MND Australia International Research Update

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Appreciating the unique biology of motor neurones

The many individuals working in the motor neurone disease (MND) research field have come to appreciate just how unique motor neurones (MNs) are in their biology, in comparison to other cell types in the body. MNs have higher demands than other cells, due to their large size (they can exceed a metre in length) and the sophisticated orchestration of signalling they control throughout the body. As MND researchers continue to understand the distinguishing characteristics of MNs, and the changes that occur selectively inside them that contribute to MND, the establishment of effective treatment plans for patients comes steadily closer to reality.

Like snowflakes, no two motor neurones are the same

When we speak of MND, we are usually referring to amyotrophic lateral sclerosis (ALS); indeed, in most instances in this report the term MND is used in place of ALS. However, the term MND encompasses a group of clinically variable neurological diseases, which all involve the progressive loss of MNs and muscle deterioration. Another type of MND called spinal muscular atrophy (SMA) is attributable to reduced levels of the protein SMN. A perplexing aspect of ALS, SMA and other MNDs, is understanding why MNs carrying the same genetic defects and exposed to the same environmental stress conditions, have different susceptibilities to becoming diseased and dying. To try and answer this question, Natalia Rodriguez-Muela and her group in Massachusetts and New York in the US examined MNs taken from both SMA and ALS patients. They showed that there was large variability in the levels of SMN per cell, and those with low levels were more susceptible to death. So Natalia and her group next tested out a drug that increased the levels of SMN in the MNs, and this treatment was able to promote survival in both SMA and ALS-derived MNs. This study shows that SMN has a broader role in the survival of MNs than has previously been appreciated, and that drugs that increase SMN levels in MNs can promote the survival of MNs in different MNDs.

Calculating the risk of MND

MND is a complex disease. This means that there is no single cause for it in people, but rather it results from interactions between a person's genes, their environment and lifestyle. MND shares this level of complexity with cancer, heart disease and diabetes. MND researchers are working hard to identify all the genetic and environmental factors that can combine to trigger a person's MNs to become diseased, and are continuing to come a long way, particularly in genetics. Researchers have identified mutations in several genes which cause MND. In addition, they have discovered many other gene variants that contribute in a smaller way to a person's risk of developing MND but which act in combination with each other and with as yet unknown environmental triggers to increase the likelihood of developing the disease.

MND Research Shorts

- *The accumulation and clumping of TDP-43 and FUS proteins in spinal MNs are known to contribute to the development of disease in these cells. Researchers in Bangalore, India, have discovered that the signalling protein VEGF is able to partially reverse this process and thus is of therapeutic value for MND.*
- *There is urgent need for clinicians to be able to accurately diagnose MND patients and to work out the severity of their condition in order to develop the most effective treatment plan for each individual. Helping to address this, Sweden and UK-based researchers have found that the concentration of NFL protein in the cerebrospinal fluid of MND patients allows them to determine disease severity and predict survival.*
- *A study carried out in Chicago, USA, has demonstrated that a protein called HGF, previously shown to protect MNs from death, can safely be taken by patients with MND. With this promising finding, trials are ongoing to assess how effectively this treatment alleviates patient symptoms over the long-term.*
- *A large collaborative study carried out by researchers across Europe, the UK, North America and Taiwan has confirmed that a specific mutation in the ATXN2 gene predicts an individual's risk of developing MND. This mutation in the DNA sequence can be of different sizes. The larger the mutation size, the greater the risk of MND.*

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Sonic the Hedgehog in the nervous system

We have a protein in our cells called Sonic Hedgehog (Shh). Shh is essential to the developing nervous system and continues to play an important role in adult life by contributing to cell growth and the transformation of cells into different cell types. It is also critical for maintaining integrity of the blood-brain barrier, a membrane that separates the circulating blood from the fluid that surrounds the brain and spinal cord (cerebrospinal fluid; CSF). And if those are not enough responsibilities for this little protein, it is also protective against toxicity resulting from excessive stimulation of neurones and from an imbalance of harmful free radicals. All of these features are of importance in MND. Shh belongs to the hedgehog gene family, so named because in the study that led to the discovery of the first hedgehog gene in fruit flies, absence of the gene caused the fly embryos to be covered with small pointy projections resembling the spines of a hedgehog. The Shh gene was named after SEGA's video game character Sonic the Hedgehog, after its discoverer, Dr Robert Riddle, had seen one of his daughter's Sonic comics. In previous studies, it has been reported that Shh signalling is defective in MND patients. Wanting to investigate this further, Anna Drannik and her colleagues in Ontario, Canada, investigated the role of Shh biological activity in the CSF of MND patients. Anna's group found that Shh activity was compromised and showed that there was an inhibitor of Shh signalling in the patients' CSF. Further investigation is needed to understand these findings and identify this mysterious inhibitor.

