MND Australia
International Research Update

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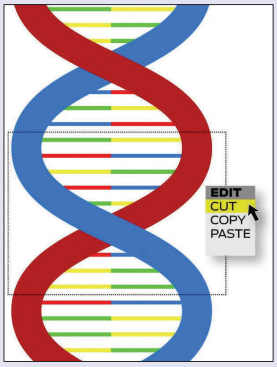
While the genetic complexity of MND is notorious within the research world, the study of some of the main causative genes has given us incredible insight into what are shaping up to be the main pathways involved in this disease. Lately much interest has been placed on the genes encoding TDP-43 and FUS, RNA-binding proteins (RBPs) which share very similar functions in regulating the proper processing of RNA. As we will see in this report, RNA processing is fundamental to all other pathways in the cell. Several recent studies add to a growing body of evidence pointing to deregulated RNA processing as a major disease mechanism in MND.

FUS behaviour gets more than itself into trouble

It is estimated that mutations in FUS cause about 4% of inherited MND cases, and within this portion the clinical manifestation of disease varies considerably. This diversity might reflect differing mechanisms by which the various FUS mutations cause motor neurone dysfunction. Like TDP-43, FUS is mainly located in the cell nucleus, but shuttles back and forth to the cytoplasm to carry out functions in both compartments. A particularly important, but not yet fully understood role of FUS in the cytoplasm, is its association with structures called stress granules (SGs). The production of SGs is a cellular stress response mechanism. These structures hijack RNA and RBPs in an attempt to slow down cellular activities, allocating resources preferentially to processes that are essential for cell survival. Being such a busy protein, it is of high interest to many researchers to zone in on how alterations in the behaviour of FUS affect its role in RNA processing and the contribution to disease.

Sandra Jackel and her colleagues in Tubingen and Munich in Germany, used a FUS fly MND model to investigate factors involved in the import of FUS to the nucleus and any harmful effect caused by alterations to this import. The data they collected suggests that in addition to the more characterised role of a loss of nuclear FUS function in MND, over-abundance and aggregation of FUS in the nucleus is detrimental. However, illustrating the diversity of FUS-caused disease mechanisms are contrasting findings by researchers in London and Oxford. In a FUS MND family with rare juvenile disease onset and rapid disease progression, they discovered a FUS mutation that prematurely shortens the FUS protein such that it impairs its localisation to the nucleus. Examining this mutant FUS in neuronal cell culture, they found that the shift of predominant localisation from the nucleus to the cytoplasm and association with SGs correlated with neuronal dysfunction. What these different findings suggest is that deregulated behaviour of FUS is enough to wreak havoc in neurones. Discovering how to target this deregulation may prove to be a way of treating MND patients carrying FUS mutations.

RNA processing: draft copies and RNA editors



Our genes, stored in the molecular language of DNA, must first be transcribed into the similar language of RNA before the proteins they code for can be made. However, the copy of RNA that is made is more like a draft version that must be edited by RBPs.

This RNA processing is one of the most vital functions carried out in our cells. Without proper editing, the correct form of the encoded proteins cannot be made. As proteins comprise a major proportion of all the cellular machinery, and are absolutely essential for cells to function at all, interfering with their correct manufacturing is detrimental to cell health.

TDP-43 and FUS are among the cohort of RBPs in the cell. If these RNA editors themselves cannot be properly regulated, the downstream effects become amplified as the RNA and thus the proteins they help regulate become dysfunctional. With this in mind, it is not hard to imagine how RBP deregulation can lead to disease.

MND Research Shorts

- *Oxidative stress is increasingly being implicated in MND. Wint Nandar and colleagues in Pennsylvania have just reported findings suggesting that the HFE gene, associated with iron homeostasis and oxidative stress, aggravates disease progression in a SOD1 mouse MND model.*
- *Researchers at Thomas Jefferson University in the USA have begun to uncover the mechanisms by which mutations in the UBQLN2 gene cause MND. Although more work is needed, it seems that neurodegeneration is caused by some gain of toxic function by the altered UBQLN2 rather than a loss of its normal function.*
- *Within the pool of RBPs in the cell it is thought that a hierarchy exists whereby specialised RBPs regulate the processing of others. Researchers in Alabama have identified the RBP HuR as being in the "higher class" of RBPs, regulating TDP-43 and FUS. Loss of HuR-mediated TDP-43 and FUS processing was found to cause considerable neuronal toxicity. Work is needed to test the potential of HuR as an MND drug target.*
- *Further evidence for deregulated RNA processing in MND comes from a study carried out by researchers in the UK and the Netherlands. Using patient-derived tissue, they showed that loss of TDP-43 from its predominant nuclear location in diseased neurones resulted in significantly altered expression of many RBPs as well as other genes with various roles in RNA processing.*

