NATURE|Vol 441|29 June 2006|doi:10.1038/nature04960

Stem cells for the treatment of neurological disorders

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Many common neurological disorders, such as Parkinson's disease, stroke and multiple sclerosis, are caused by a loss of neurons and glial cells. In recent years, neurons and glia have been generated successfully from stem cells in culture, fuelling efforts to develop stem-cell-based transplantation therapies for human patients. More recently, efforts have been extended to stimulating the formation and preventing the death of neurons and glial cells produced by endogenous stem cells within the adult central nervous system. The next step is to translate these exciting advances from the laboratory into clinically useful therapies.

It is hoped that stem cells will provide an inexhaustible source of neurons and glia for therapies aimed at cell replacement or neuroprotection in disorders affecting the brain and spinal cord (Fig. 1). Embryonic stem (ES) cells, and stem cells from the fetal or adult central nervous system (CNS) or other tissues might all be suitable for this purpose, but human cells are probably needed for clinical application. The development of stem-cell therapies will require a detailed knowledge of disease pathology and how specific cell types in various areas of the CNS are affected. Different cell types and neuroprotective molecules will be needed depending on the disorder. In the case of some disorders, gains can probably be induced only with transplanted cells generated from stem cells *in vitro*, whereas in other conditions the stimulation of endogenous CNS stem cells may be beneficial.

Here, we consider several neurological disorders for which stem-cell-based therapy has raised particular interest. We describe the ways in which stem cells might be used to treat these conditions, discussing the prospects for and problems of translating laboratory findings into clinically useful therapies.

Parkinson's disease

The pathological hallmark of Parkinson's disease (PD) is a gradual loss of nigrostriatal dopamine-containing neurons, but degeneration also occurs in systems of non-dopaminergic neurons. The main symptoms are rigidity, poverty of movement (bradykinesia), tremor and postural instability. Current therapies centre on the oral administration of L-dopa and dopamine receptor agonists, and on deep-brain stimulation in the subthalamic nucleus. These treatments are effective for some symptoms, but are associated with side effects and do not stop the progression of the disease. To be clinically competitive, a stem-cell-based therapy must lead to long-lasting, significant improvement in mobility, ameliorate currently intractable symptoms, or counteract disease progression.

Clinical trials of the transplantation of human fetal dopaminergic neurons have shown that cell replacement can produce major, long-lasting improvement in some patients[1]. So it is promising that cells with properties of dopaminergic neurons have been generated *in vitro* from stem cells of various sources, such as ES cells and stem cells isolated from bone marrow and fetal brain[1–3]. However, whether any of these protocols could induce functional recovery of therapeutic value is unclear, because there has not yet been a clear demonstration that once transplanted in animals with experimental PD, the neurons generated *in vitro* can efficiently reinnervate the striatum, release dopamine *in vivo*, and give rise to considerable recovery from deficits resembling human symptoms[1]. To make stem-cell therapy work for PD, dopaminergic neurons with the characteristics of substantia nigra neurons[4] must be produced in large numbers. For dopaminergic neurons generated from human ES cells[5], survival after

