Role of Stem Cells in Treatment of Neurological Disorder

Ashfaq Ul Hassan, Ghulam Hassan, Zahida Rasool
SKIMS Medical College, Srinagar, Qassim University (Saudi Arabia) & Islamic University, Kashmir, India

Abstract: *Stem cells* or mother or queen of all cells are pleuropotent and *have* the remarkable potential to develop into many different cell types in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is alive. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells differ from other kinds of cells in the body. All stem cells regardless of their source have three general properties:

They are unspecialized; one of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions.

They can give rise to specialized cell types. These unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.

They are capable of dividing and renewing themselves for long periods. Unlike muscle cells, blood cells, or nerve cells—which do not normally replicate themselves - stem cells may replicate many times. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. Today, donated organs and tissues are often used to replace those that are diseased or destroyed. Unfortunately, the number of people needing a transplant far exceeds the number of organs available for transplantation. Pleuropotent stem cells offer the possibility of a renewable source of replacement cells and tissues to treat a myriad of diseases, conditions, and disabilities including Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, Cerebral palsy, Battens disease, Amyotrophic lateral sclerosis, restoration of vision and other neuro degenerative diseases as well.

Correspondence:
Dr. Ashfaq Ul Hassan
House No: A 50 Khan Colony
Chanpora, Srinagar, Kashmir, India
E mail: ashhassan@rediffmail.com

Introduction

Stem cells may be the person's own cells (a procedure called *autologous transplantation)* or those of a donor (a procedure called *allogenic transplantation*). When the person's own stem cells are used, they are collected before chemotherapy or radiation therapy because these treatments can damage stem cells. They are injected back into the body after the treatment.

The sources of stem cells are varied such as *pre-implantation embryos, children, adults, aborted fetuses, embryos, umbilical cord, menstrual blood, amniotic fluid and placenta*

New research shows that transplanted stem cells migrate to the damaged areas and assume the function of neurons, holding out the promise of therapies for *Alzheimer's disease, Parkinson's, spinal cord injury, stroke, Cerebral palsy, Battens disease and other neurodegenerative diseases.*

The therapeutic use of stem cells, already promising radical new *treatments for cancer, immune-related diseases, and other medical conditions,* may someday be extended to repairing and replenishing the brain. In a study published in the February 19, 2002, *Proceedings of the National Academy of Sciences*, researchers exposed the spinal cord of a rat to injury, paralyzing the animal's hind limbs and lower body. Stem cells grown in exponential numbers in the laboratory were then injected into the site of the injury. It was seen that week after the injury, motor function improved dramatically,

Discussion

The following diseases have been treated by various stem cell practitioners with generally positive results and the spectrum has ever since been increasing.

Cerebral Palsy

Cerebral palsy is a disorder caused by damage to the brain during pregnancy, delivery or shortly after birth. It is often accompanied by seizures, hearing loss, difficulty speaking, blindness, lack of co-ordination and/or mental retardation. Studies in animals with experimentally induced strokes or traumatic injuries have indicated that benefit is possible by stem cell therapy. The potential to do these transplants via injection into the vasculature rather than directly into the brain increases the likelihood of timely human studies. As a result, variables appropriate to human experiments with intravascular injection of cells, such as cell type, timing of the transplant and effect on function, need to be systematically performed in animal models Studies in animals with experimentally induced strokes or traumatic injuries have indicated that benefit is possible with injury, with the hope of rapidly translating these experiments to human trials. (1)

Cerebral palsy produces chronic motor disability in children. The causes are quite varied and range from abnormalities of brain development to birth-related injuries to postnatal brain injuries. Due to the increased survival of very premature infants, the incidence of cerebral palsy may be increasing. While premature infants and term infants who have suffered neonatal hypoxic-ischemic (HI) injury represent only a minority of the total cerebral palsy population, this group demonstrates easily identifiable clinical findings, and much of their injury is to oligodendrocytes and the white matter (2)

Alzheimer 's Disease

Alzheimer's is a complex, fatal disease involving progressive cell degeneration, beginning with the loss of brain cells that control thought, memory and language. The disease, which currently has no cure, was first described by German physician Dr. Alzheimer, who discovered amyloid plaques and neurofibrillary tangles in the brain of a woman who died of an unusual mental illness.

