MND Australia

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International Research Update

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The first national MND Conference in-person after COVID

This April, MND/ALS researchers, clinicians and patients from across Australia and New Zealand will be gathering in Brisbane to discuss various aspects of MND/ALS. This is the first time this has occurred in-person since the start of the COVID-19 pandemic. There is great excitement for this conference with its excellent assortment of research-based and clinically-based information for all stakeholders (sign up at www.mndaustralia.org.au/symposium). In this article, however, we typically deal with international research. This issue brings information about some important disease processes recently identified that are associated with both onset and progression of MND/ALS.

UNC13A is depleted in ALS patients [1]

A world spanning and multidisciplinary research team led by Professor Pietro Fratta from University College London has discovered how depletion of a key gene called UNC13A contributes to ALS. This gene is particularly important for the maintenance of the long tails of motor neurons that span the human body to carry signals to muscle cells. They found that loss of TDP-43 results in the improper processing of the UNC13A gene, leading to its depletion from cells. This is an important finding as it identifies another mechanism by which TDP-43 drives MND and also provides another target for us to explore therapeutics.

Cryptic Exons of UNC13A Within our genome, genes represent tracks of DNA code, but a gene is often broken apart into tracks that code and tracks that don't, respectively called exons and introns. Since exon DNA is what we want to create a protein, we need to cut out the intron DNA when reading the gene to produce the RNA (a process called transcription) from which the protein is produced (a process called translation). The transcription process is tightly controlled and mistakes are catastrophic to cells. TDP-43 controls transcription for many genes and when TDP-43 is not working properly (as happens in ALS), parts that were meant to be removed can become included in the RNA (called cryptic exons), leading to protein translation of the target gene not occurring properly.

Mutations in UNC13A increase the risk of UNC13A depletion

The researchers not only found that UNC13A was being misprocessed by unhealthy TDP-43 in cells but also that mutations in the UNC13A gene led to an increased risk of improper exons being included in the UNC13A RNA, leading to its loss in cells. TDP-43 is a DNA and RNA binding protein which means it binds to genes and their products to control their activity. The mutations in the UNC13A gene that are considered risk factors for ALS fall within the site at which TDP-43 would bind to it suggesting that interactions between TDP-43 and UNC13A may influence levels of gene activity. This ties in interestingly with the discovery that patients carrying certain mutations in the UNC13A gene respond favourably to lithium as a potential treatment for MND. A trial is just commencing whereby Lithium will be specifically tested in patients carrying UNC13A mutations.

MND Research Shorts

Younger women are associated with having a lower risk of developing ALS as compared to men and older women, which suggests that some hormones might affect disease progression. Researchers from Tasmania have determined that female TDP-43 mice are more capable of remodelling their neurons than their male counterparts, with this effect being strongest when oestrogen levels are high. This suggests that hormonal modulation may be a possible treatment for MND.[2]

A landmark finding was that the gene Stathmin-2 was regulated by TDP-43, and that in ALS Stathmin-2 was lost due to incorrect regulation, resulting in motor neuron degeneration. Researchers from Harvard have determined that disruption of Stathmin-2 in mice resulted in significant motor neuron dysfunction and muscle denervation. This work strongly suggests that dysregulation of Stathmin-2, even in the absence of TDP-43 dysregulation, may be a feature of MND.[3]

TDP-43 is the protein associated with most cases of MND/ALS and it is also associated with half of frontotemporal dementia cases. New research from Aichi Medical Research University in Japan has found that TDP-43 aggregates are present in the tissue of patients suffering from progressive supranuclear palsy and corticobasal degeneration. This research further expands the number of diseases that TDP-43 protein may contribute to.[4]

Cells are tightly packed in our bodies and talk to each other through small protein channels. Researchers from Lund University in Sweden have determined that a particular channel, called connexin-43, mediates motor neurons talking to astrocytes and can cause motor neurons to become sick. Removing these channels only from astrocytes increased mouse survival in an animal model of MND. This suggests these channels may be a target for intervention in MND.[5]

Improving patient data using CAPTURE ALS[6]

A collaborative team from across Canada, led by Dr Nicolas Dupré from Laval University, have published a plan to establish a pipeline to optimise the collection of patient samples and data and their dissemination to researchers worldwide. This plan includes assessing patients at different time points throughout their MND disease journey, and collecting samples at these time points.

Why is this important? A key factor in the relatively difficult and slow progress of understanding MND/ALS is that the disease is so heterogeneous in its presentation. People develop disease at different ages and progression to end stage may be slow or rapid. Another challenge in understanding MND is that monitoring of patients is often not centralised (this is true for many other diseases too).