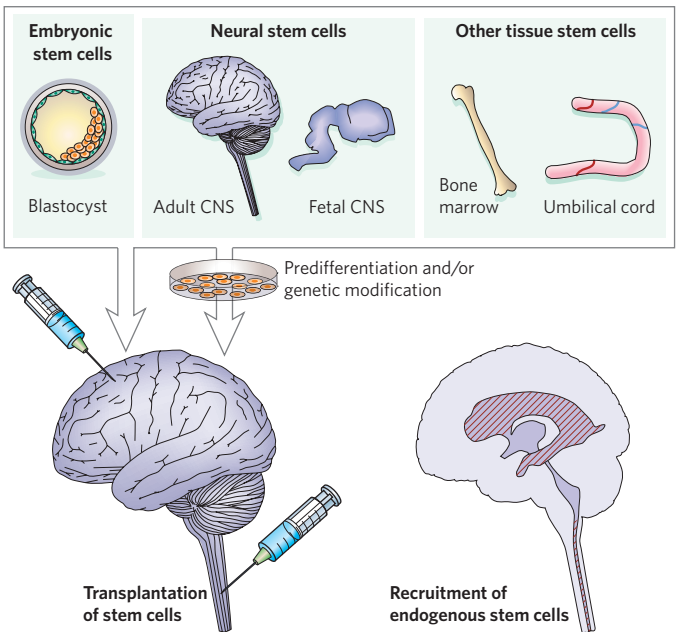

Figure 1 | Application of stem cells for neurological disorders. Stem cells would be isolated and transplanted to the diseased brain and spinal cord, either directly or after predifferentiation/genetic modification in culture to form specific types of neuron and glial cell, or cells producing neuroprotective molecules. In strategies relying on stimulation of the patient's own repair mechanisms, endogenous stem cells would be recruited to areas of the adult brain and spinal cord affected by disease, where they would produce new neurons and glia (neurogenic and gliogenic areas along lateral ventricle and central canal are shown in hatched red). Stem cells could provide clinical benefits by neuronal replacement, remyelination and neuroprotection.

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transplantation in animal models has been poor and needs to be markedly increased before clinical application. Because some patients will need implants in several areas of the brain[6], optimum recovery will require a tailor-made grafting procedure based on preoperative imaging. It will also be necessary to develop strategies that hinder disease progression. One possible approach to prevent the death of existing neurons could be to transplant human stem cells engineered to express neuroprotective molecules such as glial-cell-line-derived neurotrophic factor (GDNF)[7].

Stroke

Stroke is caused by blockage of a cerebral artery, leading to focal ischaemia, loss of neurons and glial cells, and motor, sensory or cognitive impairments. No effective treatment to promote recovery exists, so a therapy that produced even minor improvement would be valuable. Transplanted cells from different sources, such as fetal brain, neuroepithelial or teratocarcinoma cell lines, bone marrow and umbilical cord, have yielded some improvement in animals and, in one clinical trial, in humans affected with stroke[1]. In most cases, the grafts have acted by providing trophic factors that enhance cell survival and function[1]. However, for stem-cell therapy to be of major clinical value, human cells should be able to replace dead neurons, remyelinate axons and repair damaged neural circuitries.

As a first step towards this goal, human fetal neural stem (NS) cells were transplanted into the brains of stroke-damaged rats, resulting in the migration of new neurons towards the ischaemic lesion[8]. Other studies showed that monkey ES-cell-derived progenitors transplanted into the brains of mice after stroke differentiated into various types of neuron and glial cell, re-established connections with target areas[9], and led to improved motor function[10]. The therapeutic efficacy of such strategies could be improved further by genetically modifying the stem cells: for example, by overexpressing an anti-apoptotic gene[11].

Interestingly, the stroke-damaged adult rodent brain has some capacity for neuronal replacement from its own NS cells. For several months after a stroke, NS cells can generate new striatal neurons that migrate to the site of damage[1,12]. It is now important to establish whether endogenous neurogenesis can contribute to functional recovery after stroke, and whether it occurs in humans. And, because the regeneration of cortical neurons will be the basis for functional improvement in most stroke-damaged brains, we will also need to know whether the adult brain's own NS cells can be triggered to produce cortical neurons. Effective therapies will depend on strategies to increase the survival of the new neurons and to enhance their incorporation into reorganizing neural circuitries.

Huntington's disease

Huntington's disease (HD) is a fatal, intractable disorder that is characterized by chorea (excessive spontaneous movements) and progressive dementia. It is caused by the death of projection neurons in the striatum. Stem-cell therapy aims to restore or preserve brain function by replacing and protecting striatal neurons — a strategy that might be insufficient because patients also suffer progressive neocortical degeneration. In animal models of HD, cell replacement using grafts of fetal striatal neurons promotes functional recovery, and some evidence from clinical trials indicates that this can also occur in patients[1]. By contrast, stem-cell-based approaches are still in their infancy, and the reconstruction of striatal neural circuitry has not been shown in animals. However, human NS cells implanted into the brains of rats were recently found to reduce motor impairments in experimental HD through trophic mechanisms[13,14]. At this time, using stem cells for the delivery of trophic factors and neuroprotection to prevent disease progression seems a more achievable clinical goal in HD than neuronal replacement.

