Stem Cell Network
Réseau de cellules souches

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Multiple Sclerosis

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). MS is considered an autoimmune disease, as it is the patient's own immune system that creates inflammation in the brain or spinal cord. Inflammation results in the death of oligodendrocytes, cells that wrap around the axon, the main projection of the nerve cell. Axons transmit electrical signals between nerve cells. The oligodendrocytes contain myelin, a substance that provides insulation for the electrical impulses carried by axons. The loss of the insulation surrounding the axon results in "short-circuits" among the nerve impulses. This prevents the nervous system from working properly and result in disabilities for the patient – this event is called a relapse or attack. Early in the course of MS, the CNS can partially heal itself when the inflammation subsides and the disabilities lessen – this is called a remission. After a while, the CNS loses its repair capacity and the damage becomes permanent. This leads to the death of nerve cells and scarring in the CNS, which appear as lasting disabilities.

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 multiple sclerosis and frames the context for the discussion that follows about how lessons learned from stem cell research may help fight this disease. Readers may also wish to peruse additional web resources or speak with their physicians for more information about this disease.

MS is unpredictable. It can evolve rapidly or slowly with attacks that are infrequent or steadily increasing. The different clinical pictures that result are categorized into four broad types. Relapsing/remitting MS (RRMS) forms the majority (85%) of cases where patients are stable in between bouts and often completely recover. However, as the years progress there is a risk of RRMS transforming into secondary progressive MS (SPMS) where neurological function steadily deteriorates in the absence of clear relapses. However, the time between diagnosis and the start of SPMS is highly variable and can range from less than five years to more than 30 years. By contrast, malignant MS is a particular form of the disease characterized by high relapse rates and it turns into SPMS very early on. In fifteen per cent of patients, MS starts with a steady decline characteristic of primary progressive MS (PPMS) and of this group five per cent also experience acute attacks, called progressive relapsing MS (PRMS).

Causes, Symptoms and Treatments

Globally, MS affects 2.5 million people, with most individuals diagnosed between the ages of 20 and 50. Fewer than 10 per cent of cases occur in those less than 18 years of age and women are affected three times more often than men. Both environmental triggers and genetic factors are thought to play a role in the development of this disease. Unknown environmental triggers are thought to occur either during pregnancy or shortly after birth, somehow predisposing individuals to further triggers in adolescence. Curiously, geography is linked with prevalence as shown by the higher numbers of individuals with MS living temperate climates (e.g., Orkney Islands, northern North America and Europe, and southern New Zealand and Australia) as compared with tropical zones. Researchers think this phenomenon may be associated with decreases in vitamin D production in zones where sun exposure wanes with the changing seasons. The risk of developing MS also increases with higher socioeconomic status and smoking. In terms of genetic risk factors, Caucasians have a higher risk of developing MS than either Africans or Asians. In some families, the increased risk of developing the disease is due to multiple inherited genes, each contributing

incrementally and that make individuals more susceptible to acquiring the disease. Over 50 MS susceptibility genes have been identified, the most notable being linked to a stretch of DNA housing the major histocompatibility (MHC) genes that are crucial for immune responses by T cells, B cells and dendritic cells.

Although there is no simple test for MS, its diagnosis typically hinges on verifying two or more symptomatic attacks plus two or more signs that damage is occurring in the white matter of the central nervous system. Symptoms of MS are varied among individuals and include problems with balance, walking, coordination (clumsiness), numbness (pins and needles, dead feeling), vision (blurred, dimmed or lack or reduced colour perception), bladder and sexual dysfunction, constipation, speech impairment, facial weakness, and cognitive or emotional problems.

Depending on the stage of the illness and its prognosis, MS is usually treated with drugs that quell acute attacks (glucocorticoids), modify the disease course (beta-interferons, glatiramer acetate, natalizumab, fingolimod and mitoxantrone) or treat the symptoms (oral vitamin D, potassium channel blockers, baclofen). These are but a few examples of the battery of existing MS drugs, many of which work by modifying the immune response to slow the disease or delay it from worsening. Scientists believe that more successful therapies would get at the root of the inflammatory response, ridding the body of the immune cells with a memory of the triggers that promoted the attack on myelin, but also repairing and regenerating the myelin sheath.

Can Stem Cells Help?

