MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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A New Wave of Motor Neuron Disease Research in 2020

Like ripples on a pond, global efforts to defeat motor neuron disease (MND) have been advancing across the world thanks, in large part, to increased awareness raised by people affected by MND. As a marker of the increasing profile of MND, the first ever Global Walk to D'Feet MND was held in Perth last December during the 30th International Symposium on ALS/MND.

Accompanying this increased public profile is the emergence of a new wave of research building on important clues about motor neuron vulnerability. Innovative thinkers from across the world are finding out different ways to help protect motor neurons, including by clearing toxic proteins, boosting cellular resilience and maintaining connections to muscle. Following on from the Perth Symposium, collaborative efforts of people affected by MND, scientists and delegates are leading the way into a promising new year.

Gene central to motor neuron resilience identified for motor neuron diseases

A gene highly expressed in motor neurons of the eye may hold the key to improving motor neuron resilience in amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), according to a new study published in the February edition of *Acta Neuropathologica*.

ALS and SMA are motor neuron diseases (MND) defined by the loss of motor neurons required for voluntary motor movement. In both diseases, when there are disruptions in the signals between motor neurons and muscle, the muscles weaken and begin wasting away. However, in SMA and ALS, not all motor neurons are affected equally. Indeed, researchers from the Karolinska Institute in Sweden and the University of Milan have been asking why motor neurons that control eye movement appear to be spared in both diseases. Led by Eva Hedlund and Stefania Corti, they found a particular gene – Synaptotagmin 13 (SYT13) – was present at much higher levels in spared resilient oculomotor 'eye' motor neurons compared to vulnerable spinal cord motor neurons.

By increasing levels of SYT13 in motor neurons derived from ALS and SMA patient induced pluripotent stem cells (iPSCs), using gene therapy, they were able to markedly improve the health of vulnerable neurons. Similarly, increasing levels of SYT13 in transgenic animal models of SMA and ALS, reduced the extent of motor neuron loss, while also increasing the life expectancy of SMA animals by 50% and ALS (SOD1) animals by 14%. Due to the neuroprotective effects demonstrated in these studies, the authors suggest boosting levels of SYT13 may be advantageous strategy for preserving motor neurons for all forms of MND.

MND Research Shorts

- Depending on the cause, ALS is classified as either sporadic (sALS) when there is no known history of disease in a family, or familial (fALS) with an inherited genetic component. Numerous genes are now understood to be involved in fALS, with mutations inudy Mitchell Research Grant C9orf72 (40% of cases), SOD1 (20%), TARDBP (5%), FUS (<5%) and TBK1 (<5%) being identified. However, some of these genes have also been identified as playing roles in sALS, such as TARDBP (6% of cases), FUS (3%) and TKB1 (1%). This suggests that by investigating how these mutations affect the motor system, we can glean insights into understanding sporadic MND.
- Gene therapy is the process of delivering genetic material into cells to correct or edit a faulty or missing gene. Recently, at the University of Illinois, bioengineers used gene therapy to stop the toxic mutant SOD1 protein being produced in a MND animal model. Described in the journal Molecular Therapy, using the CRISPR gene-editing technique, they dramatically slowed disease progression, improved muscle function and extended lifespan in this model. Although still in its early days, such advances in gene therapy hold promise for personalised treatment that can target those specific genes underlying genetic cases of MND.
- A collaboration of scientists from Spain have been testing a specific neurotrophic factor in muscle to see if it can protect the muscle-neuron connections, the neuromuscular junction (NMJ). Specifically, using gene therapy they boosted the level of a protein called Neuregulin 1 in a SOD1 mouse model of ALS. They were able to not only improve the integrity of the NMJ, but reduce motor neuron degeneration and neuroinflammation in the spinal cord. Remarkably, the neuroprotective effects of Neuregulin 1 were observed in both male and female SOD1 animals, which is suggestive of a broad reaching efficacy.
- Researchers from the University of Malta may have identified a common link between TDP-43, FUS and SOD1 disease-causing mechanisms. Defects in an enzyme called Gemin3 appears to worsen motor dysfunction caused by these ALS-causing genes in a fruit fly model. A lack of common molecular mechanisms that explain how MND-causing genes affect the motor system has hindered attempts to develop therapeutics. Identifying common factors, such as Gemin3, may lead to the development of therapeutics that are effective for a wide range of people with MND.

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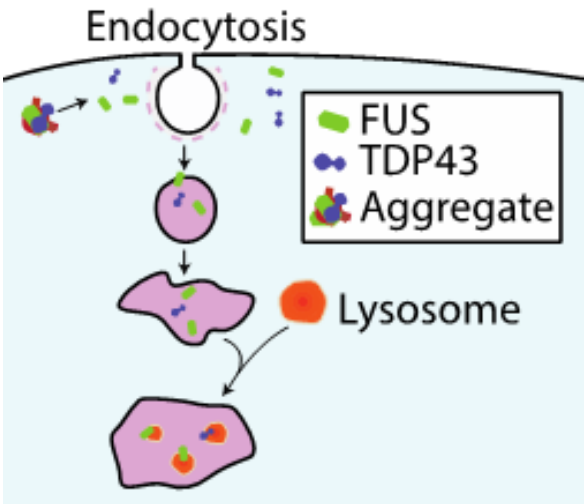
Supercharging Clearance of Abnormal Protein Aggregates - Endocytosis, an Unlikely Yet Promising Strategy

In MND a classical hallmark of affected motor neurons is the accumulation of abnormal protein 'clumps' or aggregates. These protein aggregates appear in the cytoplasm of motor neurons, and are made up of abnormal proteins that are thought to impede normal cell functions, leading to cell stress and degeneration.

