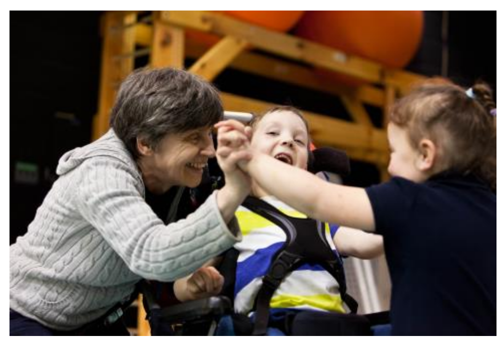
May 2018

On the Uptake

childhood disability LINK

Current State of Stem Cell Treatments for Cerebral Palsy: A Guide for Patients, Families and Service Providers



A substantial growth in stem cell research shows promising results for Cerebral Palsy

Mayada E Stephanie Beldick, Ph.D.
Michael G. Fehlings, Ph.D.
Krembil Research Institute, University Health Network
Institute of Medical Sciences, University of Toronto

Stem Cells and Cerebral Palsy

Cerebral palsy (CP) is caused by injury to the early developing brain, leading to lifetime neuro-motor deficits that are often accompanied by other symptoms, such as visual and cognitive impairments. When damage occurs to the brain during the sensitive perinatal period, the resident brain cells are unable to promote proper growth and development of the brain. **Neurons** and **oligodendrocytes** die and/or fail to mature, and the **white matter tracts** that connect various brain regions with each other and the spinal cord become damaged. This means that different parts of the brain have trouble communicating, which can cause impairments. However, if we can fix some of these broken messengers, this has the potential to help patients with cerebral palsy.

Stem cell transplantation is a **regenerative therapy** that has the potential to replace the damaged and non-functional cells in the brains of CP patients, as well as to provide support to the remaining neurons and oligodendrocytes. There are many kinds of stem cells, each with different and unique characteristics.

What Are Stem Cells?

There are two characteristics that make stem cells unique from other cells in the body:

1) They can divide and make copies of themselves over extended periods of time
2) They can specialize—or **differentiate**—

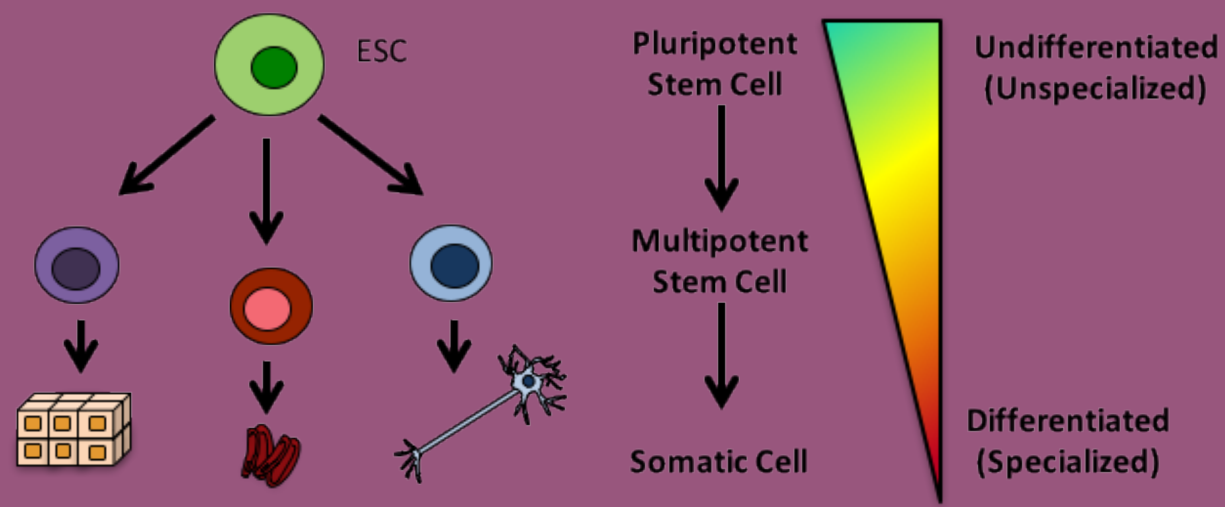


Figure 1: ESCs are classified as pluripotent (undifferentiated) stem cells. ESCs differentiate into multipotent stem cells (e.g. NPC, MSC), which have a limited differentiation capacity and are found in adult tissues. Somatic cells arise from multipotent stem cells and they are fully differentiated (e.g. skin cell, red blood cell, neuron).

into more specified functional cell types, such as heart, lung, or brain cells.

Stem cells can be sourced from various locations, including embryos (embryonic stem cells, or ESCs), children or adult tissues. Somatic (fully differentiated) cells can be induced into behaving like embryonic stem cells (called induced pluripotent stem cells, or iPSCs). iPSCs are particularly special in that the somatic cells used to create them can be sourced directly from the patient. In this way they eliminate the need for stem cell donors and help to minimize the risk of transplant rejection.

Stem cells taken from children or adults can be found in most bodily tissues, including the brain and spinal cord. These stem cells are more specialized than those found in the embryo, and can only differentiate into the cell types of the tissue in which they are found. For example, neural stem cells (NSCs) are found in the brain and spinal cord and can only differentiate into the cells found there. Other tissue-specific stem cells exist, like mesenchymal stromal cells (MSCs), umbilical cord stem cells, and hematopoietic stem cells (HSCs).

