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The benefits and risks of stem cell technology

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Abstract

The potential impact of stem cell technology on medical and dental practice is vast. Stem cell research will not only provide the foundation for future therapies, but also reveal unique insights into basic disease mechanisms. Therefore, an understanding of stem cell technology will be necessary for clinicians in the future. Herein, we give a basic overview of stem cell biology and therapeutics for the practicing clinician.

Keywords

medicine; stem cell; induced pluripotent stem cell; embryonic stem cell; regenerative therapy

Introduction

Stem cell technology will transform medical practice. While stem cell research has already elucidated many basic disease mechanisms, the promise of stem cell–based therapies remains largely unrealized. In this review, we begin with an overview of different stem cell types. Next, we review the progress in using stem cells for regenerative therapy. Last, we discuss the risks associated with stem cell–based therapies.

Stem cell types

There are three major types of stem cells as follows: adult stem cells (also called tissue-specific stem cells), embryonic stem (ES) cells, and induced pluripotent stem (iPS) cells.

Adult stem cells—A majority of adult stem cells are lineage-restricted cells that often reside within ‘niches’ of their tissue of origin. Adult stem cells are characterized by their capacity for self-renewal and differentiation into tissue-specific cell types. Many adult tissues contain stem cells including skin, muscle, intestine, and bone marrow (Gan *et al*, 1997; Artlett *et al*, 1998; Matsuoka *et al*, 2001; Coulombel, 2004; Humphries *et al*, 2011). However, it remains unclear whether all adult organs contain stem cells. Adult stem cells are quiescent but can be induced to replicate and differentiate after tissue injury to replace cells that have died. The process by which this occurs is poorly understood. Importantly, adult stem cells are exquisitely tissue-specific in that they can only differentiate into the mature cell type of the organ within which they reside (Rinkevich *et al*, 2011).

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Thus far, there are few accepted adult stem cell–based therapies. Hematopoietic stem cells (HSCs) can be used after myeloablation to repopulate the bone marrow in patients with hematologic disorders, potentially curing the underlying disorder (Meletis and Terpos, 2009; Terwey *et al*, 2009; Casper *et al*, 2010; Hill and Copelan, 2010; Hoff and Bruch-Gerharz, 2010; de Witte *et al*, 2010). HSCs are found most abundantly in the bone marrow, but can also be harvested at birth from umbilical cord blood (Broxmeyer *et al*, 1989). Similar to the HSCs harvested from bone marrow, cord blood stem cells are tissue-specific and can only be used to reconstitute the hematopoietic system (Forraz *et al*, 2002; McGuckin *et al*, 2003; McGuckin and Forraz, 2008). In addition to HSCs, limbal stem cells have been used for corneal replacement (Rama *et al*, 2010).

Mesenchymal stem cells (MSCs) are a subset of adult stem cells that may be particularly useful for stem cell–based therapies for three reasons. First, MSCs have been isolated from a variety of mesenchymal tissues, including bone marrow, muscle, circulating blood, blood vessels, and fat, thus making them abundant and readily available (Deans and Moseley, 2000; Zhang *et al*, 2009; Lue *et al*, 2010; Portmann-Lanz *et al*, 2010). Second, MSCs can differentiate into a wide array of cell types, including osteoblasts, chondrocytes, and adipocytes (Pittenger *et al*, 1999). This suggests that MSCs may have broader therapeutic applications compared to other adult stem cells. Third, MSCs exert potent paracrine effects enhancing the ability of injured tissue to repair itself. In fact, animal studies suggest that this may be the predominant mechanism by which MSCs promote tissue repair. The paracrine effects of MSC-based therapy have been shown to aid in angiogenic, antiapoptotic, and immunomodulatory processes. For instance, MSCs in culture secrete hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) (Nagaya *et al*, 2005). In a rat model of myocardial ischemia, injection of human bone marrow-derived stem cells upregulated cardiac expression of VEGF, HGF, bFGF, angiopoietin-1 and angiopoietin-2, and PDGF (Yoon *et al*, 2005). In swine, injection of bone marrow-derived mononuclear cells into ischemic myocardium was shown to increase the expression of VEGF, enhance angiogenesis, and improve cardiac performance (Tse *et al*, 2007). Bone marrow-derived stem cells have also been used in a number of small clinical trials with conflicting results. In the largest of these trials (REPAIR-AMI), 204 patients with acute myocardial infarction were randomized to receive bone marrow-derived progenitor cells vs placebo 3–7 days after reperfusion. After 4 months, the patients that were infused with stem cells showed improvement in left ventricular function compared to control patients. At 1 year, the combined endpoint of recurrent ischemia, revascularization, or death was decreased in the group treated with stem cells (Schachinger *et al*, 2006).

