MND Australia
International Research Update

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This report comes from Cambridge University in the UK, where Isabella Lambert-Smith is continuing her PhD project on placement for nine months in the laboratory of Professor Steve Oliver (Systems Biology and Biochemistry). This opportunity for international experience nurtures international collaboration and exchange of ideas.

MND Research Shorts

- *Collaborating researchers in Illinois, Indiana and Ohio have evidence supporting the theory that mutant SOD1-linked MND can be initiated with events that cause disconnection between motor neurones and their target muscle fibres. This damage triggers further motor neurone dysfunction and subsequent degeneration.*
- *One of the most important blood antioxidants found in mammals, uric acid (UA), may be relevant as a marker of MND and potential therapeutic target. Researchers from Israel have reported on significantly lower blood plasma levels of UA in MND patients than in healthy disease-free individuals.*
- *Molecular dynamics simulation studies carried out by researchers in Tamil Nadu, India, have revealed changes in the structure of the MND-associated protein VAPB that may indicate the way in which mutant VAPB is involved in MND.*
- *Researchers in Italy have found that levels of the protein neurofilament light chain (NFL) in the cerebrospinal fluid could be used as a reliable marker of disease progression in sporadic MND patients.*

Too much excitement to handle

The main function of motor neurones, relaying electrical impulses from the brain to the muscles, relies on tight regulation of the neurotransmitter molecules that convey these impulses from cell to cell. Unfortunately for motor neurones, when these neurotransmitters get out of hand, the neurones become overexcited (hyperexcited). This can be toxic for the neurones, an event called excitotoxicity. This is thought to be one of the mechanisms leading to neurodegeneration in MND.

Proteins called glutamate transporters are responsible for clearing one of the main neurotransmitters, glutamate, from the gap (synapse) that lies between neighbouring neurones. These transporters reside on the surface of glial cells that help support neurones. A transporter called EAAT2 is responsible for the majority of synaptic glutamate clearance and decreases in the levels of EAAT2 have been implicated in MND. However, simply increasing the levels of EAAT2 in motor neurones does little to help diseased motor neurones in mouse models or in human clinical trials. Researchers in the lab of Davide Trotti at Thomas Jefferson University in Pennsylvania, who previously found that a fragment of EAAT2 is joined to a modifier molecule called SUMO and accumulates on the inside of glia in a mouse model of MND, have now examined the specifics of this SUMO-modification and its role in disease.

Trotti and his colleagues found that a portion of full-length, non-fragmented EAAT2 is always sumoylated in cells, and that the pool of sumoylated EAAT2 does not change as disease progresses, which indicates that disease mechanisms do not drive this sumoylation. They did discover, however, that EAAT2 that is sumoylated moves preferentially to the inside of cells, whereas non-sumoylated EAAT2 resides at the cell surface where it can carry out its function in clearing glutamate from the synapse. It seems that the balance of sumoylation and desumoylation of EAAT2 is important for controlling glutamate levels in the synapse and preventing excitotoxicity. Trotti's group also found that promoting EAAT2 desumoylation caused an increase in glutamate clearance, further supporting this. The work of these researchers poses a novel way of preventing MND-associated excitotoxicity through pharmacological targeting to promote EAAT2 desumoylation.

Even more to a SUMO than meets the eye

Structural modifications to proteins that take place after they have been synthesised in the cell form an important part of the dynamic processes which keep cells functioning normally. There are many different molecules that assist in these modification processes. One example is the protein known as SUMO. SUMO molecules attach to the proteins to be modified, a process called **sumoylation**.

Proteins that have been modified by SUMO have altered behaviour and often localise to different parts of the cell than their non-sumoylated counterparts.

Maintenance of the balance of sumoylated proteins is important for cells. Alterations in this balance have been found in neurodegenerative diseases, including MND.

