Stem cells: An overview with respect to cardiovascular and renal disease

Rajnish Kumar, Anju Sharma[1], Ashok Kumar Pattnaik[2], Pritish Kumar Varadwaj[1]

Department of Biotechnology, Amity University, Lucknow, Uttar Pradesh, [1]Department of Bioinformatics, Indian Institute of Information Technology, Allahabad, Uttar Pradesh, [2]Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India

Address for correspondence:
Mr. Rajnish Kumar, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.
E-mail: 12.rajnish@gmail.com

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Abstract

In recent years, there has been a tremendous increase in the understanding of stem cell biology. Stem cells have clonogenic and self-renewing capabilities, and under certain conditions, can differentiate into multiple lineages of mature cells. Recent studies have shown that adult stem cells can be isolated from a wide variety of tissues, including bone marrow, peripheral blood, muscle, and adipose tissue. The potential clinical applications lead to an extended interest in the use of stem cells in many medical disciplines. In this article, we present an overview of stem cells with special reference to cardiovascular and renal diseases treatments by stem cells.

Key words: Cardiovascular disease, renal disease, stem cells

INTRODUCTION

Stem cells are cells found in multicellular organisms. They retain the ability to renew themselves through mitotic cell division and can differentiate into a diverse range of specialized cell type.[1] Two broad types of mammalian stem cells are embryonic cells that are found in blastocysts and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of specialized embryonic tissues.[2] In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, and also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues. As stem cells can be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture, their use in medical therapies has been proposed.

Stem cells are undifferentiated cells that go on to develop into any of the more than 200 types of cells the adult human body holds. The stem cells are formed in the bone marrow (the spongy cavity in the center of large bones). Each stem cell receives chemical signals that direct it to become erythrocytes, leukocytes, or a small cluster of platelets. This growth process occurs in the bone marrow space, and normally only mature cells are released into the peripheral blood stream.[3] Adult stem cells have been identified in many organs and tissues. One important point to understand about adult stem cells is that there are a very small number of stem cells in each tissue. Stem cells are thought to reside in a specific area of each tissue where they may be constantly replicating at a controlled rate to maintain a ready pool of supply when needed. The adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, adipose tissue, spleen, kidneys, and liver [Figure 1].

MAJOR HISTORY RESEARCHES ON STEM CELLS

In a major breakthrough in 1908, Russian histologist Alexander Maksimov[4] proposed the term "stem cell" for scientific usage. Scientific evidence of adult neurogenesis in ongoing stem cell activity in the brain was presented by Joseph Altman *et al.* in 1960.[5] The presence of self-renewing cells in mouse bone marrow was later illustrated

