Writer: Maya Chaddah
Editor: Lisa Willemse
Reviewer: Ivar Mendez

Stem Cell Network
Réseau de cellules souches

Originally published by the Stem Cell Network May 2012

Parkinson's Disease

Research is a dynamic enterprise that generates a wealth of knowledge. It provides a forum for debating ideas and working them into evidence-based theories. The clinical trial setting puts these theories to the test and may lead to evidence-based medicines that can alleviate symptoms or cure disease. But the process of taking research from bench to bedside is a lengthy one, and demands not only vision but also years of hard work and dedication on the part of scientists, physicians and patients. This document presents basic information about Parkinson's and frames the context for the discussion that follows about the future application of stem cells to treat this disease. Readers may also wish to peruse additional web resources or speak with their physicians for more information.

About Parkinson's

Parkinson's Disease is a chronic disease of the central nervous system (CNS) marked by the progressive loss of the neurons in the brain that produce dopamine. Dopamine is a crucial neurotransmitter that conveys messages from dopamine neurons in the substantia nigra pars compacta to the striatum, the part of the brain mediating the control and coordination of movement.

Globally, Parkinson's strikes about 5 million people of all races and occupations making it one of the most common neurodegenerative disease, second only to Alzheimer's. The symptoms of Parkinson's appear when about 80 per cent of dopamine neurons are lost. That typically does not occur until age 60, although there have been cases reported in people as young as 20 years of age. Similar to other neurodegenerative diseases, the vast majority of Parkinson cases occur sporadically, whereas only 10-15% of cases are familial and are linked to multiple genes that can be inherited among family members.

Symptoms and Causes

The cause of Parkinson's Disease remains a mystery, and the symptoms, patterns of progression and response to treatment are quite variable. Scientists have long known that the lack of dopamine is a major contributor, and in some cases genetics and environment are also contributing factors.

The telltale signs of Parkinson's are uncontrollable tremors in the hands, feet or face, rigidity, slowness of movement (bradykinesia), difficulty initiating movement and increasing problems with balance, gait and posture. These symptoms are associated with loss of dopamine neurons, but there are also other symptoms unrelated to loss of dopamine, including reduced eye blink, soft voice, difficulty swallowing (dysphagia), freezing, loss of smell (anosmia), pain, mood disorder, sleep disturbances, cognitive impairment, as well as blood pressure, gastrointestinal, urinary and sexual dysfunction. Falling and dementia characteristically occur during the late stages of the disease and these too are symptoms unrelated to the loss of dopamine neurons.

Scientists have identified upwards of 16 genes known to play a role in Parkinson's, most of which contribute to abnormal protein folding and accumulation, or mitochondrial dysfunction. As yet, there are no conclusive environmental factors causing the disease, but counted among such risk factors are pesticides, rural living, and drinking well water. Contrary what might be expected, smoking and caffeine may in fact decrease the risk of Parkinson's. Studies on twins have shed some light on the importance of environment versus genetics at different developmental ages, with environmental factors playing a more substantial role in older people and genetic factors contributing more to disease development in younger individuals.

Writer: Maya Chaddah
Editor: Lisa Willemse
Reviewer: Ivar Mendez

Originally published by the Stem Cell Network May 2012

Treatment

Because many symptoms are attributed to lack of dopamine, most treatments for Parkinson's focus on dopamine replacement therapies. The gold standard for treating Parkinson's is a drug called levodopa, which is a dopamine precursor. It is often administered in conjunction with an agent that provides more time for the body to convert levadopa to dopamine. However, side effects and complications of levadopa have fuelled the search for other drugs, which although less effective, do show some benefits. These drugs include dopamine agonists (drugs that stimulate dopamine receptors), and drugs that block dopamine metabolism (such as rasagiline). Other treatments are neuroprotective in their aim in that they try to prevent the death or slow down the demise of the brain's own dopamine-producing neurons. Deep brain stimulation is a surgical technique that stimulates regions of the brain with electrical impulses in an attempt to control symptoms.

