Recovery and Rehabilitation in Stroke
Stem Cells
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Abstract—The recent demonstration that neurons for transplantation can be generated from stem cells and that the adult brain produces new neurons in response to stroke has raised hope for the development of a stem cell therapy for patients affected with this disorder. In this review we propose a road map to the clinic and describe the different scientific tasks that need to be accomplished to move stem cell–based approaches toward application in stroke patients. (Stroke. 2004; 35[suppl I]:2691-2694.)

Key Words: acute care ■ rehabilitation ■ stem cells ■ stem cell transplantation

The main aim of cell therapy is to restore function in the diseased human brain by replacing dead neurons with new neurons through transplantation or stimulation of neurogenesis from endogenous stem/precursor cells. This approach seems to be more suitable for disorders like Parkinson disease, in which the main pathology is a relatively selective degeneration of a specific type of neuron, the nigrostriatal dopamine neuron. In stroke, occlusion of a cerebral artery leads to focal ischemia and subsequent damage in a restricted central nervous system region. To repair the human brain after stroke may seem unrealistic because of the atrophy and loss of many different neuron and glial cell types. It could be argued, however, that reestablishment of even only a fraction of damaged neuronal circuitries might have significant implications. The clinical trials with intrastriatal transplantation of human embryonic mesencephalic tissue in patients with Parkinson disease have provided proof-of-principle that cell replacement can work in this disorder. The grafted neurons can survive and reinervate the striatum, release dopamine, become functionally integrated into host neuronal circuitries, and give rise to clinical benefit. However, 2 recent sham surgery-controlled trials showed only modest improvement, which illustrates that present cell replacement procedures for Parkinson disease patients are far from optimal.

In contrast to Parkinson disease, there is so far no convincing evidence that neuronal replacement can work in stroke patients. In the only clinical trial reported so far, 12 patients with stroke affecting the basal ganglia received implants of neurons generated from the human teratocarcinoma cell line NTera-2 (NT-2) into the infarcted area. This cell line gives rise to neurons after a complex induction process. The improvements in some of the patients correlated with increased metabolic activity at the graft site. This finding could be interpreted as graft function, but may also reflect inflammation or increased activity in host neurons. Autopsy in 1 patient revealed a population of grafted cells expressing a neuronal marker 2 years after surgery.

In this brief review, we will discuss the prospects of stem cell therapy to repair the brain after stroke. Stem cells are immature cells with prolonged self-renewal capacity and, depending on their origin, the ability to differentiate into multiple cell types or all cells of the body. Hypothetically, neurons and other cells useful for brain repair in stroke could be made from stem cells of four different sources: embryonic stem cells from the blastocyst, neural stem cells (NSCs) from the embryonic or adult brain, or stem cells in other tissues, eg, bone marrow.

Can Cell Therapy Work in Animal Models of Stroke?
Stem/precursor cells from different sources have been tested for their ability to reconstruct the forebrain and improve function after transplantation in animals subjected to stroke (Table 1). The transplants, including a mouse neuroepithelial stem cell line, the human NTera-2 cell line, and human bone marrow cells, have been reported to partly reverse some behavioral deficits. However, in most cases, the underlying mechanisms are unclear and there is little evidence for neuronal replacement. Only few grafted cells have survived and they have not exhibited the phenotype of the dead neurons. Moreover, it is unknown if the observed grafted cells are functional neurons and establish connections with host neurons.

Despite the poor evidence for significant neuronal replacement in these studies, improvement of various stroke-induced behavioral deficits has been observed. How is this possible?
In this context, it should be pointed out that stem cell transplantation probably can lead to clinically valuable improvements through several mechanisms. First, the tissue damage per se can stimulate plastic responses or interfere with neural activity in the host. Second, the transplants can act as biological minipumps and release a missing transmitter or secrete growth factors. These factors can stimulate plastic responses and improve the survival and function of host neurons. Third, the grafts can restore synaptic transmitter release by providing a local reinnervation. Fourth, and this is true neuronal replacement, the grafts can become integrated into existing neural and synaptic networks, and reestablish functional afferent and efferent connections. Recent findings in rodents suggest an alternative approach to cell therapy in stroke based on self-repair. Stroke leads to increased generation of neurons from NSCs in the subventricular zone (SVZ), lining the lateral ventricles.11–13 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. However, because more than 80% of the new neurons die during the first weeks after stroke, they only replace a small fraction (about 0.2%) of the mature striatal neurons which have died.11

