DECEMBER 2017

MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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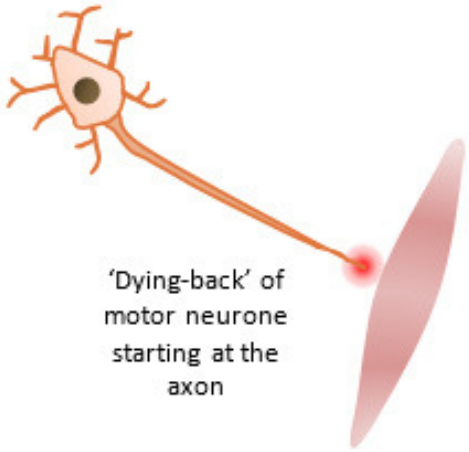
A season of celebration

'Tis the season – to celebrate the progress made by scientists researching motor neurone disease (MND) throughout 2017. It has been a productive year marked by many encouraging discoveries that provide us with new strategies to diagnose MND and significant insights into its underlying causes. Many of us will be continuing our research over the festive season, fuelled by fresh motivation and the promise of what's to come in 2018!

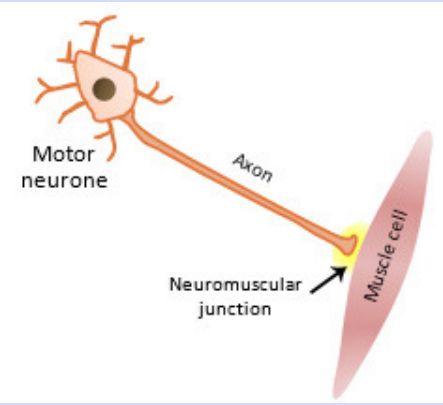
Head to toe, or toe to head? A 'dying back' mechanism in FUS-linked MND

About 5% of people with hereditary MND have genetic defects in the *FUS* gene that encodes the FUS protein and regulates RNA molecules. RNA is the intermediate molecule generated from DNA that then provides the instructions to produce proteins encoded by each gene. Genetic defects in *FUS* result in the production of mutant, abnormal FUS protein that loses its ability to regulate RNA. In the motor neurones (MNs) of people with FUS defects, FUS protein becomes abnormal and sticky, and clumps together with other proteins to form protein deposits. In recent years, several groups of researchers have discovered FUS may have additional roles at the synapse (see box below). Here it may help regulate RNA that is transported down from the nucleus to produce proteins needed for synapse function. However, until now relatively little has been known about FUS-linked MND, with the majority of researchers around the world focusing on SOD1-linked MND. This led Eva So and her colleagues at King's College London to develop a mouse model of FUS-linked MND and examine if any disease-related changes occur at the neuromuscular junction (NMJ: see box below). Strikingly, they found the NMJs in the mice deteriorated significantly before there was any loss of MNs. Associated with NMJ loss was deterioration of the MN's energy-generating machines, the mitochondria. Eva's findings confirm the role of FUS at the synapse and NMJ, and also suggest there is likely to be a 'dying-back' mechanism in FUS-linked MND in which the MN axon is the first part of the MN to degenerate, leading to degeneration of the entire cell.



Genes, axonal transport and synapse function

Synapses are tiny connecting gaps between neighbouring neurones in the brain and spinal cord, and between neurones and muscles throughout the body. Synapses enable neurones to transmit signals to their connecting neurones or muscle cells. MNs are the largest cells in the body; from the main body of the cell, which is relatively tiny, there is a remarkably long projection, called the axon, along which electrical signals are transmitted. Consequently a MN's synapse with its neighbouring cell is usually located considerably far away from its nucleus.



RNA that is transcribed from DNA needs to be transported from the nucleus all the way down the axon to the synapse, where it gets translated into proteins that are crucial for synapse function. In many neurodegenerative diseases, dysfunction of the synapse is believed to be one of the earliest events in the disease process. Multiple researchers have identified the degeneration of the specialised synapse between MNs and muscle cells, the neuromuscular junction (NMJ), to be an early feature of MND.

MND research shorts

A pronounced feature of MN degeneration is inflammation in the brain and spinal cord. Researchers in Mexico have discovered increased levels of adipsin in the cerebrospinal fluid of people with MND. Adipsin is a hormone produced by fat cells that is involved in the immune system, and is believed to play a role in some autoimmune disorders. Researchers now need to investigate the clinical significance of increased adipsin in the development of MND.

Researchers suspect that iron metabolism is disrupted in MND. Accumulation of iron is associated with other neurodegenerative diseases. A study carried out by researchers in France and Belgium has demonstrated accumulation of iron in several brain regions in MND patients. This was associated with tiny bleeds in the brain, highlighting the occurrence of vascular damage in MND.

One of the most promising avenues for therapy in MND is viral-delivered gene therapy. This involves the use of machinery isolated from viral particles to deliver therapeutic molecules to MNs that help correct genetic defects. Researchers in China and the USA have shown slow injection of viral-delivered therapeutic molecules into the spinal cord of MND model mice yields a relatively more effective response than fast injection. Researchers will need to take this into consideration in future therapeutic trials.

The largest genetic studies of MND have been carried out on people of European ancestry. These studies have advanced our understanding of MND, however it is likely there are MND-causing genetic defects of ancient origin that are shared across ethnic groups. To address this, a huge collaborative project was carried out by scientists in Australia, China, the Netherlands, UK and USA. They explored the genomes of thousands of individuals with MND across different ethnicities, and found significant association of two novel genes with MND. These genes, *GPX3* and *TNIP1*, interact with other known MND genes. Further investigation of their roles in MND will now need to be carried out.