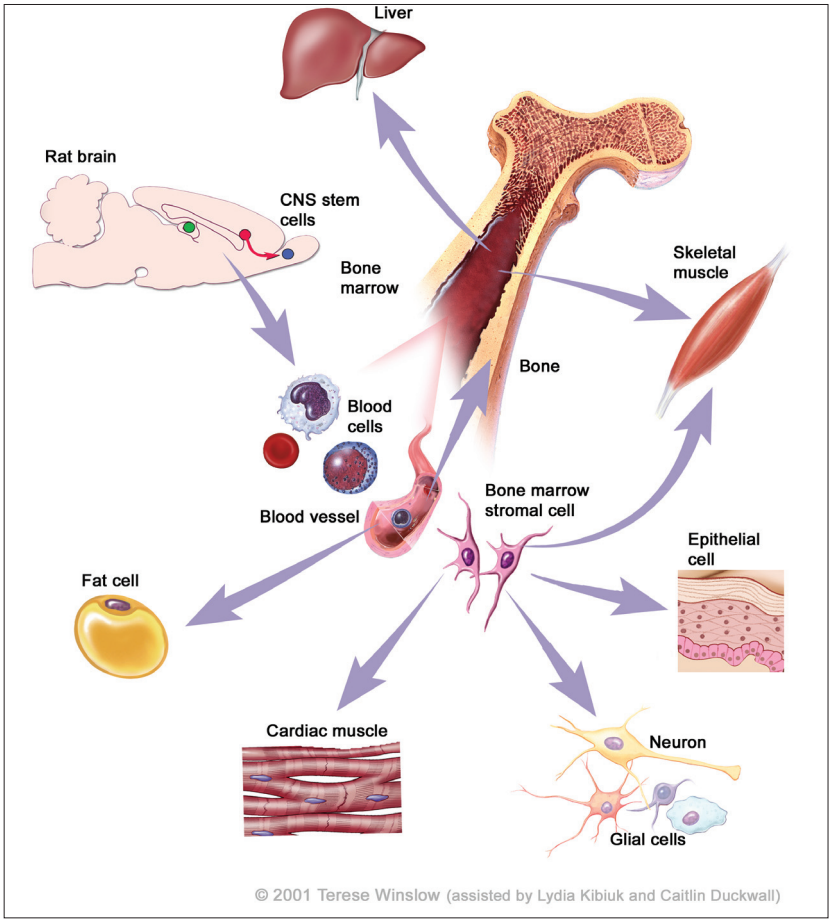

Figure 1: Sources of stem cells (Courtesy: Terese Winslow, Lydia Kibiuk, and Caitlin Duckwall)

in 1963 by McCulloch *et al.*[2] A lot of work was carried out all around the globe related to stem cells. In 1968, the first successful bone marrow transplant between two siblings was done, which brought a new revolution in medical science. Hematopoietic stem cells were discovered in human cord blood in the year 1978. Martin *et al.*[6] derived mouse embryonic stem cells (ESCs) from the inner cell mass in 1981. Gail Martin is attributed for coining the term "embryonic stem cell." Neural stem cells were cultured *in vitro* as neurospheres after 11 years in 1992. The first evidence of cancer stem cell was observed in 1997. Leukemia is shown to originate from a hematopoietic stem cell (HSCs). A year later, James Thomson and co-workers at University of Wisconsin–Madison derived the first human ESC line.[7] Several reports of adult stem cell plasticity were published in 2000. The first early human embryo (four- to six-cell stage) was cloned by scientists at Advanced Cell Technology for the purpose of generating ESCs.[8] Working on parallel lines in 2004–2005, Korean researcher Hwang Woo-Suk claimed to have created several human ESC lines from unfertilized human oocytes. By the end of year 2005 another claim was put forward by researchers at Kingston University in England; they discovered a third category of stem cell, dubbed cord-blood-derived embryonic-like stem cells (CBEs), derived from umbilical cord blood. In 2006, journal *Cell* published the work of Kazutoshi Takahashi and Shinya Yamanaka,[9] namely, Rat Induced Pluripotent Stem Cells. Year 2007 has seen a many new findings in the arena of stem cells. A new type of stem cell was discovered by scientists at Wake Forest University led by Dr. Anthony Atala and Harvard University in early 2007.[10] In the same year (2007), research reported by three different groups showed that normal skin cells can be reprogrammed to an embryonic state in mice.[11] By the end of 2007, a Nobel Prize was awarded to Mario Capecchi, Martin Evans, and Oliver Smithies in Physiology and Medicine for their work on ESCs from mice using gene-targeting strategies producing genetically engineered mice (known as knockout mice) for gene research.[12] Two important works dealing with the induction of pluripotent stem cells was published by Kazutoshi Takahashi *et al.*[13] and by Junying Yu *et al.*[14] In 2008, Wong *et al.*[15] determined the role of gap junctions in embryonic and somatic stem cells. Vanessa Hall[16] found porcine ESCs as a possible source for cell replacement therapy. Danijela Menicanin *et al.*[17]

carried out the genomic profiling of mesenchymal stem cells in 2009. In a recent study by Xu *et al.*[18] in May 2010, the core signaling regulatory mechanism for pluripotent stem cell survival and self-renewal was revealed.

STEM CELL PROPERTIES

Stem cells differentiate into progenitor cells which are far more specific and developmentally committed to a cell line. Most progenitor cells are multipotent or unipotent; therefore, they are also compared to adult stem cells. But they are in "center" between stem cells and fully differentiated cells. Progenitor cells are usually found in adult organisms where they act as a repair system for the body. They replenish special cells and also maintain blood, skin, and intestinal tissues. Examples of progenitor cells include satellite cells in muscles, bone marrow stromal cells, etc.[19]

Self-renewal: They have the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.[20]

Potency: Stem cells have the capacity to differentiate into specialized cell types. Potency includes totipotency and pluripotency. Sometimes, multipotent and unipotent progenitor cells are referred to as stem cells [Figure 2].[2]

