MND Australia International Research Update

Isabella Lambert-Smith
Australian Rotary Health PhD Scholar, University of Wollongong

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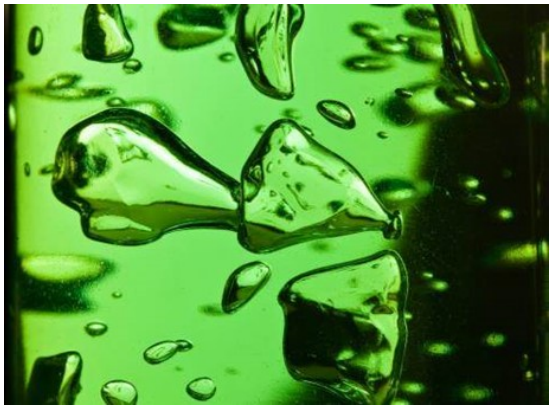
Leaps and bounds in MND research

Motor neurone disease (MND) researchers around the world have been very productive these last few months. A wealth of knowledge has been shared about the intricacies of motor neurones (MNs) and the involvement of other types of cells and environmental factors in MND. Some researchers have also developed new imaging and biochemical tests for diagnosis and disease stage assessment, and a new tool to help in working out a way to stop the spread of MND through the body.

Vulnerable motor neurones are thoroughly saturated in MND



With more than 50 genes identified as being associated with MND and each of them involved in diverse cellular processes, it is no wonder researchers have struggled to pin-point if there is a common underlying cause of this disease. A second major mystery of MND is why certain types of MNs become diseased and degenerate, while others are unaffected. One thing that *is* universal to all cases of MND, and only in the MNs that are specifically affected, is the presence of clumps of proteins called inclusion bodies. Dr Justin Yerbury and Isabella Lambert-Smith have been part of a team of collaborating researchers at the Universities of Wollongong and NSW in Australia, the University of Cambridge, UK, and in Spain and the USA, investigating why all MND cases involve certain proteins clumping together in MNs. The researchers discovered the more than 60 proteins found in inclusion bodies are “supersaturated”; that is, they exist inside MNs at such high levels they exceed their solubility. Thus, they are always on the brink of aggregating out of the watery solution that fills up cells. Notably, these proteins are supersaturated only in MNs, not in other tissue types. The results suggest that a unifying feature amongst all cases of MND is a dangerous collapse of the MN’s ability to maintain all of the proteins in cells at sustainable levels. Importantly, this demonstrates that the development of an effective way of elevating the activity of mechanisms that maintain protein equilibrium in MNs will be an important part of a MND treatment strategy.

A bouquet of cell types contribute to MND

MNs are the cells that are selectively affected in MND, and only select sub-types of MNs at that. For many years, scientists held the view that individual cells function independently, and that diseases that affect a specific type of cell are caused by damage only within that select population. However, this view is changing for many diseases, particularly neurodegenerative diseases. Just as bouquets of flowers and perfumes owe their unique smell to the contribution of multiple different components, MN damage in MND is believed to be caused by the combined effect of multiple different cell types. These different cells include glia, the non-neuronal cells that usually support MNs and Schwann cells that function in wrapping MN axons with an insulating fatty layer.

MND Research Shorts

- *Researchers at Flinders University, South Australia, have developed the first urine sample test for MND prognosis and progression, which can be used in clinical trials of therapeutic drugs. This test is based on the levels of the p75 protein in urine samples, which are one of the most easily accessible biological sample types available.*
- *Calcium is crucial for MNs to transmit messages to each other. However, in MND calcium levels can be very high and overstimulate MNs, which is toxic. Researchers in Hungary and Italy have discovered that a drug called talampanel reduced calcium levels in MNs when given presymptomatically, preventing toxic increases in calcium levels. If MND can be detected in people presymptomatically, talampanel could become an effective treatment option.*
- *Understanding the exact cascade of degeneration that occurs in MNs is important for identifying potential disease targets. A study carried out on a MND mouse model by researchers in Italy and Spain has highlighted the usefulness of an imaging technique called diffusion-tensor magnetic resonance imaging (DTI). DTI revealed that degeneration begins in the long processes (axons) that extend from MNs in the spinal cord. DTI could be adapted for use in humans to aid in assessing MND progression and treatment efficacy.*
- *Researchers in Singapore and the USA have discovered that the major MND protein, TDP-43, contributes to the onset of disease by acting inside MNs but not to the progression. Progression was driven by TDP-43 acting on other cells, called glia.*

