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Conference News

Potassium Channel Helps Microglia Scope Out the Scene

Microglia use dynamic projections to continuously survey their surroundings for evidence of injury or disease. At the Joint Keystone Symposia on Neurodegeneration/Microglia in the Brain, June 12-16 in Keystone, CO, David Attwell of the University College London reported that this process of probing may depend on an outwardly-rectifying potassium channel called THIK-1 (Two-pore domain Halothane-Inhibited K+ channel). Using imaging, electrophysiology, and pharmacology on mouse brain tissue slides, Attwell and colleagues observed that the THIK-1 potassium current was triggered by P2Y12 purinergic receptor signaling. Intriguingly, THIK-1 was not required for motility to sites of injury, but was necessary for extension and retraction of microglial projections, as well as for important immune functions.

Removed from the Brain, Microglia Change Their Stripes

At the "Microglia in the Brain" Keystone Symposium, scientists tackled the quandary of how to study microglia, considering how dramatically these cells change once removed from their natural milieu. Christopher Glass, University of California, San Diego showed that microglia lose expression of their unique transcripts within just 8 hours of removal from the brain. Brad Friedman, at Genentech in South San Francisco, analyzed the transcriptomes of microglia to identify co-regulated genes, and identified a tentative "neurodegenerative disease cluster" of genes whose expression changed similarly in several mouse models or in response to specific ligands. Erik Boddeke, of the University of Groningen, The Netherlands, presented data on discrepancies between microglia-specific genes in humans and mice, which sparked questions about reliability of mouse data for research on microglia.

Research News

Knockout Mice Boost Evidence for Role of C9ORF72 in Immune Function

The GGGGCC nucleotide repeat expansion in the C9ORF72 gene is the most common known genetic cause of ALS and FTD, but debate remains on whether its detrimental effects are conferred through loss or gain of a key function. A new knockout mouse model of C9ORF72, described in the July 13 Science Translational Medicine and presented last year (see Oct 2015 conference news) strengthens the case for an important role of the gene in immune regulation, which is lost due to the repeat expansions. The knockout mice developed fatal autoimmunity, resulting in ataxia, internal hemorrhaging, respiratory failure, and a shorter lifespan. These results and other C9 null models (see March 2016 news) suggest that therapeutic approaches should avoid ablation of wild-type C9ORF72 expression in mutation carriers.

iPSC-derived Motor Neurons May Need to Age to Better Model ALS

In the July 18 in Nature Neuroscience, researchers report important progress toward characterizing and improving induced pluripotent stem cell (iPSC) models of ALS. By comparing the transcriptomes of iPSC-derived spinal motor neurons (MNs), fetal and adult spinal tissues, and spinal MNs extracted from control and ALS patients' postmortem samples, the researchers found that the gene expression signatures of iPSC-derived MNs resembled fetal tissue more than adult MNs. They further characterized gene networks that are active in different stages of maturation and aging of spinal MNs, and showed that ALS leads to dysregulation of these networks. The findings suggest that activation of key maturation pathways in iPSC-derived MN models of ALS may yield cellular models that more closely mimic human disease.

New CHMP2B Mouse Model Develops ALS- and FTD-like Symptoms

Mutations in charged multivesicular body protein 2B (CHMP2B), a protein involved in vesicle trafficking and autophagy, were identified as a rare cause of frontotemporal dementia (FTD), and were also associated with ALS and ALS/FTD. Previously generated transgenic models of CHMP2B mutations did not exhibit a motor phenotype (see Sept 2015 news), but a new mouse model described in June 21 online in Human Molecular Genetics, exhibits symptoms and pathology reminiscent of both ALS and FTD. Homozygous transgenic mice developed a progressive gait abnormality, with reduced muscle strength and decreased coordination culminating in generalized paralysis, accompanied by denervation of neuromuscular junctions but not motor neuron death. The mice also exhibited behavioral disturbances, such as decreased social interaction. This model may serve as a tool to investigate pathways involved in both ALS and FTD.

New Method Enables Single-Cell Gene Expression Analysis of Motor Neurons In Situ

A new technique, termed laser capture microscopy with transcriptome sequencing (LCM-seq"), has enabled researchers to conduct transcriptome analysis on single cells in situ, overcoming limitations posed by small tissue samples and limited cell numbers. In the July 8 Nature Communications, researchers show applications of this approach to neurons from mouse spinal cord, human post-mortem tissues, and histologically stained brain tissue. Using spatial information, which is preserved since the cells are not dissociated, LCM-seq was used to identify unique transcriptional profiles for motor neurons (MNs) based on their spatial location in the spinal cord. The researchers hope

to use LCM-seq to analyze single MNs in ALS to elucidate pathways underlying selective MN vulnerability to disease.

