Overview of stem cells

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INTRODUCTION

Stem cells are those cells that have the capability of self-renewal and differentiation. First identified in the hematopoietic system, they are likely to be present in many other tissues. Stem cells have altered the care of individuals with hematologic, oncologic, dermatologic, ophthalmologic, and orthopedic conditions. The range of possible applications of stem cells to medicine extends beyond the conception of stem cells as replacement parts (table 1).

The evolving role of stem cells in clinical medicine is developing along at least three lines:

- Stem cells as therapy (either to replace cell lines that have been lost or destroyed, or to modify the behavior of other cells)
- Stem cells as targets of drug therapy
- Stem cells to generate differentiated tissue for in vitro study of disease models for drug development

This topic will review the biology of stem cells and present an overview of their use in clinical and research settings, as well as ethical considerations that have generated much controversy.

Hematopoietic stem cells are discussed separately. (See "Overview of hematopoietic stem cells" and "Sources of hematopoietic stem cells".)

Hematopoietic stem cell transplantation for specific clinical conditions is discussed in multiple related topics.

DEGREES OF STEM CELL POTENCY

All stem cells share two cardinal features: they are capable of self-renewal and they can differentiate. Self-renewal is the ability of cells to proliferate without the loss of differentiation potential and without undergoing senescence (biologic aging). Self-renewal does not imply that each cell division results in two exact replicas of the stem cell; daughter cells may be either stem cells or more differentiated cells. Indeed, stem cells are hypothesized to be able to divide symmetrically (in which both daughter cells are either stem cells or differentiated cells) or asymmetrically (yielding one stem cell and one more differentiated cell) (figure 1) [1,2].

The potency of a stem cell is defined by the types of more differentiated cells that the stem cell can make (table 2). Stem cells can be either totipotent, pluripotent, multipotent, or unipotent.

- Totipotent cells have the capability to produce all cell types of the developing organism, including both embryonic and extraembryonic (eg, placenta) tissues.
- Pluripotent cells can only make cells of the embryo proper, but make all cells of the embryo including germ cells and cells from any of the germ layers. Therefore, they can make any cell of the body.
- Multipotent cells can only make cells within a given germ layer. For example, multipotent stem cells from a mesodermal tissue like the blood (ie, hematopoietic stem cells) can make all the cells of the blood, but cannot make cells of a different germ layer such as neural cells (ectoderm) or liver cells (endoderm).
- Unipotent cells make cells of a single cell type. An example is a germ cell stem cell that makes the cells that mature to become egg or sperm, but not other cell types.

Classically, the potency of cells has been thought to be tied to the time of embryonic development of the organism. That is, cells that arise from the first few cell divisions following fertilization of the egg are generally the only cells that have totipotency. Pluripotent cells were thought to be limited to cells derived from either the inner cell mass of the blastocyst (a pre-implantation stage of development occurring approximately 7 to 10 days after fertilization in the human) or nascent germ cells in the embryo. Cells cultured and cell lines established from these structures are called embryonic stem (ES) cells and embryonic germ cells respectively. It is now known that pluripotent cells can arise from other cells types as well. (See 'Induced pluripotent stem (iPS) cells' below.)

Once the primitive streak forms in embryonic development (day 10 to 14 post fertilization in the human), it is thought that most stem cells are restricted to be either multipotent or unipotent. These have often been called 'adult' stem cells. If they are derived from tissue other than the germ cells, they may be called 'somatic' stem cells. Such cells would include cells derived from the cord blood, sometimes mistakenly considered equivalent to ES cells in the popular press.

SOURCES OF STEM CELLS

Stem cells can be derived from human embryos or somatic tissues in the adult or they can be created by inducing greater potency in an already differentiated somatic cell.

Embryonic stem (ES) cells — Embryonic stem cells are typically derived from a preimplantation blastocyst (7 to 10 days post fertilization). The most frequent techniques used to derive ES cells disrupt the blastocyst from which the cells are derived. Ethical considerations have prompted research into other stem cell sources. (See 'Ethical considerations' below.)

Adult stem cells — Adult stem cells are thought to be present in most, but not all, tissues and to persist throughout life (figure 2). They are thought to provide the basis for tissue maintenance and response to injury. This is particularly true for tissues where there is high cell turnover, such as the blood, skin, and intestine, where stem cells have been clearly defined experimentally [3-5].

There is also evidence for a possible stem cell population for some tissues where the rate of cell turnover is lower (such as muscle, brain, and kidney) [6,7]. A report suggesting the possibility of lung stem cells was retracted [8,9].

For some tissues, including the islet cells of the pancreas, it is not clear whether adult stem cells exist; it is possible that stem cells are a durable source of replacement cells in some tissues but not in others. Division of mature cells may be the basis for replacement after loss of some cells in other tissues. The implications of this are that mature cells are thought to only have a limited number of cell divisions, as opposed to stem cells. Therefore in settings of extensive injury, a tissue that depends upon residual mature cells to replace the injured cells may be more limited in its regenerative capacity than tissues that can rely on resident stem cells. This is one hypothesis for the failure of repair of pancreatic islet damage in type I diabetes mellitus, whereas extensive cell damage to the blood with cancer chemotherapy can result in complete restoration of tissue function.

Induced pluripotent stem (iPS) cells — The concept of the close relationship between stem cell potential and stage of development dramatically changed in 2006 [10]. In a remarkable set of experiments, Shinya Yamanaka and his colleagues took genes that were expressed in pluripotent ES cells, but not generally in mature cells, and introduced them into mature cells. They did so in a manner such that the genes would now be "ectopically" expressed, ie, expressed in a cell type where the gene is normally not expressed. A small number of the mature cells reverted back to a highly immature cell state that resembled an ES cell. This process, now called reprogramming, induced a pluripotent state in a previously differentiated cell type (figure 3). These cells are therefore called induced pluripotent stem (iPS) cells.

