MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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This issue of the International Research Update is brought to you by Dr. Luke McAlary from the University of Wollongong. Luke is the 2020 recipient of MND Research Australia's prestigious Bill Gole MND Postdoctoral Fellowship and brings a wealth of knowledge to this publication. MND Australia is very grateful to have Luke on board to author the International Research Update.

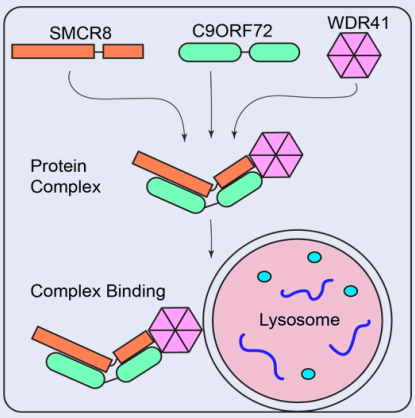
We are still moving forward

Motor neurone disease (MND) researchers worldwide are still working hard on improving patient outcomes, discovering new biochemical pathways, and examining potential treatments. This issue of the international research update focuses mainly on the basic science that is being performed in the area of MND. Basic science is the study of how things happen. In regards to MND, basic science is focused on understanding the most fundamental causes of disease. How do mutations affect protein structure and function? How does stress differentially affect MND cells and healthy cells? Here we touch on the structure and a potential function of C9ORF72 protein, a possible route of cell regeneration, an FDA-approved compound that has promising effects in mice, and a strategy for slowing disease progression by reducing inflammation.

A 'structural' study looking at how proteins interact with each other in the neuron reveals how C9ORF72 may contribute to MND

Using cryo-electron microscopy, Professor James Hurley (University of California, Berkeley) and colleagues solved the 3D structure of an important protein complex formed by the C9ORF72 protein. This complex plays an important role in various cell-signalling pathways that affect processes such as glial cell activation, protein degradation, and regulation of the motor neuron cytoskeleton.

Loss or gain of function? Or both? A focus is usually placed upon mutated repeated sections (hexanucleotide expansions) in the C9ORF72 gene, which lead to the generation of repetitive RNA sequences, which invariably lead to the expression of toxic repetitive protein sequences which damage neurons. What is often less considered, is that the hexanucleotide repeats in the C9ORF72 gene also cause 'haploinsufficiency' (lower expression of a gene that results in abnormal cell function). Therefore, an understanding of the normal role of C9ORF72 protein is essential to determining if the lower levels of the gene in C9ORF72-MND patients plays a role in the disease.



C9ORF72 structurally linked to various cellular processes.

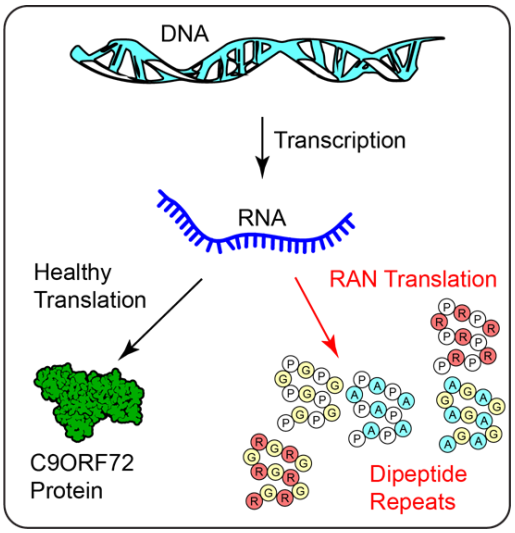
Cells have many 'molecular switches' by which they control numerous processes that occur within them. If certain switches are not turned off or are turned on for too long, problems can occur. It appears as though C9ORF72's ability to form a protein complex with the proteins SMCR8 and WDR41 is important for the proper functioning of lysosomes (compartments in cells that degrade old or improperly folded proteins). If lysosomes are not working properly then protein can build up in cells which can be very damaging. Neurons are particularly sensitive to such a protein build-up.

MND Research Shorts

- Amyloid is a protein structure that is strongly associated with a range of neurodegenerative diseases. Researchers from University California Los Angeles used cryo-electron microscopy to determine the shape of MND-associated amyloid formed by the protein hnRNPA2. Many proteins associated with MND have the capability to form these highly toxic structures that can rapidly grow and multiply. Knowing the exact structure of hnRNPA2 amyloids will be important for understanding ways of blocking or dissolving these toxic structures.
- Incorrect folding of SOD1 protein is associated with SOD1-linked MND. Researchers from the University of Liverpool and Nagoya University collaborated to test the ability of the compound ebselen to help SOD1 fold correctly in mice. They found that treatment of mice with ebselen delayed symptom onset in SOD1 mice. They also have many ebselen derivative compounds in their development pipeline.
- The key disease-associated protein TDP-43 shows both healthy and toxic responses to cellular stresses. Researchers from the Chinese Academy of Sciences recently determined that in stressed neurons, TDP-43 condenses into oil-like droplets within the cell, with a long non-coding RNA called NEAT1. Mutated TDP-43, such that is associated with MND, does not undergo this condensation during stress. This suggests distribution of molecules within the cell plays a core role in MND.
- Evidence is growing to support the notion that misfolded proteins are not always specific to a certain disease. TDP-43 aggregates due to misfolding can be found in Alzheimer's and Parkinson's patients. Researchers from the University of Kentucky have findings that suggest older adults with mild cognitive impairment commonly showed the existence of a number of aggregated proteins including tau, amyloid-β, α-synuclein, as well as TDP-43. This research supports the notion that proteins with a high aggregation propensity are common features of neurodegeneration.

