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Review Article

Are Stem Cells the Magical Medical Therapy of the Future?

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Abstract

Stem cells are characterized based on two basic characteristics—a capability for self-renewal and a capability to develop into specialized cells. The type of specialization often depends on the cell's function and location, such as those of acid and protein secreting cells in the stomach or insulin secreting cells in the pancreas. On the other hand, the capability for self-renewal and specialization enables a nerve stem cell, for example, to grow into a mature nerve cell and another self-renewing cell that perpetuates the next cycle of self replication and specialization. Stem cells can also be categorized into embryonic stem cells and adult stem cells. Pluripotent embryonic stem cells are derived from the inner cell mass of the blastocyst and adult stem cells are undifferentiated cells found in post-embryonic tissues or organs. The primary roles of adult stem cells are to maintain and repair the tissues or organs in which they reside. The pluripotency of embryonic stem cells, which give rise to various cell types, and the ability of adult stem cells to repair tissue damage are the "magic fix" that regeneration medicine is suggesting. Whether the function of stem cells is hematopoietic or non-hematopoietic, researchers all over the world are striving hard to harness the use of stem cells for medicine. As the progress of stem cell research moves steadily forward, let us pause for a minute and pose a question. Are stem cells really going to be the magical medical therapeutic component of the future? (*Tzu Chi Med J* 2009;21(1):12–17)

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1. Introduction

A recent report in *Science* describing a breakthrough in the conversion of human somatic cells into pluripotent embryonic stem cell lines by the introduction of four genes (1) has stirred up a new wave of inspiration and enthusiasm in stem cell technology and stem cell therapy. Concomitantly, a similar report appearing in the journal *Cell* made similar observations on the generation of induced pluripotent stem cells by the transduction of four defined transcription factors (2). But what are stem cells? Why are they getting so much attention from the general public and professionals alike, and what is so special about them?

According to a report prepared by the United States National Institutes of Health (3), stem cells are special

cells that possess the unique capacity to renew indefinitely. They can give rise to specialized cell types, such as heart cells, nerve cells, muscle cells and skin cells, that make up the organism. In addition, stem cells are uncommitted progenitors that remain uncommitted until they receive signals to develop into specialized cells to perform their committed biological functions [3].

Three types of stem cells have now been identified—embryonic stem cells, embryonic germ cells, and adult stem cells. Embryonic stem cells are obtained from a group of cells called the inner cell mass, which is part of the early stage of the embryo termed the blastocyst (a blastocyst is developed from a fertilized egg). Embryonic germ cells are derived from the primordial germ cells of the gonadal ridge of a 5–10-week-old fetus. Adult stem cells are undifferentiated cells in a postembryonic differentiated tissue or organ and are capable of renewing themselves and producing specialized cell types of the tissue or organ from which they originate [3]. Adult stem cells derive from a wide range of tissues and may exist in every major tissue type. For example, umbilical cord blood (UCB) and the umbilical cord (UC) [4–8], placenta [9,10], mammary gland [11], olfactory bulb [12], adipose tissue [13,14], heart [15], central nervous system [16], epidermis [17,18], hair follicle [18], eye [19,20], bone marrow [4,21,22], and teeth [23,24] have all been reported to contain adult stem cells. A well recognized adult stem cell is the bone marrow supportive element called the mesenchymal stem cell (MSC). MSCs display enormous expansion ability and, under appropriate circumstances, can differentiate into neuronal, muscle, adipose, cardiac and cartilage cells [3]. These are the types of cells that cell-based therapy intends to exploit for therapeutic applications [4,21,22]. Other applications for MSCs have focused on immune regulation. *Ex vivo*-expanded MSCs isolated from humans have been demonstrated to suppress the activity of immune cells including T cells, B cells, antigen presenting cells and natural killer cells [3,25]. This potential function of MSCs is of value in the taming of graft rejection and graft versus host disease, which inevitably occur in bone marrow transplantation [3].