More to motor neurone excitability than previously thought

The degree to which motor neurones become overexcited is one factor that correlates with patient survival. Researchers from Harvard Medical School in Boston have carried out work using induced pluripotent stem cells (iPSCs) from MND patients to investigate this more closely. Previous studies on motor neurone excitability have used a mutant SOD1 mouse model of MND. However, the various genetic forms of MND each need to be modelled to gain a full understanding of the disease process. Brian Wainger and colleagues at Harvard used MND patient iPSCs with mutations in C9orf72, FUS and SOD1 genes to demonstrate the occurrence of hyperexcitability in the different genetic forms of MND and they looked at the mechanisms involved. Previously it has been widely thought that excessive sodium currents were the main contributor to hyperexcitability. The only approved drug for MND, riluzole, targets this action. However the findings of this study suggest that the activity of potassium channels in neurones play an additional and significant role. Testing this with retigabine, a drug that targets potassium channels, these researchers observed a reduction in the excitability of motor neurones and increase in their survival rate. Understanding the mechanisms of overexcitability in MND in more detail will be an important avenue to follow which may lead to the development of a more effective method of treatment than use of riluzole alone.

A cellular Trojan Horse in MND?

There has been gathering evidence that suggests a role in motor neurone degeneration for the factors that are secreted by disease-activated glial cells. Eugenia Ranno and collaborators in Italy and the Netherlands have generated results demonstrating that the molecule endothelin-1 (ET-1), which activated glia release in increased amounts under different pathological conditions, is abundantly expressed in the spinal cord of transgenic mutant SOD1 mice and in individuals with sporadic MND. ET-1 had a toxic effect on motor neurones, suggesting ET-1 may contribute to toxicity in motor neurones. This opens up the potential of pharmacological targeting of ET-1 levels as a strategy to slow down the progressive loss of motor neurones in MND.

Mimicking the action of growth signals to rescue motor neurones

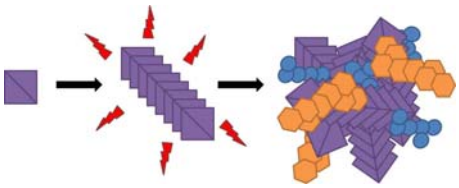
Neurotrophins are molecules important for the development, growth and survival of motor neurones. Neurotrophins function as signals that direct cells on how to develop into neurones and to continue functioning normally. Brain-derived neurotrophic factor (BDNF) is a neurotrophin known to be important in this process. The flavonoid compound 7,8 -DHF is a potent and selective small molecule that mimics the effects of BDNF. Orhan Korkmaz and fellow researchers from Boston in the US studied the neuroprotective effects of 7,8-DHF in a mutant SOD1 mouse model of MND. They found that chronic administration of 7,8-DHF significantly improved motor deficits and preserved motor neurones in the spinal cord, an encouraging finding.

TDP-43 misbehaviour wreaks havoc for motor neurones

The protein TDP-43 is now well known as having an important role in MND. In healthy cells TDP-43 is found predominantly in the nucleus where it carries out its main function of regulating the synthesis of proteins from genes. In MND, however, TDP-43 is found to move from the nucleus to the cytoplasm, where it accumulates in aggregated clumps of proteins. These aggregates are found both in people who carry mutations in the gene for TDP-43, as well as in most other cases of MND. With these observations, it has been unclear whether TDP-43 causes disease through a gain of toxic activity as it forms aggregates in cells, or whether its depletion from the nucleus and subsequent loss of function are to blame. Zuoshang Xu and fellow researchers from Massachusetts in the US generated a mouse model of MND in which they could test whether a partial, rather than complete, loss of TDP-43 function is enough to cause disease. They found that despite this partial loss of TDP-43 function in all types of cells and tissues in the mouse model, only motor neurones showed significant signs of dysfunction and toxicity. This is striking evidence that even partial loss of TDP-43 function is enough to induce neurodegeneration, and that motor neurones are particularly vulnerable to this dysfunction.

Linking stress in the cell environment with SOD1 toxicity

Researchers from the University of North Carolina have gained insight into one of the ways in which SOD1 is involved in MND, and how it may be therapeutically targeted. Although there have been studies showing that, in many cases, the dysfunction and death of motor neurones in MND involves the misfolding and aggregation of SOD1, there has been little investigation into the specific SOD1 structures that are toxic and the factors leading to these pathological changes. Rachel Redler and a team of biochemists at UNC examined this by making ingenious use of a special marker that only detects pathologically misfolded SOD1. They found that SOD1 oligomers, structures made of several SOD1 molecules joined together, are more toxic than individual misfolded SOD1 molecules. Redler's team also found that a protein modification involved in the cell's stress response to harmful free radicals caused an increase in the abundance of toxic SOD1 oligomers. These findings reveal a specific mechanism by which disease-related changes in SOD1 occur, and a way in which they can be targeted pharmacologically.



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