SEPTEMBER 2017

MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

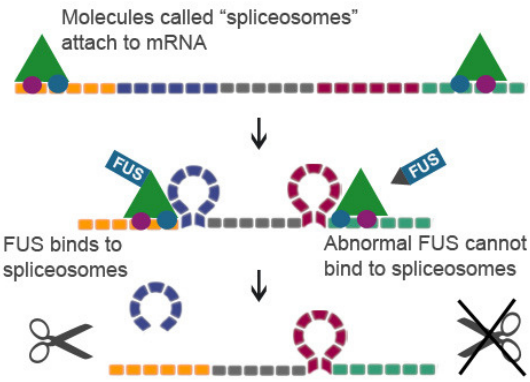
Isabella Lambert-Smith, Australian Rotary Health PhD Scholar, University of Wollongong

MND research heats up

As the weather warms up with the start of spring in Australia, so do the latest studies by motor neurone disease (MND) researchers around the world. Recently, researchers have solved a few mysteries about how some of the MND-causing genes contribute to motor neurone (MN) degeneration and discovered similarities between different diseases that give us clues on how to treat MND.

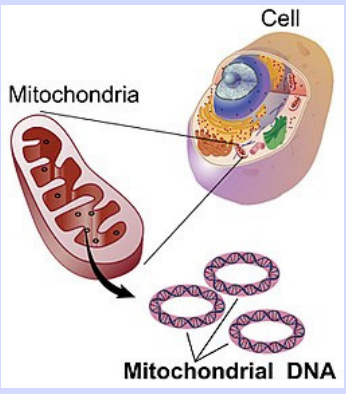
FUS and SMN interact in gene splicing

Although MND is commonly referred to as a single disease, it is actually a group of diseases that all involve the degeneration of MNs. Amyotrophic lateral sclerosis (ALS) is the most common form of MND. Spinal muscular atrophy (SMA) is a genetic disease that most often affects children. Like adult MND, SMA affects the MNs of the spinal cord, causing muscle weakness and wasting. SMA is caused when there is a deficiency of the MN protein called SMN. Changes in the gene encoding a protein called FUS are responsible for a significant fraction of ALS cases, and in many cases abnormal forms of the protein are found clumped together with other proteins in diseased MNs. FUS normally regulates a biological mechanism called gene splicing. In our DNA, about 40-60% of our 30,000 genes undergo splicing. This mechanism is important for cutting out regions of the DNA sequence that don't actually code for proteins (see box). Abnormal FUS proteins are unable to regulate splicing, and also capture other components of the machinery that carry out splicing. This is strikingly similar to what happens to the SMN protein in SMA patients, suggesting that disrupted gene splicing in MNs may be a common theme in both diseases. Alessia Mirra and her colleagues in Rome, Italy, followed this lead and tested the relevance of FUS and SMN in a mouse model of FUS- associated ALS. They found that these FUS-ALS mice shared crucial molecular features that characterise mouse models of SMA, including defective splicing of genes that are vital for MNs. Of note, when Alessia's team altered SMN levels in the MNs of these mice, the degeneration caused by FUS abnormalities stopped. These findings strongly suggest that a complex interplay exists between FUS and SMN in the regulation of gene splicing in MNs. Further research focus should therefore be directed towards strategies that target this pathway of gene splicing.



Our unique instruction manuals

Our DNA has about 30,000 genes that contain all the instructions for the growth and maintenance of our body; all the instructions that make us unique. Each gene codes for a protein molecule. Proteins are the tiny workers of the cell that carry out all the functions needed for life. Gene *expression* is a multistep process in which information from genes is used to manufacture proteins. In the first step, the DNA sequence of the gene is *transcribed* into a messenger RNA (mRNA) molecule. This mRNA then goes on to be *translated* into the corresponding protein molecule. Before it is translated, the mRNA needs to be spliced. mRNAs contain both information for the actual protein plus extraneous material that needs to be cut out. The protein-coding information is then spliced together to make a mature mRNA, which is in turn translated into a protein. Most of our DNA is packaged into chromosomes inside the cell nucleus, however tiny structures inside cells called mitochondria have 37 genes of their own DNA, called *mitochondrial DNA*. Fascinatingly, we each inherit our mitochondrial DNA from our mothers. There are some genetic testing services that use mitochondrial DNA to trace our maternal ancestry. There's also a popular idea that there exists a "Mitochondrial Eve", a woman from whom all humans inherited their mitochondrial DNA.



By National Human Genome Research Institute [Public domain], via Wikimedia Commons

MND Research Shorts

Nerve cells contain molecules called glycosphingolipids that facilitate cell metabolism. Glycosphingolipids become damaged in MND, which in turn disrupts metabolic processes. Researchers across France and the UK have discovered a way of restoring proper metabolism of these molecules in MND model mice, showing that targeting glycosphingolipid metabolism may be a therapeutic option.

Inflammation in the nervous system is a prominent feature of MND, with inflammatory molecules called cytokines infiltrating the brain and spinal cord in patients. Researchers in Beijing, China, have identified the specific cytokines in the blood that indicate whether or not a person has MND. If this finding is substantiated by further tests, the cytokine may be a useful tool for early MND diagnosis.