Functionally speaking, stem cells may be totipotent or pluripotent. The totipotent cells of the very early embryo have the capacity to differentiate into all postembryonic tissues and organs while pluripotent stem cells have the capacity to give rise to cells of all three germ layers of the embryo—the ectoderm, endoderm and mesoderm. Generally speaking, embryonic stem cells at days 4–5 are considered to be totipotent, whereas inner cell mass embryonic stem cells, embryonic germ cells and adult stem cells are regarded as pluripotent [3]. Therefore, it is the capacity and the plasticity of the stem cells that has received attention in recent years and the term stem cell was considered unequivocally equal to regenerative medicine or, to use a lay term, a "magic wonder".

What evidence do we have, however that embryonic stem cells and adult stem cells hold promise for cellular therapy? The following few reports are noteworthy.

2. Myocardial infarction

Today, despite improvements in pharmacologic and invasive treatment, myocardial infarction and ischemic heart failure are still leading causes of morbidity and mortality worldwide. An article published in *Cytotherapy* demonstrated that transplantation of embryonic stem cell-derived cardiomyocytes improves cardiac function in infarcted rat hearts [26]. Another report found that injection of bone marrow cells in the peri-infarcted left ventricle of mice resulted in myocardial regeneration [27]. Additionally, recent studies by Henning et al [28] and Hirata et al [29] described the application of human UCB in treating acute myocardial infarction in rats. Both groups of researchers injected UCB mononuclear cells immediately after coronary artery occlusion in rats. Compared with the controls, the animals treated with UCB cells had reduced infarct size, and improved myocardial contractility and ejection fractions [28,29]. After reviewing an array of studies in humans, the author of an editorial in the *New England Journal of Medicine* noted that, although the ability of infused bone marrow cells to generate cardiomyocytes may be questioned and only a remnant amount of the transplanted cells remained in the heart, cytokines or growth factors through paracrine secretion could indirectly promote mobilization of endogenous progenitors to the vicinity of the lesion area to repair damage and initiate angiogenesis. However, a failure of cell therapies to achieve a therapeutic effect on cardiac injury was also observed. The author rationalized that the heterogeneity of bone marrow cell populations applied for treatment were to be considered for various outcomes in cell therapy. This helps explain why similar treatment protocols can yield different results [30]. It appears, therefore, that transplantation using embryonic stem cells, bone marrow cells and UCB cells could offer alternative cell therapies for the repair of necrotic myocardium. All these studies suggest that embryonic and adult stem cells may be potentially valuable for the regeneration of an infarcted heart.

3. Cerebral stroke

Cerebral stroke is a medical emergency and can cause permanent neurological damage and death if not promptly diagnosed and treated. It is a leading cause of death and adult disability in many countries.

To combat this devastating traumatic brain injury, attention has turned to stem cell therapy. Vendrame et al [31] reported on the infusion of human UCB cells in a rat model of stroke. The treatment dose-dependently reduced behavioral deficits and the infarct volume. Similarly, in a severe combined immune deficient mouse model, $CD34^+$-selected cord blood cells were injected into middle cerebral artery occlusion-inflicted rats 48 hours after stroke. Neovascularization at the border of the ischemic zone was observed, followed by endogenous neurogenesis [32]. Further animal studies and clinical trials in humans are necessary to consolidate the efficacy and safety of stem cell therapy for stroke patients. Nevertheless, at this time, one may be cautiously optimistic about the future promise of stem cell therapy for cerebral stroke.

4. Spinal cord injury

The prevalence of spinal cord injury (SCI) is increasing as a result of motor vehicle accidents, violence, falls and diving accidents. Spinal cord injury causes damage to white matter or myelinated fibers that carry sensation and motor signals to and from the brain. It also causes damage to gray matter in the central region of the spine causing segmental losses of interneurons and motoneurons. In addition to the loss of motor function and sensation below the point of injury, individuals with SCI often experience other complications. Undoubtedly, any medical treatment that can alleviate SCI and help patients with SCI regain mobility will be welcome. In an animal study that used rhesus monkeys, implantation of bone marrow MSCs generated *de novo* neurogenesis and the SCI inflicted animals achieved functional recovery [33]. In humans, Kang et al [34] described a patient with SCI who was transplanted with multipotent stem cells from human UC blood. The patient showed improved sensory perception and mobility both functionally and morphologically 19 years and 6 months after the spinal cord injury [34]. Although there have been few successful outcomes with MSC and cord blood transplantations in SCI, the results definitely inspire high hopes for a curative medical treatment for this condition.