Totipotent: Stem cells are produced from the fusion of an egg and a sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. These cells can differentiate into embryonic and extraembryonic cell types.[21]

Pluripotent: Stem cells are the descendants of totipotent cells and can differentiate into cells derived from any of the three germ layers.[22]

Multipotent: Stem cells can produce only cells of a closely related family of cells (e.g., HSCs differentiate into red blood cells, white blood cells, platelets, etc.).[22]

Unipotent: Cells can produce only one cell type, but have the property of self-renewal which distinguishes them from nonstem cells (e.g., muscle stem cells).[23]

Homing: It's a process by which stem cells reach to the different parts of the body.

Plasticity: It's the ability of stem cells to mix with different cells.[20]

IDENTIFICATION OF STEM CELLS

Stem cells can be identified by using methods such as clonogenic assays, where single cells are characterized by their ability to differentiate and self-renew. They are isolated based on a distinctive set of cell surface markers.[24] Adult brain contains neural stem cells and progenitor cells that are capable of generating new neurons. Active continuous neurogenesis is limited to the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus. Newborn neurons gradually become fully functional and are integrated into the existing circuitry of the olfactory bulb and the hippocampus. The transition from stem cells to fully differentiation neurons, the neuronal differentiation

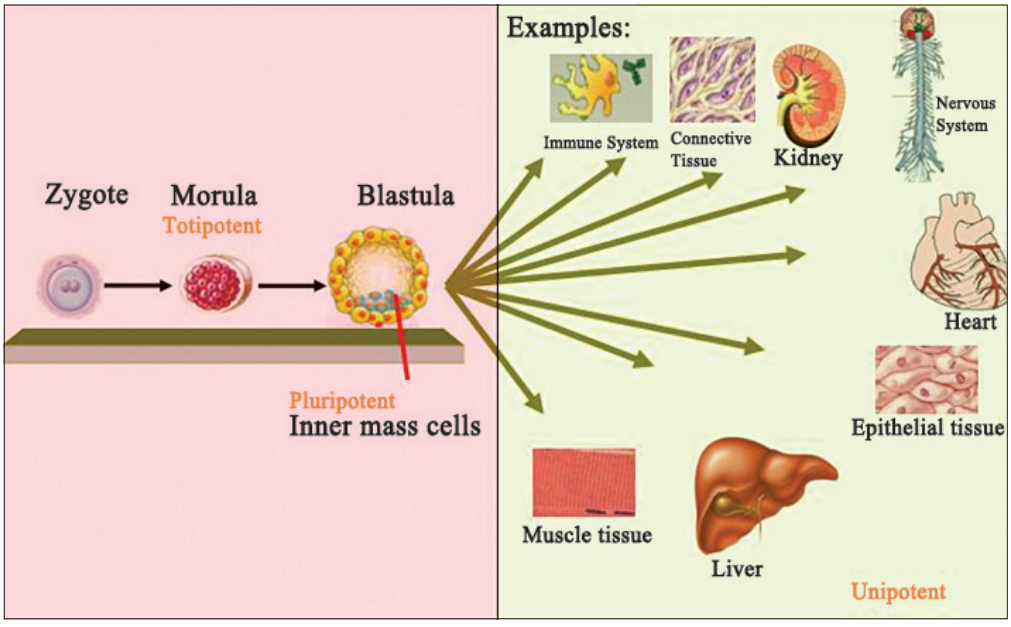

Figure 2: Different potencies of stem cells.

cascade, occurs through defined steps, and different classes of neuronal precursors can be distinguished by their morphology, expressed markers, and mitotic activity. Cells in these classes can be identified by immunophenotyping, labeling with thymidine analogs, and infection with retro- and lentiviral vectors. Encinas et al.[25] generated a series of reporter mouse lines in which neural cells and progenitor cells expressed various fluorescent proteins (GFP, CFPnuc, H2B-GFP, DsRedTimer, and mCherry) under the control of the regulatory elements of the nestin gene. Using these lines, they were able to dissect the neuronal differentiation cascade into several discrete steps and to evaluate the changes induced by various neurogenic and antineurogenic stimuli. In particular, nuclear localization of the fluorescent signal in nestin-CFPnuc mice greatly simplifies the distribution pattern of neural cells and progenitor cells and allows accurate quantitation of changes induced by neurogenic agents in distinct classes of neuronal precursors.[25]