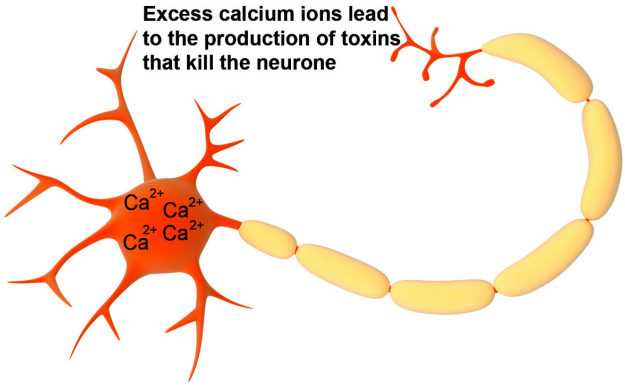
Researchers in France and Russia have discovered that dysregulated levels of zinc in MNs contribute to the disease-associated clumping of TDP-43. This knowledge launches us forward in determining a way to target and ameliorate this damaging mechanism.

Mitochondria become dysfunctional in MND and can cause damage in MNs by producing harmful free radicals. Collaborating researchers in Japan and the UK investigated how TDP-43, one of the main causative genes in MND, contributes to mitochondria dysfunction. They found that TDP-43 has a novel role in regulating the functions of mitochondria by controlling the cell's use of mitochondrial DNA (see box). The next step is for researchers to figure out how to target this process to alleviate ensuing dysfunction.

mnd Australia

New molecular tool kit to decipher calcium imbalance in MND

All of the neurones in our body rely on the fine-tuned coordination of thousands of different molecules and metal ions (atoms with electric charge). One of the most important ions is calcium. Calcium is needed by nerves to transmit signals. It needs to be kept at precise concentrations in different compartments inside neurones in order for signals to be transmitted correctly. MNs are particularly sensitive to harmful cell overloads of calcium as they possess low levels of the proteins that regulate calcium concentration. Calcium overloads in neurones cause overstimulation and the generation of free radicals and other toxins that cause cell damage and death. This phenomenon is referred to as excitotoxicity and it is one of the main contributors to MN injury in MND. Rosa Pia Norante and her fellow researchers in Padova, Italy are working to understand the calcium-related routes of MN dysfunction and damage. They generated a molecular tool kit of probes that target calcium in different compartments specifically inside MNs. These calcium probes will allow researchers to measure calcium responses and movements in cells in response to different stimuli for the first time. This will enable researchers to identify exactly where the calcium disturbances occur that cause excitotoxicity and MN degeneration.



Chains of TDP-43 prevent MND-associated protein clumping

In the vast majority of people with MND and a type of dementia called Frontotemporal dementia (FTD), their affected neurones contain clumps of different proteins mixed up with one very noticeable protein, called TDP-43. In addition to its presence in disease-associated protein clumps, TDP-43 is genetically associated with both of these diseases. This has led many researchers to investigate the exact role of TDP-43 in MND and FTD, a challenging task as detailed understanding of TDP-43's 3D structure has been near impossible to study. That is, until Tariq Afroz and fellow researchers in Zurich, Switzerland, figured out how to examine it in intricate detail in diseased human tissue. Using a suite of ingenious biochemical techniques, they demonstrated that TDP-43 in its normal, physiological state in cells exists as short chains of several TDP-43 molecules joined together head-to-tail. This precise head-to-tail arrangement actually blocks the parts of the protein that can become sticky and cause clumping. Tariq's work excitingly indicates that stabilising these functional TDP-43 chains may have therapeutic potential by preventing disease-associated clumping and restoring the normal cellular activity of TDP-43.

Potential strategy to repair the blood-spinal cord barrier

The circulatory system is separated from the brain and spinal cord by a membranous barrier called the blood-central nervous system barrier (B-CNS-B). It protects the CNS from toxins that may be present in the blood and thus is vital for a healthy and functional CNS. The B-CNS-B is made up of specialised cells called endothelial cells (ECs) that regulate the flow of substances into and out of the CNS. In MND the ECs degenerate and the B-CNS-B loses its ability to defend the CNS. To combat this B-CNS-B breakdown in MND, Svitlana Garbuzova-Davis and her colleagues in Florida, USA investigated the potential of bone marrow. Bone marrow is a primary source of stem cells that produce ECs as well as other cell types. Stem cells that specifically produce ECs have a signal on their surface known as CD34. Svitlana's team wanted to determine the potential of human bone marrow CD34 cells transplanted into symptomatic SOD1-MND mice to repair the B-CNS-B. Remarkably, the transplanted cells integrated into numerous capillaries of the B-CNS-B. This strengthened the B-CNS-B and protected the cells that surround and support MNs. While further study is needed to confirm these findings and further explore the effects of bone marrow CD34 cell transplantation, it indicates that this approach could be developed and combined with other therapeutic options to develop an effective treatment strategy.

A protein army to clear TDP-43 clumping

After a protein is produced in a cell, its structure often needs to be modified by folding so that it assumes the correct shape to perform its function; a process similar to origami. Throughout a protein's lifetime in the cell – which varies from minutes to years depending on the specific protein – it can also undergo abnormal modifications that change its shape into a non-functional, sticky form. Ping Wang and his colleagues in North Carolina, USA, have discovered that when a molecular structure called an acetyl is attached to TDP-43 it unfolds and becomes sticky. This causes TDP-43 to clump together with other proteins in MNs. Cells contain an arsenal of proteins, called chaperones that fold newly made proteins and refold old proteins, which have been unfolded and become sticky. Ping and his group tested whether or not they could make the chaperone army come to TDP-43's rescue and refold it back into its functional shape. In a cell culture MND model, they activated a protein called HSF1, essentially the "General" of the chaperone army, which coordinated a chaperone response that was able to refold TDP-43 molecules and clear away protein clumps. This group's work has highlighted the potential of folding and refolding mechanisms as therapeutic targets to alleviate MN dysfunction associated with TDP-43 protein clumps.

Structure of TDP-43 protein

MND Research Institute of Australia – the research arm of MND Australia
PO Box 430, North Sydney, NSW 2059
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