The ability to induce pluripotency has changed the landscape of stem cell biology along several lines.

- First, it indicates that the state of a given cell (ie, its level of differentiation) can be manipulated, resulting in drastic shifts in cell function. Cells have a plasticity that is far greater

than previously recognized and can be programmed by specific manipulations to achieve a different cell state. A keratinocyte derived from the skin can be induced to become a pluripotent stem cell, essentially rewinding the cell's history to revert to an embryonic-like state.

- Second, a cell taken from an individual can be induced to become a cell type capable of forming any other cell type in that individual's body. This means, for example, that a skin or blood sample obtained from a patient with a degenerative brain disorder can be converted into a pluripotent cell. The iPS cell can then become a source for generating the neural cells affected by the disease. Thus, disease models can be generated using human cells for disorders where obtaining primary tissue, or developing reliable animal models, has been difficult.

- Third, iPS from a given individual represents a highly personalized source of cells. While technologies to generate iPS currently involve genetic manipulation, it is anticipated that other methods will be developed to generate iPS that are genetically identical to the individual. Such cells could be used to assess 'personalized' drug therapies and may represent a source of immunologically identical cells for transplantation.

Further modifications of the iPS methodology are under active development. As an example, treatment of somatic cells with a cocktail of small molecule compounds was shown to alter gene expression in a similar pattern to that induced by ectopic expression of embryonic genes [11]. These advances raise the prospect of future use of iPS for therapeutic purposes. (See 'Preclinical studies using iPS cells' below.)

CLINICAL APPLICATIONS: CELL REPLACEMENT

The paradigm for stem cells as a means of replacing injured or diseased tissue was first explored in response to the threat of nuclear warfare after World War II. Research on overcoming the effects of radiation injury led to the first demonstration of stem cells, whose existence had been hypothesized since the early twentieth century. In 1963, researchers in Toronto demonstrated that a bone marrow-derived cell could replace all the blood elements and rescue an otherwise lethally-irradiated animal by simple infusion of donor cells into the blood [12].

This demonstration quickly led to clinical testing and application. Over the ensuing twenty years, hematopoietic stem cell transplantation has become a standard means of treating individuals with hematologic malignancies as well as clinical and acquired bone marrow failure states, including radiation injury. In 1975, it was reported that cultured cells from the skin could result in the generation of large numbers of cells sufficient to provide an autologous cutaneous barrier in patients with severe burns [13]. Thus both unmanipulated stem cells from bone marrow and manipulated stem cells from skin have tremendous clinical utility in otherwise fatal settings.

In addition to treatment for hematologic disease and burns, stem cells are now used for bone grafting in orthopedics and for corneal generation from limbal stem cells in ophthalmology. The presence of stem cells in other tissue types has led to the preclinical testing of stem cell therapies for other disorders, including those involving muscle and nerve tissue. The potential use of stem cells to restore missing, lost, or damaged tissues plays a central role in the field of regenerative medicine, which seeks to improve organ function by regenerating tissue [14].

Preclinical examples using human ES cells — Human embryonic stem (ES) cells have been successfully differentiated in vitro into multiple cell types for therapeutic uses, including oligodendrocytes, pancreatic cells, cardiomyocytes, motor and dopaminergic neurons, and hematopoietic precursor cells [15]. The therapeutic potential for ES cell-derived somatic cells has been demonstrated in animal models of retinal blindness, Parkinson disease, Huntington disease, spinal cord injury, myocardial infarction, and type I diabetes mellitus.

Retinal disease — Human ES cell-derived retinal photoreceptors have been used to improve visual function in blind mice [16]. Following intraocular injection, retinal cells derived from human ES cells migrated into the appropriate retinal layers and expressed markers of differentiated rod and cone photoreceptor cells. Subretinal transplantation of the cells into the subretinal space of mice modeling Leber's congenital amaurosis restored light responses to the animals. In a subsequent study, ES cell-derived photoreceptors transplanted into the eyes of adult mice were able to integrate and mature into outer segment-bearing photoreceptors [17]. (See 'Clinical use of human ES cells' below and "Retinitis pigmentosa: Treatment", section on 'Retinal cell transplantation'.)

Parkinson disease — A highly enriched population of midbrain neural stem cells was derived from mouse ES cells [18]. The dopamine neurons generated by these stem cells showed electrophysiologic and behavioral properties expected of neurons from the midbrain. These ES-derived neurons survived after being transplanted into rats with symptoms of Parkinson disease, showed appropriate electrophysiological properties, and ameliorated pathologic movements in the animals. Subsequently, functional improvement was seen with use of human ES cell-derived dopaminergic neurons after transplantation in a rat model of Parkinsonism [19]. Similarly, transplantation of differentiation stage defined ESC-derived neuronal progenitors resulted in dopamine neuron engraftment, with robustly induced recovery of motor deficits in hemiparkinsonian mice [20].

Huntington disease — Degeneration of gamma-aminobutyric acid (GABA) neurons in the basal ganglia underlies motor dysfunction in Huntington disease (HD). Human ES cells that have been differentiated into forebrain GABA neurons have been transplanted into the brains of mice in an HD model [21]. These ES-cell-derived neurons were able to repopulate the substantia nigra, receive glutamatergic and dopaminergic inputs, and restore motor neuron function.

Spinal cord injury — Transplantation of human ES-derived oligodendrocyte progenitor cells into adult rats, seven days after the induction of a spinal cord injury, was shown to enhance remyelination and promote improved motor function [22]. Transplanted cells survived, redistributed over short distances, and differentiated into oligodendrocytes, demonstrating their therapeutic potential after recent spinal cord injury.