Potential targets of neuroprotective drug therapies are mechanisms that might contribute to the death of dopamine neurons in the brain. Such mechanisms might include inflammation, accumulation of intracellular calcium, oxidative stress, overactive neurotransmission, mitochondrial dysfunction, proteolytic stress, and apoptosis (a form of cell death). However, to date there are still no drugs that can slow disease progression and that is why scientists are devoting considerable efforts towards developing novel treatment approaches based on gene therapy, delivery of trophic factors and stem cells.

Can Stem Cells Help?

Most drug therapies to treat Parkinson's are based on ameliorating the disease symptoms. Although some drugs demonstrate modest effects, the requirement of escalating the dose as the disease progresses results in too many side effects for the patient. There are no stem cell treatments yet developed to treat Parkinson's but researchers are hoping to harness their regenerative power with the end goal of restoring the normal dopamine-related function of the brain.

Stem cell therapy offers a very targeted treatment approach for achieving this goal because the majority of motor deficiencies in Parkinson's relate clearly to the failure of one specific kind of cell – the dopamine neuron – to do its job. It has long been known that when dopamine is reintroduced into the central nervous system in animal models as well as human patients, the symptoms of Parkinson's abate. This observation has prompted scientists to test a variety of different stem cells (see below) for their ability to become functional dopamine neurons or to provide protective growth factors for the neurons at risk. In theory, mobilizing or transplanting these cells or their progenitors into the brain could contribute to some degree of functional recovery in patients with Parkinson's. Researchers are also interested in the more long-term goal of testing whether stem cells could be applied to alleviate the many symptoms of Parkinson's that are unrelated to the loss of dopamine in the brain.

There remain a litany of unanswered questions around using stem cells to treat Parkinson's. Which stem cells are best for treating Parkinson's? What is the best way to introduce cell transplants into the brain and which stem cells will yield the best results? Which cues do brain neural stem cells use to differentiate into dopamine neurons? Which cell markers can be used to track the stem cells that survive, multiply and successfully produce dopamine neurons under different conditions? Which signals in the brain environment allow transplanted cells to survive, integrate and function properly? These and other questions form the basis for the research that is underway around the world.

Fetal stem cells

Over the last 18 years, hundreds of patients around the world have been transplanted with fetal cells in clinical trials for Parkinson's, albeit with limited success. Positron emission technology (PET) scans have confirmed that the transplanted neurons could grow and make functional connections which somewhat reduced the severity of symptoms. However, the results were variable, and recent studies demonstrating that transplanting fetal nigral cells results in movement disorders despite decreasing levadopa dosages have sparked some debate about the usefulness of fetal cell transplants. In addition, for ethical as well as practical reasons, fetal tissue is not the best long-term source of renewable cells. As an alternate to fetal stem cells, investigators are turning to adult neural stem cells and embryonic stem cells as potential sources of dopamine neurons.

Writer: Maya Chaddah
Editor: Lisa Willemse
Reviewer: Ivar Mendez

Originally published by the Stem Cell Network May 2012

Endogenous stem cells

Scientists have also considered whether a patient's own (endogenous) stem cells could be mobilized to repair the damage caused by Parkinson's. Adult neural stem cells are located in the brain's white matter and can multiply and form all the major brain cells, including neurons. Numerous transplant studies into rodents have proven that although adult neural stem cells can multiply and home to a site in the brain that is stripped of neurons, they appear to be limited in their potential to differentiate into dopamine neurons unless first being genetically reprogrammed.

Embryonic stem cells

Embryonic stem cells can be readily grown and differentiated into all the cells in the body. Although studies in animals using embryonic stem cell transplants are very encouraging, there continue to be two main challenges that impede the translation of results to clinical trials. The first is that in some animal models, embryonic stem cells carry the risk of developing tumours. The second is that after many years, it is possible that some of the transplanted dopamine neurons may fall prey to the disease and thus end up contributing to the disease rather than making it better. This phenomenon has been seen in some studies but not in others perhaps owing to the transplantation methodology used.

Neural stem cells

Obtaining pure populations of dopamine neurons may be the best way to avoid the problems inherent in using embryonic stem cells. The capacity of neural cells to regenerate is dependent on growth hormones (such as GNDF) and other signaling molecules that help the cells survive and grow. In principle, therefore, the right combination of growth factors should allow stem cells to be cultivated to a point where they are committed to becoming dopamine neurons which could then implanted in the brain.