Amyotrophic lateral sclerosis

In amyotrophic lateral sclerosis (ALS), dysfunction and degeneration of motor neurons occur not only in the spinal cord (lower motor neurons) but also in the cerebral cortex and brainstem (upper motor neurons). Muscle weakness progresses rapidly and death occurs within a few years. There is no effective treatment. A stem-cell therapy must restore or preserve the function of both upper and lower motor neurons, and new neurons must become integrated into existing neural circuitries. Recent reports have shown that it is possible to generate lower motor neurons *in vitro* from stem cells of various sources, including ES cells and those from the fetal CNS[1,15,16]. Mouse ES-cell-derived motor neurons establish functional synapses with muscle fibres *in vitro*[17,18] and extend axons to ventral roots after transplantation into adult rats[17]. But whether these neurons can integrate into existing neural circuitries and restore motor function has not been established.

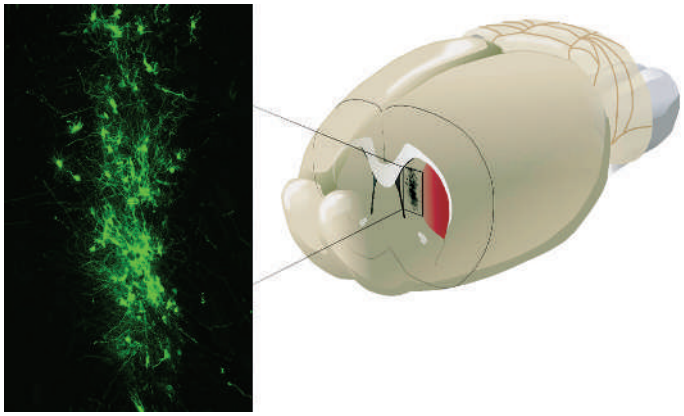

Figure 2 | Transplantation of stem cells into injured brain. Human fetal NS cells labelled with green fluorescent protein survive for at least 1 month and differentiate into cells morphologically resembling neurons after grafting in close proximity to the stroke-damaged rat striatum (red area).

Whereas neuronal replacement in ALS patients seems a distant goal, using stem cells to prevent motor neurons from dying is a more realistic and shorter-term clinical approach. This prospect is supported by studies showing that human embryonic germ cells delivered into the cerebrospinal fluid of rats with motor neuron injury can migrate into the spinal cord and induce motor recovery, probably through neuroprotection[19]. The efficacy of this approach could be improved by genetically modifying the stem cells to secrete molecules that promote motor neuron survival. For instance, a recent study showed that human cortical progenitors that were engineered to express GDNF survived implantation into the spinal cords of ALS rats and released the neurotrophic factor[20].

Alzheimer's disease

Alzheimer's disease (AD) is characterized by neuronal and synaptic loss throughout the brain, involving the basal forebrain cholinergic system, amygdala, hippocampus and several cortical areas. Patients' memory and cognitive performance is progressively impaired; they develop dementia; and are likely to die prematurely. Current therapies, such as treatment with acetylcholinesterase inhibitors to enhance cholinergic function, give only partial and temporary alleviation of symptoms.

The pathological changes seen in AD offer an extremely problematic situation for cell replacement. Given the widespread and progressive damage in the brains of patients with AD, it is unlikely that the mechanisms for instructing transplanted NS cells to differentiate into new neurons will be intact. In theory, cognitive decline caused by the degeneration of basal forebrain cholinergic neurons could be prevented by transplanting cholinergic neurons generated from NS cells *in vitro*. But to provide long-lasting symptomatic benefit, this approach would require the existence of intact target cells within the patient's brain, and these are highly likely to be damaged.

However, because stem cells can be genetically modified and have migratory capacity after transplantation, they could be used for the delivery of factors that can modify the course of the disease. In support of this approach, basal forebrain grafts of fibroblasts that produce nerve growth factor (NGF) — which counteracts cholinergic neuronal death, stimulates cell function and improves memory in animal models — have been of some benefit in patients with AD[21].