Myocardial infarction and heart failure — The safety and efficacy of stem cell-based therapy in patients with acute myocardial infarction or ischemic cardiomyopathy are under investigation, but so far there is no clear, consistent evidence of therapeutic benefit. (See "Overview of the non-acute management of ST elevation myocardial infarction", section on 'Hematopoietic stem cell therapy' and "Investigational and emerging strategies for management of heart failure", section on 'Cell therapy'.)

Diabetes mellitus type I — Efficient direct differentiation of human ES cells to insulin-producing pancreatic beta cells has been achieved [23,24]. The differentiated cells expressed key markers of mature pancreatic beta cells; they displayed glucose-stimulated insulin secretion comparable to adult beta cells; and they secreted human insulin into the serum of mice shortly after transplantation in a glucose-regulated manner, ameliorating hyperglycemia in diabetic mice.

Clinical use of human ES cells — In 2015, the first phase 1/2 study reported on the safety and tolerability of human ES cell use for the treatment of patients with retinal disease; this involved nine patients with dry age-related macular degeneration and nine patients with Stargardt's macular dystrophy [25]. Human ES cell differentiation resulted in greater than 99 percent pure retinal pigment epithelium (RPE), of which 50,000 to 150,000 RPE cells were injected into the subretinal space. Graft survival was demonstrated by an increasing subretinal pigmentation consistent with transplanted retinal pigment epithelium in the majority of patients. Patients were treated with low-dose tacrolimus and mycophenolate mofetil for immunosuppression beginning one week before the procedure and continuing for six weeks, followed by six additional weeks of mycophenolate mofetil only. There was no evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted tissue with a median follow-up of 22 months. Improvement in visual acuity was noted in the injected eye in 10 of 18 patients.

This initial report of human ES cell-derived progeny transplantation into the retinas of 18 patients suggested apparent medium- to long-term safety and tolerability of this treatment in humans, with possible efficacy as well. Subsequent trials exploring transplantation of human ES cell-derived RPE cells in macular degeneration using various approaches appear to confirm safety of this procedure with varying clinical benefit in small numbers of patients [26,27].

Other than in macular degeneration, the use of human ES-based cellular therapy has been reported in patients with severe ischemic left ventricular dysfunction [28]. Human ES cell-derived cardiovascular progenitors embedded in a fibrin patch were epicardially delivered through a coronary artery bypass procedure in six patients. Technical feasibility was shown to produce

clinical-grade human ES cell-derived cardiovascular progenitor cells as well as short- and medium-term safety, paving the way towards adequately powered efficacy studies.

Additional studies assessing the dosage, efficacy, and long-term safety in larger number of patients are required prior to widespread clinical application of human ES cell transplantation. The spectrum of disorders that ES-cell based therapies can treat is expected to increase. Clinical trials with ES-derived cell products have been initiated or designed in the areas of spinal cord injury, type 1 diabetes mellitus, and amyotrophic lateral sclerosis [29].

Preclinical studies using iPS cells — The recognition that a somatic cell taken from an individual can be induced to become a pluripotent stem cell (ie, capable of forming any other cell type in the body) provides unprecedented opportunities for regenerative medicine. Easily accessible patient cell types, such as skin fibroblasts or blood cells, can be reprogrammed to induced pluripotent stem (iPS) cells. These pluripotent cells are envisioned to then be differentiated into mature cells that may be deficient in diseases such as islet cells for type I diabetes, or into tissue-specific adult (stem) cells. The cells can theoretically be used for tissue regeneration in the same patient (figure 4).

In such a way, iPS cell technology could overcome two important obstacles associated with human ES cells: immune rejection after transplantation and ethical concerns regarding the use of human embryos. The approach would be particularly powerful in monogenic diseases, where "patient-specific" iPS can be generated, the diseased gene in those cells potentially corrected, and the gene-corrected cells transplanted to restore organ function. This field is rapidly evolving, although there remains a great deal of research needed to make such a schema viable in the clinical setting.

Many of the studies to evaluate iPS cells as a source of cell replacement are being conducted in rodents. These studies permit testing of basic principles in a physiologic setting and are therefore useful, particularly where murine models of human diseases have been generated. For two such models, Parkinson disease [30] and hemophilia A [31], iPS cells have been generated and used to differentiate cells that could then be transplanted for therapy.

Other technologies developed for gene therapy have also been used to test whether iPS cells can be used to create gene corrected cells for transplantation. One proof-of-principle study used a mouse model of sickle cell disease in which the mouse hemoglobin genes contained the mutations known to cause sickling in human sickle cell anemia. Investigators generated iPS cells from skin cells of the mouse and introduced a normal hemoglobin gene allele to replace the sickle hemoglobin gene (using the gene targeting technology used to engineer mouse strains for research) [32]. They then generated blood stem cells from the gene corrected iPS cells. Transplantation of these cells into sickle cell anemic mice improved the disease phenotype. This represents a model for the use of iPS cells as cell therapy in the setting of genetic disorders.

Similarly, neural cells derived from mouse iPS cells have been used to ameliorate Parkinson disease and spinal cord injury in experimental mouse models [33,34].

The approach of using iPS cells to correct a genetic defect has been tested using human cells. As examples:

- Fanconi anemia – A normal version of the gene mutated in Fanconi anemia was introduced into fibroblasts from patients with Fanconi anemia, and the gene-corrected cells were reprogrammed to generate patient-specific iPS cells [35]. The iPS cells carrying the normal gene were able to generate blood cell types in a manner similar to cells from normal volunteers. This study indicated that skin cells from patients with an abnormal gene can be used to generate gene-corrected iPS cells that might serve as a source of cells for transplantation. (See "Inherited aplastic anemia in children and adolescents".)

