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Stem Cells: General Features and Characteristics

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1. Introduction

Stem cells are a group of cells in our bodies, with capacity to self-renew and differentiate to various types of cells, thus to construct tissues and organs. In science, it is still a challenge to understand how a fertilized egg to develop germ layers and various types of cells, which further develop to multiple tissues and organs with different biological functions. In the battle to fight against diseases, stem cells present potencies to repair tissues by cell therapy and tissue regeneration. The study of stem cells turns to be a major frontier in 21 century biology and medicine.

There are many types of stem cells, differing in their degree of differentiation and ability to self-renewing. Gametes cells (eggs or sperms) are stem cells they will develop to a whole body with various tissues after fertilizing. Embryonic cells derived from the part of a human embryo or fetus, are stem cells also with full potential to differentiation. Adult stem cells are partially differentiated cells found among specialized (differentiated) cells in a tissue or organ. Based on current researches, adult stem cells appear to have a more restricted ability of producing different cell types and self-renewing compared with embryonic stem cells.

Cancer stem cells are a sub-group of cancer cells that respond the escaping of cancer chemotherapy and the relapse of tumors. This concept has a great impact on the strategy of cancer chemotherapy and anti-cancer drug design. The new understanding of stem cell has been applied to treat leukemia (induced differentiation) and bone/blood cancer (bone marrow transplants) for many years and has achieved great success.

In the medicine applications, the induced pluripotent stem cells (iPS) reveal a special significance, as they can be induced to derive from many adult tissues or organs by treatment of protein factors. Their features can be similar to the natural embryo stem cells. They provide the source for stem cells without an ethnic conflict.

2. Stem cells

Stem cells are certain biological cells found in all multicellular organisms. They are in small portion in body mass, but can divide through mitosis and differentiate into diverse specialized cell types and can self renew to produce more stem cells. Different types of stem cells vary in their degree of plasticity, or developmental versatility. Stem cells can be classified according to their plasticity and sources.

Classification		Characteristics
Sources/types	Embryonic stem cells	are pluripotent stem cells derived from the inner cell mass of the blastocyst, an early-stage embryo.
	Adult stem cells	Endodermal Origin: Pulmonary Epithelial SCs, Gastrointestinal Tract SCs, Pancreatic SCs, Hepatic Oval Cells, Mammary and Prostatic Gland SCs, Ovarian and Testicular SCs
		Mesodermal Origin: Hematopoietic SCs, Mesenchymal Stroma SCs, Mesenchymal SCs, mesenchymal precursor SCs, multipotent adult progenitor cells, bone marrow SCs, Fetal somatic SCs, Unrestricted Somatic SCs, Cardiac SCs, Satellite cells of muscle
		Ectodermal Origin : Neural SCs，Skin SCs，Ocular SCs
	Cancer stem cells	have been identified in almost all caner/tumor, such as Acute Myeloid leukemic SCs ($CD34^+/CD38^{-}$), Brain tumor SCs ($CD133^+$), Breast cancer SCs ($CD44^+/CD24^-$), Multiple Myeloma SCs ($CD138^+$), Colon cancer SCs ($CD133^+$), Liver cancer SCs ($CD133^+$), Pancreatic cancer SCs ($CD44^+/CD24^+$), Lung cancer SCs ($CD133^+$), Ovary cancer SCs ($CD44^+/CD117^+$), Prostate cancer SCs ($CD133^+/CD44^+$), Melanoma SCs ($CD4^+/CD25^+/FoxP3^+$), Gastric cancer SCs ($CD44^+$).
	Induced pluripotent stem cells	a type of pluripotent stem s artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of specific genes.
Cell potency	Totipotent cells	Zygote, Spore, Morula; It has the potential to give rise to any and all human cells, such as brain, liver, blood or heart cells. It can even give rise to an entire functional organism.
	Pluripotent cells	Embryonic stem cell, Callus; They can give rise to all tissue types, but cannot give rise to an entire organism.
	Multipotent cells	Progenitor cell, such as hematopoietic stem cell and mesenchymal stem cell; They give rise to a limited range of cells within a tissue type.
	Unipotent cells	Precursor cell

Table 1. Classification of stem cells (SCs)

2.1 Embryonic stem cells

Human embryos consist of 50–150 cells when they reach the blastocyst stage, 4-5 days post fertilization. Embryonic stem cells (ES cells) are derived from the inner cell mass of the blastocyst. They present two distinctive properties: they are able to differentiate into all derivatives of three primary germ layers (pluripotency), and they are capable of propagating themselves indefinitely, under defined conditions (Ying & Chambers, 2003).