Induced pluripotent stem cells

As well as being able to make dopamine neurons, induced pluripotent stem cells provide other important advantages for treating neurological disease such as Parkinson's. They can be used to create patient-specific cells lines for testing existing drugs and developing new ones. The induced pluripotent cell technology has also been used to make induced motor neurons (iMNs) from adult somatic cells, and researchers are excited about the prospect of similarly creating induced dopamine neurons for studying and treating patients with Parkinson's disease.

Mesenchymal stem cells

On the immediate horizon, mesenchymal stem cells offer an intriguing approach to treating Parkinson's disease. These stem cells can be harvested directly from a patient's bone marrow, as well as from other tissues, and therefore when injected back into the patient, they may be able to minimize the likelihood of transplant rejection. Studies have shown that it is possible to differentiate mesenchymal stem cells into neurons but the real power of these cells likely resides in their ability to produce growth factors that support damaged neurons.

Canadian contributions

The importance of being able to scale-up the production of stem cells for the purposes of clinical applications cannot be understated. In most cases, it is critical for the stem cells to be expanded first in the laboratory before being transplanted into the patient. Working to overcome this challenge, researchers at Dalhousie University and the University of Calgary pioneered a bioreactor protocol to scale up the production of human neural stem cells. More recently, this team has gone on to vary the conditions under which the neural stem cells are grown to better understand the cellular events and interactions required for the expansion process. Taken together, their work should contribute greatly towards the future clinical application of stem cell research for Parkinson's Disease.

To date, one of the key Canadian contributions to international research on Parkinson's is the Halifax Protocol for injecting cells safely into the human brain. Researchers from Halifax, Toronto, Montreal and Calgary collaborated to develop what is now widely recognized by neurosurgeons as the international standard for safe and effective brain repair using cell implantation. Novel surgical instruments to implant stem cells safely into the human brain such as the computerized Halifax Injector System have also been developed in Canada

Canadian researchers have also devoted significant attention to the ethical considerations in treating Parkinson's through stem cell implantation. They wish to encourage this debate in tandem with laboratory research in anticipation of future clinical trials.

Clinical studies

Many pre-clinical studies use animals such as mice, rats, monkeys, and pigs that can serve as living models of Parkinson's in which to test transplanted stem cells or their progeny. However, translating knowledge and success from animal models to human trials requires controlling for multiple parameters, from the source and type of stem cell used to the culture in which they are grown, the method of activating cell differentiation, the protocol for injecting them into the brain, and the factors ensuring cell survival. Progressing to the next level requires a multi-disciplinary network of scientists, clinicians and laboratories working together to arrive at safe and effective protocols for transplanting stem cells into the brain. This process takes considerable time, effort and funding, and as yet there are relatively few clinical trials testing the safety and efficacy of stem cells for treating Parkinson's.

Currently listed on clinicaltrials.gov are two early phase trials from India and China transplanting mesenchymal stem cell into Parkinson's patients. Very small numbers of patients are enrolled in these trials. Although the primary concern is safety, the trialists are also keen to assess the outcome in terms of protection to to the patients.

The results from clinical trials addressing stroke, spinal cord injury, cancer and other degenerative diseases may also offer hope to people who suffer from Parkinson's. The lessons learned from such studies may also apply to Parkinson's and contribute to the goal of regenerating, restoring or protecting the normal function of the central nervous system in patients with this disease.

Web Resources

For more information about Parkinson's disease in general and the possible application of stem cells in particular, readers may wish to peruse the recommended sites below.

- Parkinson Society Canada: http://www.parkinson.ca/
- National Parkinson Foundation (US): http://www.parkinson.org
- European Parkinson's Disease Association: http://www.epda.eu.com
- Parkinson's Disease Society (UK): http://www.parkinsons.org.uk
- The Michael J. Fox Foundation: http://www.michaeljfox.org
- Brain Repair Centre: http://www.brainrepair.ca/
- National Institute of Health: http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm