MND Australia Research Update

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How do motor neurones become sick - the chicken or the egg?

Motor neurone disease (MND) occurs due to the selective dysfunction of the neurones that control skeletal muscles. As these neurones start to become sick they withdraw their nerve endings from the muscle and the muscle stops working. We still don't fully understand why these neurones selectively stop working and what triggers the start of their demise. Scientists around the world are trying to work out what this trigger is and where it comes from.

Understanding where MND starts is a challenging problem that can be likened to the question of which came first, the chicken or the egg? Specifically, it is unclear whether the trigger to neuronal death starts in the brain or spinal cord where the cell bodies of motor neurones live, and this causes the nerve endings to withdraw from the muscle or if it starts in the muscle, where the nerve endings live and this triggers the neurones to withdraw. MND is a very complex disease and there is evidence to support both the neuronal cell body origin (the chicken) and the muscle origin (the egg).

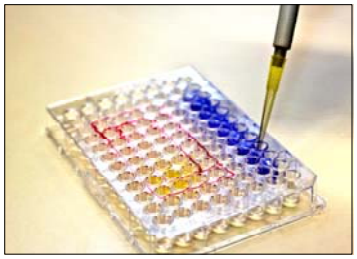
It is important to answer this compelling question because if we know where neuronal death starts then we know where to direct therapies. A targeted therapy which stops neuronal death at the very start should be the most effective in tackling this devastating disease.

A paper published in the May edition of the highly respected journal *Cell Metabolism* tackled one aspect of this conundrum. Sandrine Da Cruz and colleagues at the University of California, San Diego investigated the effect of making muscles stronger on the progression of disease in MND mice. They achieved this by super charging the mitochondria, the muscle's power plants, through a specific gene known as PGC-1α. They found that this genetically engineered mouse could run faster and for longer, however the disease progressed at the same rate. These findings show that while having healthier muscles will keep them working for longer it will not prevent the development of MND, suggesting that the trigger may not be coming from the muscle. Not only does this add another piece to the puzzle regarding where MND starts, it also suggests that this gene, PGC-1α, may be a therapeutic target to make healthier muscles that keep functioning for longer when motor neurones begin to stop working.

Mopping up of calcium in motor neurones

Calcium is the most abundant mineral in the body, which is vital in a number of functions including building and maintaining bone and tooth strength, regulating our heartbeat, helping our blood clot and, importantly, translating messages sent from cell to cell. Neurones rely on calcium to maintain the balance of their electrical and chemical signals. The concentration of calcium is very tightly regulated in neurones because whilst it is vital for them to work properly, too much of it can be very harmful. Researchers in Marseille, France have discovered an important deficit in a protein that regulates the level of calcium in MND. Calreticulin is a protein inside the neurone that mops up excess calcium. Experiments conducted by Nathalie Bernard-Marissal and others have shown that this protein stops doing this 'mopping up' job properly in MND. What is interesting is that the function of this protein decreased specifically in the neurones that are most at risk of dying. This finding contributes to our understanding of why certain types of neurones get sick faster than others in this disease. Essentially, while it might appear that the neurones which are getting sick have all the same proteins that the healthy neurones do, just having the protein is not enough. The proteins need to be doing their jobs properly as well.

Disease in a dish



Scientists culture neurones in a dish to answer a variety of important research questions. Culturing neurones, the method called *in vitro*, has a lot of advantages including easily reproducible results, simplification of complex systems and relative cost effectiveness. One of the biggest disadvantages of culturing neurones in a dish has long been that they lack the normal connections they would have in the body. Research performed by Joy Umbach and colleagues at the University of California, Los Angeles has developed a model to overcome this problem. They have developed a new method of culturing motor neurones derived from human stem cells. What they were able to do is isolate single neuromuscular junctions – the important structures which connect the neurone and the muscle. Furthermore they were able to show that these junctions were electrically active which means that they have formed a connection like they would in the body. With this method they will now be able to investigate the junction health of neurones derived from people with MND to see if that will give any clues about disease prognosis.

