Stem cell therapy for human brain disorders

**OLLE LINDVALL and ZAAL KOKAIA**

**Laboratory of Neurogenesis and Cell Therapy, Section of Restorative Neurology, Wallenberg Neuroscience Center, University Hospital, Lund, Sweden; Laboratory of Neural Stem Cell Biology, Section of Restorative Neurology, Stem Cell Institute, University Hospital, Lund, Sweden; and Lund Strategic Research Center for Stem Cell Biology and Cell Therapy, Lund, Sweden**

**Stem cell therapy for human brain disorders.** Transplantation of stem cells or their derivatives, and mobilization of endogenous stem cells in the adult brain, have been proposed as future therapies for various brain disorders such as Parkinson’s disease and stroke. In support, recent progress shows that neurons suitable for transplantation can be generated from stem cells in culture, and that the adult brain produces new neurons from its own stem cells in response to injury. However, from a clinical perspective, the development of stem cell–based therapies for brain diseases is still at an early stage. Many basic issues remain to be solved and we need to move forward with caution and avoid scientifically ill-founded trials in patients. We do not know the best stem cell source, and research on embryonic stem cells and stem cells from embryonic or adult brain or from other tissues should therefore be performed in parallel. We need to understand how to control stem cell proliferation and differentiation into specific cell types, induce their integration into neural networks, and optimize the functional recovery in animal models closely resembling the human disease. All these scientific efforts are clearly justified because, for the first time, there is now real hope that we in the future can offer patients with currently intractable diseases effective cell-based treatments to restore brain function.

The basic principle of cell therapy is very simple: to restore brain function that has been lost due to damage or disease by replacing dead cells with new healthy cells through transplantation. Given the complexity of human brain structure and function, this prospect may seem remote. However, if cell replacement will work in the human brain, it could provide radical new therapies for severe neurodegenerative disorders like Parkinson’s disease and stroke. Whether it will work or not will depend on, first, if the grafted neurons can survive and form connections in the patient’s brain and, second, if the patient’s brain can integrate and use the grafted neurons.

Available evidence supporting that cell therapy may work in patients with brain disorders mainly originates from clinical trials with intrastriatal transplantation of human embryonic mesencephalic tissue, rich in postmitotic dopamine neurons, in Parkinson’s disease patients. These studies demonstrate that grafted dopamine neurons can survive, reinnervate the striatum, and restore dopamine release for up to 10 years despite an ongoing disease process, which destroys the Parkinson’s disease patient’s own dopamine neurons [1, 2]. Several open-label trials have reported clear clinical benefit [3, 4]. Some patients have even been able to withdraw L-DOPA treatment for several years and resume an independent life [2]. However, other patients have showed only modest or no improvement after grafting [5, 6], which illustrates that transplantation procedures are far from optimal. Taken together, the clinical trials with transplantation of embryonic mesencephalic tissue in Parkinson’s disease patients provide proof-of-principle for the cell replacement strategy in the human brain.

It is unlikely that transplantation of human embryonic mesencephalic tissue will become a treatment for large numbers of Parkinson’s disease patients. Problems with tissue availability and standardization of the graft lead to too much variation in functional outcome. The most important goal for cell therapy research in Parkinson’s disease is now to develop strategies to generate large numbers of functional dopamine neurons in preparations which are standardized and quality-controlled. The stem cell technology has the potential to provide solutions to these technical issues. Results from clinical trials and animal models have identified a set of requirements which probably have to be fulfilled by the stem cell-derived neurons in order to induce marked clinical improvement after transplantation: (1) the cells should release dopamine in a regulated manner, and need to have the molecular, morphologic, and electrophysiologic properties of substantia nigra dopamine neurons, which should be replaced [7]; (2) when tested prior to clinical application, the cells must be able to reverse motor deficits in animal models of Parkinson’s disease resembling the symptoms in patients; (3) the yield of cells should be sufficient to allow for 100,000 or more grafted dopamine neurons to survive long-term in each human putamen [8]; (4) The grafted dopamine neurons should reestablish a dense terminal network in most parts of the denervated striatum; and (5) the grafts have to become functionally integrated into host basal ganglia-thalamo-cortical neural circuitries [9].