Dr. Evans first published a technique for culturing the mouse embryos in the uterus and derivation of ES cells from these embryos (Evans & Kaufman, 1981). Dr. Martin demonstrated that embryos could be cultured *in vitro* and ES cells could be derived from these embryos (Martin, 1981). In 1998, a research team led by James Thomson reported the success of isolating and growing human embryonic stem cells in cell culture (Thomason, et al., 2000).

The studies of gene expression in these SE cells have identified many proteins associated with the "stemness" phenotype and can serve as markers for ES cells. After several decades of investigates, a list of SE-specific markers has been established (The National Institutes of Health resource for stem cell research)，such as 5T4, Nanog, ABCG2, Oct-3/4, Alkaline Phosphatase/ALPL, Oct-4A, E-Cadherin, Podocalyxin, CCR4, Rex-1/ZFP42, CD9, SCF R/c-kit, CD30/TNFRSF8, sFRP-2, CDX2, Smad2, Chorionic Gonadotropin, lpha Chain (alpha HCG), Smad2/3, Cripto, SOX2, DPPA4, SPARC/Osteonectin, DPPA5/ESG1, SSEA-1, ESGP, SSEA-3, FGF-4, SSEA-4, GCNF/NR6A1, STAT3, GDF-3, SUZ12, Integrin alpha 6/CD49f, TBX2, Integrin alpha 6 beta 4, TBX3, Integrin beta 1/CD29, TBX5, KLF5, TEX19, Lefty, THAP11, Lefty-1, TRA-1-60(R), Lefty-A, TROP-2, LIN-28, UTF1, LIN-41, ZIC3, c-Myc etc.

The potential to generate virtually any differentiated cell type from embryonic stem cells (ESCs) offers the possibility to establish new models of mammalian development and to create new sources of cells for regenerative medicine and genetic disease and toxicology tests in vitro (Aznar, et al., 2011). To realize this potential, it is essential to be able to control ESC differentiation and to direct the development of these cells along specific pathways. Current embryology has led to the identification of new multipotential progenitors for the hematopoietic, neural, and cardiovascular lineages and to the development of protocols for the efficient generation of a broad spectrum of cell types including hematopoietic cells, cardiomyocytes, oligodendrocytes, dopamine neurons, and immature pancreatic β cells (Murry & Keller, 2008). Today, the most challenges are to devise and optimize effective protocols to induce differentiation of the ES cells into functional adult cells, and to demonstrate the functional utility of these cells, both in vitro and in preclinical models of human disease. For example，effective protocols are expected not only to promote ES cells differentiation into hepatocytes, but also to induce hepatic functions such as albumin secretion, indocyanine green uptake and release, glycogen storage and p450 metabolism. Several recent protocols are efficient to produce high-purity (70%) hepatocytes in cultures, when these are transplanted into mice with acute liver injury, the human ES cells derived endoderm is capable to differentiate into hepatocytes and repopulated the damaged liver (Agarwal, et al., 2008). However, due to the difficulty in controlling of proliferation and differential potential, and the most controversial issue on ethical concerns, the applications of human ES cells are currently limited *in vitro* and in animal studies.

On January 23, 2009, Phase I clinical trials for transplantation of oligodendrocytes (a cell type of the brain and spinal cord) derived from human ES cells into spinal cord-injured individuals received approval from the U.S. Food and Drug Administration (FDA), marking it the world's first human ES cell human trial (CNN.com, 2009). The study leading to this

scientific advancement was conducted by Hans Keirstead and his colleagues at the University of California, Irvine and supported by Geron Corporation of Menlo Park, CA. In October 2010 researchers enrolled and administered ESCs to the first patient at Shepherd Center in Atlanta (Vergano, 2010).