ES cells—Embryonic stem cells are derived from the inner cell mass of the developing embryo during the blastocyst stage (Thomson *et al*, 1998). In contrast to adult stem cells, ES cells are pluripotent and can theoretically give rise to any cell type if exposed to the proper stimuli. Thus, ES cells possess a greater therapeutic potential than adult stem cells. However, four major obstacles exist to implementing ES cells therapeutically. First, directing ES cells to differentiate into a particular cell type has proven to be challenging. Second, ES cells can potentially transform into cancerous tissue. Third, after transplantation, immunological mismatch can occur resulting in host rejection. Fourth, harvesting cells from a potentially viable embryo raises ethical concerns. At the time of this publication, there are only two ongoing clinical trials utilizing human ES-derived cells. One trial is a safety study for the use of human ES-derived oligodendrocyte precursors in patients with paraplegia (Genron based in Menlo Park, California). The other is using human ES-derived retinal pigmented epithelial cells to treat blindness resulting from macular degeneration (Advanced Cell Technology, Santa Monica, CA, USA).

iPS cells—In stem cell research, the most exciting recent advancement has been the development of iPS cell technology. In 2006, the laboratory of Shinya Yamanaka at the Gladstone Institute was the first to reprogram adult mouse fibroblasts into an embryonic-like cell, or iPS cell, by overexpression of four transcription factors, Oct3/4, Sox2, c-Myc, and Klf4 under ES cell culture conditions (Takahashi and Yamanaka, 2006). Yamanaka's pioneering work in cellular reprogramming using adult mouse cells set the foundation for the successful creation of iPS cells from adult human cells by both his team (Takahashi *et al*, 2007) and a group led by James Thomson at the University of Wisconsin (Yu *et al*, 2007). These initial proof of concept studies were expanded upon by leading scientists such as George Daley, who created the first library of disease-specific iPS cell lines (Park *et al*, 2008). These seminal discoveries in the cellular reprogramming of adult cells invigorated the stem cell field and created a niche for a new avenue of stem cell research based on iPS cells and their derivatives. Since the first publication on cellular reprogramming in 2006, there has been an exponential growth in the number of publications on iPS cells.

Similar to ES cells, iPS cells are pluripotent and, thus, have tremendous therapeutic potential. As of yet, there are no clinical trials using iPS cells. However, iPS cells are already powerful tools for modeling disease processes. Prior to iPS cell technology, *in vitro* cell culture disease models were limited to those cell types that could be harvested from the patient without harm – usually dermal fibroblasts from skin biopsies. However, mature dermal fibroblasts alone cannot recapitulate complicated disease processes involving multiple cell types. Using iPS technology, dermal fibroblasts can be de-differentiated into iPS cells. Subsequently, the iPS cells can be directed to differentiate into the cell type most beneficial for modeling a particular disease process. Advances in the production of iPS cells have found that the earliest pluripotent stage of the derivation process can be eliminated under certain circumstances. For instance, dermal fibroblasts have been directly differentiated into dopaminergic neurons by viral co-transduction of forebrain transcriptional regulators (Brn2, Myt1l, Zic1, Olig2, and Ascl1) in the presence of media containing neuronal survival factors [brain-derived neurotrophic factor, neurotrophin-3 (NT3), and glial-conditioned media] (Qiang *et al*, 2011). Additionally, dermal fibroblasts have been directly differentiated into cardiomyocyte-like cells using the transcription factors Gata4, Mef2c, and Tbx5 (Ieda *et al*, 2010). Regardless of the derivation process, once the cell type of interest is generated, the phenotype central to the disease process can be readily studied. In addition, compounds can be screened for therapeutic benefit and environmental toxins can be screened as potential contributors to the disease. Thus far, iPS cells have generated valuable *in vitro* models for many neurodegenerative (including Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis), hematologic (including Fanconi's anemia and dyskeratosis congenital), and cardiac disorders (most notably the long QT syndrome) (Park *et al*, 2008). iPS cells from patients with the long QT syndrome are particularly interesting as they may provide an excellent platform for rapidly screening drugs for a common, lethal side effect (Zwi *et al*, 2009; Malan *et al*, 2011; Tiscornia *et al*, 2011). The development of patient-specific iPS cells for *in vitro* disease modeling will determine the potential for these cells to differentiate into desired cell lineages, serve as models for investigating the mechanisms underlying disease pathophysiology, and serve as tools for future preclinical drug screening and toxicology studies.