MND Research Institute of Australia - the research arm of MND Australia
PO Box 430 North Sydney NSW 2059 • Ph: 61 2 8287 4989
email: research@mndaustralia.org.au • website: www.mndresearch.org.au
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Cigarettes, fatty meat and dairy products may pose increased risk for MND

The environment we live in and our other lifestyle choices are known to affect our risk for developing diseases like cancer. More and more evidence, however, suggests that the risk of developing MND is also affected by these external factors. Several different environmental pollutants called dioxins, polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) have been associated with neurodegenerative diseases. These chemicals activate a protein, called the aryl hydrocarbon receptor (AHR), which regulates certain genes and the production of proteins. Peter Ash and a group of researchers in Boston, USA, believed that these pollutants may increase MND risk by causing the AHR to produce excessive amounts of TDP-43 and cause it to clump together in the protein inclusions found in all people with MND. To test this, they examined the levels of TDP-43 in MND models after treating the model MNs with drugs that activate AHR, including a chemical that is an abundant carcinogen in cigarette smoke. They found that these AHR activators increased the levels of TDP-43 by 3-fold, providing the first evidence that environmental AHR activators in the form of dioxins, PAHs and PCBs, increase TDP-43, the principal pathological protein associated with MND. Dioxins, PCBs and PAHs are widespread in the environment, including in the fatty tissue of meat products, dairy, fish and shellfish. They are established risk factors for cancer and autoimmune diseases, and now may also be a public health concern for MND.

Algal blooms and MND risk

Overgrowths of algae called algal blooms, in water systems like lakes, are becoming a persistent problem in many areas of the world, including parts of Australia. Some algal blooms produce harmful “cyanotoxins”, including beta-N-methyl-amino-L-alanine (BMAA) and links have been made to an increased risk for MND. For example, clusters of MND cases have been reported near algal bloom outbreaks in France, Japan, and New Hampshire and Wisconsin in the USA. Nathan Torbick and a multidisciplinary team of scientists from New Hampshire and Florida, USA, carried out an extensive field study across northern New England to investigate the potential role in MND risk of lake water quality, algal blooms and the toxins they produce. They measured algal concentration as a sensor of algal bloom exposure, and demonstrated that increased algal concentration was associated with higher MND risk. Nathan’s study provides further support for the theory that cyanotoxins increase the risk for MND, and that algal blooms are a public health threat.

MND-causing *p62* genetic mutations interfere with MN energy production

One of the mechanisms believed to underlie the development of disease in MNs is dysfunction in the mitochondria that are the tiny powerhouses of the cell, which like wind turbines or other generators, produce energy. Fernando Bartolome and collaborators across Spain, France, the UK and USA, have just uncovered further insight into how mitochondria become dysfunctional in people carrying mutations in the *p62* gene. These mutations caused deficiency in the p62 protein, and this essentially caused a lack of a molecule called NADH, which is like the rotor in wind turbines that uses the wind to spin a generator to create electricity. Inside the cell, the generator is a molecular machine called ATP synthase, and electricity is in the form of ATP, which is the universal energy currency of the cell. There was also increased production of reactive oxygen species (ROS), which are molecules that can cause considerable damage inside cells. This work shows us that mutations in *p62* can lead to deficiency in the production of energy in MNs, as well as raise the levels of harmful ROS, by interfering with mitochondrial function.

Stopping the spread of MND

The spreading of clumped protein assemblies called inclusion bodies from cell-to-cell is a major factor in the progression of neurodegenerative disorders. Like weeds, these inclusion bodies are able to propagate and disperse to increase their path of destruction. Sivan Peled and fellow researchers in Tel Aviv, Rehovot and Haifa, Israel, established a cell culture model to study the MN-to-MN transmission of TDP-43, one of the major culprits of MND, and α-synuclein, the main protein involved in Parkinson’s disease. They developed a sophisticated technique whereby they could pass individual MNs through a tiny fluid-filled tube into the line of view of a camera, and thus image each MN separately. This allowed them to image and quantify individual inclusion body transmission events. Sivan’s team believe that this novel single cell approach may help them figure out the mechanism of transfer of clumped proteins and help in the development of therapeutic agents that could block the disastrous spreading, akin to stopping weed growth with herbicides.