MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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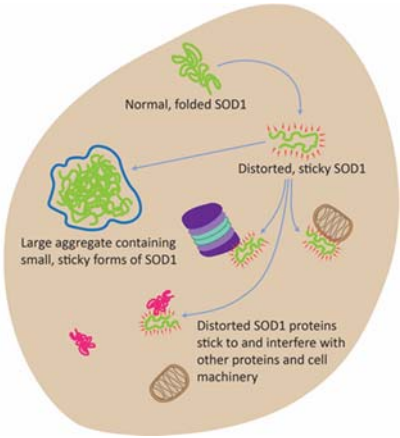
Progress in understanding MND accelerates

Motor neurone disease (MND) researchers are pulling out all stops so far in 2018. Incredible progress has been made in identifying new therapeutic targets and improving old ones. There has also been major headway made in deciphering the complicated mechanisms by which MND-linked genes cause motor neurone (MN) damage and death. No doubt about it, progress in understanding and treating MND is accelerating with each passing day.

To aggregate, or not to aggregate: that is the question

When researchers examine the MNs of MND patients, what they see most often are clumps of abnormally-shaped proteins. They call these clumps 'aggregates', and they are one of the hallmark features of MND. Proteins are the workers of the cell, and usually they do their jobs well. However, proteins can only do their jobs when they keep in tip-top shape. This is because they are made of sticky parts and functional parts. The way they're shaped is necessary to keep their sticky parts on the inside and their functional parts on the outside (see box below). In MND, however, many proteins lose their shape and become sticky. This is bad news for all the other parts of the MN as the distorted proteins end up sticking to other proteins or to critical parts of the cell's machinery, impairing their function. Some proteins are notorious for losing their shape in MNs; one of the most infamous is SOD1.

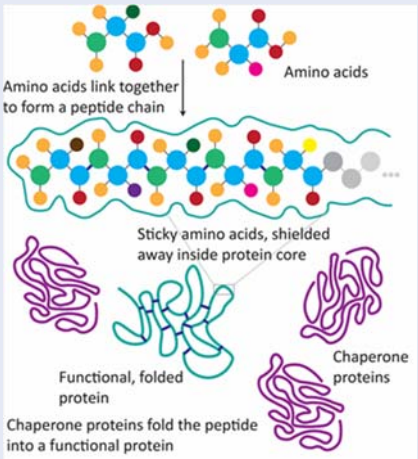


For years researchers have debated whether it is the sticky SOD1 molecules themselves, or the aggregates they form, that are toxic.

To try to determine this, Cheng Zhu and his fellow researchers in North Carolina, USA designed mutant forms of SOD1 that would either form into large aggregates or remain as small sticky SOD1s. Additionally they tested two mutant forms of SOD1 that cause particularly aggressive forms of MND. They then injected these into MNs and monitored their health. They found that the MNs treated with the mutant aggregate-forming SOD1 were healthier than MNs treated with any of the other mutants. In contrast, the small sticky SOD1s caused the greatest amount of MN death. These results show that it is the small forms of mutant SOD1 that are most toxic, and that MNs may collect these into aggregates as a mechanism to protect from its toxic effects.

The many levels of protein structure

There are thousands of different proteins that each have specific jobs to keep cells functioning. Just like machines that have a functional shape, proteins must be kept in shape to carry out their jobs. They are made up of building blocks, called amino acids, that link together to form peptides. Peptides are then assisted by chaperone proteins that fold peptides into functional proteins. The folds are secured by strong links, called bonds, that form between designated amino acids. Some amino acids are sticky and can interfere with other machinery in the cell, so folding isn't only necessary for protein functionality, its critical for keeping the sticky parts shielded away inside the protein core.



MND Research Shorts

- *Inflammation in the nervous system is a significant contributing factor to the rate of MND progression. Researchers in China have discovered that this inflammation can be reduced by increasing the levels of a protein called IGF1 in microglia, a type of support cell that looks after MNs. This allowed the microglia to suppress the inflammatory response and prevent death of MNs.*
- *Over the past 15 years, researchers have investigated the therapeutic potential of cannabinoids, the chemicals in the cannabis plant, for MND. A study carried out in Spain has revealed that increasing the amount of the cannabinoid-interacting CB2 protein, located on the surface of microglia, can slow MN death. This could be a therapeutic option for MND linked to the SOD1 and TARDBP genes.*
- *Researchers in Italy have revealed findings that really hit two birds with the one stone. Investigating blood samples from MND patients, they detected considerably reduced levels of TLQPs, small fragments of the VGF protein, compared to the levels present in blood of healthy individuals. This demonstrates that levels of TLQPs in the blood can be used to aid in early diagnosis of MND. On top of that, the researchers found that adding extra TLQPs to MNs in an MND model protected against cell death.*
- *Riluzole is one of two medications that have been approved to treat MND. Unfortunately, the blood-brain barrier (BBB) limits the effectiveness of riluzole and many other drugs targeted to the nervous system. However, researchers in the USA have devised a drug delivery system that can penetrate the BBB. They have achieved this by generating microscopic spheres made of fat molecules, called liposomes, that can pass through the BBB. Inside the liposomes they package tiny doses of riluzole with another chemical that prevents MNs from pumping riluzole back out. This strategy will be tested to improve riluzole therapy for MND.*

A new pharmalogical lead for SOD1-linked MND

When a protein is first made inside the cell, it usually doesn't have any shape and exists as a linear chain of amino acids (see box on page 1). Immediately upon being made, the protein chain is folded up into its characteristic shape through the formation of bonds between amino acids sitting at different points in the chain. One of the most important bonds in SOD1 is called a disulphide bond, but in *SOD1*-linked MND it gets broken, causing SOD1 to unfold and for its sticky parts to be exposed. A drug called ebselen that is currently used to treat a variety of conditions, including stroke and bipolar disorder, has recently been discovered to reduce the toxicity caused by mutant SOD1.