During the rapid development of medicine application of EC cells, safety is always a big concerning. The major concern is the risk of teratoma and other cancers as a side effect of ES cell applications, as their possibility to form tumors such as teratoma (Martin, 1981). The main strategy to enhance the safety of ESC for potential clinical use is to differentiate the ESC into specific cell types (e.g. neurons, muscle, liver cells) that have reduced or eliminated ability to cause tumors. Following differentiation, the cells are subjected to sorting by flow cytometry for further purification. While ESC are predicted to be inherently safer than iPS cells because they are not genetically modified with genes such as c-Myc that are linked to cancer. Nonetheless ESC express very high levels of the iPS inducing genes and these genes including Myc are essential for ESC self-renewal and pluripotency (Varlakhanova, et al., 2010), and potential strategies to improve safety by eliminating Myc expression are unlikely to preserve the cells' "stemness".

2.2 Embryonic germ stem cells

Embryonic germ (EG) cells are derived cells from primordial germline cells (PGCs) in early development. EG cells share many of the characteristics of human ES cells, but differ in significant ways. Human EG cells are derived from the primordial germ cells, which occur in a specific part of the embryo/fetus called the gonadal ridge, and which normally develop into mature gametes (eggs and sperm).

PGCs are mainly isolated from fetal tissue in a narrowed time window (Chapman, et al., 1999). These isolated cells are subsequently allowed to grow and divide in vitro. After one to three weeks in vitro, the human PGCs had formed dense, multilayered colonies of cells that resembled mouse ES or EG cells. Cells in these colonies expressed SSEA-1, SSEA-3, SSEA-4, TRA1–60, TRA-1–81, and alkaline phosphotase. A small, variable percentage (1 to 20 %) of the PGC-derived cell colonies spontaneously formed embryoid bodies. The growth medium for embryoid body cultures lacked LIF, bFGF, and forskolin (Roach, et al., 1993).

The range of cell types in the human PGC-derived embryoid bodies included derivatives of all three embryonic germ layers-endoderm, mesoderm, and ectoderm-based on the appearance of the cells and the surface markers they expressed. This result was interpreted to mean that the PGC-derived cells were pluripotent, however, it was not possible to demonstrate pluripotency in vivo by generating the formation of teratomas in mice (Shamblott, et al., 2001).

2.3 Fetal stem cells

Fetal stem cells are primitive cell types found in the organs of fetuses. Fetal stem cells are capable to differentiate into two types of stem cells: pluripotent stem cells and hematopoietic stem cells. Neural crest stem cells, fetal hematopoietic stem cells and pancreatic islet progenitors have been isolated in the fetuses (Beattie, et al., 1997). Fetal blood, placenta and umbilical cord are rich sources of fetal hematopoietic stem cells.

Human fetal stem cells have been used by many people including children and adults suffering from many of mankind's most devastating diseases (Sei, et al., 2009). Fetal neural stem cells found in the fetal brain were shown to differentiate into both neurons and glial cells (Villa, et al., 2000). Human fetal liver progenitor cells have shown enormous

proliferation and differentiation capacity to generate mature hepatocytes after transplantation in immunodeficient animals (Soto-Guitierrez, et al., 2009). Suzuki et al. showed that a single cell in the c-Met^{+}CD49f$^{-\ low}$c-Kit^{-}CD45^{-}Ter119^{-} fraction from mid-gestational fetal liver has the capacity for self-renewal in vitro and for bipotential differentiation, indicating that this defined fraction contains hepatic stem cells (Suzuki, et al., 2002). Hepatic stem/progenitor cells can be enriched in mouse fetal hepatic cells based on several cell surface markers, including c-Met, Dlk, E-cadherin, and Liv2. Rat Dlk cells isolated from mid-gestational fetal liver exhibit characteristics expected for hepatic stem/progenitor cells. Thus, fetal liver cells may be suitable for overcoming the limitations in engraftment and to allow a functional correction of the disease phenotype (Khan, et al., 2010), as well as in use of artificial liver devices.

Hematopoietic cells are fetal stem cells in the umbilical cord after the birth of a baby. The only potential of these cells are to produce blood cells (Lee, et al., 2010). However, in current medicine practice, they are quite effective in treating blood diseases such as leukemia and anemia. It is a mature medical service today to store the frozen umbilical cord blood of a new born baby, and to use for leukemia, anemia and other predispositions if needed in future (Navarrete & Contreras, 2009).

The tissue rejection problems for fetal cell's application similar to those encountered in kidney and heart transplants may limit the usefulness of fetal stem cells. Further research to overcome this barrier is a hot topic in this field.

