Stem Cell Therapy for Your Brain

By Jacqueline Silva

There are a variety of mental and neurological problems that plague the human population. Some statistics indicate that 1 in 6 people have some form of mental illness [1]. Some mental illnesses are temporary, like acute anxiety or depression resulting from life changes or stress. Other neurological problems are permanent, like autism spectrum disorder (ASD) and schizophrenia. Some disorders are progressively degenerative like Alzheimer's Disease (AD). Researchers have been struggling to understand the mechanisms behind the causes of these permanent and degenerative neurological disorders. Much progress has been made recently, especially in the last five years, in developing therapies to reverse neurological abnormalities. Stem cell therapy has been one of the most promising areas of research.

Our brain, like the rest of our organs, develops in the womb from a small group of precursor cells called stem cells. Stem cells that will become brain cells are neural stem cells (NSCs). In the early embryo NSCs initially form a tube, and as development proceeds they produce cells that migrate outward, eventually forming the upper layers of the brain capable of higher-level thinking [2]. As the NSCs produce new cells and migrate outward, they also differentiate into many different types of brain cells: neurons and support cells for neurons (called glia). When cells undergo this process of differentiation, it means that the new cells have different genes "turned on or off." In fact, the distinction between any different cell types in the body is the different pattern of genes that are on or off; when a gene is "on" the cell is making a specific protein coded for by that gene, and when a gene is "off" the cell is not making a protein from the gene.

The cells of the body do not function in isolation. Cells communicate with each other by sending out molecular signals. Surrounding cells respond to those signals by changing their behavior. This can include changes in the functions being carried out by the cell, changes in cell-to-cell communication, and even changes in where the cell will migrate to in the surrounding tissue. Environmental factors can also act as signals that affect gene expression and cellular behavior. For example, the cells of a developing embryo in the womb can be affected by molecules circulating in the mother's blood, which could be proteins produced by mom or toxic

substances. Exposure to brain-reactive substances while the brain is developing in the womb is one of the major risk factors for the development of neurological disorders [3, 4, 5].

In general, neurons are tree-shaped, with hundreds of branches reaching out and connecting with other neurons. This neural connectivity is part of the brain's composition and affects its function. Immune cells in the brain are in charge of pruning the connections between neurons. This helps to create stronger connections between some neurons, while removing connections between other neurons. Two waves of neural pruning take place as children develop. As we see on the public service announcements on television, the first five years of life are very important for stimulating neural connections in order to maintain them. This is because the first wave of neural pruning takes place during this time. The second wave of typical neural pruning takes place in the teenage years before brains reach the maturity of adulthood.

While the neural pruning process may be an evolutionary device to help us become sharper and more focused on the mental skills that help us survive into adulthood, it becomes a detrimental developmental process for some individuals predisposed to neurological disorders and mental illnesses. Improper brain development that may have occurred in the womb is then exacerbated by the natural pruning process. The rearrangement of neural connections during childhood development may suddenly reveal abnormalities [6]. These abnormalities may have been hidden before due to a more balanced and uniformly connected brain composition.

Neurological disorders present themselves at various stages of life. ASD is an early developmental disorder in which symptoms typically arise before the age of three. In contrast, the average age of onset of schizophrenia and bipolar disorder ranges from late adolescence to mid-twenties, during or after the second wave of pruning. Neurodegenerative diseases cause an unnatural wave of neural pruning, which leads to reduced connections between neurons and neuron death. Symptoms of neurodegenerative diseases, like AD, usually appear in people in their mid-60s, but there are also early onset forms of neurodegenerative diseases. For example, early onset AD can affect people in their 30s and 40s and Huntington's disease affects adults of all ages [7]. The loss of neurons causes a person to deteriorate in brain and bodily functions until death.

