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As the name suggests, motor neurone disease is a disease in which the neurones that control muscle function, the motor neurones, are dysfunctional and eventually die. This loss of motor neurones from the nervous system gives rise to the outward symptoms of loss of muscle control and wasting. However, motor neurones may not be the only dysfunctional cells that contribute to MND. There are other cells that work closely with neurones within the nervous system that may directly and indirectly affect the viability of motor neurones. Indeed, most of the brain and spinal cord is made up of cells that are not neurones; these cells are known as **glia**. The word glia comes from the Greek word for glue. Glia are so named due to the belief that the glia was literally held the neurones together. Of the glia, **astrocytes** are one of the most abundant and may turn out to be one of the most important cell types in motor neurone disease.

There have been many reports on the role of astrocytes in MND so far in 2010. In this report we will look at these, and some of the other MND research going on all around the world.

Astrocytes respond to spinal fluid of MND patients

It is well known that astrocytosis is associated with all cases (sporadic and familial) of MND. This response of the astrocytes is usually found in the areas of the brain and spinal cord where motor neurones are found. The precise reason for their 'activation' (see '*what is astrocytosis*' at right) remains a mystery. Some think that this is a direct response to the dying motor neurones. However, research just published, led by Dr Shobha from the National Institute of Mental Health and Neurosciences in India, suggests that astrocytes in the laboratory can be activated by human spinal fluid taken from MND patients. This finding is important because it means that there is an unknown signalling molecule in the nervous system of MND patients that can activate astrocytes. This in turn may have consequences for motor neurone function since active astrocytes can release neurotransmitters, such as glutamate, and other molecules that can be detrimental, such as calcium. If the researchers can find the signal that activates astrocytes it may lead to a potential target for future therapies.

Stimulating astrocytes to clean up glutamate

Much of the brains signaling between neurones is performed by the release and uptake of a substance called glutamate. However, if there is too much glutamate the neurones can be 'over stimulated' which is bad news for the neurone. This effect is called excitotoxicity. One of the astrocytes' main functions is to clean up the excess glutamate so this does not occur.



Picture the game 'Hungry Hippos'. The balls are the glutamate and the 'arms' of the astrocytes are represented by the hippos. The astrocytes' job (like the hippos') is to remove the glutamate from the synapse (in our analogy, the game board). In MND patients, uptake of glutamate is thought to be impaired. To compound this deficiency, work coming from Italian researchers found that MND mice have astrocytes that are more likely to release the glutamate that they have cleaned up. The researchers tested the response of astrocytes to a neurotransmitter called GABA. When the cells from MND mice were treated they released more glutamate than cells from mice without MND. Thus, as a whole, regulation of glutamate levels by astrocytes may be impaired in MND patients. With this in mind, a group of researchers from China led by Dr Ran Gu have used **adult** stem cells taken from adipose (fat) tissue. These stem cells can be manipulated to form a variety of cell types. In this case the researchers used them to form cells that would communicate with astrocytes, stimulating them to clean up glutamate. In the mutant G93A SOD1 MND mice the cells did indeed stimulate glutamate removal. The researchers say these adult stem cells from fat tissue may be a potential treatment for MND.

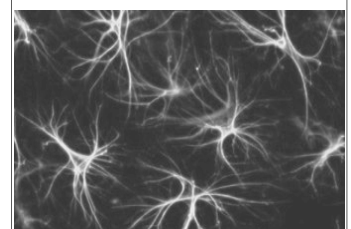
What are astrocytes?

Astrocytes are a non-neuronal cell of the nervous system. Astrocytes get their name from their star-like shape (astro means star, as in *astronomy*).

Astrocytes have a number of functions in the brain. Firstly, they can act as scaffolding for neuron movement, including the long axons of motor neurones. They actively participate in the regulation and metabolism of neurotransmitters used by neurones to send signals to other neurones and muscles. In fact, they themselves are thought to be involved in the signaling process. In addition, astrocytes are known to act as scavengers to remove debris from dead or dying neurones.

What is astrocytosis?

Astrocytosis is defined as an increase in the number and size of astrocytes in a specific area of the brain or spinal cord. This is sometimes also referred to as 'activation' of astrocytes and not only involves changes in their shape and number, but also changes in their ability to clean up debris from dying cells and alters their production of bioactive signaling molecules which they use to communicate with other cells.