Adult cardiac stem cells in mice are marked by c-Kit, Sca-1, or their ability to efflux Hochest dye due to the expression of ATP-binding cassette transporter.[26-28]

These cells exhibit distinct characteristics with regard to their surface marker expression and biological properties.[29] The c-Kit positive stem cells are clonogenic and self-renewing and capable of *in vitro* differentiation into cardiomyocytes, smooth muscle cells, and endothelial cells. In the human fetal kidney (HFK), self-renewing stem cells residing in the metanephric mesenchyme (MM)/blastema are induced to form all cell types of the nephron till the 34th week of gestation. The definition of useful markers is crucial for the identification of HFK stem cells, because Wilms' tumor, a pediatric renal cancer, initiates from the retention of renal stem cells. Dekel *et al.* hypnotized that surface antigens previously upregulated in microarrays of both HFK and blastema-enriched stem-like Wilms' tumor xenografts (NCAM, ACVRIIB, DLK1/PREF, GPR39, FZD7, FZD2, and NTRK2) are likely to be relevant markers.[30]

ISOLATION OF STEM CELLS

Noguchi *et al.*[31] have established a method for isolating mouse pancreatic stem cells. In their study, pancreatic stem cells were isolated from 8-week-old mice. After purification on a density gradient, the density range of 1.062–1.11 contained pancreatic stem cells. The islets from the layers were deleted by dithizone staining and hand-picking under a dissecting microscope. The remnant cells were then cultured, inoculated into 96-well plates, and cloned by limiting dilution. One of the wells contained cells, named HN no. 5 cells, which expressed ductal cells markers, such as cytokeratin-19. HN no. 5 cells differentiated into insulin-producing cells and albumin-producing cells by induction medium.

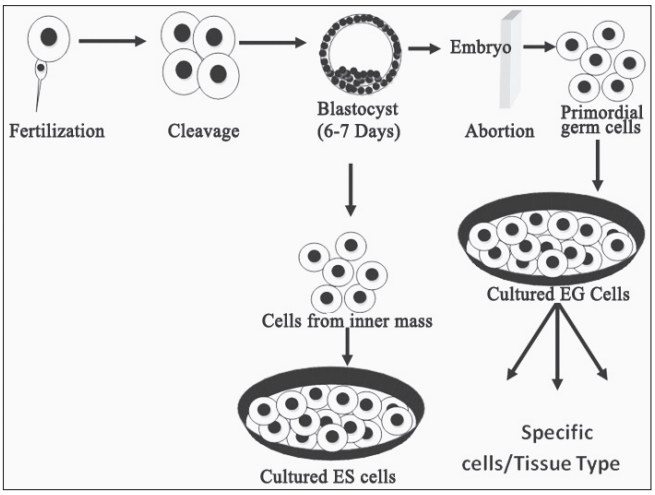

Figure 3: Isolation of embryonic stem cells[32]

The isolation of stem cells for use starts from the abortion of embryo/fetus at the age of 5–9 weeks. The primordial germ cells are isolated and cultured. The cultured ESCs are then selected for the specific tissue type. Embryonic stem cells can also be isolated from the blastocyst stage at the age of 6–7 days. These cells from inner mass are then cultured as ESCs and then specific cell and tissue types are isolated [Figure 3].[33]

STEM CELL TRANSPLANT PROCESS

The process of isolation of stem cells is similar for both autologous and allergenic stem cell transplants. However, in the case of autologous transplants, the patients undergo the stem cell collection procedure prior to receiving high-dose chemotherapy and their cells are frozen and stored until needed. In allergenic transplants, a stem cell donor typically undergoes the collection procedure just before the transplant is performed. Autologous transplants are performed more frequently. After the stem cells are collected, or at some later date, the patient receives high-dose chemotherapy, and diseased cells are destroyed. For example, the chemotherapy drug melphalan is the most commonly used drug in cancer. Within a few days after completing the high-dose chemotherapy, the stored adult stem cells are transplanted or infused into the patient's bloodstream. The infusion process is similar to blood transfusion. The frozen bags of adult stem cells are thawed in a warm water bath and infused into a vein over a period of 2–4 h. The infused stem cells travel through the bloodstream and settle in the target tissues, where they

begin to produce new cells.[34]