© 2005 by the International Society of Nephrology
Cells with at least some properties of mesencephalic dopamine neurons have been generated in vitro from stem cells of four different sources: embryonic stem cells, neural stem cells in the embryonic and adult brain, and stem cells in other tissues (e.g., bone marrow) [10]. Currently, the most effective production of dopamine neurons suitable for transplantation has been reported from mouse embryonic stem cells [10]. Large numbers of dopamine neurons can also be generated from human embryonic stem cells [11], but the survival after transplantation in animals models has been poor. A general problem with the stem cell–derived neurons described so far is that it we still do not know to what extent they can reinnervate the denervated striatum after transplantation and release dopamine in vivo, and if they can improve behavioural deficits resembling Parkinson’s disease motor symptoms in patients.

It should be emphasized that the availability of virtually unlimited numbers of dopamine neurons, generated from stem cells, will not automatically mean that we have a clinically competitive cell therapy for Parkinson’s disease. We have to define better selection criteria for patients with respect to stage and type of disease, and determine the preoperative degeneration pattern so that we know what needs to be repaired. The clinical transplantation procedure should be tailor-made with respect to dose and location of grafted cells based on preoperative imaging so that the repair of the dopamine system in striatum and extrastriatal areas is as complete as possible in each patient’s brain. The risk for teratoma from embryonic stem cells, and the consequences of the introduction of new genes in stem cell–derived neurons should also be carefully evaluated after transplantation in experimental animals.

The possibility to restore brain function by transplantation of stem cells or cells predifferentiated in vitro from stem cells is being explored also in stroke [10]. In addition, recent findings in rodents have suggested an alternative approach to cell replacement therapy in this disorder based on the adult brain’s ability to produce new neurons from its own neural stem cells. Stroke leads to increased generation of neurons from neural stem cells in the subventricular zone, lining the lateral ventricles [12–14]. These immature neurons migrate into the damaged striatum, where they express markers of striatal medium spiny projection neurons. Thus, the new neurons seem to differentiate into the phenotype of most neurons destroyed by the ischemic lesion.

Currently, there is a lot of enthusiasm about the therapeutic potential of endogenous neurogenesis in stroke [15]. However, we still have very little knowledge about the importance of endogenous neurogenesis for brain repair, and how the various steps of neurogenesis are regulated after stroke. Also, we do not yet know if the new neurons are functional and become integrated into host neural circuitries. A major scientific challenge is to develop strategies to promote survival of the new neurons formed after stroke because many of them die. Several factors can increase adult neurogenesis by stimulating formation and/or improving survival of new neurons [e.g., fibroblast growth factor-2 (FGF-2), epidermal growth factor (EGF), stem cell factor, erythropoietin (EPO), brain-derived neurotrophic factor (BDNF), caspase inhibitors, and anti-inflammatory drugs [16, 17]. Inflammation has been shown to be detrimental for neurogenesis in the dentate gyrus [18, 19]. Because stroke causes inflammation, these data suggest that inflammation-mediated suppression of neurogenesis may limit the effectiveness of neuroregenerative responses in this disorder.

Stem cell–based approaches for the first time offer real hope that we in the future will be able to offer patients with currently intractable brain disorders effective treatments. However, we need to know much more about mechanisms of cell proliferation, differentiation and survival, and of regeneration and functional recovery. Research on different sources of stem cells and on endogenous neuroregenerative responses should continue in parallel. It is important to emphasize that the biologic problems that have to be solved in order to develop safe and effective stem therapies are complex and should not be underestimated.

ACKNOWLEDGMENTS

Our own research was supported by the Swedish Research Council, EU project LSHBCT-2003–503005 (EUROSTEMCELL), and the Söderberg, Crafoord, and Kock Foundations. The Lund Stem Cell Centre is supported by a Center of Excellence Grant in Life Sciences from the Swedish Foundation for Strategic Research.

Reprint requests to Olle Lindvall, M.D., Ph.D., Laboratory of Neurogenesis and Cell Therapy, Section of Restorative Neurology, Wallenberg Neuroscience Center, University Hospital, SE-221 84 Lund, Sweden. E-mail: olle.lindvall@med.lu.se

REFERENCES