MND Australia
International Research Update

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What's in a name? More than motor neurone dysfunction in MND

As we can gather from the name itself, MND affects the motor neurones (MNs) that connect the brain and spinal cord to the muscles. These motor neurone cells, which are the largest cells in the body, are particularly vulnerable to the damage that all cells accumulate with aging, leading to their dysfunction and eventual deterioration. However it is becoming evident that the molecular changes inside MNs that lead to dysfunction perhaps do not always happen in isolation. Supportive cells called glia that surround the MNs, may have a part to play. In the first part of this report we'll see how the work of two different research groups has shed light on some ways in which a type of glia called microglia are involved in the disease process.

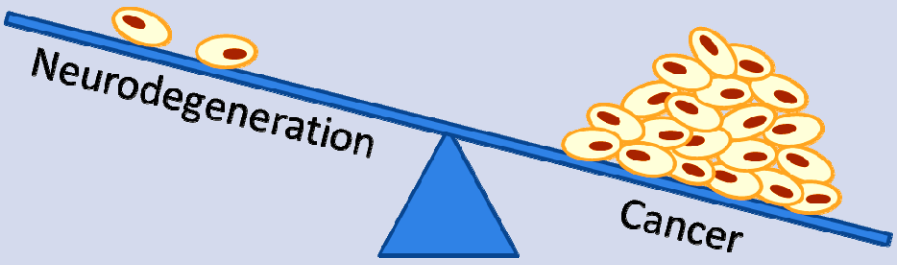
Glia aren't always so supportive

Molecules of RNA, which are the copies of information-storing DNA that are used to make proteins in our cells, can provide us with very useful insight into the specific changes that occur in cells with disease. Transcriptomics is an area of study that utilises the RNA profile of diseased cells to better understand what is going wrong. Using this approach, Harun Noristani and fellow researchers in France and Spain have analysed the RNA profile of microglia from a SOD1 MND mouse model to discover, surprisingly, involvement of the breast cancer gene Brca1. Brca1 belongs to a large class of genes called tumour suppressor genes, so named because they prevent tumour growth by slowing down cell division and regulating normal cell death. Looking at microglia in the spinal cord of these mice, Noristani's group found that Brca1 was upregulated, thus causing the opposite effect of cancerous cells and accelerating cell death. Also investigating the involvement of microglia in MND are Weihua Zhao and collaborators in Texas and California. They wanted to uncover whether the involvement of the protein TDP-43 in MND is purely due to its effects inside MNs, or mediated through signalling between MNs and microglia. Interestingly they found that TDP-43 was not toxic to MNs in the absence of microglia. TDP-43 interacted with microglia via a protein called CD14 that sits on the microglial cell surface, and this interaction initiated a cascade of inflammatory pathways that was toxic to MNs. They narrowed down on the key molecules in this cascade, some of

Cancer and neurodegeneration: the two extremes of a disease spectrum

Most of us think of cancer and neurodegeneration as two very different kinds of disease, kind of like they're sitting on opposite ends of a disease seesaw, with the former involving out-of-control cell growth while the latter involves accelerated cell death. What's interesting is that more and more genetic links are being discovered between these seemingly polar opposite disorders. In fact, some epidemiological studies have shown that individuals with Parkinson's, Alzheimer's and Huntington's diseases have a reduced risk of developing cancer, and vice versa; in some cases, people with a family history of cancer may have a reduced risk of Alzheimer's disease.

These associations between different neurodegenerative diseases and cancer largely remain to be further tested, however genetic studies are showing great potential as a way to unravel this fascinating link. Already scientists have found that these disorders share common functionally disrupted molecular pathways, including genes involved in control of the cell cycle, the repair of DNA and molecules called kinases that switch different proteins

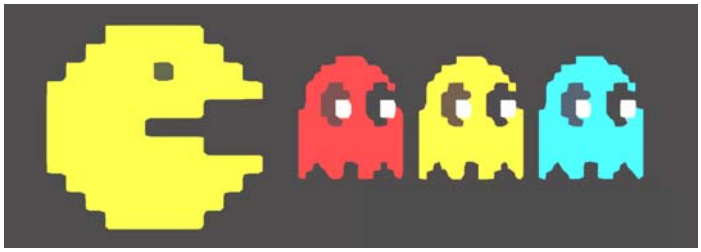


MND Research Shorts

- *Aggregation of abnormal proteins in MNs is one of the most widespread and intriguing features of MND, yet examining aggregate structure in live tissue is an ongoing challenge faced in the lab. A Swedish study has addressed this by showing that the behaviour of the SOD1 protein in test tubes mirrors what happens inside MND model mice, an encouraging finding.*
- *Motor neurone survival during disease is strongly impacted by their levels of growth factors, which are molecules involved in neurone growth and maintenance. Belgian researchers investigated whether a growth factor receptor called c-kit has a role in MND, using an MND mouse model. They found that reducing its levels in the mice was detrimental to MN function and mouse health, highlighting its protective properties.*
- *Mutations in the C9ORF72 gene represent the most common genetic cause of MND. It is believed that one way C9ORF72 mutations cause disease is by deficiency in the levels of the non-mutant form of C9ORF72. US researchers have discovered that a type of drug called a bromodomain inhibitor increases the levels of normal C9ORF72 and thus may compensate for genetic deficiency.*
- *An important cell signalling system called the Notch pathway plays a critical role in MND. Scientists in China examined the protective effects of lithium and valproic acid in MND to find that they*

