment from the ALS Association to support ALS ONE initiatives. The Massachusetts-based partnership was founded to bring together leaders in the field of ALS from Massachusetts General Hospital, the ALS Therapy Development Institute (ALS TDI), University of

Massachusetts Medical School and Compassionate Care ALS (CCALS), in order to accelerate ALS therapy development and improve patient care. The partner organizations are collaborating and coordinating their efforts across a variety of research and clinical programs, including improving accessibility of multidisciplinary ALS clinical care, establishing a clinical network for trials, developing new biomarkers and technologies, and testing gene therapies targeting the C9ORF72 expansions associated with ALS/FTD.

Funding Opportunities:

We have updated all the NIH funding opportunities applicable to ALS research. Check out the full list of funding opportunities.

December 2016

MDA Investigator-Initiated Research Grants. Letter of Intent due Dec 15, 2016.

MDA Young Investigator Development Grants. Letter of Intent due Dec 15, 2016.

NEW! TARGET ALS New Collaborative Projects. Letter of Intent due by December 15, 2016.

January 2016

NEW! NINDS Exploratory Clinical Trials for Small Business. Application due by January 5, 2017.

CIRM Funding Opportunity: DISC1: The Inception Awards. Application due by Jan 20, 2017.

Full List of Funding Opportunities >>

Job Opportunities:

The ALS Research Forum has an opening for a Science Communications Program Director. More information can be found here.

NEW! Postdoctoral Position, University of Central Florida. Orlando, FL.

NEW! Assistant Professor, Barrow Neurological Institute. Phoenix, AZ.

Postdoctoral Position. RIC Sensory Motor Performance Program, RIC, Chicago, IL.

Postdoctoral Position - Fenghua Hu Lab. Cornell University, Ithaca, NY.

Biostatistician, Research Fellow, University of Dublin, Ireland.

Full List of Job Opportunities >>

Upcoming Meetings:

December 2016

December 7-9, 2016: Dublin, Ireland: International Symposium on ALS/MND.

March 2017

Mar 29-Apr 2, 2017: Vienna, Austria:International Conference on Alzheimer's and Parkinson's Diseases.

April 2017

Apr 22-28, 2017: Boston, MA. American Academy of Neurology Annual Meeting. **Abstracts due October 24, 2016.**

July 2017

July 23-28, 2017: Stowe, VT: Gordon Research Conference on ALS and Related Motor Neuron Diseases. Applications due June 25, 2017.

Full List of Upcoming Meetings>>

Resources:

ALS Drugs in Development Database

ALSGene

Alzforum ALS Mouse Model Database

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

Target ALS Core Facilities

Download the Working with ALS Mice Manual Here

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