Motor neurone disease: how could stem cells help?

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Motor neurone disease is a rare but very serious neurodegenerative disease. Current treatments can relieve the symptoms but there is no cure. How could stem cells help?

Did you know?



Lou Gehrig, a successful baseball player in the 1920s and 30s who retired when he was 36 as the result of ALS



Motor neurons made from iPS cells generated from ALS patients



Stephen Hawking, world-renowned theoretical physicist and author of the book, A Brief History of Time, was diagnosed with motor neurone disease aged 21

What is motor neurone disease?

The term motor neurone disease (MND) describes several different conditions that all affect nerve cells called motor neurons. Motor neurons are found in the brain and spinal cord. Their job is to relay signals from the brain to the muscles in the body to control movement. In MND, damage to the motor neurons disrupts these signals, leading to progressive paralysis. Patients may suffer from a variety of problems such as uncontrollable twitching, muscle stiffness, difficulties in speaking, swallowing and even breathing. Over time, the muscles begin to weaken and waste, making symptoms progressively worse.

The most common form of MND is amyotrophic lateral sclerosis (ALS), which accounts for approximately 60-70% of all cases. It is generally known as Lou Gehrig’s disease in the USA.

What causes motor neurone disease and how is it treated?

Some forms of MND are inherited: they run in a family. Around 10% of MND falls into this familial category. For example, mutation – or change – in a gene called superoxide dismutase 1 (SOD1) was the first genetic cause of MND to be identified and results in ‘familial ALS’. This familial form of the disease affects patients in exactly the same ways as other forms of ALS.

Most MNDs are not inherited and the causes of the disease are not known. These ‘sporadic’ or non-inherited MNDs are thought to be caused by a combination of genetic changes and the patient’s environment and lifestyle. Scientists think that the motor neurons stop working not only because of changes inside the cells themselves, but also because of damage to the immediate surroundings of the motor neurons in the body. There is evidence that other types of cells found in the nervous system may play a role.

To date there is no cure for motor neurone disease. Current treatments focus on relieving symptoms to improve quality of life for patients. The only available treatment that affects the progression of the disease is the drug Riluzole, but its beneficial effects are very limited. Scientists are now searching for more effective treatments.

How could stem cells be used to treat motor neurone disease?

So far we know very little about how and why motor neurons are damaged and degenerate in MND. Many different factors seem to be involved in causing the onset and progression of this disease. To cure patients, a therapy will need to address most if not all of the damaging changes that are happening in the body.

Researchers are now studying [stem cells](http://www.eurostemcell.org/faq/what-are-stem-cells) to learn more about what goes wrong in MNDs and to investigate whether they could be used in new treatments. There are several different types of stem cells that offer different possibilities for research and therapies.

**Using stem cells to study and understand MNDs**
The motor neurons that are affected by MNDs are located in the brain and spinal cord. This means that it is very difficult to study the disease in patients, or to get samples of damaged cells for closer examination in the laboratory. In 2008, a team of [scientists at Harvard University in the USA](http://www.ncbi.nlm.nih.gov/pubmed/18669821%20) used skin cells from an ALS patient to tackle this problem. The researchers first transformed the skin cells into [induced pluripotent stem cells (iPS cells)](http://www.eurostemcell.org/factsheet/reprogramming-how-turn-any-cell-body-pluripotent-stem-cell) - lab-grown stem cells that behave like embryonic stem cells and have the ability to make all the different cells of the body. They then used the iPS cells to make motor neurons, which showed signs of ALS. Many other researchers have since grown motor neurons in the same way.

These lab-grown motor neurons provide a powerful tool to look at human cells in the disease condition, find new clues about what's wrong with them and examine how they influence each other or are affected by other types of cells in their surroundings. Researchers can use cells grown from different patients to explore the differences and similarities between the various forms of MND. The ability to grow large numbers of motor neurons also allows scientists to test potential drugs to treat the disease.

**Using stem cells as a therapy**
Although some types of stem cells can be used to grow motor neurons in the laboratory, scientists think it is unlikely that just transplanting lab-grown neurons into patients will prove the most effective way to treat MND. The transplanted cells would have to replace both groups of motor neurons that are affected by the disease (in the brain and the spinal cord) and would also have to create the right connections within the complex circuits that link the muscles with the brain. Because there are many factors that contribute to motor neuron damage in MND, it is also possible that the transplanted healthy cells would soon be damaged too.

For all these reasons, scientists feel that a great deal more laboratory research should be done before moving into clinical trials with transplanted lab-grown motor neurons. Researchers are currently investigating which kinds of stem cells could be used to address the many different aspects of this disease, and how each type of stem cell may be most useful. It is likely that a combination of approaches will be necessary because a successful therapy will need to achieve a number of things:

* Protect the patient’s existing motor neurons, support their growth and encourage an increase in the number of healthy motor neurons
* Correct any damaging conditions in the environment surrounding the motor neurons in the body
* Target not only the spinal cord but also the connection points between the motor neurons and the muscles themselves, to enable the neurons to carry signals to and from the muscle.

Several types of stem cells are being tested for their potential to overcome these issues, including embryonic stem cells and mesenchymal stem cells. Cells called ‘neural progenitor cells’, which are responsible for making new neurons in the body, are also being investigated. Among the most promising cells so far are spinal cord stem cells, which can produce both motor neurons and cells called glia. Glia secrete many of the proteins known as growth factors that help motor neurons develop. It may also be possible to use non-neuronal cells such as glia to prevent further damage to motor neurons and encourage repair by providing a working version of the protein SOD1, which does not function properly in some types of MND.

Current clinical research & stem cell transplantation

Laboratory studies suggest that certain types of stem cells may be effective for ALS treatment in the future. For example, researchers have transplanted mesenchymal stem cells or neural progenitor cells into mice with motor neuron damage similar to that found in ALS. Studies on each of these types of cells show that the disease progresses more slowly in these animals, they have less motor neuron loss, and their lifespan improves. Human neural progenitor cells have also been genetically engineered to release a growth factor that helps motor neurons grow and has been shown to help protect motor neurons in rats. In addition, research in large animals and human patients has shown that it is possible to transplant these engineered cells safely into the human spinal cord.

An [early clinical trial](http://clinicaltrials.gov/ct2/show/study/NCT01348451?term=stem+cells+AND+NeuralStem&rank=1)examining the safety of injecting human spinal cord stem cells directly into the spinal cords of ALS patients was completed in June 2012. Twelve patients participated in the trial and none of them had adverse reactions to the treatment. This is a promising first indication of the feasibility of such an approach and suggests it would be safe. More research is now needed to investigate what happens to the transplanted cells once they are in the spine and how effective they are at helping to repair damage.

Can stem cells be used to treat MND now?

In summary, although stem cells are already very useful in MND research, there are currently no approved stem cell therapies for MNDs. Using stem cells in future therapies might give us the opportunity to treat many if not all of the underlying causes of MNDs and help the body restore its own healing capacities. However, more research is needed to establish which types of stem cells may be able to help and how they might best be used to provide safe and effective treatments.