SPECTRUM OF STEM CELL, RESEARCHES AND ITS CURATIVE VALUE– A REVIEW

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Summary

Stem cells are characterized by the ability to renew themselves through mitotic cell division and differentiating into a diverse range of specialized cell types. The two broad types of mammalian stem cells are embryonic stem cells that are found in blastocyst, and adult stem cells found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. Adult organisms, stem cells and progenitor cells act as a repair system of the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs such as blood, skin or intestinal tissues. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia. In the medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, parkinson's disease, spinal cord injuries, amyotrophic lateral sclerosis and muscle damage, amongst a number of other impairments and conditions.

Keywords: Stem cell, Embryonic stem cells, Adult stem cell, Pluripotent, Neural.

Introduction

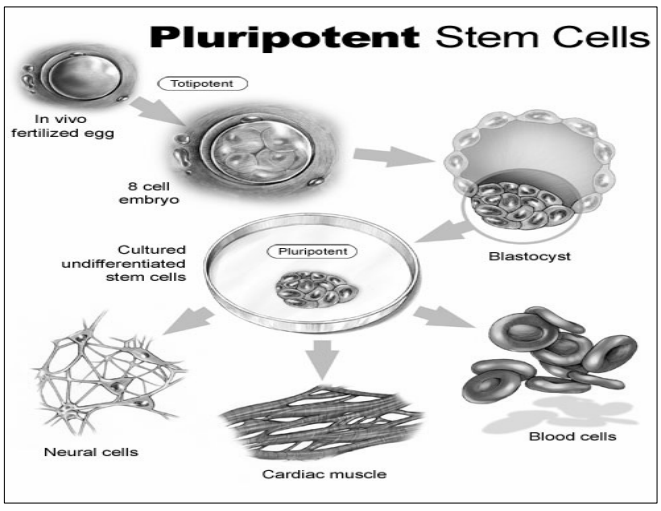
All human beings develop from the union of an egg and a sperm. The result is a fertilized egg or zygote, a single cell that divides into other cells, which together constitute the early embryo these stem cells are unspecialized cells that develop into the specialized cells that make up the different types of tissue in the human body. They are vital to the development to growth, maintenance and repair of our brains, bones, muscles, nerves, blood, skin, and other organs. Embryonic stem cells derived from the inner cell mass of an early stage embryo known as a blastocyst. In particular human embryos reach the blastocyst stage 4-5 days post fertilization, at which time they consist of 50-150 cells.

Especially adult stem cells are undifferentiated cells, found throughout the body after embryonic development that multiply by cell division to replenish dying cells and regenerate damaged tissues. Also known as somatic stem cells (from Greek Σωματικός, meaning of the body), they can be found in juvenile as well as adult animals and humans.

Research in the stem cell field grew out of findings by Canadian scientists Ernest A. McCulloch and James E. Till in the 1960s (2, 30). Stem cell research is at the very forefront of scientific and medical innovation redefining the conventional boundaries of biomedical research. As the human body's master cells, embryonic stem cells reproduce indefinitely and can develop into various cell types within the human body. Consequently stem cells have the potential to be used to repair or replace damaged cell tissue, and to treat or cure a variety of diseases and injuries. This extraordinary potential has stimulated worldwide debate on the ethical, therapeutic, and regulatory issues surrounding stem cells applications.

Potential definition

Stem cells are precursor cells that branch into multiple types of tissues and there are important distinctions. However, regarding how developmentally plastic these cells are; that is, how many different paths they can follow and to what portion of a functioning organism they can contribute. Totipotent stem cells can give rise to a whole organism as well as to every cell type of the body. Pluripotent stem cells are capable of giving rise to a plurality of tissue types (Fig.1), but not to a functioning organism. Multipotent stem cells are more differentiated cells (that is, their possible lineages are less plastic or more determined) and thus can give rise to a more limited number of multiple tissue types. For example, a specific type of multipotent stem cell called a mesenchymal stem cell produces bone, muscle, cartilage, fat and other connective tissues. A better known example is the capacity of bone marrow stem cells to constantly renew red and white blood cells. In addition stem cells can generate new cells while maintaining their own numbers.



(**Fig. 1.** Pluripotent, embryonic stem cells originate as inner mass cells within a blastocyst. The stem cells can become any tissue in the body, excluding a placenta. Only the morula's cells are totipotent, able to become all tissues and a placenta).