Regenerative therapy

Cardiovascular—Despite substantial improvements in therapy, cardiovascular disease remains the leading cause of death in the industrialized world. Therefore, there is a particular interest in cardiovascular regenerative therapies. The potential of diverse progenitor cells to repair damaged heart tissue includes replacement (tissue transplant), restoration (activation of resident cardiac progenitor cells, paracrine effects), and

regeneration (stem cell engraftment forming new myocytes) (Codina *et al*, 2010). It is unclear whether the heart contains resident stem cells. However, experiments show that bone marrow mononuclear cells (BMCs) can repair myocardial damage, reduce left ventricular remodeling, and improve heart function by myocardial regeneration (Hakuno *et al*, 2002; Amado *et al*, 2005; Dai *et al*, 2005; Schneider *et al*, 2008). The regenerative capacity of human heart tissue was further supported by the detection of the renewal of human cardiomyocytes (1% annually at the age of 25) by analysis of carbon-14 integration into human cardiomyocyte DNA (Bergmann *et al*, 2009). It is not clear whether cardiomyocyte renewal is derived from resident adult stem cells, cardiomyocyte duplication, or homing of non-myocardial progenitor cells. Bone marrow cells home to the injured myocardium as shown by Y chromosome-positive BMCs in female recipients (Deb *et al*, 2003). On the basis of these promising results, clinical trials in patients with ischemic heart disease have been initiated primarily using bone marrow-derived cells. However, these small trials have shown controversial results. This is likely due to a lack of standardization for cell harvesting and delivery procedures. This highlights the need for a better understanding of the basic mechanisms underlying stem cell isolation and homing prior to clinical implementation.

Neurologic—Although stem cells have the capacity to differentiate into neurons, oligodendrocytes, and astrocytes, novel clinical stem cell-based therapies for central and peripheral nervous system diseases have yet to be realized. It is widely hoped that transplantation of stem cells will provide effective therapy for Parkinson's disease, Alzheimer's disease, Huntington's Disease, amyloid lateral sclerosis, spinal cord injury, and stroke. Several encouraging animal studies have shown that stem cells can rescue some degree of neurological function after injury (Daniela *et al*, 2007; Hu *et al*, 2010; Shimada and Spees, 2011). Currently, a number of clinical trials have been performed and are ongoing.

Dental—Dental stem cells could potentially repair damaged tooth tissues such as dentin, periodontal ligament, and dental pulp (Gronthos *et al*, 2002; Ohazama *et al*, 2004; Jo *et al*, 2007; Ikeda *et al*, 2009; Balic *et al*, 2010; Volponi *et al*, 2010). Moreover, as the behavior of dental stem cells is similar to MSCs, dental stem cells could also be used to facilitate the repair of non-dental tissues such as bone and nerves (Huang *et al*, 2009; Takahashi *et al*, 2010). Several populations of cells with stem cell properties have been isolated from different parts of the tooth. These include cells from the pulp of both exfoliated (children's) and adult teeth, the periodontal ligament that links the tooth root with the bone, the tips of developing roots, and the tissue that surrounds the unerupted tooth (dental follicle) (Bluteau *et al*, 2008). These cells probably share a common lineage from neural crest cells, and all have generic mesenchymal stem cell-like properties, including expression of marker genes and differentiation into mesenchymal cells *in vitro* and *in vivo* (Bluteau *et al*, 2008). different cell populations do, however, differ in certain aspects of their growth rate in culture, marker gene expression, and cell differentiation. However, the extent to which these differences can be attributed to tissue of origin, function, or culture conditions remains unclear.

Risks

There are several issues determining the long-term outcome of stem cell-based therapies, including improvements in the survival, engraftment, proliferation, and regeneration of transplanted cells. The genomic and epigenetic integrity of cell lines that have been manipulated *in vitro* prior to transplantation play a pivotal role in the survival and clinical benefit of stem cell therapy. Although stem cells possess extensive replicative capacity, immune rejection of donor cells by the host immune system post-transplantation is a primary

concern (Negro *et al*, 2012). Recent studies have shown that the majority of donor cell death occurs in the first hours to days after transplantation, which limits the efficacy and therapeutic potential of stem cell-based therapies (Robey *et al*, 2008).

