# MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

DECEMBER 2019

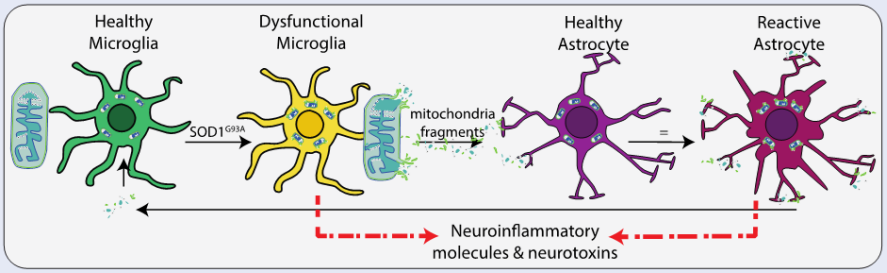
**Dr Rosemary Clark, Bill Gole MND Postdoctoral Fellow, University of Tasmania**

## A road to new insights in 2019

Motor neuron disease (MND) researchers have been paving the way towards new discoveries in 2019. Great progress has been made over the last year in understanding the factors that contribute to the development of MND. In particular, there has been impressive steps taken toward determining the underlying factors involved in sporadic MND (which occurs with no family history of disease) and the broader role of neuroinflammation in the disease. With each month, exciting new research has been emerging across the globe, adding valuable insight into how we consider the disease and how best to design therapeutic interventions to treat it.

### Fragmentation of mitochondria - providing the flame for neuroinflammation

Neurodegeneration may be spread throughout the MND brain by stressed out cells that spit out mitochondrial fragments, according to a study published in last month's edition of Nature Neuroscience. Mitochondria are small organelle structures that reside within all cells to provide the necessary energy for cellular functions. In MND there is extensive evidence of mitochondrial dysfunction.




**Cell-to-cell transmission of mitochondrial fragments fuelling neuroinflammation.**

Researchers from the Stanford University School of Medicine, led by Professor Daria Mochly-Rosen, have identified that fragmented mitochondria particles could fuel the inflammatory response in the disease. Investigating how this occurred the team found that the spread of mitochondrial fragments relied upon a type of brain immune cell called microglia. When the SOD1-G93A protein, the mutated protein underlying most genetic MND cases, was over-produced in microglia, the cells became dysfunctional, released fragmented mitochondrial components, which led to the activation of another brain immune cell called the astrocyte. Activated astrocytes then released toxic neuroinflammatory molecules that damaged neurons and also released their own mitochondrial fragments (see image).

In this manner, the authors speculate that neuroinflammation could be spread by adjacent microglia and astrocytes throughout the MND brain. Collectively, this may be an important finding for MND, as clearing damaged and fragmented mitochondria, or interrupting the pathological microglia-to-astrocyte spread of dysfunction, could provide neuronal protection and slow the neuroinflammatory cascade.

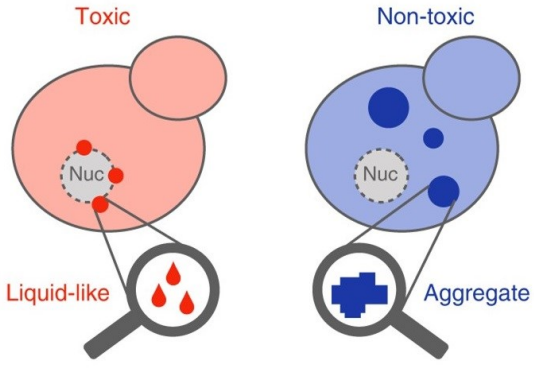
### Proteins 'clumping' may help protect motor neurons

In MND, a particular protein called TDP-43 is typically found abnormally clumped within affected motor neurons. Normally TDP-43 is found in the nucleus, the central part of the cell, but in MND it moves to the cytoplasm, the outer-region of the cell, where over time it appears to change its structure so that it accumulates and aggregates into protein clumps. Similar to other neurodegenerative diseases, such as dementia, it has been thought that this aggregated form of TDP-43 may be toxic to motor neurons. However, evidence for this has been unclear until now.

Ben Lehner and fellow colleagues from Spain have been exploring the idea that aggregated TDP-43 may not be the toxic form of the protein that leads to cell death in MND. By developing a technique that would allow them to mutate the structure of TDP-43, the team of researchers and bioengineers set out to investigate which structural conformation of the TDP-43 protein was most toxic. In a series of elegant experiments the team generated over 50,000 mutations in the TDP-43 protein to cause it to become either more, or less, aggregated.

Surprisingly, they found that the protein was most toxic when it formed a liquid-like state, and less toxic when it aggregated. Indeed, mutations that caused the liquid-like TDP-43 to form around the periphery of the cell's nucleus were most toxic.

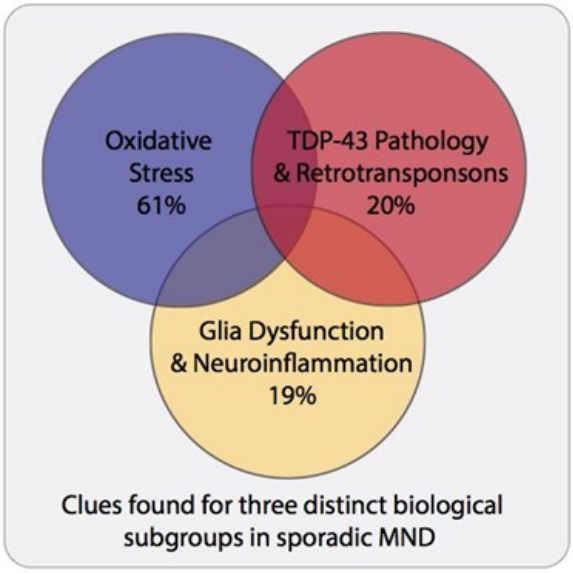
The authors suggest that aggregates of TDP-43 may in fact accumulate in cells to protect them from this ***more* toxic form of liquid-like TDP-43**. This finding is quite important as it suggests that therapeutic interventions that focus on nullifying the liquid-like state of the abnormal TDP-43 protein might be most effective.