2.4 Bone Marrow (BM) stem cells

Adult BM mainly comprises two populations of precursor cells, *hematopoietic stem cells* (HSCs) and marrow stromal cells (MSCs) (Lagasse, et al., 2000). HSC and MSC are both multipotent stem cells. HSCs are present in circulating blood and umbilical cord blood (UCB) and are able to sustain production of all blood cells throughout life. MSCs can be isolated from several other tissues, including adipose tissue, placenta, amniotic fluid, UCB and fetal tissues are able to differentiate into osteocytes, adipocytes, chondrocytes, smooth muscle cells and haematopoietic supportive stroma (Herzog, et al., 2003; Yagi, et al., 2010).

Human HSCs have been defined with respect to staining for Lin, CD34, CD38, CD43, CD45RO, CD45RA, CD59, CD90, CD109, CD117, CD133, CD166, and HLA DR (human). In addition, metabolic markers/dyes such as rhodamine123 (which stains mitochondria), Hoechst33342 (which identifies MDR type drug efflux activity), Pyronin-Y (which stains RNA), and BAAA (indicative of Aldehyde dehydrogenase enzyme activity) have been described. The positive markers useful for MSC identification are CD106, CD105, CD73, CD29, CD44, and Sca-1 (Domen, et al., 2006).

Bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) are the current clinical procedures to restore stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy. The isolation of a large number of potent HSC/MSC sets the basis of new methods for tissue regeneration and cell therapy (Körbling & Freireich, 2011). Nevertheless, the procedure of BM extraction is traumatic and the amount of material extracted is limited. Therefore, exploring new sources and isolation techniques for obtaining such cells is of great interest.

2.5 Adult stem cells

Adult stem cells are any stem cells taken from mature tissue. Because of the stage of development of these cells, they have limited potential compared to the stem cells derived

from embryos and fetuses (Robinson, 2001). Most adult stem cells are lineage-restricted (multipotent) and are generally referred to by their tissue origin (mesenchymal stem cell, adipose-derived stem cell, endothelial stem cell, dental pulp stem cell, etc.) (Barrilleaux, et al., 2006; Gimble, et al., 2007). They play important roles on local tissue repair and regeneration.

The application of adult stem cells in research and therapy is not as controversial as embryonic stem cells, because the production of adult stem cells does not require the destruction of an embryo. Additionally, because in some instances adult stem cells can be obtained from the intended recipient (an autograft), the risk of tissue rejection is essentially non-existent in these situations. Consequently, more USA government funding is being provided for adult stem cell research (US Department of Health and Human Services, 2004).

2.6 Hepatic stem cells

Liver transplantation is the primary treatment for various end-stage hepatic diseases, but is hindered by the source of donor organs and by complications associated with tissue rejection and immunosuppression. Thus, the regenerative capabilities of adult hepatocytes, liver progenitors and stem cells are being studied with great interest.

Adult hepatocytes remain a low mitotic rate during periods of tissue homeostasis. However, extensive documents have been established of these mature hepatic cells to re-enter the cell cycle and to restore damaged parenchyma through both cell hypertrophy and hyperplasia following acute hepatic parenchymal loss when surgical resection or hepatotoxin. Under these circumstances, liver mass is restored primarily through the activation of hepatocytes (Fausto, et al., 2006), suggesting mature hepatocytes could serve their own physiologic precursors (Koniaris, et al., 2003). As evidence, the isolated adult hepatocytes have been showed suitable for the treatment of liver diseases in both animal and human livers. After transplantation of primary adult hepatocytes into Gunn rat, an animal model for UDP-glucuronosyl transferase (UGT1A1) deficiency (Crigler-Najjar syndrome type I), the high bilirubin level is markedly reduced (Matas, et al., 1976). This view is also supported by the current clinical practice of that the hepatocyte transplantation can cure or alleviate congenital metabolic diseases of the liver (Sokal, et al., 2003).