- Huntington disease (HD) – The abnormally expanded cytosine-adenine-guanine (CAG) trinucleotide repeat region of the huntingtin gene was corrected to normal length in fibroblasts derived from a patient with HD [36]. These fibroblasts were reprogrammed to generate patient-specific iPS cells, which were then differentiated into gamma-aminobutyric acid (GABA)-producing neurons. When transplanted into mice, the neurons were able to populate the basal ganglia and express GABA. In cell culture, the neurons showed normalization of signaling pathways, reduced susceptibility to cell death, and improved mitochondrial function, all of which are thought to be involved in the pathogenesis of HD. (See "Huntington disease: Genetics and pathogenesis".)

Clinical studies using iPS cells — Progress has led to the first exploration of iPS cell-derived cells in transplant strategies in humans. iPS cell-derived retinal pigment epithelium (RPE) cells have been transplanted in a clinical study in Japan in age-related macular degeneration [37]. The investigators show feasibility of transplanting a sheet of RPE cells differentiated from autologous fibroblast-derived iPS cells in a single patient. The graft was well tolerated and visual acuity had not changed one year after the intervention. Before transplantation, the iPS cell-derived cells were screened for acquired mutations. A second patient that was selected for this clinical trial did not receive the transplant after testing revealed DNA alterations in the iPS cell-derived RPE cells. The efficacy and safety of iPS cell-derived transplants, therefore, remains to be determined. (See "Age-related macular degeneration: Treatment and prevention", section on 'Unproven and ineffective therapies'.)

Challenges in the clinical use of stem cells as replacement — The use of stem cells to replace abnormal or missing cells is conceptually compelling. The successful use of stems cells for bone marrow and skin therapies, and the identification of stem or progenitor populations in a number of tissue types, offers great promise for expanded clinical applications. There is the additional potential that human pluripotent cells may be a source of virtually any cell type. However, several

complexities must be addressed before widespread application becomes feasible, including those discussed in the following sections.

Tissue integration — The first issue is how transplanted cells will integrate into surrounding tissue to achieve a physiologically beneficial effect. This is of particular relevance where coordination of complex networks of cells is essential, such as in the heart and brain where aberrant circuits can result in serious adverse events. Although extensive testing is needed, one encouraging observation is that some cells appear to have an inherent capacity to incorporate into existing structures. As an example, in an animal model, human endothelial cells derived from ES cells were able to organize into tubular structures and integrate into the host vasculature when inserted as dispersed cells into a host tissue [38].

Oncogenesis — A second concern is the potential for transplanted cells to form tumors. This is of particular importance when using pluripotent cells, since these are characterized by the ability to form teratomas (neoplastic tumors containing cells corresponding to all three embryonic layers) in animal models [10,39]. Thus, the differentiation state of transplanted cells will need to be defined with high precision to avoid delivery of residual pluripotent cells that may differentiate aberrantly in vivo. Evidence also suggests that oncogenesis is not restricted to pluripotent cells. In one case, a child was given cultured fetal brain cells intrathecally and subsequently developed multiple CNS tumors of donor origin [40]. The culture process may enable the outgrowth of genetically abnormal cell types that could be of potential danger [41]. The specifics of what types of testing will be required for pluripotent or other cells to assure genetic integrity of transplanted cells is an active area of consideration.

The issue of malignant potential of cells is of greatest concern in induced pluripotent stem (iPS) cells. The methods of greatest efficiency for reprogramming cells are currently retrovirus or lentivirus-based, and therefore run the risk of mutagenesis by virtue of viral integration into the host genome. In addition, some of the genes used to induce reprogramming have known oncogenic potential (eg, c-Myc) [42]. Progress in reducing the number of gene products needed for reprogramming, and in the use of either non-integrating viruses or small molecules to supplant retrovirus-based reprogramming, is ongoing [43-47]. These developments may mitigate the concerns about insertional mutagenesis, but will not entirely assuage concern for altered growth control of modified cells, particularly those with pluripotency.

Directed differentiation — A third concern is the ability to direct the differentiation state of the cells to be used. Generating the proper cell type from pluripotent cells remains a significant challenge for some cell types. Protocols have now been devised to create some neural cell types of clear clinical importance [48]. However, for other tissues, such as the blood, the cell types created most closely resemble embryonic blood cells and are not capable of engrafting the bone marrow without further and undesirable genetic manipulation [49].

Achieving the right stage of differentiation is another consideration in development of the stem cell derived cell therapies. It may be most desirable to generate progenitors, rather than fully mature terminally differentiated cells in some tissues so that the replaced cells do not quickly senesce and die.

Uniformity and consistency — Finally, the uniformity and consistency of the cell product may be difficult to achieve across different donor sources of cells.

These hurdles are not likely to be prohibitive, but each will require considerable effort and attention.

OTHER CLINICAL APPLICATIONS

Disease modifiers — Beyond use of stem cells for cell replacement, the ability of certain stem cells to alter disease without engrafting has been explored as a means of modifying cellular response to injury or aberrant immune activity. Such non-engrafting stem cells are hypothesized to provide complex signals, affecting disease outcome without directly replacing injured cells.

The identification of a population of cells in the bone marrow that could form a number of mesenchymal cell populations ex vivo led to the concept of a mesenchymal stem cell [50,51]. This population of cells is defined primarily by its ability to form colonies in tissue culture, and by the ability of single cells derived from the colonies to differentiate into osteoblasts, adipocytes or chondrocytes in vitro. Identification of these cells in the body, and understanding of how they function in vivo, remains controversial.

