MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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A new year brings new research opportunities

Although last year provided many hardships to the global community, the roll out of the COVID-19 vaccines is expected to begin alleviating the effects of the pandemic. There will, of course, be a lag period to return to the economic levels that permit advanced research projects and allow for generous charity, but we are well on our way.

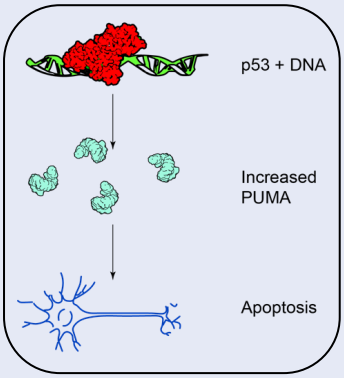
This issue of the international research update has no specific focus, but rather entails a broad range of topics that have been investigated in relation to Motor Neuron Disease (MND). The broadening scope of MND research is expected to yield new ideas and opportunities for the MND community.

Transcriptional factors as disease mechanisms[1]

Researchers from Stanford University in the USA have identified a specific transcription factor which plays a significant role in prompting neurodegeneration in C9orf72 models of MND. Transcription factors are proteins that control and regulate the DNA-to-RNA step in protein production, thereby controlling the levels of a specific protein that may be produced within a cell. Transcription factors are very important for instructing cells on how to operate by controlling which genes can be activated and how active those genes should be.

Tumour protein P53

The transcription factor identified in this work is called 'tumour protein p53' or p53 for short. As its name implies, p53 is responsible for preventing cells from becoming cancerous. As such, it is the most frequently mutated gene found in cancer cases. In the case of the research referred to here, p53 is the transcription factor that controls the production of a protein known as PUMA.



P53 upregulated modulator of apoptosis (PUMA)

PUMA protein is situated in a very important pathway in the cell called 'apoptosis'. Apoptosis is a form of controlled and regulated cell death. The authors identified that, in C9orf72 models of MND in different species, p53 transcription factor promoted the expression of PUMA, which led to cell death in mice, flies, and human cells. By removing p53 from the models, the researchers saw a robust decrease in the toxic effects of C9orf72 in their models.

Potential for future treatment?

Much of the research we do in science is levelled at two major ideas: killing cells or keeping cells alive. Cancer research is focused on killing cells, whereas neurodegenerative disease research is focused on keeping cells alive. P53 appears to sit at the interface of these two major medical challenges. In this model it appears that reducing p53 can protect neurons. However, any treatment that prevents p53 from doing its normal job may lead to the formation of cancer cells. This being said, the pathways within cells, where proteins talk to each other, are large and complicated, and manipulation can be targeted at specific points in these pathways to increase the therapeutic value.

MND Research Shorts

- The endoplasmic reticulum of cells is a key player in promoting proper protein folding, a role which is carried out with the help of 'chaperone' proteins. Researchers from the University of Manchester in the UK have shown that upregulating the expression of a protein called ERp57 slows degeneration and prolongs life in the SOD1 mouse model. This provides information to another gene as a potential therapeutic target.[2]
- TDP-43 is thought to have a primary role in MND as a cause, therapeutic target and potential biomarker. Researchers from the University of Milano-Bicocca in Italy examined the blood serum of MND patients for the presence of antibodies against TDP-43 in the hope that they would be higher due to TDP-43 in MND patients. They found that MND patients had a much greater amount of TDP-43 reactive antibodies in their blood serum, signalling this method as a potential diagnostic and prognostic.[3]
- The risk of developing MND is increased for those who have served in the military, although the reason for this is unknown. Researchers from the University of Colorado in the USA examined if veterans diagnosed with MND were more likely to commit suicide as compared to veterans without MND. They found that the risk was ~4 times higher for MND diagnosed veterans to commit suicide. This research underpins the need for effective therapies but also compassionate and effective mental health interventions for MND patients and veterans alike.[4]
- Evidence has shown that TDP-43 can spread from cell-to-cell in a prion-like manner in cells and animals, however the question remained if this spreading causes MND. Researchers from Zhengzhou University in China have shown that the spread of TDP-43 in mice also causes MND-like symptoms. This research supports the notion that MND may be a disorder in which protein aggregates spread and cause disease in a manner similar to prion diseases.[5]

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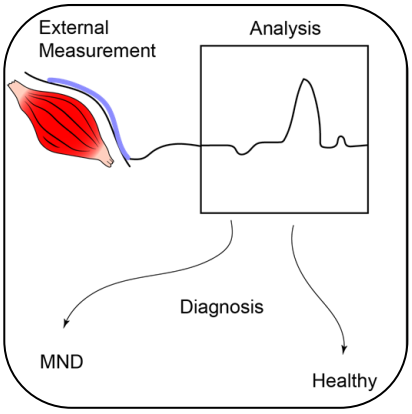
Non-invasive diagnosis[6]

Research published by scientists from King's College in the UK has pointed towards a promising method of making non-invasive diagnoses of MND. At the current time, there is no one test that allows for the diagnosis of MND and neurologists must conduct a physical examination of patients. This process takes time and is not always certain. The method proposed in the research referred to here uses an advanced system of electrodes that can be applied to a patient's skin.