Use of stem cells in cardiovascular diseases

Cardiovascular diseases like myocardial infarction, complex congenital heart disease, and subsequent heart failure are a leading cause of morbidity and mortality. Currently, the grafts for replacement therapy or repair are imperfect and subject patients to one or more ongoing risks including thrombosis, limited durability, increased susceptibility to infection, and need for reoperations due to lack of growth in children and young adults. Tissue engineering has emerged as a novel and potentially.[35]

Curative approaches for the replacement of impaired myocardium or reconstruction of the congenital malformations were also developed. In general, cells are seeded in three-dimensional (3D) matrices of (biodegradable) polymers to form 3D living tissue products having structural or functional properties that can be used to restore, maintain, or improve tissue function. In analogy to cardiac tissue grafts currently used in pediatric cardiac surgery, 3D engineered myocardial constructs are expected to provide directed contractile function and to survive and electrically couple to the host myocardium. In addition, they can be designed in appropriate shape and size. Thus, tissue constructs should

1. have clearly defined contractile properties;
2. be large in size;
3. become vascularized and integrated into the host myocardium; and
4. improve contractile function of the diseased myocardium [Figure 4].

Previous reports have shown the feasibility and safety of tissue-engineered myocardial constructs with neonatal cardiomyocytes; in addition, the surgical resection of the nonviable myocardium after infarction and replacement with tissue-engineered cardiac grafts could improve the cardiac function and prevent congestive heart failure. Stem cells have clonogenic and self-renewing capabilities and under certain conditions, can differentiate into multiple cell lineages. Embryonic stem cells are omnipotent cells derived from the inner cell mass of blastocysts. However, unresolved ethical and legal issues, concerns about the tumorigenicity of the cells, and the need to use allergenic cells for transplantation currently hamper their use in clinical studies. Postnatal adult stem cells, with the ability to proliferate and self-renew *in vitro* and the capacity to differentiate into specialized cell types, are an important potential cell source. It indicates that tissue-engineered myocardial constructs with stem cells may potentially offer advantages over current replacement options. Hopefully, the engineered myocardial constructs may fulfill the requirements of native heart muscle and, in the long run, may allow replacement of the injured heart and repair of congenital cardiac defects.

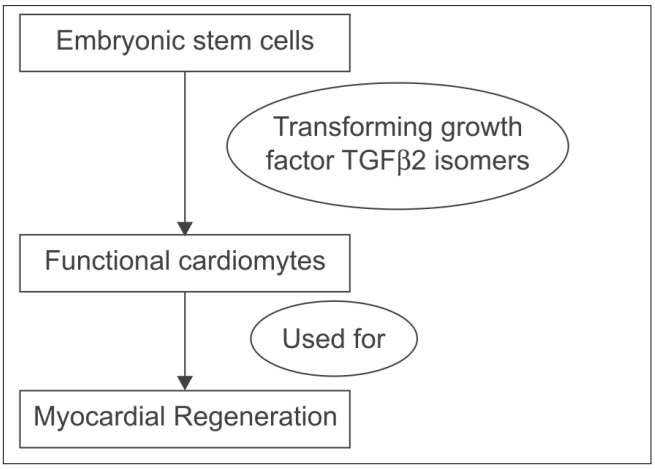

Figure 4: Different steps of generation of heart muscles

The induction of autologous stem cells provides a powerful source for all types of cell regeneration and would be a great advantage in myocardial tissue engineering. Newly formed cardiomyocytes, vascular smooth muscle cells, or endothelial cells in the ischemic heart can be obtained by the transplantation of bone marrow-derived or circulating stem cells, resulting in functional improvement with a partial recovery of contractility or reduced cardiac remodeling. In addition, under certain conditions, postnatal adult stem cells have the potential to transdifferentiate into cardiomyocytes, smooth muscle cells, and endothelial cells which may fulfill the requirements of myocardial tissue engineering. Myocardial stem cells (MSCs) are isolated from the bone marrow; they present an attractive stem cell source for tissue engineering due to ease of procurement and extraordinary potential for *in vitro* expansion in the undifferentiated state. MSCs lack tissue-specific characteristics but under the influence of appropriate signals can differentiate into specialized cells with a phenotype distinct from that of the precursor. It has been seen that MSCs could differentiate into cardiomyocytes and develop into functional phenotypes of myocardial cells after treatment with the demethylating agent 5-azacytidine, formed myotube-like structures, began beating spontaneously after 2 weeks, and beat synchronously after 3 weeks.[36] Electron microscopy revealed a cardiomyocyte-like ultrastructure. These cells had several types of action potentials, such as sinus node-like and ventricular cell-like action potentials.[37]