Studies using model organisms are showing promise in the use of NSC transplantation as a therapy for the reduction or reversal of neurological symptoms [8, 9]. The transplanted NSCs respond to signals from the patient's brain cells by generating new neuron subtypes in the

appropriate composition. The NSCs grow, divide, differentiate, and migrate. The new neurons that are produced change the composition of the brain and improve neural connectivity. Researchers have measured the effects of these changes in the brain and, in some cases, have seen a reversal in neurological dysfunctions [8, 9]. While there is still much work to be done to ensure neural stem cell therapies can be safely administered to humans, the scientific community is very hopeful. Most neurological disorders have very limited treatment options and no cures. The current progress in the field of regenerative medicine suggests that stem cell therapies will eventually provide effective treatments or cures for a litany of neurological disorders.

References

[1]. Substance Abuse and Mental Health Services Administration, *Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings*, NSDUH Series H-47, HHS Publication No. (SMA) 13-4805. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

[2]. Martínez-Cerdeño, V., Cunningham, C.L., Camacho, J., Keiter, J.A., Ariza, J., Lovern, M., & Noctor, S.C. (2016a). Evolutionary origin of Tbr2-expressing precursor cells and the subventricular zone in the developing cortex. *The Journal of Comparative Neurology*. 524(3), 433-47. doi: 10.1002/cne.23879.

[3]. Bauman, M.D., Iosif, A.M., Ashwood, P., Braunschweig, D., Lee, A., Schumann, C.M., Van de Water, J. & Amara, D.G. (2013). Maternal antibodies from mothers of children with autism alter brain growth and social behavior development in the rhesus monkey. *Translational Psychiatry*, 3, e278. doi:10.1038/tp.2013.47

[4]. Camacho, J., Jones, K., Miller, E., Ariza, J., Noctor, S.C., Van de Water, J., & Martínez-Cerdeño, V. (2014). Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice. *Behavioural Brain Research*. Jun 1;266:46-51. doi: 10.1016/j.bbr.2014.02.045.

[5]. Martínez-Cerdeño, V., Camacho, J., Fox, E., Miller, E., Ariza, J., Kienzle, D., Plank, K., Noctor, S. C., & Van De Water, J. (2016b). Prenatal Exposure to Autism-Specific Maternal Autoantibodies Alters Proliferation of Cortical Neural Precursor Cells, Enlarges Brain, and Increases Neuronal Size in Adult Animals. *Cerebral Cortex*, 26(1), 374-383.

[6]. Tang, G., Gudsnuk, K., Kuo, S-H., Cotrina, M.L., Rosoklija, G., Sosunov, A., Sonders, M.S, Kanter, E., Castagna, C., Yamamoto, A., Yue, A., Arancio, O., Peterson, B.S., Champagne, F., Dwork, A.J., Goldman, J., & Sulzer, D. (2014). Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits. *Neuron*; 83(5), 1131–1143. doi: http://dx.doi.org/10.1016/j.neuron.2014.07.040

[7]. "Huntington Disease." *National Institutes of Health*. U.S. Department of Health and Human Services, 8 July 2015. Web. 02 Mar. 2017.

[8]. Martinez-Cerdeno, V., Noctor, S.C., Espinosa, A., Ariza, J., Parker, P., Orasji, S., Daadi, M.M., Bankiewicz, K., Alvarez-Buylla, A., & Kriegstein, A.R. (2010). Embryonic MGE Precursor Cells Grafted into Adult Rat Striatum Integrate and Ameliorate Motor Symptoms in 6-OHDA-Lesioned Rats. *Cell Stem Cell*, 6(3), 238-250. doi: http://dx.doi.org/10.1016/j.stem.2010.01.004

[9]. Matchynski-Franks, J.J., Pappas, C., Rossignol, J., Reinke, T., Fink, K., Crane, A., Twite, A., Lowrance, S.A., Song, C., & Dunbar, G.L. (2016). Mesenchymal Stem Cells as Treatment for Behavioral Deficits and Neuropathology in the 5xFAD Mouse Model of Alzheimer's Disease. *Cell Transplantation*, 25, 687-703. doi: http://dx.doi.org/10.3727/096368916X690818