Liver oval cell, a blast-like cell and with the capability of self renewing and multipotent differentiation, is considered as the liver-specific stem cell. It can be identified only in the setting of chronic liver injury, when resident hepatocytes are unable to enter the cell cycle to restore liver mass. (Newsome, et al., 2004; Shafritz, et al., 2006). In multiple independent studies, these liver oval cells have been shown to present molecular markers of adult hepatocytes (albumin, cytokeratins 8 and 18), bile duct cells (cytokeratins 7 and 19, OV-6, A6), fetal hepatoblasts (AFP), and haematopoietic stem cells (Thy -1, Sca-1, c-kit). A recent study provides direct evidence that active Wnt/β-catenin signaling occurs preferentially during the transit amplifying of oval cell population and β-catenin clearly localizes to proliferating oval cells (Sekine, et al., 2007). Although it is not clear yet whether such a cell mass expanding in vitro is sufficient enough for clinical applications and its possible risk on carcinogenesis, oval cells isolated from the liver represent a promising source for cell-based therapy.

Human fetal liver progenitor cells have shown enormous proliferation and differentiation capacity to generate mature hepatocytes after transplantation in immunodeficient animals (Dan, et al., 2006). Hepatic stem/progenitor cells are enriched in mouse fetal hepatic cell fraction, identified with several cell surface markers including c-Met, Dlk, E-cadherin, and

Liv2. A single cell in the c-Met^{+}CD49f$^{-\ low}$c-Kit^{-}CD45^{-}Ter119^{-} fraction from mid-gestational fetal liver revealed the capacity of self-renewal in vitro and bipotential differentiation, indicating the containing of hepatic stem cells in this defined fraction, while the hepatic progenitor cells lack the capacity of self-renewal. As an in vitro cultivation protocol of fetal hepatic stem cells has been established, the fetal liver cells may be promised for the hepatic cell amount in engraftment and the functional correction of the disease phenotype (Khan, et al., 2010), which should be better over the artificial liver devices.

Extra hepatic stem cells have been demonstrated to be involved in liver regeneration too in mice and rats studies (Herzog, et al., 2003). For example, cells from multiple extra hepatic tissues (including BM, umbilical cord and umbilical cord blood (UCB), and amniotic fluid) may differentiate into hepatic cells with some or many hepatic features, and some of them have shown the ability of liver repopulation in vivo. Remarkable trans-differentiation of HSCs to hepatocyte-like cells has been described, mainly in animals with BM/HSC transplantations followed by induction of liver damage. Lagasse et al demonstrated that highly purified HSCs repopulated not only the haematopoietic system, but also the livers with hereditary tyrosinaemia, rescuing these animals from liver failure (Lagasse, et al., 2000). The published reports have suggested that MSCs may differentiate into hepatocyte-like cells both in vitro and in vivo. The cellular mechanism of trans-differentiation of MSCs to hepatocyte-like cells in vivo might be due to cell-fusion, while other reports suggested cell-autonomous trans-differentiation (Alvarez-Dolado, et al., 2003; Vassilopoulos & Russell, 2003).

2.7 Pancreatic stem cells

Pancreatic islet transplantation has demonstrated an efficient way to achieve the long-term insulin independence for the patients suffering from diabetes mellitus type 1. However, because of limited availability of islet tissue, new sources of insulin producing cells that are responsive to glucose are required. Development of pancreatic beta-cell lines from rodent or human origin has progressed slowly in recent years. To date, the best candidate sources for adult pancreatic stem or progenitor cells are: duct cells, exocrine tissue, nestin-positive islet-derived progenitor cells, neurogenin-3-positive cells, pancreas-derived multi-potent precursors; and mature β-cells.

The first report to describe in vitro generated insulin-producing islet-like clusters was based on the expansion of mouse pancreatic duct cells (Gupta, et al., 1999). Afterwards, Bonner-Weir et al (Bonner, 2000) generated the same type of insulin-producing islet-like clusters from cultivated islet buds developed from human pancreatic duct cells in vitro. Our previous study also provided evidence of that GLP-1 is able to induce pancreatic ductal cells with the expression of IDX-1 to differentiate into insulin producing cells (Hui H, 2001), and is able to stimulate glucose-derived de novo fatty acid synthesis and chain elongation during cell differentiation and insulin release (Bullota A，2003). These data indicated pancreatic ductal cells are potential tissue source for insulin-producing islet cells. However, at this time, the expansion capacity of these cultivated cells is still limited, and protocols for in vitro amplification need further optimization for a sufficient number of fully differentiated cells to allow a successful transplantation.