Highlights from the 25th International Symposium on ALS/MND

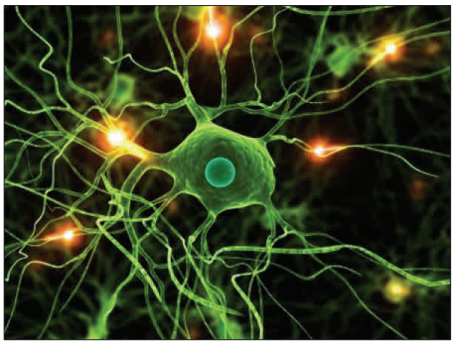
The 2014 International Symposium, hosted by ALS Liga Belgium in the breathtaking city of Brussels, was off to a brilliant start on Friday 5th December. Chairing the symposium for the last time after years of dedication was Professor Wim Robberecht, who, together with the symposium committee, organised an exciting and thought-provoking program of platform and poster presentations by scientific and clinical researchers from around the world. Reported here are a few selected research highlights that were presented in the scientific sessions over three very stimulating days.

A fresh perspective: speeding up the clinical testing of new drug candidates

The global community of MND researchers have been working hard for years to narrow down on the biological pathways involved in the development and progression of this devastating disease. The fruits of this labour have been rapidly ripening in recent years with many groups identifying potential drug targets in the various genetic variants of MND. As more genes continue to be implicated, potential drug targets will continue to be identified, causing a significant bottleneck in the testing of these drug candidates; a process that requires considerable investment of human and financial resources.

In the first talk of the symposium, Alfred Sandrock of Biogen Idec spoke about advancing the drug testing process by identifying key criteria for predicting and evaluating the viability of a drug candidate before it transitions from the research to development phase. He also spoke about replacing animal models with induced pluripotent stem cells (iPSCs) derived from MND patients for pre-clinical drug trials, highlighting their usefulness as a test system.

Epilepsy and MND: altered electrical activity a key disease target?



Kevin Eggan from the Harvard Stem Cell Institute and Howard Hughes Medical Institute gave an exciting presentation on an approach his lab has been using to generate iPSC-motor neurones (iPSC-MNs) from patient-derived blood and skin cells, and how they have used them to discover a new drug candidate for MND. Studying iPSC-MNs from patients with different genetic mutations, Kevin's group found that they shared alterations in their electrical activity not found in cells from healthy individuals. Importantly, they also discovered that the drug *retigabine*, already used to treat epilepsy, reversed the aberrant changes in electrical activity.

An initial trial of *retigabine* to test the safety of the treatment in MND patients will begin at the end of 2014.

iPSCs: Patients' own cells may lead the way to an effective MND treatment

Further highlighting the worth of iPSCs derived from MND patient tissue is the work presented by Ruxandra Mutihac of the University of Oxford. Ruxandra and her group have generated iPSC-MNs from patients carrying the C9ORF72 mutation, and used them to discover aberrant changes that are specific to this MND genetic variant. Calcium ion signalling is fundamental to motor neurone function. This team of researchers identified disruption of this pathway in the C9ORF72-iPSC-MNs that was associated with cell stress and increased susceptibility to a type of cell death called apoptosis, which is believed to be abnormal in MND. As was raised by Alfred Sandrock in his talk on testing drug candidates, Ruxandra spoke about the possibility of using these C9ORF72-iPSC-MNs as a tool for drug screening and development.

Catastrophic cliffs: motor neurones living on the edge

In a talk that cut straight through to the heart of MND genetics research, John Hardy of Reta Lilla Weston Research Laboratories, UCL Institute of Neurology, analysed the current state of genetics research and discussed the common problems that need to be addressed. Sifting through the wealth of genetic data to date, he described how the genes implicated in MND seem to be mapping to specific molecular pathways; in particular, the ubiquitin-proteasome system (UPS), the cell's main "garbage disposal" machinery for recycling proteins.

They have also mapped the genes implicated in the neurodegenerative diseases frontotemporal dementia (FTD) and spinocerebellar ataxias (SCAs), discovering that these map to specific pathways.

As these diseases affect different types of neurones, these discoveries highlight that specific neuronal classes may be particularly susceptible to deregulation of certain molecular pathways; as put by Professor Hardy, "catastrophic cliffs" where neurones sit vulnerably at the edge.

Working from this fresh perspective may help researchers not only identify other MND-associated and causative genes, but also to accurately define the exact pathways involved in these complex neurodegenerative diseases.