Preclinical Stem Cell Research for Cerebral Palsy

CP researchers have been studying various cell types, including ESCs and iPSCs that have been induced into becoming NSCs and MSCs, as well as NSCs found in the adult rodent brain. Results have been promising in these animals, as stem cell transplantation has resulted in modest functional improvements and positive anatomical changes within the brain. Although these results are promising, it is important to remember that this has not yet been tested in the human brain.

Dr. Michael Fehlings and his laboratory (Krembil Research Institute, University Health Network and University of Toronto) are currently investigating NSCs for the treatment of CP. NSCs have a unique benefit over other cell types to treat CP; their ability to differentiate into brain cells provides them with the greatest potential to appropriately integrate into the injured brain and replace the damaged and non-functional cells.

In preclinical models, a few of the hurdles that need to be overcome are: improving cell survival in the brain following transplantation, reducing the risk of tumour formation that can result from ESC and iPSC-derived cells, and understanding how we can force our transplanted cells to integrate better into the existing neuronal pathways. Researchers are continuing to piece together this complex puzzle to improve outcomes for patients with CP and minimize risks associated with stem cell therapy.

Despite these challenges, the knowledge gleaned from how stem cells function and incorporate into the damaged central nervous system is incredibly useful. This information has helped researchers to advance their strategies for cell transplantation, as well as to better understand the function of NSCs following brain injury.

Stem Cell Therapy Clinical Trials

There are several registered clinical trials around the world using stem cells to treat CP, many of which are making use of HSCs, MSCs, and umbilical cord stem cells. To date, the findings of one study have been published. This study had three groups of child participants: Those receiving conventional rehabilitation therapy only, those receiving a drug called erythropoietin (shown to have promise in treating CP) along with conventional rehabilitation therapy, or those receiving umbilical cord

Childhood disability LINK is a bilingual website linking Information and New Knowledge on childhood disability to service providers and families. The website also focuses on enhancing the awareness and understanding of research on a variety of issues in childhood disability. Please visit us at: www.childhooddisability.ca.

Want to learn more on the topic? Suggested readings:

Basics of stem cells:
http://stemcellfoundation.ca/en/
https://stemcells.nih.gov/info/basics/1.htm

Stem cells in CP:
http://stemcellfoundation.ca/en/diseases/cerebral-palsy/

Information on clinical trials:
https://clinicaltrials.gov/
http://stemcellfoundation.ca/en/toward-treatments/clinical-trials/

Stem cell tourism:
http://stemcellfoundation.ca/en/tag/stem-cell-tourism/
https://www.cirm.ca.gov/patients/stem-cell-tourism
http://www.nytimes.com/2016/06/23/health/a-cautionary-tale-of-stem-cell-tourism.html

blood (containing stem cells) in addition to erythropoietin and conventional rehabilitation therapy. The study found that the group who received stem cells showed greater improvements on cognitive and motor assessments when compared to the other treatment arms.

While the growth in the number of clinical trials over the past half-decade is exciting and holds promise for the future of stem cell therapies for CP, there is still a long way to go. None of the clinical trials to date have used NPCs or iPSC-sourced cells, which, as described above, have unique advantages.

Risks and Limitations of Stem Cell Therapy

It must be cautioned that stem cell therapy is still an experimental technique that is not ready to be adopted as the standard of care for patients with CP. Once injected into the body, stem cells cannot be removed and so understanding any negative side-effects, including possible tumour formation, is a must. Other limitations are related to the large-scale manufacturing and regulation of stem cell therapies.

In the laboratory, it is feasible to use petri dishes to culture stem cells for animal experiments, however manufacturing stem cells in mass quantities for consistent and widespread clinical use is understanding of the mechanisms underlying how stem cells work will help these agencies to better define guidelines for their use in the clinic. Basic scientists, clinicians, industry partners, regulatory agencies, and patient advocates all need to work together to help stem cell therapies move forward.

The promise of stem cell therapy is great and heralds a potential revolution in medicine by providing new therapies for previously untreatable conditions. However, it is unlikely to provide a one-stop magic bullet to alleviate all clinical symptoms. In the case of CP, stem cell therapy is likely to result in small incremental improvements in function that in turn will lead to noticeable improvements in the quality of life for most patients. Additionally, at present it is not known for how long the beneficial effects of stem cell transplantation will last, and if multiple transplantations of stem cells over several years will be required to improve or maintain functional recovery.

As a community, it is important that we manage our expectations of stem cell therapies. As mentioned above, this treatment is still undergoing development and is not yet widely accepted in the clinic. While stem cell therapies have huge potential for the future treatment of CP, the study of these cells is a lengthy process that requires extensive investment of time and money. Support of the research that is moving stem cell therapies forward will help to fast-track this therapeutic to the forefront of medicine within the next 20 years.

Take Home Points

- Stem cell therapy for cerebral palsy has the potential to replace damaged brain cells (regeneration) and provide support to the remaining cells
- There are many types of stem cells, with neural stem cells holding the greatest potential for brain repair
- More preclinical research is needed to understand how stem cells work after transplantation, and how to scale-up stem cell production for use in the clinic

Glossary

Central nervous system — The brain and spinal cord

Neurons – Cells in the brain that send signals in order to communicate with other regions of the brain and the body.

Axons – Long processes attached to neurons that relay electrical signals. Analogous to wires in an electrical circuit.

Oligodendrocytes – Produce myelin, a fat that insulates neuronal axons so that neurons can send signals quickly.

White matter tract – A bundle of axons connecting two different regions of the central nervous system.

Differentiate — The ability to transform into specialized cell types found in the body. Once differentiated, the cells cannot go back to their previous state.

Pluripotent – A term used to describe certain stem cells that can differentiate into all the different cell types found in the human body.

Somatic cell – A fully differentiated cell found in the human body (for example, a skin cell).