A recent genetic lineage study (Dor, et al., 2004) claimed the replication success of pre-existing β-cells and that turned to be the dominant pathway for the formation of new β-cells in adult mice. Another similar study (Seaberg, et al., 2004) also showed a cloned isolation of multi-potential precursor cells from mouse adult pancreas called pancreas-derived multi-potent precursors. These precursor cells arise from single islet and duct cells.

The generation of insulin-producing cells from pancreatic exocrine tissue has recently been reported (Baeyens, et al., 2005). Both exocrine and endocrine pancreatic originate from a domain of the foregut endoderm, which expresses the pancreatic duodenal homeobox factor (Pdx-1) at early developmental stages. The inactivation of this gene leads to a non-pancreatic phenotype, demonstrating its major role in both exocrine and endocrine pancreatic development. In addition, signaling induced by soluble factors is a prerequisite to pancreatic lineage specification and triggers the emergence of pancreatic precursors expressing Pdx-1. Moreover, as Baeyens et al (ibid.) indicated, there were data suggesting the existence in vivo of acinar-islet transitional cells and the "spontaneous" trans-differentiation of acinar cells to insulin-expressing cells. Altogether, these may suggest that a population of acinar cells, in the presence of certain soluble factors, is competent to adopt an endocrine fate.

Some reports suggest that pancreatic precursor cells express nestin (Zulewski,2001), an intermediate filament protein that is a marker of neural stem cells. These nestin-positive islet-derived progenitor cells also express insulin, glucagon, and Pdx-1 as well as low with levels of insulin secretion. However, other studies suggest that nestin expression is not related to pancreatic precursor identity.

Recent data indicate that Ngn-3-positive cells are endocrine progenitors both in the adult pancreas and in the embryo and that Ngn-3 expression is not seen outside the islets (Gu, et al., 2002). Nevertheless, low levels of Ngn-3 expression within a population of duct cells are not excluded by these studies.

Pancreatic stem cells (PSCs) have the potential to differentiate into all three germ layers. Major markers present on the surface of PSCs include Oct-4, Nestin, and c-kit. DCAMKL-1 is a novel putative stem/progenitor marker, can be used to isolate normal pancreatic stem/progenitors, and potentially regenerate pancreatic tissues.

2.8 Eye stem cells

Human cornea is transparent and clear for vision. Unique to other human organs, there is no blood vessels to provide nutrition in corneas. It is the corneal stem cell existing in the nearby limbus ring, differentiate and move to the center of corneas to renew the transparent and clear cornea around every four months. Stem cells in human cornea play a unique and significant role to maintain the corneal function.

Human corneal stem cells locate on cornea limbus, which is between the colored and white part of the eye (where it joints the sclera). During homeostasis and following injury to the corneal epithelium, the limbal corneal stem cells divide to produce daughter transient amplifying cells that proliferate, migrate onto the central cornea and become terminally differentiated to replace the lost cells (Moore JE, 2002). When a stem cell divides, each new daughter cell has the potential to either remain a stem cell or become a differentiated corneal cell. The microenvironment within the corneal basement membrane is expected the primary factor responsible for the corneal terminal differentiation (Daniels JT, 2001). However, in the case of limbal stem cell deficiency, either due to injury or diseases, it is unable for the corneal ocular repairing and regeneration. In certain corneal disorder such as Keratoconus, some stem cell markers, such as CD34, p63, were reported significantly decreased from normal to keratoconus corneas (Daniels JT, 2001). It is speculated that many corneal disorders such as in keratoconus, anirdia and alkali burns are likely associated with the corneal stem cell deficiency.

Cornea transplantation is widely used to treat certain corneal diseases such as keratoconus. Due to the limited source of donated corneas, corneal stem cells are explored, instead of

corneal buttons. In a pioneering test on cornea damage patients, stem cells were taken from the biopsied limbus tissue, grew into healthy corneal tissue in a little over two weeks, and the healthy tissue was then grafted onto the damaged eye. In the study of 112 patients between 1998 and 2006, 77% of patients had a successful first or second graft. While the opaque cornea became clear again, the vision restored. As human cornea is the most tolerant organ to accept xenograft, the corneal stem cells might be among the first large scale produced stem cells for medical application.