The potential for these mesenchymal stem cells to form muscle led to exploration of their use in the setting of ischemic injury of the heart. While initial indications suggested that the cells may directly contribute to generating cells in the area of injury, it has subsequently been shown that the cells do not engraft [52]. Rather, it is proposed that they provide complex signals, in a paracrine manner, that may alter the ability of the heart (and other tissues) to respond to ischemic injury [53-55]. This concept remains highly contested, in part because the mechanisms by which stem cells may function in this capacity are not clear. The mesenchymal stem cell populations studied are highly variable and have been variably reported to secrete a number of factors including indoleamine 2, 3-dioxygenase, prostaglandins, interleukin-6, hepatocyte growth factor, inducible nitric oxide synthase, and tumor growth factor (TGF)-beta 1 [56].

It has been proposed that the mesenchymal stem cell population is capable of altering immune function and may therefore modulate injury responses as in ischemia, or mitigate the effects of immune mediated diseases. Mesenchymal stem cells have been tested in clinical trials in humans in settings of graft versus host disease following allogeneic hematopoietic stem cell transplantation, and in inflammatory bowel disease. For each, there has been controversy regarding the impact of the cells and the mechanism by which the cells may be acting. (See

"Investigational therapies in the medical management of Crohn disease", section on 'Stem cell therapy' and "Treatment of acute graft-versus-host disease", section on 'Mesenchymal stromal cells'.)

While this use of stem cell populations as disease modifying cell platforms is an area of active investigation, the concept should not be considered proven at this time. The prospect that mesenchymal cell populations may have the ability to arrive at sites of injury and provide paracrine signals is an exciting and potentially important application of stem cell biology, but it is not yet a defined therapy.

Drugs targeting endogenous stem cells — There is emerging recognition that stem cells resident in adult tissues may be targets for pharmacologic interventions with the goal of altering the function of endogenous stem cells. This approach may avoid concerns related to tissue integration of exogenous cells.

Growing understanding of the signaling processes that induce activation of stem cells, or modify their differentiation, makes this approach one of growing interest. Analogous to the use of erythropoietin to modify the activity of red cell progenitors, agents with similar effects on stem cells might generate reconstitution of other types of blood cells in the case of hematopoietic stem cells, or other mature cell types for other tissue stem cells.

Some studies have identified agents capable of altering stem cell activity in settings of injury to the bone marrow or the bone [57,58]. As an example, a prostaglandin E2 (PGE2) derivative was identified in a chemical screen to be a potent positive regulator of vertebrate HSCs in zebrafish, increasing self-renewal capacity and engraftment [59]. In a subsequent phase 1 trial, the potential of PGE2 to promote hematopoietic stem cell engraftment was tested in the setting of hematopoietic cell transplantation using umbilical cord blood (UCB) in patients with hematologic malignancies [60]. Ex vivo modulation of UCB cells using the PGE2 derivative was found to be safe with durable, multilineage engraftment of PGE2-treated hematopoietic stem cells. Accelerated neutrophil recovery, coupled with preferential long-term engraftment of the PGE2-treated hematopoietic cells suggested clinical efficacy in this trial.

PGE2 similarly supports the expansion of human colon stem cells in cell culture, leading to the idea that in vivo manipulation of PGE2 metabolism may modulate stem cells and regeneration of multiple tissues. In support of this view, a preclinical study in mice demonstrated that treatment with small molecules capable of increasing PGE2 levels in the bone marrow and other tissues led to accelerated hematopoietic recovery after hematopoietic cell transplantation and promoted tissue regeneration after colon and liver injury [61].

Disease models — Stem cells offer the possibility of creating in vitro disease models that may improve molecular understanding of disease and accelerate the development of new therapies. Human cells from affected individuals with diseases affecting the nervous system, for example,

have been extremely difficult to obtain for in vitro analysis. With stem cell approaches, it is possible to generate sufficiently large numbers of cells to study the molecular basis of functional deficits associated with the disease or to be used in the development and testing of new drugs.

The development of induced pluripotent stem (iPS) cells has led to a number of efforts to create in vitro disease models amenable to genetic and small molecule study. A major goal of such efforts is to identify compounds capable of altering the progression of cell events corresponding to disease progression. These efforts depend upon robust cell culture systems that resemble the in vivo context closely enough to be useful for drug evaluation. Fulfillment of this requirement still needs validation.

Two early examples depict use of iPS cells to create a disease model for further study of human disease pathogenesis and treatment.

- iPS cell lines were created from patients with familial dysautonomia (FD), a rare fatal sensory autonomic neuropathy caused by a point mutation in the IKBKAP gene involved in transcriptional elongation [62]. The investigators demonstrated tissue-specific missplicing of IKBKAP in purified FD-iPSC-derived lineages, suggesting a mechanism for disease specificity. Functional studies revealed marked defects in neurogenic differentiation and migration behavior, recapitulating disease characteristics. FD-iPSCs were subsequently used for validating the potency of candidate drugs to reverse aberrant splicing and ameliorate neuronal differentiation and migration. (See "Hereditary sensory and autonomic neuropathies", section on 'HSAN3 (Familial dysautonomia)'.)

- In another study, iPS cells were generated from skin fibroblasts from a child with spinal muscular atrophy [63]. These cells expanded robustly in culture, maintained the disease genotype, and generated motor neurons that showed selective deficits compared to those derived from the child's unaffected mother.

iPS cells have also been used to generate disease models for a wide variety of (genetic) diseases, including neurological, hematological, metabolic, and cardiovascular disorders. These studies have generated novel insights into the molecular mechanisms driving these disorders and platforms for drug screening [64].

An additional application of stem cell biology to disease modeling is in the setting of cancer. The model hypothesizes that there is a definable population of malignant cells that can be demonstrated to have the two cardinal features of stem cells (self-renewal and differentiation capacity). These cells, like stem cells in normal tissues, would replace more mature cells whose lifespan is limited. They are therefore hypothesized to be the cells that enable persistence and perhaps metastasis of tumors.