CAPTURE ALS plans to lessen these challenges by standardising clinical scoring of patients, building a widely available biorepository and promoting the participation of ALS patients in research. All of this is planned to occur across multiple sites in Canada, requiring extensive expertise and involvement from many stakeholders.

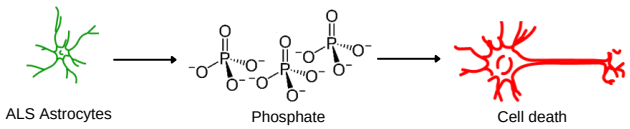
What might be discovered from this? Often, understanding disease from clinical measurements becomes a game of numbers. The more information you have, the more confident you can be about your final result. Problems with this occur when different types of examination or samples are collected in assessing patients. By standardising the entire process, the Canadian team has a good chance of identifying prospective biomarkers and more clearly defining changes in patient health throughout their disease course.

A similar approach is already underway in Australia where we are currently working to combine the SALSA genomics database with the Australian MND Registry under the MiNDAUS program – www.mindaus.org

Excessive inorganic phosphate release[7]

An international research team led by Dr Brigitte van Zundert from Andrés Bello National University in Chile has published work suggesting that increased levels of inorganic phosphate are found in MND-patient spinal cord samples, and that astrocytes are to blame for this.

Astrocytes and MND A component of MND is the non-cell autonomous death (i.e. caused by surrounding cells) that is observed. This means that even healthy motor neurons can die because the surrounding astrocyte cells release toxic molecules. Unravelling the reasons why astrocytes become toxic, and what the toxic molecule(s) might be has been intensely researched for a long time in the MND field.

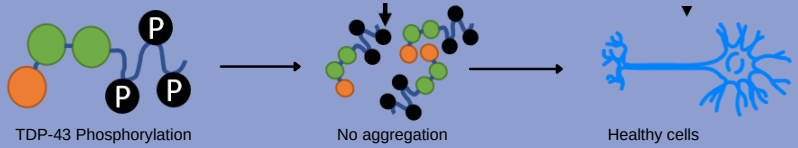


Polyphoshphates Phosphate is typically found in a form where the phosphate group is surrounded by 4 oxygen molecules. Phosphate is an essential molecule for cellular function due to the requirement of cells to use various forms of phosphate in cell-signalling and metabolism. Like anything, too much or too little may be toxic to cells. Polyphosphates are just phosphate molecules that form chains, and some are good to have in cells (e.g. polyphosphates ATP and ADP are critical elements in energy production) but others can be harmful.

Astrocytes release polyphosphates The researchers found that human samples from ALS patients had increased levels of polyphosphates and that astrocytes originating from patient samples generated increased amounts of polyphosphates. The main take away is that researchers determined that removing these polyphosphates from samples prevented those samples from being toxic to motor neurons. This strongly suggests that polyphosphates may be a key molecule that induces motor neuron death in MND.

TDP-43 solubility is increased upon phosphorylation[8]

Researchers led by Dr Dorothee Dormann from the Johannes Gutenberg University in Germany have expertly unravelled a long-held assumption regarding TDP-43 and its aggregation in ALS. They found that a post-translational modification called phosphorylation led to an increase in solubility of the TDP-43 molecule. This is important because there has long been debate as to whether TDP-43 phosphorylation leads to its aggregation or is a protective mechanism to prevent aggregation.



Post-translational modifications and phosphorylation

Post-translational modifications are alterations to proteins that occur following their translation, i.e. when the cell changes a protein molecule after it has been formed. These include attachment of molecules, removal of parts of proteins, binding of metals etc. One of the most prolific modifications is called phosphorylation, which is the attachment of a phosphate molecule to a specific site on a protein. Phosphorylation is a very important modification that can make proteins active, turn proteins off, or make proteins move to a certain position in the cell.

TDP-43 aggregates and phosphorylation

We have known for some years now that the insoluble aggregates composed of TDP-43 in cells is partly composed of phosphorylated TDP-43. What has been puzzling has been whether phosphorylated TDP-43 ends up in these aggregates, or if the aggregates are phosphorylated after they form. The article here suggests that the phosphorylation of TDP-43 in cells leads to an increased solubility and less aggregation. Also, they found that phosphorylation of TDP-43 did not alter its ability to move from nucleus to cytoplasm, indicating that targeting the phosphorylation of TDP-43 may be a potential therapeutic route in MND/ALS.

References

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