Another frontier of stem cell applications in human eyes is the aged-related macular degeneration (AMD). Macular degeneration is a retinal degenerative disease which causes progressive loss of central vision. The risk of developing macular degeneration increases with age. This disease most often affects people over fifties, and is the most common cause of blindness in the elderly. The impact of AMD on patients includes, but not limits, vision impairment, difficulty with daily activities, increased risk of falls, more depression and emotional distress. It affects the quality of life for millions of elderly individuals worldwide (Pulido JS, 2006). It is not only a health challenge, but also a severe social problem across the world, no mater your ethnic group and gender.

The macula is the central portion of the retina responsible for perceiving fine visual detail. Light sensing cells in the macula, known as photoreceptors, convert light into electrical impulses and then transfer these impulses to the brain via the optic nerve. Central vision loss from macular degeneration occurs when photoreceptor cells in the macula degenerate.

During the stem cell treatment, macular patients are treated by implanting autologous (from selves) stem cells behind the eye via retrobulbar injection under local anesthesia. These re-injected stem cells have the potential to transform into multiple types of cells and are capable of regenerating damaged tissue. Stem cell treatment is so far the most promising approach to restore the vision from AMD among many strategies.

2.9 Cancer stem cell

Cancer stem cells theory is a finding on stem cell biology and an application of stem cell features on cancer studies. Cancer stem cells are those stem cells in tumor mass. They specifically are with the ability to give rise to all cell types found in a cancer sample. According to the hypothesis, the original tumor is developed and formed from these cancer stem cells by self-renewal and differentiation into multiple cell types. Cancer stem cell population consists of only a small potion of tumor mass (around 0.1-1% of total mass) and can be distinguished from the other cells in tumor mass by special cell surface antigens (such as $CD34^+$). Both stem cells and cancer stem cells share the characters of stemness, the capacity of differentiation, the multi-potential differentiation (Gupta PB, 2009). However, the unique character of cancer stem cells, different from normal stem cells, is the growth out of control. They, or their descendants, lost the behavior of “contact inhibition of growth”, the most important character of a non-cancer cell.

During conventional cancer chemotherapies, the differentiated or differentiating cells are likely to be killed while the cancer stem cells, due to their stemness and inactivity, could remain untouched, therefore to escape from chemotherapies. It is believed they serve as “cancer seeds” and respond to the cancer relapse and metastasis by rising new tumors. Based on the concept of cancer stem cells, it is beneficial to include an induction of the cancer stem cell differentiation during chemotherapies (Perkel JM, 2010). This will be expected to increase the efficacy of chemotherapies and improve the survival rate of cancer patients.

2.9.1 Identify cancer stem cell in various types of cancers

The existence of cancer stem cells has been debated for many years until the first conclusive evidence was published in 1997 in Nature Medicine. Bonnet and Dick (Bonnet D, 1997) isolated a subpopulation of acute myeloid leukemic cells that express a specific surface antigen CD34, but lacks the antigen CD38. The authors established that the subpopulation, $CD34^+/CD38^-$, is capable of initiating tumors in NOD/SCID mice that is histologically similar to the donor. Later, Blair A et al reported a similar but slightly different cancer stem cell phenotype of $CD34^+/CD71^-/HLA^-/DR^-$ in acute myeloid leukemic cells (Takaishi S, 1998).

Evidence also comes from the rational of histology, the tissue structure of tumors. Many tumors are very heterogeneous and contain multiple types of cells. These multiple types of cells are believed to be developed from single cells (or a cluster of cells), rather than assembled by multiple cells. If the descendants of these multiple types of cells come from a same ascendant, this implies that the ancestor must have the capacity to generate multiple cell types. In other words, it possessed multi-differential potentials, the fundamental character of stem cells (Bonnet D, 1997).

Tumor type	Surface antigens	Year reported	Reference
Acute Myeloid leukemic	$CD34^+/CD38^-$	1997	Bonnet D, 1997
Brain tumor	$CD133^+$	2003	Singh SK, 2003
Breast cancer	$CD44^+/CD24^-$	2003	Al-Hajj M, 2003
Multiple Myeloma	$CD138^+$	2004	Matsui W, 2004
Colon cancer	$CD133^+$	2007	O'Brien CA, 2007
Liver cancer	$CD133^+$	2007	Ma S, 2007
Pancreatic cancer	$CD44^+/CD24^+$	2007	Li C, 2007
Lung cancer	$CD133^+$	2008	Eramo A, 2008
Ovary cancer	$CD44^+/CD117^+$	2008	Zhang S, 2008
Prostate cancer	$CD133^+/CD44^+$	2008	Maitland NJ, 2008
Melanoma	$CD4^+/CD25^+/FoxP3^+$	2008	Schatton T, 2008
Gastric cancer	$CD44^+$	2009	Takaishi S, 2009