Surface Potential Quantification Engine (SPiQE)

The tool is called SPiQE and is the result of a collaboration between King's College and Imperial College. SPiQE works by detecting and differentiating between voluntary and involuntary muscle activity. MND patients often present with muscle fasciculations, which are involuntary twitches of muscles, early in the disease course. Early detection and accurate determination of muscle twitching has been proposed as a potential diagnostic, but non-invasive measures have not been as accurate as one would hope. SPiQE overcomes the deficiency in accuracy.

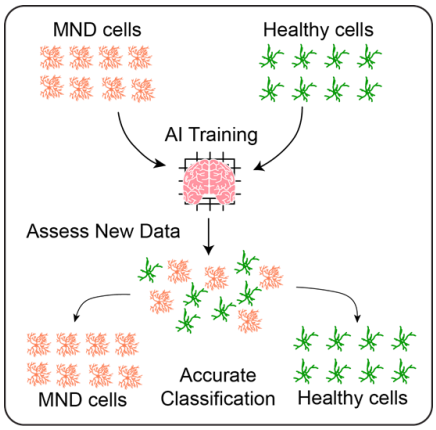


Delineation between MND, other neurological diseases and controls

As a show of its accuracy and power, SPiQE was capable of measuring the muscle activity of MND patients, healthy patients, and people suffering from neurological disorders that are not MND. Amazingly, SPiQE was capable of differentiating between each category. Although this work is only in its infancy, it has the potential to provide neurologists and patients with more effective knowledge during the early stages of MND, which is critical in patient care and wellbeing.

When intelligence isn't enough, make it artificial[7]

Researchers from Kyoto, Japan, have used their expertise in artificial intelligence to help researchers with one of the current problems in scientific research: big data. Big data is the collection of large amounts of diverse data. Humans are smart enough to process, as well as understand and interpret the data, but we are too slow. Artificial intelligence is capable of processing large amounts of data very quickly, but cannot understand and interpret the data at the level a human does. A combination of the two provides a very useful research tool.



A picture says a thousand words

We all know that pictures have a lot to say. The researchers here took many thousands of pictures of cells from healthy patients and MND patients. By measuring quantitative features of the images of cells and telling the AI whether those images were MND or healthy, they could train the AI to accurately predict whether cells were from an MND patient or not.

Application to both diagnosis and treatment

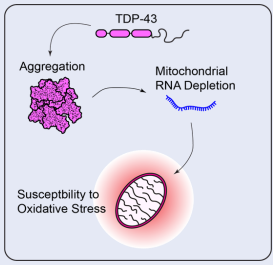
This method has fantastic applications to MND research that span from basic research to medical and pharmacological interventions. Researchers could use such a technology to efficiently undertake large-scale screens for drugs that return MND patient cells to being healthy as determined by the AI. Likewise, more accurate and effective diagnosis could be made by procuring cells from suspected MND patients and analysing them with this system.

Back to oxidative stress[8]

Researchers from University of California, San Diego in the USA have revitalised the idea that oxidative stress may contribute to the cause and progression of MND. Originally, the identification of SOD1 protein mutation in MND caused researchers to propose that oxidative damage to cells was a substantial factor in the disease as SOD1 is involved in the oxidative stress pathway. However, subsequent research showed that this is not the entire story, prompting researchers to look elsewhere. The researchers of this work decided to investigate how TDP-43, another key MND protein, may cause toxicity in cells by looking at what genes change in expression level in response to TDP-43 toxicity.

TDP-43 aggregation depletes other proteins from the cell

TDP-43 is a protein with a role in managing RNA, the molecules that transfer gene information into the creation of proteins. If TDP-43 is not acting properly, some proteins do not get generated in the cell and thus their function is lost. The researchers found that the accumulation of clumps (aggregates) of TDP-43 resulted in other proteins being caught up in these aggregates, and that the loss of TDP-43's role caused other proteins to not be expressed.



Mitochondrial genes

We've all heard it before, "the mitochondria are the powerhouse of the cell". This fact places mitochondria in a very important role and one that is very sensitive to perturbation. Although mitochondria contain their very own genome, in humans they require genes from the cell nucleus to still function properly. The researchers here found that many of the genes depleted by TDP-43 aggregation were those very genes important for proper mitochondrial function. The depletion of these genes makes mitochondria more susceptible to stress, which has consequences such as the generation of oxidating molecules and the loss of cellular energy for proper functioning.

References

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