Researchers at the University of Arizona have been investigating ways to help remove these cytoplasmic protein aggregates from cells. Associate Professor Ross Buchan and his team have been looking at ways to remove aggregates that are positive for TDP-43 (TAR DNA binding protein) and FUS (fused in sarcoma), which are both commonly found in the aggregates of motor neurons in MND.

Encouragingly, by investigating processes that occur within cells, they were able to identify a specific process called endocytosis, which seemed to be involved in controlling this clumping. When endocytosis was sped up, aggregates were cleared from cells and toxicity suppressed, but when the process was inhibited (or slowed down) FUS and TDP-43 mediated toxicity worsened, leading to increased accumulation of aggregates. This is quite a surprising finding as endocytosis is not typically thought to have roles in removing proteins from cells. In fact, endocytosis helps cells bring nutrition into a cell from outside – the equivalent of a cell eating or drinking.



In their latest work, published in the January edition of *Molecular and Cellular Biology*, Buchan and his team were able to show that endocytosis was impaired when both TDP-43 and FUS were independently expressed in the outer regions of the cell (the cytoplasm) where they do not normally belong (as happens in MND-associated clumping) this process of endocytosis was impaired. This may explain why these aggregates accumulate in people who have abnormal TDP-43 or FUS. Future studies will determine whether we can target endocytosis to enhance the clearance of aggregates as a therapeutic strategy.

Neurons that fire too much triggering TDP-43 pathology

An exciting link to TDP-43 has been found by researchers from the Kings College London, and the University of Michigan. In a compelling series of experiments, Associate Professor Sami Barmada and colleagues have discovered that a phenomenon called hyperexcitability can drive the emergence of cytoplasmic TDP-43 pathology.

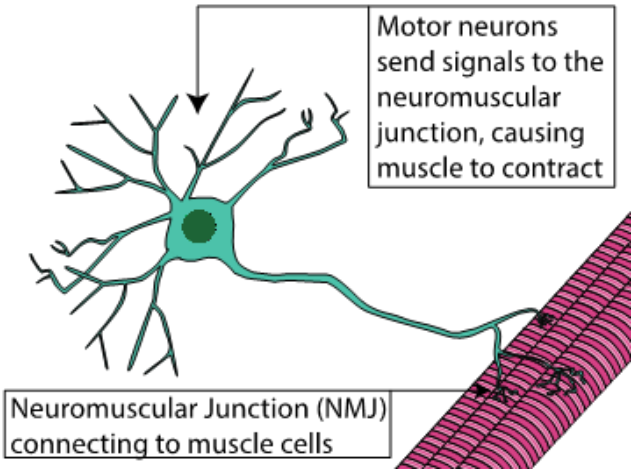
This is rather exciting as the protein TDP-43 is found in 97% of sporadic ALS, clustered in aggregates within the affected neurons cytoplasm, where it is thought to trigger cellular dysfunction, as described above.

Hyperexcitability (or too much firing) is a common feature of motor neurons in both sporadic and familial ALS. Indeed, the emergence of cortical hyperexcitability within the brain has been linked to symptom onset and disease progression in people with MND. This new study, published in the *Journal of Clinical Investigation* suggests that this abnormal hyperexcitability may have a large role in the mis-localisation of TDP-43 protein to the cytoplasm of motor neurons. Normally TDP-43 is found within the nucleus of cells, where it is not believed to be toxic, and as such it will be exciting to see if attempts to reduce this hyperexcitability reduces sporadic TDP-43 pathology and protects cells.

Modelling Neuron-Muscle Communication in MND

Motor neurons make contact with muscle at the neuromuscular junction (NMJ), where they release signals to direct muscle tissue to contract (see figure). In MND, this NMJ is degraded, resulting in muscle weakness or paralysis. Due to the importance of this small structure, a number of research groups have been trying to find ways to better study and create biological models of NMJs, so they can find more effective ways to protect them.

A functional human neuromuscular system model: In a world first, a group from the Max Delbrück for Molecular Medicine (based in Berlin, Germany) have been able to develop a functioning human cell model of a neuromuscular system. By reprogramming human stem cells into motor neurons and muscle (using induced pluripotent stem cells (iPSCs)), group leader Mina Gouti and her team were able to combine the cells together in a dish using a range of biological factors that encouraged them to form functional connections. Not only were the NMJ connections between muscle and motor neuron functional but, exceptionally, they also caused the muscle cells to contract. This is super exciting as future studies could use this technique to model NMJ dysfunction in MND by reprogramming stem cells from human MND patients. Such a model would represent a significant advance in the capacity to study key aspects of disease pathology and test potential drug therapies.



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