Published in final edited form as:
Brain Res. 2014 October 10; 1584: 1–2. doi:10.1016/j.brainres.2014.09.011.

RNA metabolism in neurological disease

Fen-Biao Gao, Ph.D. and
Department of Neurology, University of Massachusetts Medical School, Worcester, MA 01605, United States fen-biao.gao@umassmed.edu

J. Paul Taylor, M.D., Ph.D.
Department of Cell and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, United States jpaul.taylor@stjude.org

There is a growing appreciation of a role for altered RNA metabolism in a broad range of neurological diseases. For two decades we have recognized that fragile X syndrome and spinal muscular atrophy (SMA) are associated with the loss of function mutations affecting expression of the RNA-binding proteins FMRP and SMN, respectively. Later it was discovered that the pathogenesis of some microsatellite expansion disorders, including the myotonic dystrophies and some spino-cerebellar ataxias, involve the sequestration of RNA splicing factors. The emerging field that was focused on the role of RNA metabolism in neurological diseases reached a watershed moment in 2006 when it was recognized that the RNA-binding protein TDP-43 is a prominent component of the pathological inclusions characteristic of sporadic and familial forms amyotrophic lateral sclerosis, frontotemporal dementia and related diseases. The subsequent identification of disease-causing mutations in the RNA-binding proteins TDP-43, FUS/TLS, hnRNPA1 and hnRNPA2B1 in rapid succession provided the field momentum and led to the 2011 symposium "RNA-binding Proteins in Neurological Disease". As the field continued to grow, drawing in more investigators and chalking up more discoveries, we elected to organize a follow up meeting. This symposium, "RNA Metabolism in Neurological Diseases" held over two days in November 2013, drew> more than 350 participants, including oral presentations by 27 investigators and poster presentations by over 100 investigators covering diverse topics, including updates on the genetic origins of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), the mechanisms of disease associated with microsatellite repeat expansions in RNA, the role of unconventional, repeat-associated non-ATG ("RAN") translation in repeat expansion diseases, cellular and animal models of GGGGCC repeat expansion in C9ORF72, RNA defects in Alzheimer's disease (AD), Parkinson's disease (PD) and SMA, RNA granules, microRNAs, and RNA-targeted therapies. To complement this meeting, a special issue of *Brain Research* is presented here, with 12 papers describing some of these topics as well as research that could not be accommodated in the meeting.

A highlight of the meeting was the extensive discussion of unstable microsatellite expansion diseases. **Maurice Swanson** and colleagues present a historical perspective of these diseases, including myotonic dystrophy, fragile X-associated tremor-ataxia syndrome, and *C9ORF72-related* FTD/ALS. They review current concepts regarding potential pathogenic mechanisms in these diseases, including toxic gain-of-function mediated by RNA and the possibility of toxicity mediated by peptide products produced by RAN translation. Detailed

discussions of these mechanisms in the context of different microsatellite diseases will allow readers to grasp their commonalities and disease-specific features.

Several groups have reported that pathogenic GGGGCC expansions are accompanied by reduced expression of *C9ORF72* transcripts, yet the basis for this reduction is unknown. **Leonard Petrucelli** and colleagues previously demonstrated trimethyla-tion of histones H3 and H4 in brain samples from carriers of pathogenic GGGGCC expansions. A related report examined blood, spinal cord and frontal cortical tissue of c9FTD/ALS patients, reporting a high frequency of hypermethylation of the CpG island located at the 5′ end of the *C9ORF72* locus. In this issue, Petrucelli and colleagues take the story further, reporting for the first time hypermethylation within the *C9ORF72* promoter in cerebellar tissue.

The microtubule-associated protein tau is widely dispersed in neurons, distributed over the entirety of the axonal compartment. The mechanisms responsible for the localizing tau protein throughout the cell are unknown. In this issue **Jean-Marc Gallo** and colleagues report the results of a fluorescence in situ hybridization study that illustrates that MAPT mRNA in axons is associated with RNA transport granules and components of the translational machinery, suggesting that the spatial distribution of tau protein is controlled by transport of tau mRNA followed by local translation.

