MND Australia
International Research Update

Dr Luke McAlary, Bill Gole MND Postdoctoral Fellow, University of Wollongong

An excellent meeting of international researchers to tackle the problem with protein aggregation

I am writing this article after having finished organising and attending a conference on protein aggregation and disease in Wollongong New South Wales. Whilst protein aggregation plays a role in many neurodegenerative diseases, MND-focused research constituted a sizable bulk of presentations and posters at the conference. This focus on MND is highly encouraging and stimulating.

This issue of the MND international research update highlights research improving patient monitoring, targeting mitochondria, degrading toxic C9 RNA, and identifying patients who may respond better to CuATSM.

Patient monitoring to improve care for patients[1]

A common issue in the care of MND patients is that the time and resources available to monitor progression is inadequate. This is due to the cost and difficulty in providing continuous in-person care and monitoring. A research group from the Netherlands has proposed and tested how e-monitoring (think telehealth or online healthcare) of patients would be received and how useful it would be to provide more effective assessment.

Multiple ALS care teams were encouraged to join the program, which was implemented across 10 care teams. First, the research team engaged the care teams and their patients to explain and describe the proposed care trial. Next, the researchers advised the care teams and patients on the implementation of the e-monitoring. The monitoring itself was performed using a mobile phone application where patients would record their weight, well-being, and functional status, along with regular online check ins from a healthcare coach specialised in ALS care.

The research team found that most patients adhered to the schedule and were very happy to use the mobile phone application and check in regularly with a health coach. The major complaints from patients were that the mobile application itself was slow and sometimes difficult to log on to, and that use of the application made them confront their condition more often than they would have liked. The healthcare coaches reported that they disliked the inability to integrate the mobile phone application with their own patient monitoring software.

Considering the difficulty associated with sending experts to various locations to determine the status of patients, this sort of approach could be a game-changer in many ways. First and foremost, it provides patients a routine and consistent model of care.

Secondly, it may allow for a larger cohort of patients to be monitored over time so that more accurate estimates and predictors of disease progression could be generated. This information would be invaluable for clinical trials. However, consideration would have to be given to finding a balance between frequency of monitoring and convenience and intrusiveness for patients and carers.

Mitochondria are a fragile component in cells[2]

You may have heard the phrase that 'mitochondria are the powerhouse of the cell', which is a brief way of describing the role this organelle plays in cell biology. More specifically, mitochondria are small organelles within cells that carry out the oxidative phosphorylation to generate the main energetic molecule that cells use, ATP i.e. they literally power the cell. When mitochondria get sick, cells get sick, so one would imagine that this important organelle would be well-protected by cells. In fact, mitochondria can be found to be sick in most neurodegenerative diseases, suggesting that perhaps they are a good target for us to attenuate these disorders.

A team of researchers from Washington University in the USA theorised that by using some new drugs that keep mitochondria healthy they may effectively slow disease in MND models. To test this theory, they utilised patient-derived cell models and the SOD1 animal model of MND. They treated these models with compounds that activated and protected mitochondria from becoming sick.

Tests of the drugs in human cells showed that the mitochondria were well-protected in cells derived from patients with SOD1-associated, FUS-associated, and TDP-43-associated cases of ALS. The team found that the drugs were capable of improving mitochondrial health in all these cases by measuring how mobile the mitochondria were. They then tested the drug in mice, finding that a sustained dosage was protective in the animals too.

This research provided more information that mitochondria are a good target in MND. I would propose that the next step that these researchers should take is to combine this drug with others. By targeting multiple pathways in disease, we may see better outcomes as compared to a single drug treatment.