Although mouse and human ES cells have traditionally been classified as being immune privileged, a recent study used *in vivo*, whole-animal, live cell-tracing techniques to demonstrate that human ES cells are rapidly rejected following transplantation into immunocompetent mice (Swijnenburg *et al*, 2008). Treatment of ES cell-derived vascular progenitor cells with inter-feron γ (to upregulate major histocompatibility complex (MHC) class I expression) or *in vivo* ablation of natural killer (NK) cells led to enhanced progenitor cell survival after transplantation into a syngeneic murine ischemic hindlimb model. This suggests that MHC class I-dependent, NK cell-mediated elimination is a major determinant of graft survivability (Ma *et al*, 2010). Given the risk of rejection, it is likely that initial therapeutic attempts using either ES or iPS cells will require adjunctive immunosuppressive therapy. Immunosuppressive therapy, however, puts the patient at risk of infection as well as drug-specific adverse reactions. As such, determining the mechanisms regulating donor graft tolerance by the host will be crucial for advancing the clinical application of stem cell-based therapies.

An alternative strategy to avoid immune rejection could employ so-called 'gene editing'. Using this technique, the stem cell genome is manipulated *ex vivo* to correct the underlying genetic defect prior to transplantation. Additionally, stem cell immunologic markers could be manipulated to evade the host immune response. Two recent papers offer alternative methods for 'gene editing'. Soldner *et al* (2011) used zinc finger nuclease to correct the genetic defect in iPS cells from patients with Parkinson's disease because of a mutation in the α -Synuclein (α -SYN) gene. Liu *et al* (2011) used helper-dependent adenoviral vectors (HDAdV) to correct the mutation in the Lamin A (LMNA) gene in iPS cells derived from patients with Hutchinson–Gilford Progeria (HGP), a syndrome of premature aging. Cells from patients with HGP have dysmorphic nuclei and increased levels of progerin protein. The cellular phenotype is especially pronounced in mature, differentiated cells. Using highly efficient helper-dependent adenoviral vectors containing wild-type sequences, they were able to use homologous recombination to correct two different *Lamin A* mutations. After genetic correction, the diseased cellular phenotype was reversed even after differentiation into mature smooth muscle cells. In addition to the potential therapeutic benefit, 'gene editing' could generate appropriate controls for *in vitro* studies.

Finally, there are multiple safety and toxicity concerns regarding the transplantation, engraftment, and long-term survival of stem cells. Donor stem cells that manage to escape immune rejection may later become oncogenic because of their unlimited capacity to replicate (Amariglio *et al*, 2009). Thus, ES and iPS cells may need to be directed into a more mature cell type prior to transplantation to minimize this risk. Additionally, generation of ES and iPS cells harboring an inducible 'kill-switch' may prevent uncontrolled growth of these cells and/or their derivatives. In two ongoing human trials with ES cells, both companies have provided evidence from animal studies that these cells will not form teratomas. However, this issue has not been thoroughly examined, and enrolled patients will need to be monitored closely for this potentially lethal side effect.

In addition to the previously mentioned technical issues, the use of ES cells raises social and ethical concerns. In the past, these concerns have limited federal funding and thwarted the progress of this very important research. Because funding limitations may be reinstituted in the future, ES cell technology is being less aggressively pursued and young researchers are shying away from the field.

Conclusion

Stem cell technology is unique in that it possesses both diagnostic and therapeutic potential. iPS cells and their derivatives have provided excellent *in vitro* models of disease processes. Moreover, patient-specific iPS cell models will serve as an invaluable tool for drug discovery and toxicology studies. The therapeutic potential of these cells to regenerate functional tissue and replace damaged tissue has vast potential. Additionally, stem cell-based therapies may enhance the body's own ability to repair itself. As previously mentioned, MSCs exert potent paracrine effects that are thought to be beneficial. For these reasons, the potential of stem cells to cure disease is virtually limitless. Nonetheless, major obstacles to safely implement these therapies remain and must be systematically addressed. Most immediate among these is the identification of stem cell populations that can be maintained and expanded in culture to provide the large numbers needed to be therapeutically useful. Additionally, the potential for cancerous transformation and immunologic rejection is largely unexplored. These issues highlight the potential danger of implementing stem cell therapies before they have been adequately studied *in vitro* and *in vivo* in animal models. More intensive characterization is required to avoid the possible lethal complications of this type of therapy. Although the current therapeutic potential of stem cell technology is in its infancy, basic research discoveries in the standardization of stem cell derivation, culture, and differentiation techniques, together with improved transplantation, engraftment, and survival strategies, will aid in the development of safer and more effective stem cell-based therapies in the future.

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