Magnitude of embryonic stem cells

In embryonic stem cells first few of the early cells are totipotent, meaning that they are each capable of giving rise to an entire organism, including all the cell types that make up the embryo and the body, and all the cell types that make up the extra embryonic supporting tissues, such as the placenta. About five to seven days after conception, a zygote will have divided into about one hundred to one hundred and fifty cells these take the form of a hollow ball called a blastocyst with a mass of undifferentiated cells inside it in these undifferentiated cells are used to generate embryonic stem cell lines. These stem cells are unspecialized cells that develop into the specialized cells that make up the different types of tissue in the human body. They are vital to the development, growth, maintenance, and repair of our brains, bones, muscles, nerves, blood, skin, and other organs.

Assessment of embryonic stem cell research

Embryonic stem cells were first isolated from mouse embryos in 1981. Animal embryos were the only source for research on embryonic stem cell unit November 1998, when two groups of U.S. group, at the University of Wisconsin, derived stem cells from one week old embryos produce via in vitro fertilization (IVF). Ongoing research at the University of Adelaide (35, 16) has applied knowledge gained from study of early mouse embryogenesis to direct mouse ES cells into homogeneous populations of differentiated cells. Soluble factors have been identified that convert ES cells homogeneously into primitive ectoderm, which can in turn be coaxed specifically into either ectoderm or mesoderm. These germ layer equivalents go on to form neural stem cells and neurons, blood and muscle cells respectively. Purification of the soluble factors has permitted their functional and molecular characterization. These factors have the ability to control differentiation and de differentiation in a way that suggests ES cells do indeed have important therapeutic prospects in both tissue repair and as a vehicle for delivery of gene therapy. Non human primate ES cells were not isolated in rhesus and marmoset monkeys until fifteen years after the first isolation of ES cells in mice. The reagents such as interleukin 6 that maintain mouse ES cells in their proliferating and undifferentiated state do not work in primate ES cells, new experimental embryology systems and reagents needed to be developed. The mouse is a good experimental model in some respects, with short generation times and cost effective maintenance, but it is often a flawed model for primate biological systems, as is evident in the case of experimental embryology. Development of non human primate ES cells defined the protocols for maintaining prolonged proliferation of primate ES cells, for confirmation of unique markers that identify ES cells and for the demonstration that ES cells could develop into different types of tissue. This work established the experimental systems for derivation of ES cells from inner cell masses of human embryos cultured to the blastocyst stage.

ES cell lines can be derived from human blastocysts (26). The ES cells will differentiate into a range of cell types, either spontaneously or in response to specific culture conditions and factors. These cell types have characteristics of neuronal ganglia, lung epithelia, gut tissue, muscle cells, bone and cartilage, among others.

The research challenges are to identify and characterize the factors and conditions that maintain, expand and direct the lineages of the cell lines, to drive exclusive differentiation of cells into desired tissue types. The Monash University group reported in March 2001that it has established four human ES cell lines, from cells extracted from blastocysts by colleagues in Singapore and derived in compliance with National Institutes of Health guidelines. These cells are available to colleagues under a standard agreement, as are human ES cell lines developed in Wisconsin and now distributed to about 30 institutions in the United States and elsewhere (33).

Multidisciplinary adult stem cells

The term adult stem cell refers to any cell which is found in a developed organism that has two properties the ability to divide and create another cell like itself and also divide and create a cell more differentiated than it self. Also known as somatic (from Greek Σωματικός, "of the body") stem cells and germ line (giving rise to gametes) stem cells, they can be found in children as well as adults (13). Pluripotent adult stem cells are rare and generally small in number but can be found in a number of tissues including umbilical cord blood (25). A great deal of adult stem cell research has focused on clarifying their capacity to divide or self renew indefinitely and their differentiation potential (9). In mice, pluripotent stem cells are directly generated from adult fibroblast cultures. Unfortunately, many mice don't live long with stem cell organs (31). Most adult stem cells are lineage restricted (multipotent) and are generally referred to by their tissue origin such as mesenchymal stem cell, adipose derived stem cell, endothelial stem cell, etc (1, 11). In a living animal, adult stem cells can divide for a long period and can give rise to mature cell types that have characteristic (Fig. 2 and 3) shapes and specialized structures and functions of a particular tissue. The following are examples of differentiation pathways of adult stem cells.