A compound similar to the components of DNA may improve the chances that stem cells transplanted from a patient's bone marrow to the brain will take over the functions of damaged cells and help treat Alzheimer's disease and other neurological illnesses. A research team led by University of Central Florida professor Kiminobu Sugaya found that treating bone marrow cells in laboratory cultures with bromodeoxyuridine, a compound that becomes part of DNA, made adult human stem cells more likely to develop as brain cells after they were implanted in adult rat brains.

It has long been recognized that Alzheimer's disease (AD) patients present an irreversible decline of cognitive functions as

consequence of cell deterioration in a structure called *nucleus basalis of Meynert* The reduction of the number of cholinergic cells causes interference in several aspects of behavioral performance including arousal, attention, learning and emotion. It is also common knowledge that AD is an untreatable degenerative disease with very few temporary and palliative drug therapies. *Neural stem cell (NSC)* grafts present a potential and innovative strategy for the treatment of many disorders of the central nervous system including AD, with the possibility of providing a more permanent remedy than present drug treatments. After grafting, these cells have the capacity to migrate to lesioned regions of the brain and differentiate into the necessary type of cells that are lacking in the diseased brain, supplying it with the cell population needed to promote recovery. [3]

Multiple Sclerosis

Malignant multiple sclerosis (MS) is a rare but clinically important subtype of MS characterized by the rapid development of significant disability in the early stages of the disease process. These patients are refractory to conventional immunomodulatory agents and the mainstay of their treatment is plasmapheresis or immunosuppression with mitoxantrone, cyclophosphamide, cladribine or, lately, bone marrow transplantation. A report on the case of a 17-year old patient with malignant MS who was treated with high-dose chemotherapy plus anti-thymocyte globulin followed by autologous stem cell transplantation. This intervention resulted in an impressive and long-lasting clinical and radiological response [4].

In other experiment treatment of 24 patients (14 women, 10 men) with relapsing-remitting Multiple Sclerosis, in the course of 2-8 years was done For treatment, used were *embryonic stem cell suspensions (ESCS)* containing stem cells of mesenchymal and ectodermal origin obtained from active growth zones of 4-8 weeks old embryonic cadavers' organs. Suspensions were administered in the amount of 1-3 ml, cell count being 0,1-100x10^5/ml. In the course of treatment, applied were 2-4 different suspensions, mode of administration being intracavitary, intravenous, and subcutaneous. After treatment, syndrome of early post-transplant improvement was observed in 70% of patients, its main manifestations being decreased weakness, improved appetite and mood, decreased depression. In the course of first post-treatment months, positive dynamics was observed in the following aspects: Nystagmus, convergence disturbances, spasticity, and coordination. In such symptoms as dysarthria, dysphagia, and ataxia, positive changes occurred at much slower rate. In general, the treatment resulted in improved range and quality of motions in the extremities, normalized muscle tone, decreased fatigue and general weakness, and improved quality of life. Forth, 87% of patients reported no exacerbations, no aggravation of neurological symptoms, and no further progression of disability. MRI performed in 1-2 years after the initial treatment, showed considerable subsidence of focal lesions, mean by 31%, subsidence of gadolinium enhanced lesions by 48%; T2-weighted images showed marked decrease of the foci's relative density.

Parkinson's Disease

Doctors firstly isolated adult stem cells from the patient's brain, they were then cultured in vitro and encouraged to turn into dopamine-producing neurons. As soon as tests showed that the cells were producing dopamine they were then re-injected into the man's brain. After the transplant, the man's condition was seen to improve and he experienced a reduction in the trembling and muscle rigidity associated with the disease. Brain scans taken 3-months after the transplant revealed that dopamine production had increased by 58%, however it later dropped but the Parkinson's symptoms did not return. The study is the first human study to show that stem cell transplants can help to treat Parkinson's.