The hypothesis has gained experimental support through the use of immunodeficient mice in whom human cancer cells can be engrafted [65,66]. A subset of tumor cells can be defined in

these animals that is capable of engrafting the tumor, while other subsets cannot. Further, the tumor-initiating subset can be sequentially transplanted to initiate new tumors and can yield the full diversity of cells observed in the original malignancy, thereby fulfilling the experimental definition of stem cells. Human acute myelogenous leukemia, breast, colon, ovarian, pancreatic, head and neck cancer, and malignant glioma have been shown to have such a subpopulation of cells [65-71].

Whether all tumors have a stem-like cell is controversial, and much of the definition depends upon engraftment in a mouse model, which is not necessarily a surrogate for function in humans. However, the model is beginning to impact the way cancer is viewed and how oncologic drugs are developed. Studies are now investigating whether drugs affect the stem-like cells and not just tumor bulk, and whether agents can target distinctive features of the stem-like cells of cancer rather than the mixture of cells comprising a malignancy.

ETHICAL CONSIDERATIONS

The first derivation of human embryonic stem and embryonic germ cells in 1998 sparked enormous interest and controversy regarding pluripotent stem cells. The initial, and still most frequent, techniques used to derive ES cells disrupt the blastocyst from which the cells are derived, raising concern that an early human life form was being destroyed. The source of the blastocyst was generally discarded material from in vitro fertilization clinics. Nonetheless, the issue of using the material for research, even if that research was intended to assuage human suffering, was morally unacceptable for many. These controversies led to policy decisions among some nations that precluded ES cell research or, as in the case of the United States, federal funding to support such research.

The advent of reprogramming to generate induced pluripotent stem (iPS) cells has provided an alternative source of pluripotent cells. It should be recognized that iPS have not yet been shown to be fully equivalent to ES cells, and ES cells still represent the best defined pluripotent cell population. However, iPS cells are increasingly the focus of research and appear to engender less ethical concern since they do not involve the use of blastocysts or embryonic tissue. The cells from animals do have the ability to contribute to a developing organism though, so other ethical concerns are not entirely mitigated.

An issue that is relevant for both pluripotent and other stem cells is how to define safety when proceeding to clinical trial. The area of cell therapies has been well explored in hematology, transfusion medicine, and hematopoietic stem cell transplant. Infusion of other cultured cell products has a well-defined safety profile for keratinocyte skin grafts and mesenchymal stem cell transplants. Several features are unique to the use of pluripotent cells, however:

- Concern regarding the placement of cells in tissues highly intolerant of aberrant growth control such as the central nervous system and heart.
- Defining the genetic integrity of manipulated cells can be extremely difficult, though may be resolvable through emerging genomic technologies.
- Whether the cells have tumorigenic potential is hard to define since even established cancers can be difficult to grow with functional in vitro or in vivo assays.
- Defining the potential to integrate as functional tissue requires in vivo settings, and animal models have only limited ability to predict events in humans.

Therefore, clinical experience will be necessary to define some of the risks in stem cell-based therapeutics, and careful design of clinical trials with a range of parameters specific to the field are in process.

Stem cells have enormous potential that is well recognized by the public, and are a source of hope for those dealing with otherwise untreatable medical problems. However, the field is in its infancy and progress is painstaking; for those desperate to get help, unproven therapies even outside of reputable centers or clinical trial are a highly tempting option. The potential for patient exploitation raises another extremely challenging area. There has been a profusion of centers in many parts of the world, often offering treatment without clear definition of what cells would be used, what the source of cells is, and what the full experience has been. Services are often offered for cash payment and with unclear provisions to monitor safety or respond to adverse events. Patients and providers should ask a range of specific questions about such therapies. The International Society for Stem Cell Research (ISSCR) has provided suggested questions and other information that may be of use (www.isscr.org).

SUMMARY AND RECOMMENDATIONS

- Stem cells are those cells that have the capability of self-renewal and differentiation. Stem cells are classified based on the type of differentiated cell they can reproduce. Pluripotent stem cells can make all cells of the embryo, including germ cells and cells derived from ectodermal, mesodermal, and endodermal germ cell lines. (See 'Degrees of stem cell potency' above.)
- Embryonic stem cells are typically derived from the preimplantation blastocyst (7 to 10 days post fertilization). Adult stem cells typically derive from tissue formed beyond 10 to 14 days post fertilization and are called "somatic" stem cells when derived from non-germ cell tissue. It is unclear whether adult stem cells are present in all tissues, such as pancreatic islet cells. (See 'Sources of stem cells' above.)

- Since 2006, it has been possible to create induced pluripotent stem (iPS) cells by "reprogramming," a process that involves gene transplantation into mature cells, with reversion to a pluripotent state. Creation of iPS cells provides the potential to use tissue culture to generate a specific tissue derived from an entirely other somatic cell. The potential for therapeutic use is great, although the need for genetic manipulation in the process limits the transference clinical application at the present time. (See 'Induced pluripotent stem (iPS) cells' above.)

- Stem cells present current and future opportunities for several different clinical applications. Hematopoietic stem cell replacement is currently a robust intervention for a number of hematologic conditions. Burn therapy, bone grafting, and corneal transplant tissues are examples of other current uses of stem cell–generated tissue. Tissue replacement treatment for other conditions (retinal disease, Parkinson disease, myocardial infarction) is in development. Concerns about the technology include integrating the transplanted cells into complex cell networks, oncogenesis of the transplant material, and the ability to generate the correct target cell types in the right stage of differentiation. (See 'Clinical applications: Cell replacement' above.)