Hematopoietic stem cells

Hematopoietic stem cells (HSC) are the most extensively studied somatic stem cell population in both humans and mice (21). HSC are capable of giving rise to all blood cell types, including red blood cells, B lymphocytes, T lymphocytes, neutrophils, natural killer cells, basophils, eosinophils, monocytes, macrophages and platelets. During adulthood, HSC reside primarily within niches in bone marrow, where cell communication with the surrounding stromal cells is critical for regulating HSC maintenance (14). Recent studies suggested that Cx32 is vital to HSC differentiation. Cx32 expression can be readily detected in Lin−c-kit+ HSC enriched cells (12). Interestingly, Cx32 knockout mice exhibit more undifferentiated HSC and fewer progenitor cells, suggesting a role of Cx32 in maturation of HSC to progenitor cells. In addition, Cx43 is also implicated in hematopoiesis. During the quiescent state, undifferentiated HSC (Lin−, Sca1+, C-kit+) do not express Cx43 mRNA (23). However, Cx43 expression can be massively up-regulated in adult mouse bone marrow upon forced stem cell division (28).Cx43 deficient mice also demonstrate clear defects in blood cell formation. However, it is not clear whether this effect is mediated by functional gap junctions or by connexon hemichannels.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) have been isolated from various tissues, including bone, umbilical cord blood and adipose (3, 34). They can readily differentiate into adipose tissue, tendon, cartilage and bone (24). Human MSC express Cx40, Cx43 and Cx45 and can communicate among them via gap junctions (18, 32). The exact identity of this MSC population remains unknown.

Neural Stem Cells

Neural stem cells share many properties with haematopoietic stem cells (HSCs). Remarkably, when injected into the blood, neurosphere derived cells differentiate into various cell types of the immune system (4). Cells that resemble neural stem cells have been found in the bone marrow, the home of HSCs (15).It has been suggested that new neurons in the dentate gyrus arise from circulating HSCs. Indeed, newborn cells first appear in the dentate in the heavily vascularised sub granular zone immediately adjacent to blood vessels. Neural stem cells are commonly cultured in vitro as so called neurospheres floating heterogeneous aggregates of cells, containing a large proportion of stem cells (27). They can be propagated for extended periods of time and differentiated into both neuronal and glia cells and therefore behaves as stem cells. However some recent studies suggest that this behavior is induced by the culture conditions in progenitor cells, the progeny of stem cell division that normally undergo a strictly limited number of replication cycles in vivo (7). Furthermore, neurosphere derived cells do not behave as stem cells when transplanted back into the brain (19).