Currently, there is a lot of enthusiasm about the therapeutic potential of endogenous neurogenesis in stroke. However, we have very little knowledge about the importance of endogenous neurogenesis for brain repair. We know that there is a neurogenic response after stroke. We know very little how the various steps of neurogenesis are regulated after stroke or if the new neurons are functional neurons and become integrated into host neural circuitries. One major problem is that the majority of the new neurons die after stroke, and very few survive long-term. Several factors can increase adult neurogenesis by stimulating formation or improving survival of new neurons, such as FGF-2, EGF, stem cell factor, erythropoietin, BDNF, caspase inhibitors, and antiinflammatory drugs.14 Recently, it was demonstrated that inflammation is detrimental for neurogenesis in the dentate gyrus.15,16 Because stroke causes inflammation, these data raise the possibility that inflammation-mediated suppression of neurogenesis plays a role for the ineffective neuroregenerative response in this condition.

In the ideal transplantation scenario, stem cells implanted directly into or around the damaged area will differentiate in situ into those cells which have died. This strategy requires that the largely unknown developmental mechanisms instructing stem cells to differentiate into specific cell types will work also in the patient’s brain. The optimum strategy would probably be to combine transplantation of NSCs close to the damaged area with stimulation of neurogenesis from endogenous NSCs. Newly generated neurons are able to migrate toward the damage11,13,17 and, at least to some extent, adopt the phenotype of those cells that have died.11,13,18 Available data provide evidence for a neurogenic potential also in the human brain. Neurogenesis from precursors in the SVZ has been demonstrated in vivo in humans,19 and precursors capable of forming neurons are found in human subcortical white matter.20

The inadequate blood supply to the ischemic core region will cause massive loss of newly formed neurons. If cells are implanted into the penumbra area (region-at-risk), they will probably be supported by collateral circulation. Adult hippocampal neurogenesis is closely associated with angiogenesis from endothelial cell precursors.21 The creation of such a vascular niche and the stimulation of vascularization after stroke will be crucial for the survival of the new neurons. Administration of vascular endothelial growth factor promotes both neurogenesis in the SVZ and angiogenesis in the ischemic penumbra region following stroke.22 However, for efficient repair after stroke it may be necessary to provide the NSCs with a platform so that they can reform appropriate brain structure and connections. A recent study in neonatal mice23 shows that if NSCs are seeded on synthetic extracellular matrix and implanted into the ischemia-damaged area, then new parenchyma composed of neurons and glia is formed and becomes vascularized.
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How Can Stem Cell Therapy Be Developed for Stroke Patients?

In order to develop stem cell therapy toward clinical application in stroke, 3 different tasks should be accomplished: The first task (Steps 1 and 2 in Figure 1) is to obtain proof-of-principle that implanted stem cells, or neurons that are generated from endogenous NSCs, can survive in large numbers in animals subjected to stroke, migrate to appropriate locations, exhibit morphological and functional properties of those neurons that have died, and establish afferent and efferent synaptic interactions with neurons that survived the insult. Magnetic resonance imaging seems ideal for noninvasive imaging at high spatial and temporal resolution of the survival, migration and differentiation of grafted cells. The second task (Step 3 in Figure 1) is to optimize the behavioral recovery induced by neuronal replacement in animal models. Strategies to improve survival, differentiation, and integration of endogenous and grafted stem cells will require detailed knowledge of how these processes are regulated. The time window after the insult when the generation of new neurons will lead to maximum restitution of neuronal circuitries and functional recovery should be determined. The third task (Step 4 in Figure 1) is to define which patients are suitable for stem cell therapy based on findings in animal models regarding which cell types can be produced and replaced. The occurrence of striatal neurogenesis after stroke focuses the interest on patients with basal ganglia infarcts. If stem cells can also generate cortical neurons and repair axonal damage, patients with lesions in the cerebral cortex may be included. A strategy for repair of infarcted white matter was suggested recently by the observation that adult neurospheres injected intravenously or intravitreally in mice gave rise to cells that migrated to demyelinated areas, differentiated into oligodendrocyte progenitors, remyelinated axons, and improved function. 

Conclusions

Recent progress shows that specific types of neurons and glia cells suitable for transplantation can be generated from stem cells in culture. We also see that the adult brain produces new neurons from its own stem cells in response to stroke. Although these findings raise hope for the development of stem cell therapies for brain repair after stroke, many basic issues remain to be solved. We need to move forward with caution and avoid ill-founded trials of patients. Before clinical trials with stem cell–based approaches are initiated, we need to know to a much greater extent how to control stem cell proliferation and differentiation into specific phenotypes, induce their integration into existing neural and synaptic circuits, and optimize the functional recovery in animal models of stroke.

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