New drugs for C9-associated ALS[3]

One of the major causes of familial MND is large expansions of repetitive code in the C9orf72 gene. Following the central dogma of biology, that DNA produces RNA, and this RNA then provides the template to produce a protein, we have three potential targeting strategies for treatment, i.e. DNA, RNA, or protein. In the case of C9-ALS, RNA targeting is likely the best option, as there is good evidence to suggest that the RNA itself is toxic to cells. Trying to just delete the gene is often too difficult and can have unforeseen side-effects

Researchers from the USA have developed a new molecule with good qualities that may potentially be used against C9-ALS. This drug binds to C9 RNA and eliminates the repeat expansions within it by forcing the cells to degrade the RNA. They tested this molecule on several models of C9-ALS and found it was effective at lowering the expression of toxic protein and lowering the RNA-toxicity in all of these models. The researchers also determined a very important feature of the molecule, that it was capable of crossing the blood-brain barrier.

The blood-brain barrier is an extremely important part of our physiology. It is a layering of tightly packed cells that separates the central nervous system from circulating blood. It allows nutrients and essential molecules to cross into the nervous system so that neurons have food, but stops most other molecules from crossing. Although this protects the brain, it can often prevent some drugs that have shown good results in pre-clinical models from proceeding further through the development pipeline, as they can often not cross this barrier.

The researchers have a very promising molecule in their hands. Considering that the molecule is capable of crossing the blood brain barrier and it appears effective in both human cells and mice, there is good potential for a clinical trial of this molecule. Although this molecule only would be effective for C9 cases, any drug that can modify ALS progression is an incredibly welcome prospect and worth pursuing.

CuATSM still showing benefit[4]

CuATSM is well known within the Australian MND community due to the ongoing clinical trial that was carried out here. For those that don't know, CuATSM is a small molecule that binds copper and is capable of carrying the copper into the central nervous system and alleviating various issues. This compound has shown great promise in multiple cell and mouse models of MND as well as early stage clinical trials.

Although successful in mice, what hasn't been explored is whether CuATSM is capable of working in multiple systems to alleviate MND pathology. Researchers from the USA set out to examine the effect that CuATSM may have on a human cell model where astrocytes and neurons were cultured together. This model is much closer to what we see in humans, where MND astrocytes can kill healthy neurons. Here, the researchers used healthy neurons in culture with diseased astrocytes, so they could examine the role that astrocytes play.

Interestingly, the researchers found in most cases that CuATSM was capable of rescuing the neurons, but not all the time. The researchers followed this thread of evidence and determined that in some patient-derived cell lines the mitochondria were unable to effectively produce energy. Those lines where the mitochondria appeared to be working OK were rescued by CuATSM, others were not.

It is becoming increasingly evident that MND is an extremely variable disease. This issue has impeded molecular characterisation and treatment of the disease. The system established here in this research exemplifies why a personalised approach to medicine is warranted (even beyond MND). It would be a good idea to establish personalised treatments for patients on the basis of culture of their cells.

MND Research Shorts

- TDP-43 regulates the expression of many genes, and perhaps in disease this regulation becomes dysfunctional. Dr Emanuele Burrati from Italy led a team that discovered that a gene called NOS1AP was dysregulated by TDP-43 in MND. This gene is part of the nitric oxide cell-stress response in neurons, suggesting that perhaps this system is involved in MND pathogenesis[5].

- Understanding how MND progresses in patients is paramount to better designed clinical trials and determining if therapies actually work. A research team from Boston USA closely examined the progression of disease in roughly 2000 patients. They found that C9-ALS patients had a more rapid progression than sporadic, but that C9-ALS patients with thyroid dysfunction had a slower progression. This suggests that alterations to thyroid function may be protective in disease[6].

- The underlying physical structure of protein aggregates (clumps) has implications for how these aggregates cause disease. Researchers from Sweden mapped the structure of SOD1 aggregates arising from several MND experimental models finding that aggregates produced in mice differ from those produced in cell cultures or from test tube. This has implications for the role that the central nervous system may play in shaping the toxic and propagative SOD1 aggregates in disease[7].

- Axons are one of the primary sites of degeneration in MND, and as such they are a target for therapy. Researchers from the USA deleted one axon gene (DLK) whilst overexpressing another (ATF3) in the SOD1 mouse. They found that this promoted survival of the mice and improved outcomes. Figuring out the interplay of genes within the motor neuron axon is important for gaining more insight into MND[8].

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