Digesting away garbage proteins

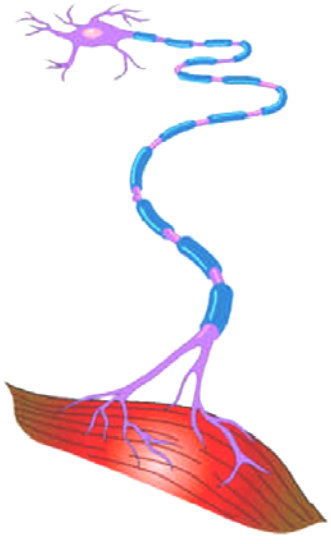
The involvement of abnormal protein accumulation in MNs in MND goes hand in hand with defects in the machinery inside cells that usually degrades and disposes of such protein "garbage". Forming an important part of this machinery are structures that regulate a process called autophagy, which



literally means "self-eating".

Autophagy involves the envelopment of garbage proteins inside the cell by small membrane-bound structures called autophagosomes, which fuse with lysosomes that contain the digestive enzymes required to break down the garbage. A protein called HDAC6 is needed to induce the fusion of autophagosomes to lysosomes, and thus needs to be present in cells in the right amount to allow autophagy to proceed. Sheng Chen and fellow researchers in Dalian and Shanghai in China examined the levels of HDAC6 in MNs in an MND mouse model and found it was much reduced at symptom onset and decreased further with disease progression. Following these findings they increased the HDAC6 levels in the MNs using a gene injection technique, with spectacular results. The higher HDAC6 levels induced the fusion of autophagosomes and lysosomes, promoted the degradation of abnormal SOD1 proteins, delayed MN degeneration and prolonged lifespan. Targeting this process and re-enabling MNs to eat away disease-promoting proteins may prove effective in restoring normal MN function in MND patients.

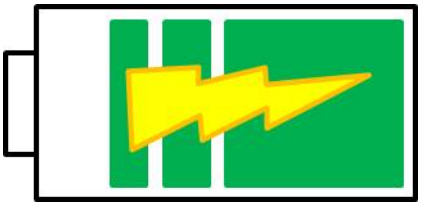
Personalising cell models of MND



The ways we're able to model MND using cells derived from MND patients are advancing to more and more sophisticated systems, allowing us to probe even the most minuscule of details in diseased cells. Maria Demestre and a team of researchers in Ulm and Tubingen, Germany, have developed the first MND model made of two different types of cells, MNs and muscle fibre cells, coming from the same MND patient. The amazing thing about this model is the interaction occurring between the MNs and muscle cells, as it is physiologically very similar to the true interaction that occurs in our bodies. These and other stem cell-based models are invaluable to research as they harbour the genetic defects causing disease, offering us the ability to study disease mechanisms in as true-to-life a context as possible.

Stressed out motor neurones and the FUS about cleaning up garbage

This same group of researchers plus collaborators in Dresden, Germany, have generated the first patient stem cell-derived model of FUS-linked MND, which accounts for approximately 5% of hereditary MND cases. In FUS-linked MND it is believed that disease ensues when the combination of abnormal FUS protein accumulation and an added "hit" of stress in motor neurones push them beyond their limits of damage. They used this model to study different FUS mutations associated with varying degrees of clinical severity. What they found was that the amount of garbage FUS protein inside motor neurones and their vulnerability to additional stress were determined by the associated severity of the underlying FUS mutation. This work confirms findings from other studies carried out in non-neuronal MND models, supporting a connection between the build-up of garbage FUS protein in motor neurones, exposure to additional stress and the severity of disease in patients.



Recharging the powerhouses of motor neurones

One of the early events in motor neurone degeneration in MND patients is the dysfunction of very important cellular structures called mitochondria, which are the energy producing powerhouses of the cell. As well as enabling our cells to produce and use the energy found in the food we eat, mitochondria also help regulate a process of controlled cell death called apoptosis. Apoptosis is important during the early development of organisms and in response to infections and other types of cellular damage, as well as for healthy tissue maintenance throughout life. Mitochondria are involved in initiating apoptosis by releasing a protein called cytochrome c into the rest of the cell, which starts off a cascade of events that lead to cell death.

A neurotransmitter called Substance P (SP) is also involved in apoptosis. There is evidence showing that SP levels are increased in the cerebrospinal fluid in the spinal cords of MND patient, thus showing involvement in the disease process. A drug compound called L-NAT interferes with the function of SP. Following promising results of the protective effects of L-NAT in a previous drug screening study, Ana Sirianni and her colleagues in the US, Canada and China examined its protective effects and mechanisms of action in mouse and human motor neurones. They found that it inhibited the production of SP as well as the release of cytochrome c,