MND Australia
International Research Update

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A productive start to 2015

In the world of medical research the work that goes into understanding how to treat a disease involves several components. The genes, proteins and other factors (coming from the person's external and internal cellular environment) involved in triggering or causing cells to dysfunction must be deciphered. The methods and techniques used to identify and study them are continually developed. And then with this knowledge and know-how, potential genes and molecular pathways can be identified to target for treatment, and ways to target them can be tested.

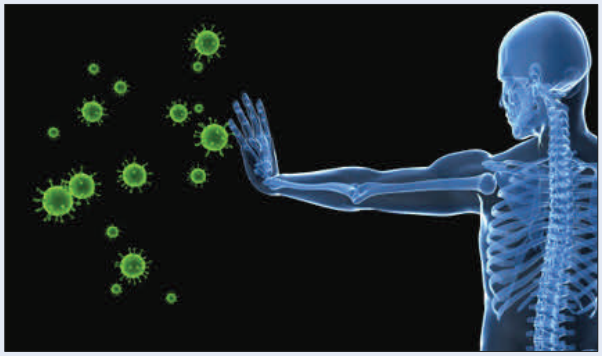
The first quarter of 2015 has been a productive one for MND research. In this report we explore new genetic mutations that have been discovered, new roles for previously identified genes and proteins in the disease process, innovative methods to uncover in detail different disease mechanisms, and new candidate drugs and treatment ideas.

Astrocytes, microglia, cytokines and neuroinflammation: How does the brain protect itself?

As most of us know, the immune system is our body's defence against disease-causing microbes, such as bacteria, viruses and parasites. However, the body's blood and immune system is, under normal circumstances, separated from the central nervous system (**CNS**; made up of the brain and spinal cord). This is to keep the CNS protected from infections in the body that could circulate through the blood to the brain and spinal cord and cause very serious harm. Instead, the CNS has its own exclusive defence system made up of specialised immune cells called **microglia** and **astrocytes**, and a large family of proteins called **cytokines**.

In response to trauma, infection and other sources of harm, the microglia and astrocytes become activated and start to produce certain cytokines. However, in some cases the cytokines can start to be produced in excessive amounts and cause the normal barrier between the brain and the blood system to open up, allowing extra defences to enter the CNS and clear the infection or injury.

Neuroinflammation occurs when this state becomes chronic. It is aimed at protecting the nerve cells, but in some cases it can end up causing more harm. There is now evidence to suggest that different cytokines control this response to different effects; some generate protection while others trigger harm. Why and how this occurs is a focus of much research effort.



Inflammation and MND

Neuroinflammation is an important disease feature in MND patients and the SOD1 MND mouse model. One cytokine in particular, called TGF-β1, has been previously implicated in MND. Fumito Endo and collaborating researchers in Aichi, Saitama and Miyagi, Japan and at Stanford in the USA undertook a study to uncover in more detail the role of TGF-β1 in MND, using a SOD1 mouse model.

The astrocytes in the spinal cords of the mice were found to be overproducing TGF-β1, which accelerated disease progression by affecting microglial activation, reducing the production of a protein important for nerve cell growth and repair, and disrupting the balance of other cytokines.

With these results Fumito and his colleagues think that targeting TGF-β1 signalling in motor neurones and astrocytes may be a promising therapeutic target in the treatment of MND.

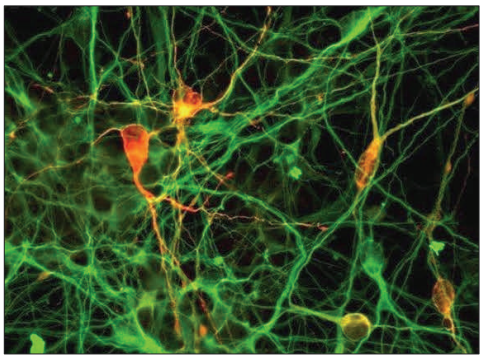
MND Research Shorts

- *The SETX gene, linked to MND, is involved in controlling the production of specific proteins from their genes. Researchers in Australia, Singapore, Switzerland, the USA and Canada have discovered that SETX may inhibit the genetic response to viral infection, suggesting a possible link between viral infection and MND with SETX mutations.*
- *p75NTR is a receptor protein that allows neurones to detect and respond to growth and survival signals during embryonic growth. In adults, only injury to neurones induces its production, including in MND. South Australian researchers have characterised p75NTR in great detail in the SOD1 MND mouse, greatly improving the usefulness of this MND model.*
- *Disruption in the protein production and packaging that is carried out in a specialised part of the cell called the endoplasmic reticulum (ER) is believed to be involved in MND. A study carried out across Canada, the USA and Chile has identified new genetic evidence for this, with findings of mutations in two ER genes in MND patients.*
- *The DNA-binding protein FUS is involved in MND and frontotemporal dementia (FTD), but its role is not well understood. However, Japanese researchers have discovered that FUS has a pivotal role in controlling the production of a protein critical for neurone-neurone communication. FUS also regulated dementia-reminiscent behaviour in their mouse disease model.*