Fukuda studied expression of alpha-1A, alpha-1B, alpha-1D, beta-1, and beta-2 adrenergic, and M1 and M2 muscarinic receptors. Stimulation with phenylephrine, isoproterenol, and carbachol increased ERK phosphorylation and second messengers. Isoproterenol increased the beating

rate, which was blocked with CGP20712A (beta-1-selective blocker). Recently, pluripotent stem cells termed multipotent adult progenitor cells (MAPCs), marrow-isolated adult multilineage inducible (MIAMI) cells, and human BM-derived multipotent stem cells (hBMSCs) have been isolated from the bone marrow.[38] These cells can be expanded *in vitro* without senescence and develop features of cardiomyocytes, endothelial cells, and smooth muscle cells under certain conditions. They show clonal *in vitro* differentiation potential to cells of the three germ lineages. The relationship between these pluripotent stem cells is not clear; however, regardless of their origin, they are extremely valuable as a source of stem cells for cell therapies and tissue engineering. Although current surgical therapy focuses on the replacement of diseased vessels even after infarction, the potential to replace the myocardial scar with viable engineered myocardial constructs at the time of revascularization offers a novel therapeutic possibility.[39,40]

Stem cell biology allows a completely new approach to the understanding and treatment of cardiovascular disease. It is important to decide which system is best for modeling the role of stem cells in cardiovascular disease. Small animal models, for example mice and rats, are useful for molecular studies owing to the wide range of commercially available transgenic animals and antibodies, although usefulness can be hampered by a shortage of experienced technicians. Meanwhile, large animal models, for example, porcine, although technically easier to work with and in some respect closer to human biology are often restricted by lack of transgenic, money, and space. Animal models are limited by the lack of a system that reproduces the entire disease process in man. However, in spite of this shortcoming, important information has already been obtained using these techniques. This pragmatic approach will eventually permit the transition of cell-based therapies into man. Bench-to-bedside progression can be most quickly accomplished by an open and active collaboration between cell biologists, physiologists, and clinicians.[41]

Induced pluripotent stem cells, commonly abbreviated as iPS cells, are a type of pluripotent stem cells artificially derived from a nonpluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of certain genes. Ethical issues associated with the production of ESCs do not apply to iPSCs, which offer a noncontroversial strategy to generate patient-specific stem cell lines.[42] Somatic cells from a patient with cardiovascular disease could be used to generate iPSCs that could then be directed to give rise to functional adult cardiac muscle cells (cardiomyocytes) that replace diseased heart tissue. iPSCs created from human 50 and murine fibroblasts 51–53 can give rise to functional cardiomyocytes that display hallmark cardiac action potentials. However, the maturation process into cardiomyocytes is impaired when iPSCs are used; cardiac development of iPSCs is delayed compared to that seen with cardiomyocytes derived from ESCs or fetal tissue. Furthermore, variation exists in the expression of genetic markers in the iPSC-derived cardiac cells as compared to that seen in ESC-derived cardiomyocytes. Induced pleuripotent cells can serve as a potential source for treatment of kidney failure, kidney damage, and other renal impairment diseases.[43] An elaborated use of stem cells in renal disease is described below.