The use of fetal-derived neural stem cells has shown significant promise in rodent models of Parkinson's disease, and the potential for tumorigenicity appears to be minimal. The authors report that undifferentiated human neural stem cells (hNSCs) transplanted into severely Parkinsonian 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates could survive, migrate, and induce behavioral recovery of Parkinsonian symptoms, which were directly related to reduced dopamine levels in the nigrostriatal

system[5] . Working with these cells, the researchers created dopamine neurons deficient in DJ-1, a gene mutated in an inherited form of Parkinson's. They report that DJ-1-deficient cells -- and especially DJ-1-deficient dopamine neurons -- display heightened sensitivity to oxidative stress, caused by products of oxygen metabolism that react with and damage cellular components like proteins and DNA. In a second paper, they link DJ-1 dysfunction to the aggregation of alpha-synuclein, a hallmark of Parkinson's neuropathology. [6,7]

In summary most of studies using aborted human embryonic tissue indicate that:

Clinical benefit does occur; however, the benefit is not marked and there is a delay of many months before the clinical change.

Postmortem examinations show that tissue grafts do survive and innervate the striatum.

PET scans show that there is an increase in dopamine uptake after transplantation.

Followup studies show that long term benefit does occur with transplantation. [8]

Stroke

During and after a stroke, certain cellular events take place that lead to the death of brain cells. Compounds that inhibit a group of enzymes called histone deacetylases can modulate gene expression, and in some cases produce cellular proteins that are actually neuroprotective -- they are able to block cell death. Great deal of research has gone into developing histone deacetylase inhibitors as novel therapeutics [9]

"One Mesenchymal stem cell (MSC) transplantation improves recovery from ischemic stroke in animals. The Researchers examined the feasibility, efficacy, and safety of cell therapy using culture-expanded autologous MSCs in patients with ischemic stroke. They prospectively and randomly allocated 30 patients with cerebral infarcts within the middle cerebral arterial territory Serial evaluations showed no adverse cell-related, serological, or imaging-defined effects. In patients with severe cerebral infarcts, the intravenous infusion of autologous MSCs appears to be a feasible and safe therapy that may improve functional recovery. [10]

Early intravenous stem cell injection displayed anti-inflammatory functionality that promoted neuroprotection, mainly by interrupting splenic inflammatory responses after intra cranial Haemorrage.

In summary, early intravenous NSC injection displayed anti-inflammatory functionality that neural stem cell (NSC) transplantation has been investigated as a means to reconstitute the damaged brain after stroke. In this study, however, was investigated the effect on acute cerebral and peripheral inflammation after intracerebral haemorrhage (ICH). STEM CELLS from fetal human brain were injected intravenously (NSCs-iv, 5 million cells) or intracerebrally (NSCs-ic, 1 million cells) at 2 or 24 h after collagenase-induced ICH in a rat model. Only NSCs-iv-2 h resulted in fewer initial neurologic deteriorations and reduced brain edema formation, inflammatory infiltrations and apoptosis. [11]

Vision restoration: Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina. The relatively easy access of the cornea, the homogeneity of the cells forming the different layers of the corneal epithelium and the improvement of cell culture protocols are leading to considerable success in corneal epithelium restoration. Rebuilding the entire cornea is however still far from reality. The restoration of the retina has recently been achieved in different animal models of retinal degeneration using immature photoreceptors [12]

Bone marrow contains stem cells, which have the extraordinary abilities to home in on injuries and possibly regenerate other cell types in the body. In this case, the cells were transplanted to confirm that bone marrow does regenerate the injured RPE. Damage to RPE is present in many diseases of the retina, including age-related macular degeneration, which affects more than 1.75 million people in the United States. [13]

Spinal cord injury: Neural stem cells (NSCs) offer the potential to replace lost tissue after nervous system injury. Thus, stem cells can promote host neural repair in part by secreting growth factors, and their regeneration-promoting activities can be modified by gene delivery.

Attempted repair of human spinal cord injury by transplantation of stem cells depends on complex biological interactions between the host and graft

Extrapolating results from experimental therapy in animals to humans with spinal cord injury requires great caution.

There is great pressure on surgeons to transplant stem cells into humans with spinal cord injury. However, as the efficacy of and exact indications for this therapy are still uncertain, and morbidity (such as rejection or late tumour development) may result, only carefully designed studies based on sound experimental work which attempts to eliminate placebo effects should proceed.