An antibody to search out sick neurones

One of the most routinely investigated mutations that occur in inherited forms of MND is the SOD1 mutation. Problems with how this protein is made can also occur in non-inherited forms of this disease making it an interesting protein to study. Recent work published in *Proceedings of the National Academy of Sciences* by Terrell Brotherton and others at the Laval University Research Centre, Quebec, Canada revealed an antibody that selectively sticks to mutant forms of SOD1. Furthermore this antibody only sticks to SOD1 in the neurones that get sick in MND. This antibody could be a powerful new tool in tackling the question of why some neurones get sick despite other neurones around them being healthy.

Motor neurone disease's signature

Axons are the information transporters of a neurone and they constantly carry signals to and from the cell body and nerve endings. The axons of motor neurones can be relatively very, very long, which makes them easily susceptible to disruptions that cause them to stop working. The degeneration of the axons of motor neurones in mouse models of MND has been well documented. However, in human MND there is significant degeneration of the axons of the upper motor neurones, which are found in the corticospinal tract. Anna King and colleagues at the University of Tasmania have recently investigated these changes in the SOD1 mouse model of MND and found widespread degeneration of axons in the spinal cord white matter. Degeneration resulted in the accumulation of specific scaffolding proteins, some of which have been identified in human tissue. These changes highlight the similarities in the degenerative process between this mouse model and human cases and the things that are similar. Future studies of the 'pathological signature' may offer insight into how axon degeneration occurs.

Seeing the way ahead

Muscular paralysis in MND is caused because the motor neurones stop working. However not all motor neurones are equal in this disease and some are more susceptible than others. The laboratory group run by Fatima Pedrosa-Domellof at Umea University, Sweden has been looking at the neurones that don't get sick. The muscles that control eye movement are generally not paralysed in MND. The work in Sweden has shown that these muscles have a lot less of their nerve endings dying back from the muscle in comparison to some of the muscles that are severely affected in MND. It is possible that there is something unique about these motor neurones that makes them resistant. Finding out what this unique property is may be useful in devising ways to prevent the loss of the more susceptible neurones.

Stay tuned

Researchers in London, UK have shed new light on how the neuroprotective drug Arimoclomol may increase the survival of MND mice. Linda Greensmith's lab at University College, London has previously shown that administration of this drug to MND mice increases their survival. The most recent paper from the Greensmith lab, published in *Amyotrophic Lateral Sclerosis*, suggests that the drug may be doing all its work at the connections between the nerve endings and their muscle. These connections are broken in MND and it is essential to find a way to stop this happening. This work suggests that Arimoclomol may be able to slow down the loss of connections long after MND has been diagnosed. However, before we get too excited, it has to be accepted that there are differences between the rodent and human disease. While the mouse model of MND is great for highlighting drugs such as Arimoclomol that may help, it does not guarantee that the drug will have the same positive effect in human patients.
The good news is that there is a clinical trial currently ongoing in the USA with this drug so stay tuned for the results.

MND Research Shorts

- Researchers in London, UK have found a neuroprotective drug that increases the survival of MND mice. This is a common drug which is already used for other illnesses and may be a successful strategy for slowing down disease progression.
- Mannick, Nicholas, Gerber and others in Monpellier, France have shown that onset of symptoms in the most well know mouse model of MND may be occurring earlier than we first thought. They showed that there were differences in resident immune cells of the spinal cord before the start of the disease in the MND mice.
- Researchers in Philadelphia, USA have investigated how toxic SOD1 is in lymphoblasts from patients with MND. They found that the toxicity of this protein was the same regardless of whether the disease was an inherited or sporadic form.
- A study conducted in Dublin, Ireland has shown that a signal that occurs between neurones and astrocytes may be getting lost in MND. This signal is important for neuronal protection and highlights the critical role of non-neuronal cells in MND.
- Research in Milan, Italy, using MRI technology to scan the brain, has identified key differences in brain network connectivity in patients with MND.

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