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Finding the cause of protein clumps

TDP-43 protein is one of the main components making up the protein deposits found in diseased MNs in people with MND. Like all other proteins, TDP-43 is made up of a specific sequence of building blocks called amino acids. When freshly made, proteins exist as linear chains of amino acids which are then folded into the protein's characteristic shape by specialised molecules. The end portion of TDP-43's chain, called its C-terminal domain (CTD), is very important in determining whether TDP-43 will remain a functional protein or bend out of shape, becoming sticky and forming disease-associated clumps with other proteins.

Most of the genetic changes in TDP-43 that cause MND occur in this CTD. Given TDP-43 is one of the most prevalent proteins in MND, figuring out the exact structural component of the CTD that drives TDP-43 to transform its shape and clump into protein deposits could help scientists devise a way to prevent this. Hao-Ru Li and a team of scientists in Taipei, Taiwan, examined TDP-43's CTD and identified a specific amino acid, tryptophan, in the CTD that is key in disrupting TDP-43's normal structure. With this knowledge, researchers can now investigate the effects of correcting disease-associated alterations in this tryptophan building block and ascertain any therapeutic potential.

Does fungal infection play a role in MND?

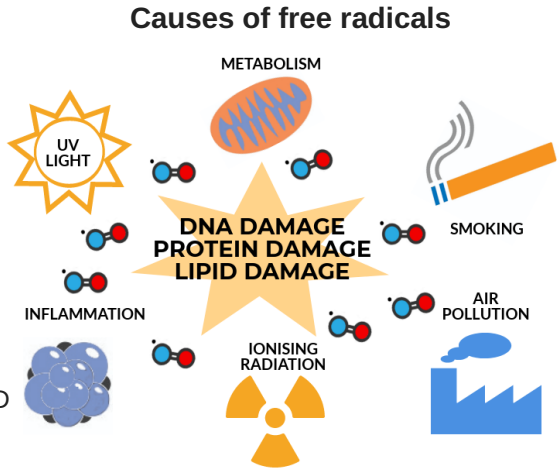
MND and other neurodegenerative diseases share many similarities, in particular, the presence of protein deposits in the affected neural tissue. Because of these known similarities, research discoveries in, for instance, Alzheimer's disease, can accelerate discoveries made in MND. Indeed, scientists researching MND often also investigate other neurodegenerative disease. This is the case for Ruth Alonso and the group she works with in Madrid, Spain. A few years ago, Ruth discovered that microbial infection may play a role in some cases of Alzheimer's disease. Her group also detected the presence of fungal proteins in the cerebrospinal fluid of MND patients. This led her to further search for fungal cells in brain and spinal cord tissue from MND patients. Fascinatingly, they found fungal cells of different fungal species both inside MNs and in the surrounding extracellular matrix, with the exact combination of species varying between different people. These novel findings could be very important in the development of appropriate therapeutic strategies targeted to each unique case of MND.

New layers of complexity in MND

The complexity of MND extends along a disease spectrum, with many individuals also experiencing cognitive and behavioural changes, and a fraction of these further developing a form of dementia known as frontotemporal dementia (FTD). There is overlap between genetic changes that are caused by the degeneration of MNs in MND and degeneration of neurones in the frontal and temporal regions of the brain. There is also considerable variability in the severity of a person's degeneration and the rate at which disease worsens, even when the same genes are involved. Erdogan Taskesen and colleagues in Amsterdam, The Netherlands, recognised that epigenetic changes in specific genes may be a possible cause of the variation in disease severity. Epigenetic changes are those that modify the activity of a gene, and the extent to which the protein it codes for is produced in cells, without actually changing the underlying genetic sequence in the DNA. Epigenetic changes are normal and very important for the growth and maintenance of all the cells and tissues throughout the body, but occasionally the changes they cause in gene activity can have damaging effects. One of the molecular systems in cells responsible for epigenetic change is DNA methylation. This is a process when a small group of connected atoms, called a methyl group, is added to the DNA molecule at the site of a specific gene. The addition of a methyl group usually represses the activity of the gene to which it is attached. Taskesen's team compared the amount of DNA methylation in the genomes of people with MND-FTD to unaffected individuals, and discovered nine genes with alterations. These genes, together with those in which actual genetic defects occur in patients, are involved in common biological pathways. As these pathways are highly likely to be critical for degeneration in both MND and FTD, researchers will now investigate them further.

Free radical damage as a marker of MND

Researchers have determined many of the mechanisms occurring in the nervous system that are involved in MND. One of these mechanisms is believed to be oxidative stress. All of our cells produce oxygen free radicals as a by-product of normal metabolism, however in times of stress cells can produce excessive amounts of these free radicals and overwhelm the cell's antioxidant defence mechanisms. This is when oxidative stress occurs, and it can cause immense damage to proteins, DNA and the lipids (fats) that are crucial to cell structure and function. Whether or not oxidative stress is one of the causes of MND or if it occurs as a result of previous damage to MNs by other mechanisms is debatable. Gordana Djordjevic and her colleagues in Niš and Belgrade, Serbia, carried out a study to measure the levels of one of the main antioxidants in our bodies, glutathione, and of proteins that have been damaged by free radicals in the cerebrospinal fluid of MND patients. Gordana found that there were higher levels of oxidatively-damaged proteins in the MND patients compared to healthy individuals, and this correlated with lower levels of glutathione. Cerebrospinal fluid levels of oxidatively-damaged proteins and of glutathione may be of use as biomarkers of MND progression, and await further study.



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The *MND Australia International Research Update* is generously supported by MND Victoria