Premature application of stem cell transplantation in humans with spinal cord injury should be discouraged. [14, 15, 16]

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Vertebral repair: Mesenchymal stem cells have also been identified and are currently being developed for bone, cartilage, muscle, tendon, and ligament repair and regeneration. These MSCs are typically harvested, isolated, and expanded from bone marrow or adipose tissue, and they have been isolated from rodents, dogs, and humans .Interestingly, these cells can undergo extensive sub cultivation in vitro without differentiation, magnifying their potential clinical use.[17] Human MSCs can be directed toward osteoblastic differentiation by adding dexamethasone, ascorbic acid, and β-glycerophosphate to the tissue culture media. This osteoblastic commitment and differentiation can be clearly documented by analyzing alkaline phosphatase activity, the expression of bone matrix proteins, and the mineralization of the extracellular matrix.[18]

Batten's Disease: Children with Batten's disease suffer seizures, motor control disturbances, blindness and communication problems. As many as 600 children in the US are currently diagnosed with the condition.[19]

Death can occur in children as young as 8 years old. The children lack an enzyme for breaking down complex fat and protein compounds in the brain, explains Robert Steiner, vice chair of paediatric research at the hospital. The material accumulates and interferes with tissue function, ultimately causing brain cells to die. Tests on animals demonstrated that stem cells injected into the brain secreted the missing enzyme. And the stem cells were found to survive well in the rodent brain. Once injected, the purified neural cells may develop into neurons or other nervous system tissue, including oligodendrocytes, or glial cells, which support the neurons[20] .

Amyotrophic lateral sclerosis: In a study that demonstrates the promise of cell-based therapies for diseases that have proved intractable to modern medicine, a team of scientists from the University of Wisconsin-Madison has shown it is *possible to rescue the dying neurons characteristic of amyotrophic lateral sclerosis (ALS), a fatal neuromuscular disorder also known as Lou Gehrig's disease*. Previously there was no effective treatments for ALS, which afflicts roughly 40,000 people in the United States and which is almost always fatal within three to five years of diagnosis. Patients gradually experience progressive muscle weakness and paralysis as the motor neurons that control muscles are destroyed by the disease

In the new Wisconsin study, nascent brain cells known *as neural progenitor cells* derived from human fetal tissue were engineered to secrete a chemical known as glial cell line *derived neurotrophic factor (GDNF),* an agent that has been shown to protect neurons but that is very difficult to deliver to specific regions of the brain. The engineered cells were then implanted in the spinal cords of rats afflicted with a form of ALS. The implanted cells, in fact,

demonstrated an affinity for the areas of the spinal cord where motor neurons were dying. The cells after being injected to the area of damage where they "just sit and release GDNF." At the early stages of disease, almost 100 percent protection of motor neurons was seen. (21)

In other study MSCs were isolated from bone marrow of 9 patients with definite ALS. Growth kinetics, immunophenotype, telomere length and karyotype were evaluated during in vitro expansion. No significant differences between donors or patients were observed. The patients received intraspinal injections of autologous MSCs at the thoracic level and monitored for 4 years. No significant acute or late side effects were evidenced. No modification of the spinal cord volume or other signs of abnormal cell proliferation were observed. The results seem to demonstrate that MSCs represent a good chance for stem cell cell-based therapy in ALS and that intraspinal injection of MSCs is safe also in the long term. A new phase 1 study is carried out to verify these data in a larger number of patients. (22)

Conclusion

Stem-cell-based technology offers amazing possibilities for the future. These include the ability to reproduce human tissues and potentially repair damaged organs (such as the brain, spinal cord, vertebral column the eye), where, at present, we mainly provide supportive care to prevent the situation from becoming worse. This potential almost silences the sternest critics of such technology, but the fact remains that the ethical challenges are daunting. It is encouraging that, in tackling these challenges, we stand to reflect a great deal about the ethics of our profession and our relationships with patients, industry, and each other. The experimental basis of stem-cell or OEC transplantation should be sound before these techniques are applied to humans with neurological disorders.

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