USE OF STEM CELLS IN RENAL DISEASES

To properly review recent findings on renal ESCs, it is worthwhile to briefly review renal embryonic organogenesis so that these stem cells may be seen in their proper developmental context. Arising from the intermediate mesoderm are the three embryonic predecessors of the kidney; the pronephros, mesonephros, and metanephros. The pronephros regresses by the fourth week of gestation. The mesonephros forms the mesonephric glomeruli and mesonephric tubules but lacks loop structures. The mesonephric duct (also called Wolffian duct) arises from the intermediate mesoderm. Mesonephric tubules, from the mesonephros, laterally connect to the mesonephric duct, which canalizes to form alumen through its connection with the cloaca. The mesonephric duct caudally sprouts the ureteric bud, which then grows into the metanephric mesenchyme. The ureteric bud then differentiates into calyces, renal pelvis, collecting tubules, and ureter through its contact with the metanephric mesenchyme, whereas the metanephric mesenchyme differentiates to form nephron epithelia. The origin of the renal microvasculature has been debated as extrarenal versus intrarenal. There is evidence that murine metanephric grafts transplanted to the quail chorioallantoic membrane developed quail endothelium, suggesting extrarenal endothelialization of the kidney. Recent evidence suggests that juxtaglomerular smooth muscle and endothelial cells of the embryonic kidney have intrarenal origins in the metanephric mesenchyme. The origin of the macrovasculature of the kidney is thought to be extrarenal, derived from the developing aorta, suggesting a chemoattractant role for the developing kidney. Therefore, stem cells of the embryonic kidney may produce or regulate precursors of the microvasculature while chemoattracting the macrovasculature, which may be important for revascularizing diseased kidneys with therapeutic stem cells in the future. It appears that the metanephric mesenchyme forms nephron epithelial cells, except for collecting duct epithelia derived from the ureteric bud.

In addition, mesenchymal cells differentiate into myofibroblasts and smooth muscle cells. This differentiation is enhanced by the presence of transforming growth factor1 and attenuated by intact collagen. Such data suggest that the mesenchyme contains renal stem cells that are at least multipotent.[44]

In searching for kidney ESCs, another location for potential insight is the mesonephros. The mesonephros and metanephros seem closely related because cells of both require the Pax-2 gene for development, along with bone morphogeneic protein-4 secreted by the surface ectoderm to drive Pax2 expression. Moreover, the mesonephros and metanephros both share close connections with the mesonephric duct and ureteric bud.[45]

Cellular studies show that the mesonephros is a location rich in stem cells. Supplanting the traditional view that the yolk sac was the first source of embryonic hematopoiesis, the mesonephros is a part of the aorta–gonad–mesonephros area now considered the first site of adult hematopoiesis. Thus, the mesonephros has a close regulatory and genetic relationship with the metanephros, as well as a wealth of stem cells for developing hematopoietic and gonadal structures, raising the theoretical possibility of a stem cell connection with the adult kidney. There is a growing body of knowledge regarding the direct transplantation of fetal metanephroi to recapitulate structure and function. Subcapsular transplantation of human fetal kidney fragments into rats resulted in the growth and differentiation of the fetal renal graft. Although this growth and differentiation of the transplanted fetal kidneys is promising, experiments to date have not shown that donor nephrons can incorporate with the recipient's collecting system to provide added renal function. To address this problem, attempts have been made to transplant fetal renal tissue into renal parenchyma. Grafts developed vascularized glomeruli (vasculature was of host origin), mature proximal tubules, and extensions of metanephric tubules into the renal medulla, but donor nephrons did not connect with native collecting ducts.

Alternatively, transplants of metanephroi into the omentum (to avoid space constraints of subcapsular or parenchymal locations) developed into normal kidney structures in animal models and showed functional capabilities evidenced by the ultrafiltration of inulin and production of concentrated urine.[46,47]

ROLE OF DIFFERENT TYPES OF STEM CELLS IN CARDIOVASCULAR AND RENAL DISEASES

HSCs are multipotent stem cells that give rise to all the blood cell types including myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells) and lymphoid lineages. Research in a mouse model indicates that cells from grafts of bone marrow or selected HSCs may act as a home to damaged skeletal and cardiac muscle or liver, and regenerate those tissues.[48] A group of researchers in NIH's intramural research program recently described this approach for treating metastatic kidney cancer.[49]

Endothelial progenitor cells (EPCs) are a population of rare cells that circulate in the blood with the ability to differentiate into endothelial cells, the cells that make up the lining of blood vessels.[50] Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) studied the therapeutic effect of infusing *ex vivo* expanded bone marrow EPCs and culture enriched EPCs derived from peripheral blood into 20 patients suffering from acute myocardial infarction (MI). After 4 months, significant enhancements were found in ventricular ejection fraction, cardiac geometry, coronary blood flow reserve, and myocardial viability.[51] According to Patschan *et al*., renal ischemia after acute kidney injury rapidly mobilizes EPCs and the transplantation of EPCs transferred partial protection after renal ischemia.[52] Moreover, according Abe-Yoshio *et al*., EPCs are involved in capillary repair of damaged glomeruli in HSV-induced glomerulonephritis.[53] Endothelial colony-forming cells (ECFCs) are a subtype of EPCs.[54] Ingram *et al*. have developed an alternative assay that quantifies colonies described as ECFCs and determines the proliferative potential of the cells that form the colony.[55]