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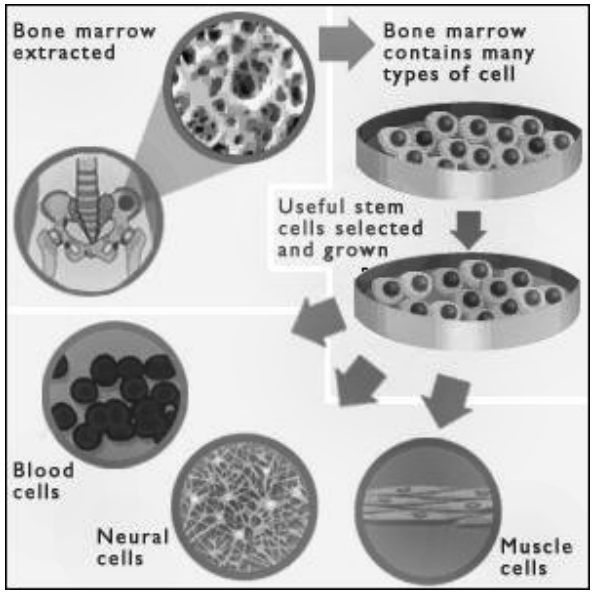
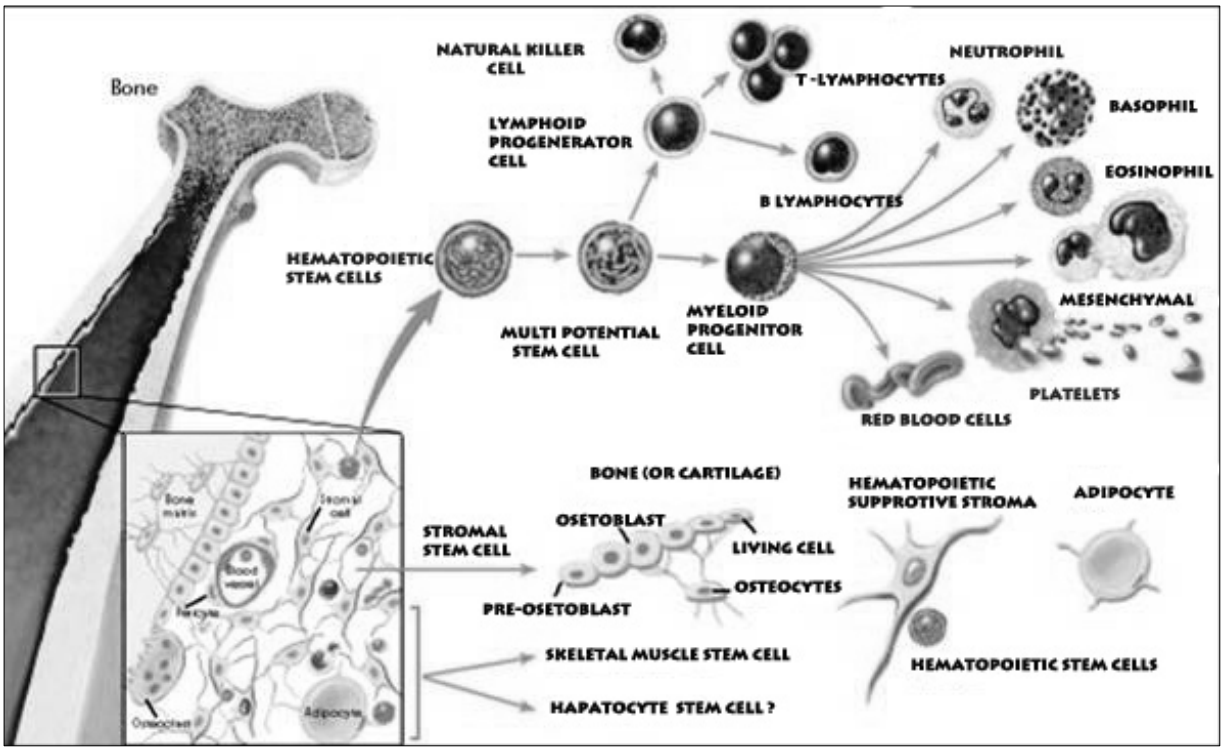


(**Fig. 2.** Separation of stem cell from bone marrow).



(**Fig. 3.** Hematopoietic and stromal stem cell differentiation).

Amazing adult stem cell and its research

While research on adult stem cells began decades ago, important new discoveries have been made in just the past few years. Scientists have found adult stem cells in many more tissues than they once thought likely, including the brain, bone marrow, blood, blood vessels, skeletal muscle, skin, liver, and other body parts. Given the right conditions, certain kinds of adult stem cells now seem to have the ability to differentiate into a number of different cell types. If this differentiation of adult stem cells can be controlled and sustained in the laboratory, these cells could become the basis of therapies for many serious common diseases and injuries. As examples of potential treatments, an NIH (National Institute of Health) list includes replacing the dopamine producing cells in the brains of Parkinson's patients, developing insulin producing cells for type I diabetes, and repairing damaged heart muscle with new cardiac muscle cells following a heart attack.

New victory of adult stem cell research

February 6, 2007, New York - The Adult Stem Cell Research Network announced that new clinical and pre clinical data on adult stem cells was presented at the 4th Annual Meeting of Cell Therapy for Cardiovascular Disease Sponsored by the Cardiovascular Research Foundation. Held at Columbia University, it attracted over 300 attendees from around the world.

Adipose Derived Stem Cells

Dr. Keith March of the Medical Center for Vascular Biology and Medicine, Professor Patrick Serruys of the Thorax Centre, Rotterdam, Netherlands and Francisco Fernandez-Aviles of Madrid, Spain all presented data related to the use of stem cells derived from a patient's own adipose (fat) tissue. Preclinical studies have demonstrated improved blood flow and a reduction of scar size when adipose derived stem cells are provided within a short time period following the heart attack by coronary infusion. Dr. March presented data that two cell types, adipose stem cells and endothelial progenitor cells, work in partnership to provide much more blood flow than either cell type can alone. Clinical studies of cells from adipose tissue have begun at a number of centers worldwide. "We are very interested to see that cells from adipose tissue are being tested in these early trials," said Dr. March, noting that the use of one's own cells from fat tissue is potentially a very practical approach.