Multiple sclerosis

Multiple sclerosis (MS) is caused by the inflammation-induced destruction of the myelin sheath that surrounds axons, leading to conduction deficits and a variety of neurological symptoms and, in some patients, major disability. Axonal loss as a consequence of acute inflammation or chronic demyelination is an important cause of functional deterioration. Immunomodulatory and immunosuppressive treatments are only partially effective.

Myelin-producing oligodendrocyte progenitor cells (OPCs) are abundant in the adult human brain[22]. Spontaneous remyelination occurs to varying degrees in the early stages of MS, and OPCs are also present in chronic demyelinated MS lesions. An important area of research is that focused on finding ways to enhance remyelination from these cells, and identifying the factors that lead to a failure of cells to produce myelin in the first place. To this end, Back *et al.*[23] recently showed that astrocyte-derived hyaluronan accumulated in demyelinated lesions from MS patients and prevented the maturation of endogenous OPCs.

The transplantation of remyelinating cells represents another approach for treating myelin loss in MS. Human adult[22] and ES-cell-derived[24] OPCs have been shown to myelinate dysmyelinated mouse brain and spinal cord after transplantation. However, a major concern is that the inflammatory environment could destroy the grafted OPCs and inhibit their maturation. Immunosuppressive and anti-inflammatory treatments might therefore be necessary. Another problem is that the demyelinated MS lesions are distributed across multiple locations throughout the CNS. An effective therapy will require the implanted OPCs to migrate to these sites. Interestingly, after systemic administration in mice, NS cells migrated to inflammatory demyelinating lesions, where some became OPCs and remyelinated axons[25]. Most cells remained undifferentiated and suppressed proinflammatory mechanisms[26].

Spinal cord lesions

Spinal cord injuries interrupt ascending and descending axonal pathways, and cause a loss of neurons and glia, inflammation and demyelination. The lesions lead to a loss of movement, sensation and autonomic control below the site of injury. There is no cure, and the most common current treatment — high-dose methylprednisolone — is of questionable value.

The transplantation of stem cells into injured spinal cord can lead to functional benefits[27,28], mainly through trophic factor secretion or the remyelination of spared axons. A recent study showed that human NS cells implanted into damaged mouse spinal cord generated new neurons and oligodendrocytes, leading to locomotor recovery[29]. However, there are risks of side effects unless NS-cell differentiation after transplantation is controlled. Astrocytic differentiation and aberrant axonal sprouting after NS-cell implantation into injured rat spinal cord can cause hypersensitivity to stimuli that are not normally painful[30].

Perhaps the most realistic short-term clinical goal is to use stem cells for remyelination, which probably occurs to some degree after lesions from endogenous OPCs[31]. One study reported that after NS-cell implantation into injured spinal cord in rats, there was a good correlation between the number of graft-derived oligodendrocytes, the amount of myelin, and the extent of functional recovery[30]. Another study reported that transplanted oligodendrocytes from human ES cells could myelinate the injured rodent spinal cord and improve motor function[32].

Perspectives

It would be premature to launch clinical trials to use stem cells to treat neurological disorders. However, steady progress supports the hope that stem-cell-based therapies to restore and preserve function in the brain and spinal cord can be developed. For each disease, it is now possible to develop a road map that defines the necessary scientific and clinical advances required for stem cells to reach the clinic. Before we apply stem-cell therapies to patients, we must be able to control the proliferation and differentiation of stem cells into specific cellular phenotypes and to prevent tumour formation. Furthermore, the efficacy of stem cells and their mechanisms of action should be demonstrated in animal models with pathology and symptomatology resembling the human disease. Even so, it may be difficult to translate data obtained in animals to humans because of species differences in the degree of neuronal plasticity and an incomplete knowledge of disease mechanisms. We must understand how to influence the pathological tissue environment, including inflammatory and immune reactions, to allow efficient repair. Finally, we must remember that however exciting the neurobiological mechanisms might be, the clinical usefulness of stem cells will be determined by their ability to provide patients with neurological disorders with safe, long-lasting and substantial improvements in quality of life. ■

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