Broadly speaking, MS research rests on two cornerstones. The first is preventing damage by modulating the immune system. The second is repairing damage by regenerating myelin and protecting neurons. Although there are drugs that address the former, there are no therapies that effectively address the latter. Because MS is a complex disease, its successful treatment will likely require a combination of new treatments that control or heal each of the disease mechanisms: autoimmunity, loss of oligodendrocytes, loss of nerve cells, and the inability of the CNS to regenerate cells of the CNS.

Although stem cells offer the promise of filling this therapeutic gap, there are currently no stem cell therapies that can cure MS. However, investigators are experimenting with a variety of different types of stem cells – hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs) and oligodendrocyte precursor cells (OLPs) – to assess if they could be used for treating MS. Embryonic stem cells are not currently being considered a viable option for MS, in part due mixed results in preclinical studies and also because of ethical considerations given their source and risk of tumour formation.

Hematopoietic Stem Cell Transplantation

Stem cells have been used for years to treat leukemia and other blood cancers through transplantation of bone marrow. As luck would have it, scientists have found that the same process, known as hematopoietic stem cell transplantation (HSCT), can be adapted to arrest the progression of MS. This procedure is particularly effective in patients who have an especially aggressive disease diagnosed early on with a poor prognosis.

In HSCT, the hematopoietic stem cells administered to a patient are either harvested from the patient's own bone marrow (autologous) or from a donor's bone marrow (allogeneic). Prior to performing HSCT, patients are given chemotherapy to destroy their immune system (referred to as immunoablative therapy). The theory behind this approach is that newly transplanted stem cells won't carrying the immunologic memory that caused the autoimmune attack in the first place and so they should be able to make new, healthy immune cells that don't attack myelin.

Many phase I/II clinical trials around the world have now tested whether AHSCT could be used to treat MS and the results are encouraging from all quarters. Like stem cell transplants for leukemia, the AHSCT procedure has certain side-effects and even a small risk of a fatal complication. For this reason, it is reserved for those patients with the most aggressive MS. However, AHSCT appears to prevent the progression of disease, even 10 years after the transplant, and especially in very active and young individuals who have a short history of RRMS. Because HSCT therapy prevents MS from progressing in these individuals, it helps to prove that MS is due in part to a learned immune response. As high doses of chemotherapy can be very toxic, researchers are testing the effects of low and medium dose chemotherapy regiments for AHSCT. The scientific community is also interested in establishing trials of AHSCT

in individuals who have less severe forms of MS.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) can be found in bone marrow, fat tissue or umbilical cord and are able to produce a variety of cells, such as bone, cartilage or fat. Many studies have shown that MSCs are also able to modulate the immune system. For example, in mouse models of MS, MSCs inhibit the proliferation of T and B cells and hinder the maturation of dendritic cells. These different immune system cells are all important players contributing to inflammation and the attack on myelin.

Many pre-clinical studies using mouse models of relapsing-remitting and chronic MS have demonstrated that transplanting MSCs can protect neurons from further damage and improve functionality of the remaining neurons. In some cases, the MSCs are making neurotrophic factors and antioxidants that promote neuronal survival while in others they are making proteins that stimulate the body's own neural precursors, perhaps leading to the formation of neurons and oligodendrocytes. An important discovery has been that MSCs are able to reduce scar formation, which is a key barrier to the repair process.

The International MSCT Study Group recently struck a consensus supporting the testing of intravenous autologous mesenchymal stem cell transplants as therapies to inhibit the autoimmune component in MS. The patients treated would be individuals for whom conventional agents modulating the immune system are not working. The group has recommended further studies to test the biological activity of mesenchymal stem cells before using them to repair tissue.

Neural stem cells

Because neural stem cells are able to differentiate into a variety of brain cells, they are considered an ideal source for replenishing depleted supplies of oligodendrocytes and neurons. Early experiments looked very promising but more recent studies have shown only very low levels of neural stem cells making oligodendrocytes and neurons. All is not lost, though, because other studies have shown that transplanted neural stem cells can stimulate the brain to make its own oligodendrocyte precursors. Transplanted neural stem cells also secrete neurotrophic factors, anti-inflammatory factors and molecules that inhibit scar formation, and researchers think that these attributes are the ones that may alleviate MS-like symptoms in mice.

Pre-clinical studies have progressed to testing the ability of human neural stem cells in primates with an MS-like disease. The results are encouraging because the symptoms are lessened, perhaps through neural stem cells modulating the immune system.