5. Duchenne muscular dystrophy

The muscular dystrophies are a group of genetic and hereditary muscle diseases characterized by defects in muscle proteins, progressive skeletal muscle weakness and death of muscle cells and tissues resulting from mutations of genes responsible for the dystrophin protein. In some forms of muscular dystrophy, smooth muscle and cardiac muscle are affected. One of the major types of muscular dystrophy is called Duchenne muscular dystrophy (DMD), which is a fatal X chromosome-linked muscle dystrophy that affects juvenile males. The most frequent symptoms are skeletal and muscle deformities and frequent falls, walking problems and eyelid drooping due to muscle weakness [35,36]. To date, no known drug can stop muscle dystrophy, but cell-based therapies may offer a potential treatment. As in human DMD, the *mdx* mouse (C57BL/10ScSn) lacks dystrophin in its skeletal muscle fibers, which makes it a useful animal model for DMD research [35,36]. In animal studies [35,36], bone marrow stem cells were injected into the tail veins of irradiated experimental *mdx* mice to determine the effects of the transplanted cells. Expression of dystrophin and MyoD (a master regulatory gene for skeletal myogenesis) was detected at different time points by immunofluorescence staining, Western blotting and reverse transcription-polymerase chain reaction [35]. The investigation found that bone marrow cells were recruited to the muscles of the experimental mice and the injected cells proceeded to muscle differentiation, recapitulating embryonic myogenesis, which partially restored the specific pathophysiologic features of dystrophic muscle in aged *mdx* mice [35]. Although it is too early to consider stem cells as a promising treatment for DMD, this report did suggest that bone marrow stem cell transplantation may be potentially useful as an alternative therapeutic approach for this condition.

6. Type 1 diabetes

The potential application of allogeneic bone marrow stem cell transplantation to alter the course of the type 1 diabetes mellitus (DM) disease process was first proposed in animal studies in the 1980s [37] and there were calls for bone marrow transplantation (BMT) to be tested in treating this disorder in the early part of the present decade. Autologous human stem cell transplantation for type 1 DM proposed by Voltarelli et al [38] involved stem cell mobilization of peripheral blood $CD34^+$ cells, immune ablation in the recipient to eliminate self-reactive lymphocytes within the body, and reinfusion and cryopreservation of autologous stem cells harvested in the beginning. The study demonstrated significant improvements in beta cell function, as measured by C-peptide levels. There were several limitations, however, which included uncertainty over whether the putative beneficial effects of the autologous stem cell transplant were due to immune reconstitution or otherwise altering the immune-mediated beta cell destruction that eventuates in the type 1 DM disease process, or were due to regeneration of beta cells [38]. Other approaches under consideration include the use of umbilical cord cells [39], embryonic or adult stem cells [40] and allogeneic BMT [41,42]. For bone marrow transplantation in rats with diabetes, it was further

suggested that successful treatment with bone marrow and mesenchymal stem cells occurred because both types of cells induced regeneration of recipient-derived pancreatic insulin-secreting cells and because mesenchymal stem cells were able to inhibit the T cell-mediated immune response against beta cells [42]. Research in this area is likely to increase in the near future and curative therapy for type 1 DM may soon become possible.