*Mutations that promote formation of insoluble cytoplasmic aggregates decrease TDP-43 toxicity (blue) , while mutations that cause the protein to stall in a liquid de-mixed phase increase its toxicity to the cell (pink).*

## New Insights Into Sporadic MND – Machine learning and Big Data Led The Way

Sporadic MND may be clustered into three distinct biological groups, according to a new study published in the October edition of Cell Reports. Using advanced machine learning algorithms, a group from the Cold Spring Harbour Laboratories in New York, have been aiming to understand if there are key pathological factors that help define or distinguish sporadic MND. Led by Associate Professor Molly Hammell, the team looked at a range of different factors and were able to identify that sporadic MND clustered into three distinct biological groups based on the presence of certain pathology and evidence of pathogenic mechanisms (see figure).



Clues found for three distinct biological subgroups in sporadic MND

While we have learnt a lot about the genetic causes of familiarly inherited MND (genes such as C9orf72, SOD1, TARDBP and FUS are heavily implicated), the cause of sporadic MND has been much harder to pinpoint. This work suggests that **oxidative stress** and **neuroinflammation** could define different types of MND in patients and gives us new clues about how mutant TDP-43 could be linked to disease.

**Retrotransposons**, also known as jumping genes, are genomic parasites that copy a genomic sequence and then insert that copy into a new location of the genome. These typically dormant 'jumping genes' become re-activated when TDP-43 becomes dysfunctional. This work is very exciting as it suggests when TDP-43 abnormally accumulates in MND, the protein can no longer keep these jumping genes silent.

Future works will need to find out how re-activation of jumping genes could contribute to disease processes in MND. Collectively, this study provides valuable insight into underlying disease mechanisms, and may help guide clinical trial design. This may also go some way to help explain why the disease is so heterogeneous between patients.

## New wave of MND research looks to the math

Scientists have long been puzzled why people who carry genetic mutations that cause MND don't develop the disease until later in life. If these mutations are so toxic, why doesn't the disease manifest sooner? If we understood why, could we stop the disease from developing all together?

Ammar Al-Chalabi and collaborators from around the world have been attempting to ask this question using some very clever mathematical modelling. By analysing incidence data from patients who had different genetic mutations, the team were able to find that certain genetic mutations may only account for a proportion of the pathogenic burden required to develop the disease. In early 2014, Al-Chalabi and colleagues first identified that multiple steps (or pathogenic factors) were required to develop MND – specifically at least 6-steps were suggested to lead to the development of the disease. In their recent 2018 study, published in the Journal of Neurology, Al-Chalabi identified that ***mutations in genes can account for more than one step in this multi-step process***, leaving fewer steps before MND begins. Indeed, modelling suggested only 3 steps were required for the development of disease when C9orf72 mutations were present, while a 2-step process was consistent in SOD1 and 4-step process for TARDBP. This work is very promising as it suggests that relatively fewer steps need to be identified in order to develop effective therapeutics.

In November this year Australian Neurologists Professor Matthew Kiernan, and Professor Steve Vucic demonstrated that the multistep model is also applicable in the Australian setting – previous modelling had been conducted in a predominantly European cohort. Further studies that lead to the identification of these steps will hold great therapeutic potential, as it could effectively unlock the combination of factors that add-up to cause MND.

### *MND Research Shorts*

- STMN2 is a protein that mediates motor neuron growth and repair. A study led by researchers from Harvard University has identified that STMN2 levels are tightly linked to TDP-43 function, which could explain why motor neurons are particularly vulnerable when TDP-43 becomes dysfunctional in MND.
- Researchers from Philadelphia have been developing methods to bind up the abnormal liquid-like form of TDP-43 they believe may be toxic in MND and frontotemporal dementia. Like a fishing expedition, the team designed TDP-43 targeting bait-balls (or bait-oligonucleotides) that catch abnormal TDP-43 and reverse neurotoxicity in a dish. The next step will be to see how these targeted 'bait-balls' perform in animal models of the disease.
- MND and frontotemporal dementia (FTD) share common disease pathology with dysfunctional TDP-43 identified in affected neurons of both, and mutations in a gene called C9orf72 also in both, so how do these diseases develop different symptoms? Researchers from Germany have shown that when the symptoms appear in MND and FTD there is a key difference in the type of inflammation present. This may provide vital clues about how to protect neurons in both MND and FTD.
- Upper motor neurons in the brain initiate a motor signal, which is then relayed to the spinal cord lower motor neurons for muscle movement to occur. Researchers from Chicago have shown that very early in disease, upper motor neuron vulnerability may be caused by problems with mitochondria – the powerhouse of the cell required to produce energy for cells.

**MND Research Institute of Australia - the research arm of MND Australia**
PO Box 117 Deakin West ACT 2600
Ph: 61 2 8287 4989 email: research@mndaustralia.org.au website: www.mndresearch.org.au

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