- Stem cell transplantation may have the ability to modify diseased tissue in a paracrine fashion, without actual engraftment. Drugs directed at endogenous tissue stem cells may modify tissue response to injury. Finally, stem cells may generate tissue to be used as laboratory models for the study of diseases where obtaining live tissue is otherwise difficult or not possible. (See 'Other clinical applications' above.)

- Ethical concerns have been raised regarding stem cell research. The use of induced pluripotent cells may mitigate concerns about disruption of embryos, but several other concerns remain to be addressed. (See 'Ethical considerations' above.)

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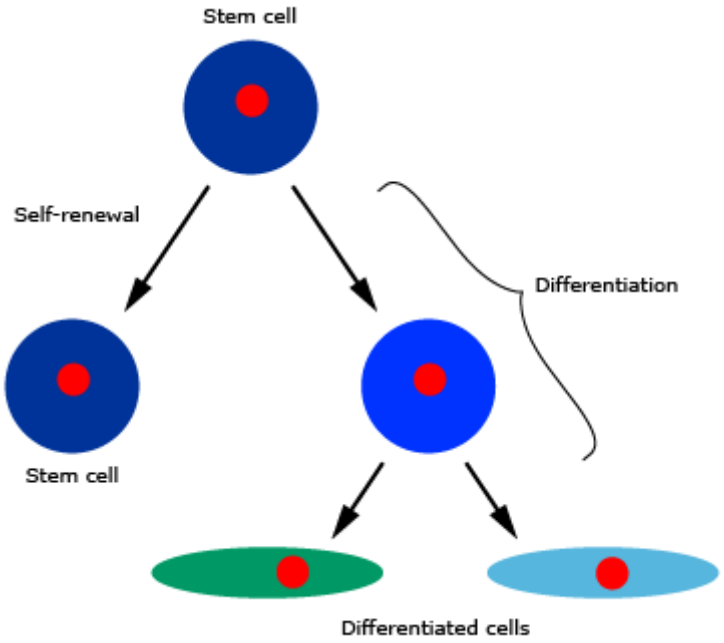
GRAPHICS

Stem cells in medicine

Cell therapy
Drugs targeting stem cells to induce tissue regeneration
Models of disease to drive drug therapy development

Graphic 69800 Version 1.0

Signature characteristics of stem cells



Stem cells have two properties that distinguish them from other cell types. Stem cells can divide and result in daughter cells that either are replicates (self-renewal) or acquire features of more mature cell types (differentiation). The balance between these two outcomes may vary depending on the stem cell type and the context, but a stem cell must be capable of either outcome.

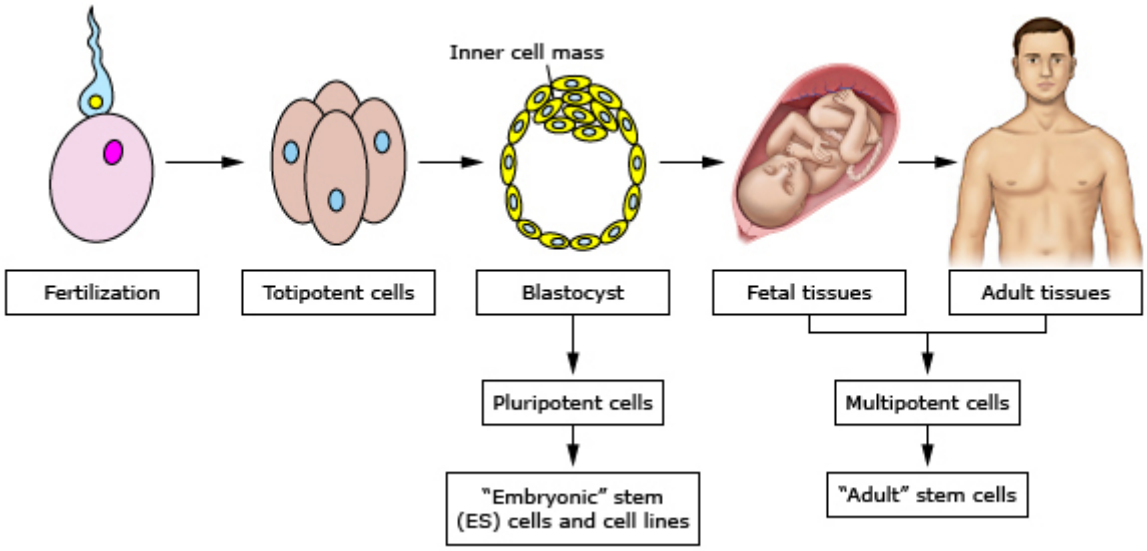
Graphic 54474 Version 1.0

Classification of stem cells

Type of cell	Capable of producing	Example
Totipotent	Embryonic and extraembryonic tissues	Within the first few cell divisions of the zygote
Pluripotent	Any cell in the body including germ cells	Inner cell mass of the blastocyst, embryonic stem cells, embryonic germ cells, induced pluripotent cells
Multipotent	Restricted to a given germ layer or tissue cell type	Hematopoietic stem cells
Unipotent	Restricted to a specific cell lineage	Germ cell stem cells