Lowering SOD1 levels in MND

Previous studies have shown that mutant SOD1 in other cell types besides motor neurones, including astrocytes, contributes to disease in mutant SOD1 MND mice. Scientists from the University of Chicago have examined lowering the levels of mutant SOD1 in MND mice. It is thought that, like water in a dam, as the level of SOD1 goes above a certain level it goes beyond the control of the cell. Using a genetic switch, they were able to lower levels in the whole mouse (not just in the brain) by 66%.



This lowering of levels of the mutant protein delayed disease onset and lengthened the life of the mouse. Interestingly, the effect on disease onset was similar to that seen when the mutant protein was lowered by only 25% but restricted to protein in motor neurones and some interneurones. These results suggest that mutant SOD1 induced motor neurone death starts in the motor neurones themselves and that other cell involvement in motor neurone disease occurs after the initiation of MND. Regardless, this study supports the value of lowering SOD1 levels in familial MND patients and asymptomatic individuals with SOD1 mutations.

Zinc and MND?

Movement of protein into 'junk piles' inside motor neurones is a hallmark of MND. In most cases the protein TDP-43, mutations of which are causative in some forms of MND, are incorporated into these junk piles. Until now, researchers have been unable to pinpoint a cause of the TDP-43 protein ending up in the scrap heap. When scientists at the University of Melbourne treated neuronal cells with zinc they observed an increase in the appearance of TDP-43 protein junk piles. The researchers suggest that these results show that changes in the zinc metabolism could affect neurodegenerative diseases such as MND.

Optimising adult bone marrow stem cells for MND treatment.

Researchers in Korea have been optimising the process of preparing adult stem cells from MND patients to put back into their brain and spinal cord. The stem cells are taken from MND patients' bone marrow and then cultured in the laboratory for a number of weeks. The researchers found that the stem cells were better off spending the least amount of time in the test tube. After only a short time in the laboratory the cells were more suitable for stem cell therapy in MND patients because of their stability and more potent anti-inflammatory and neuroprotective properties. Similar studies of bone marrow stem cells have been ongoing in Italy. The researchers found that the stem cells taken from MND patients have altered functions compared to controls and as a consequence must be carefully re-evaluated before further use in humans.

Energy dysfunction in MND?

Using the electron accelerating synchrotron, researchers from Canada discovered small deposits of creatine in MND tissue. Creatine plays a crucial role in energy metabolism in humans. Comparable creatine deposits were not found in other samples or in other regions of the brain not associated with MND. The researchers conclude that creatine deposits may be indicators of dysfunctional energy processes in some cases of MND.



Cyanobacteria and MND

Cyanobacteria are bacteria that gain their energy from photosynthesis. They are sometimes called blue/green algae. Cyanobacteria produce many neurotoxins including beta-methylamino-L-alanine (BMAA) and have been linked to cases of MND. In Enfield, Northhamshire, USA a cluster of MND cases has been diagnosed. Enfield has a lake with a history of cyanobacteria algal blooms. Researchers identified nine MND patients who lived near Lake Mascoma in Enfield, an incidence of sporadic MND that is 10 to 25 times the normally expected incidence. Researchers have suggested that this is due to exposure to high levels of toxins such as BMAA. It is unknown whether or not this cluster is due to cyanobacteria toxins, but researchers say that it is possible to be exposed to the toxins via inhalation of aerosolised toxins, consuming fish, or ingestion of lake water. Further investigation is still required to determine if the cases identified are in fact due to cyanobacteria toxins.

MND Research Shorts

- Researchers in Brazil have found two couples in which both spouses were affected by MND. Both couples lived in southeast Brazil, were married for at least 20 years and the interval of disease onset between husband and wife was short. This is consistent with an environmental trigger for MND, however, no common environmental factors could be identified.
- It has been hypothesised that free radicals may effect MND progression. In Italy researchers examined 88 patients affected by sporadic MND. They found that the patients were less able to deal with free radicals as MND progressed.
- MND severity has been correlated with blood flow in the brain as measured by MRI. The researchers in California suggest that this may be a useful way of monitoring disease progression and assessing potential treatments in MND patients.