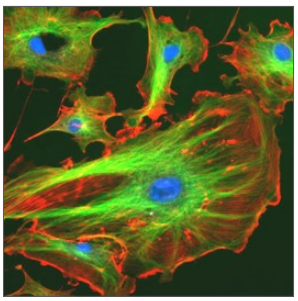
Copper delivery to SOD1 helps keep motor neurones functioning

Mutations in the copper dependent antioxidant SOD1 were the first described genetic cause of MND. Mouse models of mutant SOD1-MND have proved to be a robust experimental approach to study MND. They exhibit a prominent feature of clinical cases of MND caused by SOD1 mutations; even though the mutant SOD1 is expressed in all cell types of the body throughout life, from birth onwards, the MND symptoms only develop relatively late in life and are caused only by selective death of MNs. So the SOD1 mouse model provides the opportunity to better understand why a gene mutation that is carried in all cells of the body selectively affects the MNs in the brain and spinal cord. A drug called copper-atsm has previously been investigated as a potential therapeutic in animal models of MND and Parkinson's disease. Copper-atsm's therapeutic activity in SOD1-MND mouse models is believed to be due, in part at least, to its ability to increase the availability of copper to SOD1. In these model mice, the insufficient availability of copper to SOD1 only occurs in the brain and spinal cord. With all this information, James Hilton and his colleagues in Melbourne, Australia, and Oregon, USA, launched a study to determine whether or not copper-atsm increases the availability of copper to SOD1 in peripheral tissues or only in the brain and spinal cord. They tested this in SOD1-MND model mice and found that it delayed the onset of neurological symptoms, improved the ability of mice to move normally and extended their overall survival. This is strong evidence for copper-atsm as a treatment option for MND.

A new culprit for inflammation in motor neurones

Inflammation in the nervous system (neuroinflammation) is a major hallmark of MND. Various anti-inflammatory drugs have been tested in patients and animal models of MND, but the lack of knowledge of effective target proteins and molecules for these drugs has limited their success. Tackling this gap in knowledge, Laura Pasetto and her collaborators across Italy, Germany and the USA carried out a study that uncovered the protein PPIA as a mediator of neuroinflammation in MND. They also found that it is selectively toxic for MNs. High levels of PPIA were found in the cerebrospinal fluid of SOD1-MND model mice and sporadic MND patients. PPIA is an enzyme that accelerates protein folding and assembly. It is located both inside cells, where it is beneficial, and outside cells (extracellular PPIA), where it has some detrimental functions including inducing the production of pro-inflammatory molecules. An inhibitor of extracellular PPIA, MM218, given at symptom onset, rescued MNs and extended survival in the SOD1-MND mouse model. The treatment resulted in glia, the cells that surround and support MNs, taking on a pro-healing form. These results indicate that extracellular PPIA is a promising target for both SOD1-linked MND and sporadic MND.

A new drug to help heal the skeleton of motor neurones



All cells have a microscopic "skeleton" called a cytoskeleton that gives them structure and support. An abnormal cytoskeleton in MNs is linked to the development of MND. Our cells have proteins called Rho kinases (ROCKs) that are known to control cytoskeletal structure. One of these, ROCK2, has been reported to be present at significantly increased levels in muscle biopsies of MND patients. A few years ago, René Günther and collaborators across Göttingen, Dresden, Lübeck and Bochum in Germany published a study showing that inhibition of ROCK using different drugs strongly promoted a regenerative response in the brain and spinal cord, and was able to activate protective mechanisms inside cells. One of the drugs they tested, Fasudil, was able to extend survival time and improve motor function in MND model mice when treated at a pre-symptomatic stage. Fasudil has been studied in various neurodegenerative diseases, in which it is found to be effective when taken orally, and is able to penetrate the blood brain barrier. So with these promising findings, René's team evaluated the therapeutic effect of Fasudil starting at a symptomatic disease stage, which more realistically reflects the clinical reality. Although survival time was unfortunately not influenced, Fasudil did significantly improve motor behaviour in mice. This indicates that restoring ROCKs to normal levels in MNs and the subsequent restoration of the cytoskeleton is important in helping MNs to keep functioning, even when they're already severely damaged in disease. Given that Fasudil is a well-tolerated substance and is already in clinical use for other conditions, René's study has shown it has therapeutic potential for MND patients even at advanced stages of disease.

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