Chaperone reinforcements help maintain order in motor neurones

In MND and several other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, the affected neurones are usually characterised by the presence of solid aggregates of abnormal "garbage" proteins. Thankfully cells are naturally equipped with specialised molecular machinery to help deal with junk protein. Forming part of this machinery are proteins called molecular chaperones which, true to their name, chaperone newly made or abnormally folded proteins to assist them in either folding into their correct shape or directing them to the cells' waste disposal units. However, sometimes the junk proteins escape these molecular chaperones and accumulate into disease-associated aggregates. It seems logical then that if more molecular chaperones could be available to monitor the protein environment then aggregate accumulation could be prevented. Tamar Getter and collaborators in Israel, Germany, South Korea and the USA wanted to explore this idea and worked on making a therapeutic drug derivative of molecular chaperones. Examining the protective effects of their chemical chaperone in neurone-like cells and in a MND mouse model, they found that it prevented protein aggregation, reduced several molecular signs of stress, and furthermore improved neurological functions. This encouraging finding will hopefully lead to further studies into the potential of this and other chemical chaperones as therapeutic aids in MND treatment.

Boosting stem cell ability to rescue motor neurones



While drug therapies to help combat MND continue to be developed and tested, a very promising new line of work is the development of cell-based therapies.

Stem cells are showing strong potential as a means to provide localised protection and support to diseased motor neurones in MND patients. Localised treatment is very important as neural tissue is notoriously difficult to access by most methods of drug administration. J. Simon Lunn and a team of researchers at the University of Michigan and Neuralstem Inc. in the USA have been working through phase I and II clinical trials of human spinal stem cell (HSSC) transplantation in MND patients. With results demonstrating the safety and feasibility of this method, they also focused on understanding how the neurone-protective growth factor IGF-I (insulin-like growth factor 1) may boost the beneficial effects. IGF-I is known for its ability to promote neurone growth and protection, and has been found to be produced in large amounts by HSSCs in studies using MND model rats. Lunn's team constructed HSSCs that produced greater amounts of IGF-I than normal. These new HSSCs showed significantly enhanced protective effects on the surrounding motor neurones, and promoted their growth. This work adds much to the development of stem cell therapy to help treat MND, showing the potential of augmenting therapy using neurone growth factors.

MND and dementia: SOD1 and TBK1 form new links

MND is increasingly recognised to exist on a disease spectrum with frontotemporal dementia (FTD), with a proportion of patients suffering problems with cognitive (intellectual) function in addition to motor ability deterioration. In FTD, aggregates containing the proteins TDP-43 and FUS, which also occur in MND, form inside the affected neurones of the neocortex, which is the part of the human brain responsible for our distinctly human intellectual functions. Two different studies have now added new links to the MND-FTD spectrum; the genes SOD1 and TBK1.

Masataka Nakamura and his colleagues in the USA and Canada examined a family with MND carrying a SOD1 genetic mutation, with one patient in particular also showing symptoms of FTD. SOD1 mutations are responsible for a large percentage of hereditary MND cases. The MND patient in question was found to have SOD1 aggregates in the neurones of the neocortex. Furthermore, this mutation in other family members was associated with very aggressive motor ability deterioration and caused SOD1 aggregates to accumulate in different neuronal cell types, varying between individuals. What this suggests is that other factors come into play to alter the disease course caused by the SOD1 mutation, factors that could be genetic or coming from the surrounding cellular or external environment.

The second novel genetic link, TBK1, was discovered by Axel Freischmidt and collaborators across Europe and in New Caledonia. Through DNA sequencing and several biochemical experiments, these researchers found that reduction in the functionality of TBK1 caused by mutation was responsible for the neuronal dysfunction in MND and FTD.

Antibodies: the key to unlock the protein aggregate mystery?

We now know that protein aggregates are important in the development of neurodegenerative diseases. What we still don't understand, however, are the exact mechanisms by which they form and how they are involved in disease. The problem largely stems from the difficulty in studying their minute quantities in the CNS. A new method developed by Johan Bergh and fellow researchers at Umea University and Stockholm University in Sweden may help get around this problem. Their method uses large Y-shaped proteins called antibodies that chemically combine with specific proteins, much like a lock and key. Johan's group designed antibodies that combine with regions of the SOD1 protein that drive it to aggregate. In a SOD1 MND mouse model these antibodies allowed them to detect two different kinds of SOD1 aggregates that were associated with differences in disease progression. Interestingly, they were different to SOD1 aggregates formed artificially in the test tube, which reveals that the CNS must play a critical role in the aggregation process of disease-associated proteins.

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