In a related story, **Shin Kwak** and colleagues review evidence that reduced expression of the adenosine deami-nase ADAR2 could initiate a pathological cascade that drives the relocalization of TDP-43 from the nucleus to the cytoplasm. ADAR2 editing of mRNA encoding GluA2 impacts normal AMPA receptor assembly. Kwak and colleagues argue that ADAR2 deficiency results in abnormal assembly of AMPA receptors and increases the Ca2+ permeability of AMPA receptors with subsequent activation of the Ca2+-dependent serine protease calpain. They argue further that activation of calpain results in inappropriate cleavage of TDP-43, culminating in the accumulation of aggregation-prone TDP-43 fragments in the cytoplasm.

TDP-43 is a major component of the cytoplasmic inclusions characteristic of ALS and related diseases. In most cells TDP-43 is predominantly localized in the nucleus. In disease, however, there is a conspicuous clearance of TDP-43 from the nucleus in concert with accumulation in cytoplasmic inclusions. This observation has fueled questions about the relative contributions of loss of nuclear TDP-43 function vs. toxic gain of cytoplasmic function in disease. **David Morton** and colleagues studied the function of the *Drosophila* ortholog of TDP-43, TBPH. They identified *cacophony* mRNA as a binding target of TBPH and showed that deficiency in TBPH impairs the stability and splicing of *cacophony*. They show further that loss of TBPH function results in reduced levels of the gene product, a voltage-gated calcium channel, in the neuromuscular junction and that this is associated with a locomotor defect. These findings support the contention that loss of TDP-43 function could contribute to ALS pathogenesis.

Ben Wolozin and colleagues have contributed an article that discusses the relationship of stress granules to the pathological inclusions in ALS, FTD and related diseases. Stress granules are cytoplasmic RNA–protein assemblies composed of mRNPs that are stalled in

translation. These structures are formed in response to a variety of stimuli and represent a form of past-transcriptional regulation of gene expression. It has emerged from several quarters that the pathological inclusions in ALS, FTD and related diseases are composed largely of components found in stress granules, suggesting that pathology evolves from these structures.

Steve Perrin and colleagues describe a novel mouse model of ALS based on exogenous expression of mutant human TDP-43. They generated transgenic mice expressing TDP-43 (A315T) using the Prp promoter. These animals showed early mortality and developed ubiquitin-positive inclusions in spinal cord motor neurons, but had no neuromuscular phenotype. Rather, these investigators found a progressive defect in gastrointestinal motility, culminating in frank stasis that was primarily responsible for decreasing longevity in these mice.

MicroRNAs (miRNAs) – a class of small, noncoding RNAs that regulate mRNA translation and stability mostly through 3′ untranslated regions of target mRNAs – have been implicated in many physiological and pathological processes. Three review articles here concern the roles of these small RNAs in neurological disease. **Walter Lukiw** discusses circulating miRNAs in the human central nervous system and speculates about their potential involvement in the progression of AD. **Angélica Zepeda** and colleagues review how miRNAs can be modulated by synaptic activity and in turn contribute to synaptic function; they also discuss the roles of miRNAs in synaptic alterations in AD. **Lan Tan** and associates address the topic of miRNAs in human and animal model of epilepsy, in particular, their dysregulation and potential therapeutic use.

Recent interesting findings suggest that defects in RNA metabolism also play a key role in the pathogenesis of PD. **Bingwei Lu** and co-workers describe how different familial PD genes, such as *LRRK2, PINK1, Parkin*, and *eIF4G1*, interact with components of the ubiquitous translation initiation machinery as well as miRNA and mTOR pathways that modulate protein translation. These advances highlight the complexity of PD pathogenesis and the need to further understand the selective vulnerability of DA neurons in that disorder.

Finally, despite breathtaking progresses in our understanding of pathogenic mechanisms of various neurological diseases, there are still no effective treatments. One promising approach is oligonucleotide-based therapies. **Eran Hornstein** and colleagues summarize the types of oligonucleotides that can be used for therapy and their formulation, delivery, and potential use in AD, PD, Huntington’s disease, ALS, and SMA. Despite enormous challenges ahead, tireless efforts by all the scientists who attended this meeting and elsewhere make RNA-based therapy more realistic than ever.