Michael Capper worked with a brilliant team of MND researchers collaborating across Italy, Australia and the UK to discover that the mechanism of action of ebselen against mutant SOD1 makes it ideal for treating MND patients who carry changes (mutations) in the *SOD1* gene. Ebselen works specifically to refold SOD1 that's lost its shape by repairing the disulphide bond that holds it together. This demonstrates that ebselen is a very promising lead to help treat MND caused by *SOD1* mutations.

A rare form of MND may reveal protective mechanisms in motor neurones

Unlike many diseases that can be linked to one or a up to a few different genes, there are about 20 different genes that have now been linked to MND. It is extraordinary that mutations in so many different genes can cause the same disease in thousands of people around the world. However, there are some variations in the age of onset and severity of MND that depend on the genetic mutation involved.

Mutations in the *SETX* gene cause a rare form of MND that is quite different to most forms of MND. MND usually starts to affect the body after 40 years of age, yet MND symptoms appear during childhood and adolescence in people carrying *SETX* mutations. It causes a very slow rate of disease progression, and in most reported cases there is no effect on a person's lifespan. Not much research has gone into understanding how *SETX* mutations cause MND, as most researchers have focused their efforts on investigating the other MND-linked genes that are much more common in MND patients. But a large collaborative project lead by Craig Bennett, Somasish Dastidar and colleagues in the US, Singapore, the UK and the Netherlands has revealed that this unusual form of MND is actually very similar to the more common forms in its underlying molecular mechanisms. Researchers are now working to figure out what mechanisms and factors distinguish *SETX*-MND from other MND forms. Identifying any differences might reveal a protective mechanism that lessens the severity of this form of MND.

A police force of proteins helps protect motor neurones

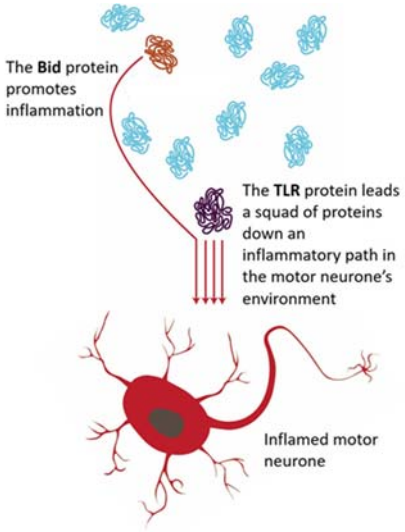
Every one of the cells in the body contain tens of thousands of different proteins that each carry out specific jobs crucial to the normal functioning of each cell. The whole population of proteins are like the population of people in a city. Proteins have jobs that serve the rest of the cell, just as people have jobs that serve others in their community. And proteins sometimes misbehave, just like people.

In the case of disease, particularly MND, some proteins exhibit downright criminal behaviour and are detrimental to the rest of the cell. Thankfully, each cell has a police-like force of proteins that are in charge of looking after the rest of the protein population. In both MND and Alzheimer's disease (AD), one of the departments in this force becomes particularly active, and this has been linked to a protective effect on MNs in MND and on certain neurons in the brain in AD. For years researchers have been trying to work out exactly what the different "police" proteins in this department are doing to cause this protective effect, and headway has finally been made.

Luigi Montibeller and Jackie de Belleroche at Imperial College London, UK discovered that in both MND and AD there are two leading police proteins, XBP1 and ATF6, that communicate to other proteins to work harder. MND and AD differed in the specific proteins that were stimulated to work harder. In MND, the activated proteins were those that have the responsibility of going around the cell to monitor the protein population and target any criminal behaviour. Now that these activated proteins have been identified, researchers can now look at using them to develop new therapeutic strategies.

Researchers identify a leading cause of inflammation in MND

A prominent feature of the diseased nervous system in MND patients is inflammation, and it is thought that the extent of inflammation contributes to the rate of MND progression.



The immune system is governed by an entire hierarchy of different proteins that control inflammation in our different tissues. One of the leading commanders of the immune system is a protein called TLR. Sinead Kinsella and her fellow researchers in Dublin, Ireland have elucidated how the TLR commander leads a whole squad of other proteins down a path that causes extensive, damaging inflammation in the MN environment. Hoping to identify any proteins in the squad that could be targeted to stop this inflammatory response, they pin-pointed the Bid protein. They found that Bid was a bit of a leader itself, and out of all the other proteins TLR was regulating, Bid had the ability to strongly promote inflammation.

The work of Sinead's team provides evidence that targeting and inhibiting Bid could be a therapeutic option to reduce inflammation in MND.

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