7. Parkinson's disease

Parkinson's disease is one of the most common neurodegenerative diseases, and it is characterized by the progressive loss of dopamine neurons in the substantia nigra of the midbrain. One of the therapeutic successes in the treatment of this disease has been the use of L-dopa. However, dopamine replacement fails to slow the rate of loss of neurons, and the beneficial effects wear off with time. Surgical treatment is not a better option because the unstable efficiency and shortage of donated embryonic mesencephalic tissue limit the application of embryonic tissue transplantation as a therapeutic option. Therefore, recent advances in stem cell research have inspired high hopes for cell based therapy as the answer to this disease [43,44]. Three types of stem cells (neural stem cells, mesenchymal stem cells and embryonic stem cells) are currently being tested in stem cell therapy for Parkinson's disease. Parish et al [45] found that, using *in vitro* differentiation of Cripto(–/–), embryonic stem cells resulted in an increase in dopaminergic differentiation and, upon transplantation into 6-OHDA lesioned Parkinson's rats, facilitated behavioral and anatomical recovery in the animals tested. Using tyrosine hydroxylase and GTP cyclohydrolase 1 transduced human neuronal stem cells in brain transplantation of Parkinsonian rats, Kim et al [46] reported functional improvement in animal models of Parkinson's disease. Similarly, mesenchymal stem cells derived from bone marrow and umbilical cord were reported to be capable of producing functional benefits in animals with Parkinson's disease [43]. Will stem cell therapy for Parkinson's disease in humans be as successful? We hope that regulated clinical trials can answer this critical question.

8. Stem cell engineering

Stem cells in tissue engineering are aimed at producing "spare parts" for the body to replace damaged or destroyed tissues and organs. Despite questions about the actual clinical feasibility of the "engineered parts", the potential for tissue engineering to produce blood vessels, skin, nasal cartilage, urinary bladders, and cardiac valves is increasing [47]. In addition, efforts to generate neuronal cells to produce dopamine for patients with Parkinson's disease and to cultivate cells of oligodendrocyte lineages for patients with multiple sclerosis may one day materialize and prove successful in cellular therapy [48]. Other applications in tissue engineering of stem cells include the generation of skin for skin grafting, formation of bones for bone reconstruction, identification and isolation of stem cells from various tissues to provide appropriate targets for prospective gene therapies [47], and restoration of damaged corneas using stem cells derived from autologous or allogeneic limbal epithelial cells [49,50]. Stem cell engineering offers an avenue of therapeutic options, which depend on the collaborative efforts of devoted scientists and medical personnel.

9. Discussion

Today, it does seem that stem cell therapy has potential clinical relevance in tissue regeneration. Organ repair is not a matter of a quick fix for various diseases and we are not even near the stage when the efficacy and safety of cell-based therapies are a matter of reality. In fact, there are questions about the coming of age of stem cell therapy [51–53]. However, there have been successful outcomes in bone marrow, peripheral blood stem cells (PBSC) and UCB hematopoietic stem cell transplantations, which were performed to treat severe anemia, metabolic disorders, immune deficiency and blood cancers. Since its successful debut 40 years ago, bone marrow transplantation has been used to treat patients diagnosed with aplastic anemia, leukemia, immune deficiency disorders, lymphomas and some forms of solid tumor [3]. With the advent of advanced technologies for PBSC and cryopreservation of UCB, hematopoietic stem cell transplantation offers a life-saving cellular therapy for those facing life-threatening diseases. Less than 1 month after the report by Yu et al [1] on the success of the generation of human embryonic pluripotent stem cell lines from somatic cells, Hanna et al [54] reported the generation of induced pluripotent stem cells from autologous skin to treat sickle cell anemia in a mouse model. This immediate progress signifies a great leap in overcoming the obstacles of histocompatibility and allogenicity, which are frequently encountered in the arena of allogeneic transplantation. On the other hand, using embryonic stem cells [55] and pluripotent stem cells [56] for treatment may result in the formation of teratoma or other forms of tumorigenicity. This must be carefully evaluated prior to actual practice [55,56]. In addition, regulations on related issues, such as safety, cell storage and transportation, outcome analysis, equipment supplies, maintenance and monitoring, and auditing, must also be in place before the clinical introduction of stem cell therapy. Vogel [55] stated that it is far from clear when

the day of stem cell therapy might arrive. Nevertheless, looking back at the history of hematopoietic stem cell transplantation of BM, PBSC, and CB provides us with optimism about the development of cellular therapy.

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