Oligodendrocyte precursor cells

The oligodendrocyte is pivotal in MS. These cells wrap their myelin-filled membranes around nerve axons to form the myelin sheath. The sheath spirals around the axon like the layers of an onion. As the disease progresses and myelin is destroyed, only some regions are remeylinated and eventually axons and neurons are injured beyond repair. In addition to being the sole provider of myelin in the CNS, the very presence of intact oligodendrocytes is thought to promote axon survival, even when the tissue is inflamed.

In terms of applying stem cells to the problem, one strategy would be to transplant into the brain oligodendrocytes created in the laboratory, from neural stem cells, embryonic stem cells or inducible pluripotent stem cells. Another strategy would be to stimulate oligodendrocyte precursors (OLPs) that are already present in the patient's brain. The first approach is tricky because the cells would have to get to multiple regions of demyelination and conditions there would already be unfavourable to remyelination. In addition, transplanting high numbers of donor cells might require lifelong immunosuppression which is not ideal. Autologous OLP's created from iPS cells may get around this issue but this technology is just starting to be developed.

The second approach addresses both these issues because immunosuppression would not be required, and OLPs

are abundantly distributed throughout the brain. Preliminary studies have corroborated the potential for this approach. In the adult central nervous system, OLPs can give rise to many cell types including oligodendrocytes; they become activated when demyelination occurs and migrate to the damaged regions in the brain where they become mature oligodendrocytes capable of making the myelin sheath. Understanding the pathways that lead to myelin formation and repair by OLPs and how these processes go awry is a priority for the field and out of such work may come novel drugs and reparative strategies.

Canadian contributions

North Americans have among the highest rates of MS in the world, with the prevalence in Canada ranging from 55,000 – 75,000. Canadian scientists are at the forefront of research on stem cell therapies for MS and are advancing the field through rigorous pre-clinical and clinical studies.

At the pre-clinical stage, researchers in Calgary and Montreal are collaborating with a team in Minnesota to test if prolactin, a pituitary hormone, can stimulate endogenous stem cells to repair damaged myelin in patients with MS. Other teams in Ottawa and Montreal are investigating how mesenchymal stem cells manage to inhibit the immune response, particularly in terms of different types of T cells. If favourable, the results from these studies will be potential targets for future clinical trials.

In one clinical trial, scientists at the Ottawa Health Research Institute (OHRI) demonstrated that immunoablative therapy and autologous hematopoietic stem cell transplantation is effective for treatment of aggressive MS. By following patients for several years after they had immunoablative therapy, scientists found that the inflammatory process could be arrested, and new lesions were not formed. Phase II trials of this treatment in patients aged 18-52 with active MS with relapsed or progression have recently been completed. With an average follow-up of five years (an 10 in some cases) the results are promising and encourage the ongoing use of this therapy for certain patients with MS.

Although this trial is among a number of phase II trials exploring various aspects of using autologous hematopoietic stem cells to treat MS, there are as yet no randomized clinical trials comparing this treatment to conventional agents for patients with earlier stages of MS. Canadian researchers in Montreal, Ottawa and Calgary are facilitating the development of a phase III trial to address this, in collaboration with international groups, such as the Centre for International Blood and Marrow Transplant Research (CIBTR) and the European Group for Blood and Marrow Transplantation (EBMT).

Clinical studies

Phase I/II stem cell clinical trials for MS are progressing at a pace around the world – in Canada, the United States, the United Kingdom, Sweden, Israel, Germany, Australia and Japan. For the most part, these early trials are testing the safety and efficacy of stem cells such as HSCTs or MSCs.

Although scientists have long envisioned using stem cells as a source for replacing myelin-forming cells lost during MS, it is becoming increasingly apparent that the application of stem cells can be much broader. Research studies have shown that stem cells are also able to modulate the immune system and protect brain cells via the secretion of growth factors and other mediators. Capitalizing on the newly recognized attributes of stem cells while pursuing the grail of regenerative therapies will hopefully lead to the translation of novel therapies to treat MS and other neurodegenerative diseases.

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Web Resources

Readers may wish to peruse the recommended sites or review the selected reading list below for more information about the application of stem cells to treat chronic wounds.

General Information

- MS Society of Canada: http://mssociety.ca
- MS Glossary: http://mssociety.ca/en/research/glossary.htm
- National MS Society: http://www.nationalmssociety.org/
- MS-UK: http://www.ms-uk.org/
- EuroStemCell: http://www.eurostemcell.org/factsheet/multiple-sclerosis-how-could-stem-cells-help
- Multiple Sclerosis International Federation: http://www.msif.org/