Bone Marrow Derived Stem Cells

Dr. Andreas M. Zeiher, MD, and a number of other researchers provided both preclinical and clinical data from the use of bone marrow derived cells. These cells seem to function primarily by promoting growth of new blood vessels, which can help preserve tissue following a heart attack. Data from clinical studies of hundreds of patients has demonstrated a noticeable improvement in heart function, especially in patients whose hearts start with low pumping ability. More clinical studies are in progress. Sponsors of bone marrow cell studies include Osiris Therapeutics and Boston Scientific Guidant.

Other character of stem cells

Stem cells capable of dividing and renewing at long periods

Unlike muscle cells, blood cells or nerve cells which do not normally replicate themselves stem cells may replicate many times. When cells replicate themselves many times over it is called proliferation. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized like the parent stem cells, the cells are said to be capable of long term self renewal. The specific factors and conditions that allow stem cells to remain unspecialized are of great interest to scientists. It has taken scientists many years of trial and error to learn to grow stem cells in the laboratory without them spontaneously differentiating into specific cell types. For example it took years to learn how to grow human embryonic stem cells in the laboratory following the development of conditions for growing mouse stem cells. Therefore, an important area of research is understanding the signals in a mature organism that cause a stem cell population to proliferate and remain unspecialized until the cells are needed for repair of a specific tissue. Such information is critical for scientists to be able to grow large numbers of unspecialized stem cells in the laboratory for further experimentation.

Stem cells can give rise to specialized cells

When unspecialized stem cells give rise to specialized cells, the process is called differentiation. Scientists are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation. The internal signals are controlled by a cell's genes, which are interspersed across long strands of DNA, and carry coded instructions for all the structures and functions of a cell. The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in the microenvironment. Stem cells have potential uses in many different areas of research and medicine, as described below. However, these applications are all likely to be 10-20 years away.

Stem cell curative value

Replacing damaged tissue

Human stem cells could be used in the generation of cells and tissues for cells based therapies this involves treating patients by transplanting specialized cells that have been grown from stem cells in the laboratory. Due to their ability to replace damaged cells in the body, stem cells could be used to treat a range of conditions including heart failure, spinal injuries, diabetics and Parkinson disease. Scientists hope that transplantation and growth of appropriate stem cells in damaged tissue will regenerate the various cell types of that tissue. For example haematopoietic stem cells (stem cells found in bone marrow) could be transplanted into patients with leukemia to generate new blood cells. Or, neural stem cells may be able to regenerate nerve tissue damaged by spinal injury.

Bone marrow stem cells use to rebuild weakened heart muscle

27 September 2005 for the first time, scientists have discovered that injections of bone marrow stem cells can help rebuild weakened heart muscle, thanks to a technique pioneered by Dr. Amit Patel, one of the leaders in stem cell therapy for heart disease, at the University of Pittsburgh Medical Center. Stem cells are primal undifferentiated cells which retain the ability to differentiate into other cell types. This ability allows them to act as a repair system for the body, replenishing other cells as long as the organism is alive. For example, recently, it was discovered that a Pennsylvania woman with heart failure has significantly improved after undergoing a stem cell treatment in Thailand via the direct injection technique pioneered by Dr. Patel. Jeannine Lewis suffered from non ischemic cardiomyopathy. She was in Class III−IV heart failure (the borderline of needing a heart transplant) and on maximal oral medical therapy. After three months, MRI and echocardiogram results showed improvement and doctors have reclassified her to Class I heart failure a significant improvement. Her shortening fraction and stroke volume have also increased.

Dallas born Patel?s interest in Stem Cell research stems from having seen "so many cardiac patients that we couldn't help with surgery or with traditional medications." Patel, 33, earned his undergraduate degree (B.S. 1993) and graduate (M.S. 1994) from Youngstown State University and then went on to earn his M.D. (1998) with distinction from Case Western Reserve University.

He received additional training at Baylor University Medical Center and University of Pittsburgh Medical Center. Among the many awards Patel has received, is the Most Distinguished Resident Award from the American Association of Physicians of Indian Origin (AAPI) at the 21st Annual Convention, Orlando, FL.

