MND Australia
International Research Update

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With much of the genetics of inherited MND discovered, we must now put this information to good use and turn our focus to understanding how these mutated genes cause MND and more importantly how to use this knowledge to treat MND. Sadly the process of 1) discovering a gene, 2) understanding how it causes disease and then 3) discovering how to stop it causing disease is a long and arduous process. However, some researchers are taking advantage of a recently (recent in terms of the history of scientific discovery) uncovered trick of biology to skip the second step in the research translation process and hope to come up with a treatment for MND sooner because of this. The trick is known as RNA interference, or RNAi for short, and may be able to slow MND by lowering the amount of times the gene is made into its product. In this report we will focus on this new genetic trick and how it might be used to treat MND, as well as looking at some of the other MND research going on all around the world. .

RNAi shaping up to be a potential treatment for MND

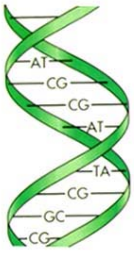
Although the idea of reducing the amount of mutant gene product using RNAi is a logical and exciting approach, delivery of the RNA molecules into the brain is not a straightforward process. Scientists have come up with a range of ways to do this; Prof Robert Brown and co-workers teamed up to use an artificially made adeno-associated virus due to its long-lasting gene expression and low toxicity. They have recently published work showing injection of the virus that expressed an artificial micro RNA targeting SOD1 into the SOD1 MND mice. This treatment knocked down mutant SOD1 levels in the brain and slowed the disease progression. At the same time Don Cleveland and Brian Kaspar and their teams have made a similar adeno-associated virus encoding a different small RNA molecule to reduce SOD1 mutants. In a late-onset mouse model, peripheral (non-brain) injection of the virus after onset of MND symptoms markedly slowed disease progression and significantly extended survival. In addition, they also report that the virus, when injected into the spinal cord of non-human primates, demonstrated significant SOD1 suppression in motor neurones. The researchers believe this sets the stage for virus-mediated therapy in human clinical trials.

What is RNA interference?

DNA is a long molecule that holds the code for our genes. These individual packets of information (genes) must be copied (into RNA) and then from this copy, made into a functional protein or enzyme.

The RNA molecule is a vital middleman or messenger that can control how much of a gene is made into its product.

RNA interference (RNAi) is a normal process in the cell that removes messenger RNA so there is less of the gene made into its product – in effect it silences the gene.



Normally the cell uses this process to stop viruses from making virus gene products inside the cell by identifying the virus RNA and destroying it by chopping it up.

So by injecting a short piece of RNA scientists can trick the cell into thinking that the gene from where it came is bad and to start chopping it up.

MND Research Shorts

- Researchers from Taiwan have claimed that sunlight deprivation and/or amount of rainfall may be related to some degree to MND incidence.
- Professor Roger Pamphlett at the University of Sydney, has found that toxins such as mercury seem to be taken up specifically by some motor neurons providing evidence for the theory of toxin involvement in some cases of MND.
- Researchers in South Carolina have conducted a study to examine self-reported environmental and occupational exposures with risk of ALS. They conclude that workers exposed to metals and pesticides may be at greater risk of ALS.
- Researchers at the University of Wollongong have shown that modifications to the already unstable mutant SOD1 by a naturally occurring protective molecule called glutathione actually causes more instability and may contribute to its accumulation.

RNAi treatment may be useful for other forms of MND

RNAi treatment may be useful for forms of MND other than those caused by SOD1 mutations. Researchers have begun to investigate the possibility of treating the largest known cause of MND, the mutations in C9ORF72. Professor Baloh and colleagues at the Cedars-Sinai Medical Center, USA used skin cells from patients with C9ORF72 mutations to generate motor neurones in the dish. These motor neurones had some features of motor neurone disease pathology. Small RNA molecules targeting the C9ORF72 gene suppressed MND like symptoms in these neurones. At the same time a similar study was also published by Prof Rothstein at Johns Hopkins Hospital, USA demonstrating the ability of RNAi to act as a potential therapeutic for MND.

Motor neurones easily stressed out?

Dr Crippa and co-workers from Milan, Italy compared what happens when you stress neurones with a mutant MND gene compared with muscle cells with the same stress. They found that muscle cells possess a much better response to stress when compared to motor neurones. In related work, Dr Lin and co-workers took SOD1 mutant MND mice and increased a molecule called heat shock factor 1 (HSF1) which has the job of coordinating the cells' response to stress. They showed that an increase in HSF1 significantly reduced body weight loss, delayed MND symptom onset and increased survival for all of the mice. Together these studies show that motor neurones are more easily stressed out and that drugs increasing their ability to deal with stress may be helpful for MND patients.

Is exposure to diesel exhaust a risk factor for MND?

Professor Roger Pamphlett and co-workers at the University of Sydney attempted to find out if occupational exposure to toxic molecules plays a part in triggering MND. They compared occupations of 611 MND patients with 775 control individuals. Of all the occupations, only truck drivers, where exposure to diesel exhaust is common, showed an increased risk of MND. A previous study has also found truck drivers to be a risk factor for MND, and almost two-thirds of occupations already identified as risk factors for MND, including military duties, have potential exposure to diesel exhaust.

Scientists find no genetic connection between MS and MND

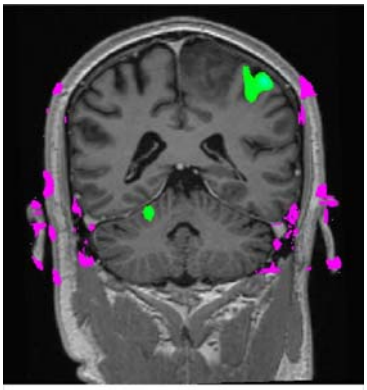
There are many features of MS and MND that are similar; both diseases affect motor neurones and both have inflammatory and neurodegenerative features. In addition, some studies have found an increased co-occurrence within individuals and families. Dr de Bakker and his team from Leuven in Belgium examined genome-wide data from 4,088 MS patients, 3,762 ALS patients, and 12,030 healthy control individuals. When the researchers studied the variation in all genes in all these cases they failed to find any evidence of an overlap in genetic susceptibility between MS and MND.

Neurone loss a case of dominoes in MND?

There has been some evidence that suggests that MND may progress from one brain region to another in an orderly process, just as dominoes start to fall from one site and continue falling in one direction. However, some argue that the distance between some neurones and regions in the brain is too considerable to sustain such a process.
A new review on the topic suggests that the affected neurones are connected by axonal projections, indicating that physical contacts between nerve cells along axons are important for the domino effect in MND pathology. If this is true it may eventually provide us with a way to stop MND progression in its tracks.

Could MND be triggered by a brain injury?

Researchers from Ulm in Germany, lead by Dr Rosenbohm performed a search of patient-and-MRI data bank and screened 1,835 patients with MND for brain injury. The researchers found 18 out of the 1,835 MND patients who had documented injuries to the part of the brain called the motor cortex which houses motor neurones. These injuries were found to precede the MND symptoms by 8 to 42 years in these cases. In 15 out of the 18 patients with injuries, the onset of MND was closely related to the injury site since symptoms were first recorded in a body region reflecting the damaged area of the brain.
The findings could mean that injury to the part of the brain where motor neurones are found may contribute in some patients to developing MND or it may mean that an injury may dictate the site of MND onset in pre-disposed individuals.



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