Graphic 78504 Version 1.0

Relationship of development to stem cell type

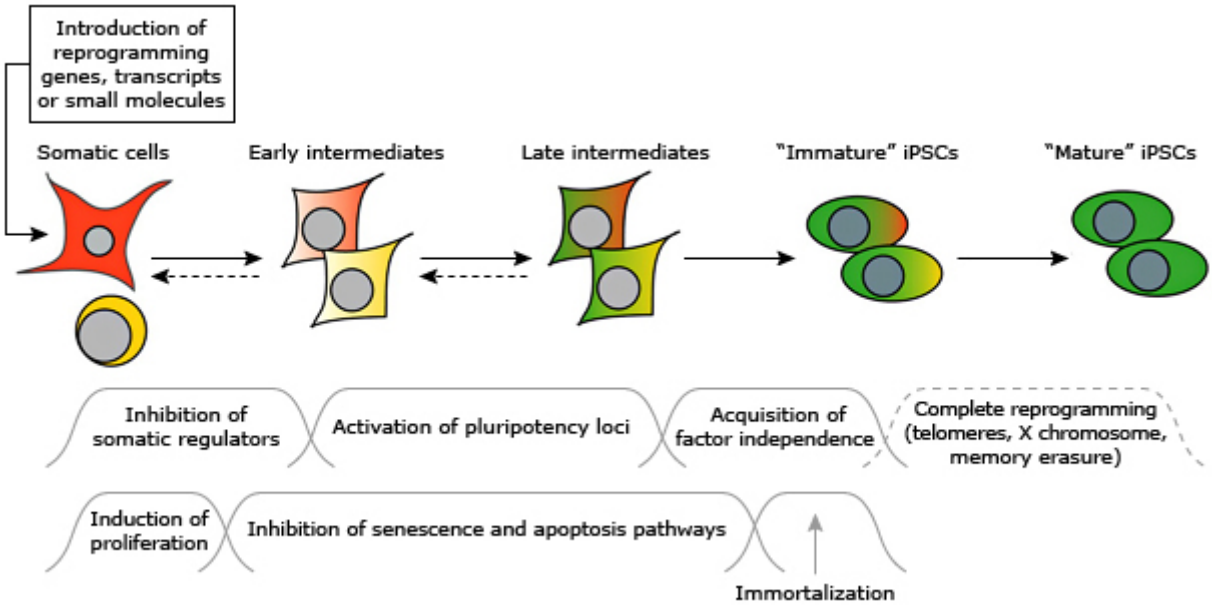


Types of stem cells and their relationship to normal development. Totipotent stem cells are thought to exist only in the first several divisions of the zygote. Stem cells become more restricted as pluripotent cells once the blastocyst is formed. By the time the primitive streak forms, most cell types in the organism become further restricted to multipotent status, with the exception of embryonic germ cell lines. The cells derived from these later stages in development have been called "embryonic" or "adult" stem cells, to reflect their different potency as stem cells. The unilinear relationship of development to stem cell potential that is depicted here is no longer a rigid dictate as it appears that highly differentiated cells can be reprogrammed to become pluripotent cells.

Redrawn based on information from The National Institutes of Health.

Graphic 67256 Version 1.0

Reprogramming adult cells to become pluripotent cells



The introduction of defined factors (as genes, mRNA, or a combination with small molecules) permits the gradual reversion of a mature, somatic cell, such as a skin fibroblast, to an induced pluripotent (iPS) cell. Sequential changes in the targeted cell are thought to proceed in an orderly manner as indicated.

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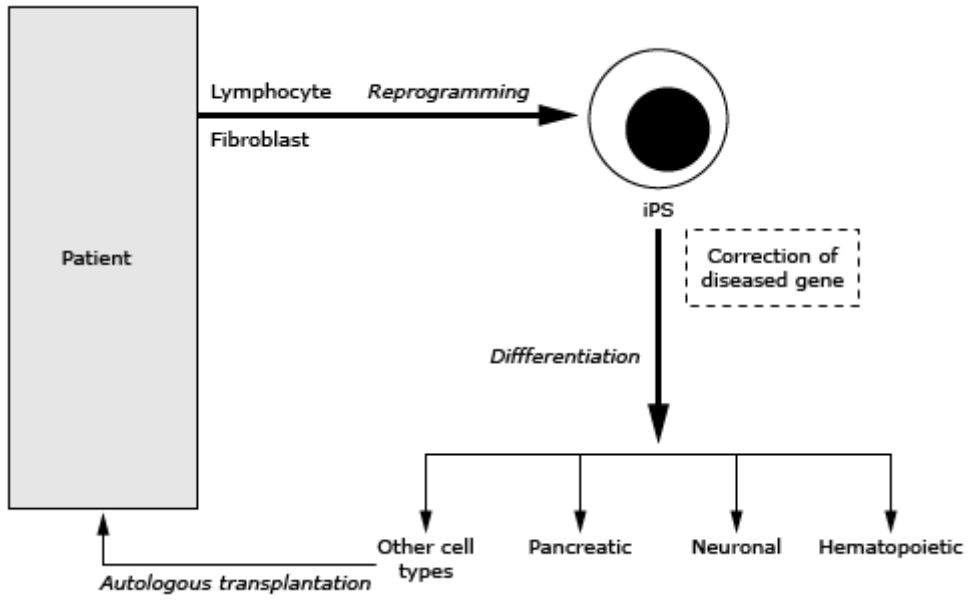
Graphic 81456 Version 2.0

Induced pluripotent stem cells (iPS) in cellular replacement therapy



Principle of use of induced pluripotent stem cells (iPS) in cellular replacement therapy. Patient cells, ie skin fibroblasts, can be obtained and reprogrammed to pluripotency ex vivo, generating iPS. These iPS can subsequently be differentiated to specific cell types which can be used for autologous transplantation. In monogenic diseases, it may be possible to correct the disease gene in iPS before transplantation.

Graphic 51751 Version 3.0

Contributor Disclosures

Marc HGP Raaijmakers, MD, PhD Nothing to disclose **Benjamin A Raby, MD, MPH** Consultant/Advisory Boards: Sanofi; Genzyme; Regeneron [Asthma]. Employment (spouse): Parexel [Hematology (CRO)]. **Jennifer S Tirnauer, MD** Nothing to disclose

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