Heart Tissue Regeneration

Recent years have seen the emergence of successful adult stem cell treatment for those who have suffered from heart attacks and heart failure. Dr. Andreas M. Zeiher, and Dr. Stefanie Dimmeler (University of Frankfurt) conducted a study of 28 heart attack patients in 2003 (5). The subjects received a transplantation of their own blood and hematopoietic (blood-forming) stem cells into their heart arteries an average of 4.7 days after their respective heart attacks. Two of the patients experienced difficulties arising from personal arterial conditions. The remaining 26 demonstrated higher levels of heart-pumping capability. The researchers reported that the heart's ability to pump blood increased from 44.1 percent to 48.9 percent. The report also indicated the average amount of dead tissue for the subjects decreased by 20 percent within four months of the stem cell implantation. In a French study, doctors found that skeletal muscle stem cells taken from a patient suffering from heart disease and implanted back into his heart successfully treated the condition. This was the first adult stem cell treatment that successfully treated cardiac degeneration (22).

Stem Cell Therapy for Sickle Cell Disease

HCT and replacement gene therapy have curative potential for SCD, and these continue to be actively investigated. HCT has a track record of success and, if applied under optimal conditions, results in clinical cure of the majority of patients. However, it is associated with short-term and long-term toxicities that limit its widespread application. Gene therapy has the potential for a lower toxicity profile compared to transplantation, but very little is known about its long-term toxicity, in particular the effects of ex-vivo manipulation of haematopoietic cells. There are well-based concerns that the genetic and cellular manipulations that are required to ensure high-level expression will carry a significant, but as yet ill-defined, risk of malignancy. In addition, there remain technical difficulties in ensuring the long-term, high-level, tissue-specific expression of replacement or anti-sickling genes, and these difficulties continue to hinder the initiation of clinical trials for gene therapy for hemoglobinopathies. In light of the high-profile nature of gene therapy and transplantation therapies, it is of utmost importance that any clinical trials be conducted in the absence of conflicting interests and with careful attention to ensuring informed consent that deals explicitly with the issues discussed above.

Testing new drugs and testing gene therapy methods

Stem cells grown in the laboratory may be useful for testing drugs and chemicals before they are trialed in people. The cells could be directed to differentiate into the cell types that are important for screening that drug. These cells may be more likely to mimic the response of human tissue to the drug being tested than animal models do.

This may make drug testing safer, cheaper and more ethically acceptable to those who oppose the use of animals in pharmaceutical testing. Stem cells may be useful for screening potential toxins in substances such as pesticides before they are used in the environment. Stem cells may prove useful during the development of new methods for gene therapy that may help people suffering from genetic illnesses.

Non-Human Sugar Molecule

Many human beings have antibodies against the non-human sugar molecule called N-glycolylneuraminic acid (Neu5Gc) circulating in their blood. Scientists hypothesize that the antibodies are produced after a person is exposed to Neu5Gc in animal products consumed as food. NIH-supported scientists have now determined that human embryonic stem cells (hESCs) grown on mouse feeder cells and supported with animal-derived cell culture products express Neu5Gc on their cell surfaces. Cultured hESCs exposed to human blood serum were marked for destruction by the immune system. However, scientists do not yet know whether transplanted cells derived from these hESCs (such as insulin-producing cells or dopamine-producing cells) would be destroyed by the immune system. This study identifies another safety concern that must be addressed before derivatives of hESCs could be used to treat patients in clinical trials (20).

Blood Vessels Regenerate

Blood vessels in skeletal muscle are composed of two cell types, endothelial and perivascular (also known as pericytes, vascular smooth muscle cells, or mural cells). Recently, scientists funded by the Muscular Dystrophy Association (MDA), Italian government, and other sources have discovered that "pericyte-derived" stem cells are located around small blood vessels in muscle tissue and have the potential to regenerate skeletal muscle in individuals with muscular dystrophy. The scientists injected the pericyte-derived cells taken from healthy human muscle tissue into immune-deficient mice missing the dystrophin protein (the cause of human Duchenne muscular dystrophy). The mice showed functional improvement in walking and holding onto a moving rod. Unlike satellite cells in the muscle that can also regenerate skeletal muscle but need to be injected directly into the affected muscle, the new pericyte-derived cells could repair the muscle and reconstitute the muscle cell population by crossing the blood vessel wall into the muscle. Therefore, if these new pericyte-derived stem cells taken from a individual's own muscle could be easily injected into the bloodstream, this would be an ideal treatment for muscular dystrophy (6).