Metformin as a potential treatment for C9ORF72-associated MND

Professor Laura Ranum (University of Florida) and her team recently showed that the drug metformin was capable of blocking the "RAN translation" process that is thought to be defective in C9ORF72-MND. The authors developed the idea that the "RNA-dependent protein kinase pathway" controls RAN translation, and that methods to block this pathway already exist.



RAN Translation? RAN (Repeat Associated Non-AUG) translation is the event where RNA can be translated into protein at the wrong start location, resulting in the production of the wrong protein. In C9ORF72-MND, this event occurs frequently on the hexanucleotide repeat RNA sequences, resulting in the generation of the multiple toxic dipeptide repeat proteins observed in this MND subtype.

Metformin. Metformin treatment was found to prevent the RAN translation of the C9ORF72 hexanucleotide repeat RNA in a mouse model of C9ORF72-associated MND. This could have promising implications for those suffering from C9ORF72-associated MND. Further encouraging news is also found in the fact that metformin is already FDA-approved (approval by the FDA is a significant hurdle in most therapy pipelines) and is currently in use to treat type 2 diabetes, meaning that the route to clinical trial should be faster. If the drug is found to be effective, its existing safety in humans will expedite its approval for the treatment of at least C9ORF72-associated MND.

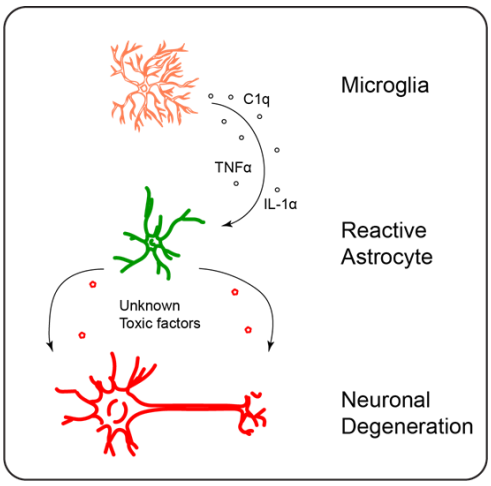
Preventing astrocyte reactivity in MND

The late Professor Ben Barres (Stanford University) and colleagues showed that by removing 3 key factors linked with inflammation SOD1-G93A MND mouse model, they could substantially slow disease progression.

Inflammation in MND? Most diseases are associated with some form of inflammatory response. Normally this inflammation aids in the fighting of microbes or repair after injury. In neurodegeneration, it is thought that inflammation gets out of control and can kill vulnerable cells like neurones. In the nervous system, astrocyte cells are responsible in part for both producing and controlling inflammation. Astrocytes are a strong focus in MND research due to their ability to release toxic factors that kill motor neurones.

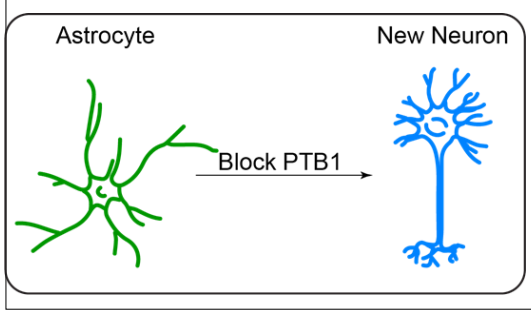
Blocking three factors slows disease progression

IL-1α, TNFα, and C1q are inflammation factors released by motor neuron support cells known as microglia. Release of these molecules in turn activates astrocytes to become inflammatory. The authors of this work showed that by knocking out these three molecules, resulted in the prevention of a subset of toxic astrocytes forming. This led to significantly improved survival and motor function in a MND mouse model. They also found that the subtype of activated astrocyte that was removed in their mouse model was present at high amounts in patient tissue samples, signifying that this inflammation pathway may be a disease factor in human disease and therefore a potential therapeutic target.



Conversion of cells into neurons in a model of Parkinson's disease

Although this research is not focused on MND, it has exciting implications for those suffering from MND. Professor Xiang-Dong Fu (University of California, San Diego) and colleagues exploited the ability of a protein called PTB1 to prevent the differentiation of cells into neurons. By stopping this protein from being expressed, they were able to effectively convert astrocytes to neurons in a mouse model of Parkinson's disease. They achieved this with both viral-based and antisense oligonucleotide (ASO)-based methods, both of which are currently being tested to deliver gene therapy in MND. This potentially highlights a way to regenerate lost motor neurones in MND patients.



Potential to regenerate lost motor neurones in MND patients. In MND, it is the motor neurones that primarily degenerate and die. Astrocytes remain relatively unaffected, although they do play a role in the death of motor neurones. Indeed, even if one could simply reprogram the surviving astrocytes into motor neurones in an MND patient, it is likely that the non-reprogrammed astrocytes would kill the transitioned motor neurons. This means we have to fully understand the underlying processes contributing MND to truly provide an effective treatment. If we had an effective treatment that could prevent the astrocyte-mediated killing of motor neurones we see in MND, we could then use the regenerative method developed here to potentially restore lost motor neurones in MND patients.

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