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Research News

Blood NfL Holds Promise as Measure of Disease Progression and Drug Effects

Neurofilament light chain (NfL) is emerging as a highly promising biomarker for neurodegenerative diseases, including ALS (see Jun 2015 news). Results published June 9 in Neuron further strengthen the case for NfL as a useful measure that can be detected in blood and CSF of both humans and mice. Importantly, its levels correlate with onset and progression of brain pathology in mouse models of synucleinopathies, tauopathy and β-amyloidosis and its levels are sensitive to artificial manipulations of this pathology. Further studies are needed to longitudinally track how NfL concentration changes throughout the course of human disease, and how it responds to therapeutic interventions, but plans already exist for evaluating NfL as a surrogate outcome measure in ongoing neurodegenerative disease clinical trials.

A Breath Test for ALS? Possible, but not There Yet

Volatile organic compounds (VOCs) in the breath of people with ALS may differ from those with cervical spondylotic myelopathy (CSM), according to findings published May 23 in Scientific Reports. In a study with 28 ALS patients and 13 CSM patients, researchers identified four metabolites that were elevated in CSM vs. ALS patients. These intriguing but preliminary findings suggest that breath VOCs may represent a novel avenue for identifying diagnostic biomarkers for ALS. More work is needed to validate these results in more patients, and to determine both their clinical utility and potential as a progression biomarker.

HIPK2 Provides Link Between ER Stress and Neuronal Death in ALS

The molecular mechanisms that drive motor neuron death in response to misfolded protein accumulation are not completely understood, but a paper in the June 15 Neuron adds one more piece to the puzzle. The researchers describe a previously-unknown role for the homeodomain interacting protein kinase 2 (HIPK2) in triggering motor neuron death in response to ER stress via the IRE1α pathway. Mouse models of SOD1-ALS with a deletion of HIPK2 lived longer and had improved motor function than

mice expressing the kinase. Furthermore, expression of activated HIPK2 was elevated in C9ORF72 ALS and sporadic ALS patients at levels that positively correlated with phosphorylated TDP-43. These findings suggest that HIPK2 could provide a promising druggable target for ALS.

ALS Astrocytes Upregulate Drug Efflux Pumps in BBB Endothelial Cells

The drug efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are expressed on endothelial cells of the blood brain barrier (BBB) and limit entry of toxins into the CNS. However, they can also block entry of beneficial drugs. Both transporters are upregulated in the spinal cord of ALS mice and in postmortem spinal cord from ALS patients, and a drug that blocks them enhances the effect of riluzole in ALS mice (see Dec 2014 news). A follow up report in the May 9 Glia online sheds light on what causes the increased expression of these transporters in ALS. Co-culture experiments with human iPSCs reveal that astrocytes expressing SOD1 or FUS mutations drive an increase in P-gp expression on BBB endothelial cells in an NFκB-dependent manner. Interestingly, these two mutations exert this effect through distinct but convergent signaling cascades.

Misfolded Proteins Escorted Out of Cells via Novel Secretion Pathway

When the proteasome becomes overwhelmed with degrading unwanted proteins, cells can discard aberrant proteins through a newly-identified misfolding-associated protein secretion (MAPS) pathway, according to a paper in the June 13 Nature Cell Biology. Scientists at the National Institute of Health have found that when misfolded polypeptides start to accumulate, the endoplasmic reticulum (ER)-associated enzyme, USP19, can recruit and deubiquitylate the unwanted proteins. The USP-protein complexes are then packaged into late-endosome-like Rab9-expressing vesicles that are released into the extracellular space. An initial venture into neurodegenerative diseases identified α-synuclein as a substrate of the MAPS pathway in HEK293T cells. However, further research is needed to see whether this pathway exists in primary neurons and *in vivo*, and if and how it applies to different misfolded protein implicated in neurodegenerative diseases, including ALS.

Deals and Partnerships

Mitsubishi Tanabe Pharma Submits New Drug Application for Edaravone to Treat ALS in the United States

The Japanese pharmaceutical company Mitsubishi Tanabe Pharma Corporation has announced the submission of a New Drug Application (NDA) to the US FD
A for edaravone for the treatment of ALS. The drug, also known as MCI-186, was approved for ALS in Japan in 2015 (see Jun 2015 news), and the same year wasgranted Orphan Drug Designation by the EMA and FDA in its oral formulation called TW001, which is under development by the Dutch biotechnology company, Treeway (seeMar 2015 news). Results of two Phase III clinical trials of the free radical scavenger conducted in Japan (see Jan 2016 news) suggested that a subgroup of ALS patients within milder respiratory symptoms benefit from the drug. It is unclear whether the FDA will approve the drug based on these data, or will request Phase III studies in the US.

Target ALS Selects RUDCR Infinite Biologics for ALS Stem Cell Core

The Target ALS Foundation has contracted with Rutgers University Cell and DNA Repository (RUCDR) Infinite Biologics, the largest university-based biorepository, to house the human ALS stem cell lines of the Target ALS stem cell core. Available cell lines from Target ALS at RUDCR can be found in the online catalog, and additional genetically modified lines are expected to be added through the course of 2016. Stem cells from the Target ALS core are provided to researchers from academia and industry without reach through to data and intellectual property generated by using the stem cells (more information can be found here).

Yumanity and NY Stem Cell Foundation Announce Discovery Collaboration
Yumanity Therapeutics, a biotechnology company focused on drug discovery for neurodegenerative diseases associated with protein misfolding, has announced a partnership with the NY Stem Cell Foundation (NYSCF) Research Institute to generate induced pluripotent stem cell (iPSC) lines for applications in drug discovery for ALS, Alzheimer's and Parkinson's disease (see Feb 2016 news). Yumanity will leverage NYSCF's Global Stem Cell Array technology for large scale production of standardized iPSCs to incorporate into the company's drug discovery platform, which integrates high-throughput phenotypic screening in yeast cells with drug candidate validation in human patient-derived iPSCs.

Funding Opportunities:

July 2016

The Paulo Gontijo Institute (PGI) International Medicine PG Award. Applications due July 1, 2016.

NEW! The AFM Telethon Research Grants. Applications due July 5, 2016.

CIRM Partnering Opportunity for Translational Research Projects. Applications due July 15, 2016.

NINDS Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases. LOI due July 18, 2016.

NEW! The ALS Assistive Technology Challenge. LOI due by July 29, 2016.

September 2016

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

Full List of Funding Opportunities >>

Job Opportunities:

Postdoctoral Position
Gladstone Institutes, Steven Finkbeiner Lab
San Francisco, CA

Director, Neuroscience Research & Drug Discovery
Verge Genomics

San Francisco, CA

Scientist 1 - CNS Discovery
Teva Pharmaceuticals
West Chester, PA
Full List of Job Opportunities >>

Upcoming Meetings: *Don't miss the abstract submission deadlines listed below!*

July 2016

July 10-14, 2016: Arlington, VA: RESNA Annual Conference.

August 2016

August 7-12, 2016: Girona, Spain: Gordon Research Conference on Neurobiology of Brain Disorders. **Abstracts due July 10, 2016.**

November 2016

Nov 10-11, 2016: San Diego, CA: RNA Metabolism in Neurological Disease. **Abstracts due July 17, 2016.**

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

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

TargetALS Core Facilities

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