Multipotent Adult Progenitor Cells (MAPCs) Regenerate Blood in Mice

In 2001, scientists isolated a special type of non-blood stem cells from human bone marrow. They named these cells multipotent adult progenitor cells, or MAPCs. MAPCs are able to generate cells of all three embryonic germ layers. Initially, MAPCs were notoriously difficult to isolate and grow in culture. In 2006, scientists reported improved MAPC isolation and culture conditions. Now a collaborative group of NIH-supported scientists successfully used mouse MAPCs to regenerate the blood-forming system in mice.

The scientists speculate that MAPCs may arise earlier in development than blood-forming stem cells, because transplanted MAPCs generated both long-term blood-forming stem cells and all types of early blood cells. Although MAPC-derived cells that did not make blood-specific proteins (i.e., not blood cells) were identified in tissues outside of the blood, they also did not make proteins characteristic of the tissue in which they were found. The scientists have not yet determined the identity of these cells. Transplanted MAPC-derived cells did not appear to form tumors in recipient mice. MAPCs' ability to grow and divide in culture and to regenerate the blood-forming system in mice provides hope that scientists may be able to use human MAPCs to treat diseases of the blood. Doctors may also be able to induce transplant tolerance in human beings by using MAPCs to generate both immune cells and tissues for repair or replacement (29).

Cure Mouse Model of Hemophilia

Hemophilia is a rare inherited disorder in which the blood does not clot normally. The disease is caused when the liver does not produce any (or insufficient amounts of) blood clotting factors. Individuals with hemophilia can be treated with infusions of blood clotting factors, but these only help for a short time. Scientists are searching for ways to permanently restore these individuals' blood-clotting ability. NIH-supported scientists used stem cells to cure mice suffering from a disorder similar to human Hemophilia B. The scientists incubated mouse embryonic stem cells for 7 days with a growth factor called FGF, for Fibroblast Growth Factor. After this treatment, the cells' protein-producing machinery stopped making templates for embryonic proteins and began making templates for proteins of early digestive system cells. When injected into the livers of "hemophilic" mice, the cells survived and made the missing blood-clotting factors. If these results can be repeated in human beings, doctors may one day be able to use human embryonic stem cells (hESCs) to restore blood clotting abilities to individuals with hemophilia (8).

Parkinson's disease

Parkinson's disease is a disorder of the central nervous system in which the substantia nigra, a part of the brain, ceases to produce dopamine, a chemical that allows for effective motion. Dennis Turner is a man who suffered from the disorder for fourteen years. His condition was characterized by strong shaking on the right side of his body, making arm coordination virtually impossible. He underwent years of medication and watched his condition gradually deteriorate. After consultation with a neurologist, he discovered the option of adult stem cell therapy and decided to have the procedure done. His own stem cells were extracted from his brain and subsequently transplanted into the left side of his brain in a 1999 procedure (17). Turner announced in a July 2004 United States Senate subcommittee hearing that he has since experienced dramatic improvement in daily activity. He stated that he went four years without symptoms of the disease. He also affirmed that he would pursue another treatment involving his own stem cells to further improve his condition. The procedure would involve a second extraction of stem cells from his brain and implantation into the right side.

Meanwhile, he explained that his treatment had enabled him to remain active; he has since gone on safaris, photographic excursions to Africa, and swimming sessions in the Atlantic. In another study, five Parkinson's patients received an injection of a normal protein known as glial cell line-derived neurotrophic factor. The factor stimulates the adult stem cells of the brain. Within a year, the patients demonstrated a 61 percent increase in physical coordination and lessening of symptoms (10).

Conclusion

Stem cell holds scientific and medical promise. Like other powerful technologies they pose challenges and risks as well. If we are to realize the benefits meet the challenges and avoid the risks, stem cell research must be conducted under effective accountable systems of social oversight and control at both national and international levels. Stem cells offer a lot of promise and expectations for developing new cell based therapeutics. Despite the difficulties in their isolation and in vitro culture, tremendous progress has been made during the last several years. These new discoveries will bring stem cells closer to the patients' beds and will give hope to patients suffering from untreatable diseases.

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