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into a variety of cell types. Studies indicate that the cell type most likely involved in cardiac regeneration is the MSC, possibly due to its arteriogenic effects rather than its cardiomyogenic properties.[56] The potential role of MSCs (also called mesenchymal stromal cells) in endogenous repair and cell-based therapies for acute kidney injury (AKI) is under intensive investigation. Preclinical studies indicate that administered MSCs both ameliorate renal injury and accelerate repair.[57]

SIDE EFFECTS OF STEM CELL TREATMENT

The side effects for stem cell treatments are similar to ones experienced during chemotherapy. These effects are also bound to happen because of the large amount of strong drugs and therapy advised toward the treatment and administration of stem cell therapy. Short-term side effects often include nausea, vomiting, diarrhea, loss of appetite, hair loss, and mouth sores or ulcers. However,

when bone marrow cells from the same patient are used, these short-term side effects are not of major concern. In some cases, skin reactions and fatigue occur due to a fall the in red blood cell count during the treatment. Serious complications include a drastic decrease in the white blood cell count because of which an individual is more prone to infections, and bleeding.[58] Various organ complications are also observed in stem cell treatment, including problems developing in the organ systems, such as liver (including hepatitis and other infections), kidneys (including kidney failure), lungs (including inflammation and congestion), and most importantly heart (including reduced pumping ability), caused by chemotherapy, radiation, or medications. This condition mainly arises because of the high doses of chemotherapy involved during the therapy. Graft versus host disease (GVHD) is a potentially serious side effect. It occurs when the body recognizes the transplanted stem cells as foreign substances and begins to attack and destroy these new stem cells.[59] Clinical trials that use stem cells for myocardial repair must address two concerns that accompany the delivery of these cells: (1) safety and (2) tracking the cells to their ultimate destination(s). Although stem cells appear to be relatively safe in the majority of recipients to date, an increased frequency of nonsustained ventricular tachycardia, an arrhythmia, has been reported in conjunction with the use of skeletal myoblasts.[60-63] While this proarrhythmic effect occurs relatively early after cell delivery and does not appear to be permanent, its presence highlights the need for careful safety monitoring when these cells are used. Additionally, animal models have demonstrated that stem cells rapidly diffuse from the heart to other organs (e.g., lungs, kidneys, liver, spleen) within a few hours of transplantation,[64,65] an effect observed regardless of whether the cells are injected locally into the myocardium. This migration may or may not cause side effects in patients; however, it remains a concern related to the delivery of stem cells in humans.

These side effects differ from person to person. One may show all of these side effects after stem cell therapy while the other might not show all. All these side effects of stem cell therapy are at their worst in the initial days after therapy and for a couple of weeks afterward. When the body regains its ability or blood counts start to rise, one may feel better.[66] Some reports suggest that autologous HSC transplantation holds potential for treatment of renal diseases such as lupus nephritis, but the safety of delivering various stem cell types (hematopoietic, mesenchymal, and endothelial precursors) is not well established. Thirabanjasak *et al.* reported a case of lupus nephritis treated by direct renal injection of autologous stem cells recovered from peripheral blood. The patient developed masses at the sites of injection and hematuria. They suspected transitional cell carcinoma but nephrectomy revealed that the masses were angiomyeloproliferative lesions.[67]

FUTURE TREATMENTS OF STEM CELLS

Stem cells have great potential to cure many diseases which have been a great threat for human beings. Certain diseases which can be cured in future with the help of stem cells include Parkinson's disease, coronary artery disease, cardiomyopathy, congestive heart failure, bone marrow transplants, leukemia, and cell replacement therapy in neurological disease.[68] Of course, there are dozens of other diseases on which stem cell research is working on, including treatments of vision or ocular disease processes like retinitis pigmentosa and corneal regeneration, as well as musculoskeletal disorders like muscular dystrophy. Stem cells promises cells cannot be denied in the 21st century, they will continue to wage an untold hope for patients around the world seeking answers and cures to formerly deadly disease processes.

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