Drug News

Brainstorm Cell Therapeutics Announces Positive Results of NurOwn Trial in ALS
Stem cell biotechnology company Brainstorm Cell Therapeutics Inc. announced positive results for its randomized, double-blind, placebo-controlled Phase II clinical trial of NurOwn in ALS, which enrolled 48 patients at 3 sites in the U.S. (see Oct 2015 news). The NurOwn technology is a candidate stem cell therapy that entails transplantation of autologous mesenchymal stem cells (MSCs) designed to secrete neurotrophic factors. The company reported that the primary objectives of safety and tolerability were met. Exploratory analysis of secondary outcomes measures revealed improvements in the ALSFRS-R slope following treatment in a greater percentage of treated patients than controls, and CSF biomarker analysis revealed an effect on neurotrophic factors and inflammatory markers. The company next plans to conduct a larger, pivotal study with repeat dosing to assess treatment efficacy following this preliminary signal of an effect.

Deals & Partnerships

Iron Horse and Euroimmun Partner to Bring First ALS Diagnostic Test to Market
Molecular diagnostics company Iron Horse Diagnostics announced a non-exclusive license agreement with Euroimmun Medizinische Labordiagnostika, a German company that specializes in *in vitro* diagnostics, to launch the first marketed ALS diagnostic test in Europe and the U.S. The diagnostic test is based on research by Bowser and colleagues pointing to pNfH (phosphorylated axonal neurofilament subunit H) and complement c3 as candidate diagnostic biomarkers for ALS (see Oct 2011 news, Ganesalingam et al., 2011, Ganesalingam et al., 2013). The CSF-based diagnostic test has been shown to be over 90% accurate, and a blood-based biomarker is undergoing further validation. These tests could significantly accelerate the timeline for an ALS diagnosis, which could improve patient care and enable earlier therapeutic interventions.

Amylyx Secures Funds for Phase II Trial of AMX0035 for ALS
Cambridge, MA-based startup company, Amylyx Pharmaceuticals has secured funding from The ALS Association and ALS Finding a Cure for a Phase II trial of AMX0035 in ALS. Amylyx's oral therapeutic candidate is a combination of two drugs, sodium phenylbutyrate (PB) and tauroursodeoxycholic acid (TUDCA), which have been shown to exert synergistic neuroprotective and anti-infammatory effects in preclinical models. Separately, each compound has exhibited efficacy in pre-clinical models (Ryu et al., 2005, Vaz et al., 2015) and demonstrated safety and tolerability in ALS clinical trials (Cudkowicz et al., 2009, Elia et al., 2016), as well as preliminary signs of efficacy. The clinical trial, which is expected to begin later this year, will test the safety and tolerability of AMX0035, as well as functional outcomes.

Funding Opportunities:

July 2016

The ALS Assistive Technology Challenge. LOI due by Jul 29, 2016.

August 2016

The Judith and Jean Pape Adams Foundation ALS Research Grants. Application due Aug 12, 2016.

Accelerating Drug Discovery for Frontotemporal Degeneration. LOI due Aug 12, 2016.

NEW! Target ALS Foundation Industry-Led Consortia. LOI due Aug 31, 2016.

NEW! Target ALS Foundation Young Investigator-Led Collaborative Projects. LOI due Aug 31, 2016.

September 2016

Frick Foundation for ALS Research Grants. Applications due Sept 30, 2016.

Full List of Funding Opportunities >>

Job Opportunities:

Director, Neuroscience Research & Drug Discovery, Verge Genomics, San Francisco, CA.

Scientist I - Electrophysiology, Research, Biogen, Cambridge, MA.

NEW! Director, Neurodegenerative Disease Research Center, Arizona State University, Tempe, AZ.

NEW! Research Associate (PhD), University College London, London, UK.

Full List of Job Opportunities >>

Upcoming Meetings:

August 2016

Aug 7-12, 2016: Girona, Spain: Gordon Research Conference on Neurobiology of Brain Disorders.

September 2016

NEW! Sept 7-9, 2015: Baltimore, MD: Neurological Disorders Summit.

NEW! Sept 25-28, 2016; Bar Harbor, ME: Molecular Mechanisms of Axon Degeneration.

November 2016

Nov 10-11, 2016: San Diego, CA: RNA Metabolism in Neurological Disease.

Nov 12-16, 2016: San Diego, CA: Society for Neuroscience Meeting.

December 2016

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

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