Table 2. Reported cancer stem cell and their surface antigens

The existence of leukemic stem cells prompted further studies in this field. Cancer stem cells have been reported in more and more other cancer types. Followed the Acute Myeloid leukemic stem cells ($CD34^+/CD38^-$), cancer stem cells have also been identified in several solid human tumors respectively.
As cancer stem cells have been identified in various organ origin cancers, it is widely accepted that cancer stem cell is a general format and fundamental concept in all cancers (or tumors).

2.9.2 The origin of cancer stem cells

Where the cancer stem cell comes from? The origin of cancer stem cells is still a hot topic of discussion and argument. Several camps regarding the issue have formed within the scientific community, and it is likely that the correct answer is not limited in one, depending on the tumor types and their developments. Up to date, there is not yet an experimental model has been established to demonstrate a tumor formation in lab, as cancer stem cells are usually isolated from end-stage of tumors rather than the initial stage to tumors. Therefore, describing a cancer stem cell as the cell of origin is often an inaccurate claim, and as hypothesis.
As cancer stem cells share the features of stem cells and of cancer cells, it is not wonder that some researchers believe they are the results of cell mutants from developing stem cells, including progenitor cells, adult stem cells, and the most likely from stem cell niche populations during development. The rational behind is that these developing stem populations are mutated and then expand such that the mutation is shared by many of the descendants of the mutated stem cell. These daughter stem cells are then much easier to becoming tumors, and because of the large amount of cells, there is more chance of a mutation that can cause cancer (Wang ZY, 2000). Adult stem cells are with extremely long lifespan to accumulate mutants that drives cancer initiation. Thus, adult stem cells have also advantages on the logical backing of the theory of tumor formation.
It has also been proposed that the cancer stem cells are mutants from cancer cells after obtaining the stem cell-like features. De-differentiation is a reasonable hypothesis, which assumes these cells acquire stem cell like characteristics by reverse-differentiation from cancer cells. This is a potential alternative to any specific cell of origin, as it suggests that any cell might become a cancer stem cell.
The tumor hierarchy is another model to propose the origin of cancer stem cells. The main point of this model claims that a tumor is a heterogeneous population of mutant cells with various stages of stem cells. In this model, the tumor is made up of several types of stem cells, some stem cell lines will be more thrive than other cell lines, as they adapt to the specific environments. Within the tumor hierarchy model, it would be extremely difficult to pinpoint the cancer stem cell's origin. It is important to bear in mind that, due to the heterogeneous nature of cancers, it is possible that any individual cancer could come from an alternative origin.

2.9.3 The impact of cancer stem cell concept on cancer therapy

The concept of cancer stem cell has a great impact on the strategy of chemotherapy and cancer treatments. The classic view of cancer is that the tumor cell (and its progeny) arises from the progressive accumulation of mutations over time, giving it growth advantage over its neighbors. It also implies that all cells in a tumor have more or less an equivalent capacity to form another tumor - relapse or metastasis. Under the classic view of cancer, the anti-

cancer drugs are designed to target rapid growth cells. However in CSC model, tumor cells have somehow been reprogrammed to be "stem-like", and thus grow slower than surrounding cells. It also implies that only CSCs have the ability to propagate new tumors. According to CSC model, the traditional therapies that target the bulk tumor are to some extent pointless, as the resulting shrinkage may look good on a CT scan, but the disease itself can still recur (Perkel JM, 2010).

Relapse and metastasis are major challenges in current cancer treatments. During the cancer chemotherapies, the cancer (or tumor) mass is initially shrink, but barely cleared up. After a while, they usually come back (relapse) with some new drug resistance features developed. It is believed the cancer stem cells serve as "cancer seeds" with stemness and inactivity features, which help them to escape from chemotherapy and survive from drug attack. They are responding to the cancer relapse. Based on this concept of CSC, it is beneficial to include an induction of the cancer stem cell differentiation before and during chemotherapies. This will be expected to increase the efficacy of chemotherapies and improve the survival rate of cancer patients. This induced differentiation strategy has achieved significant efficacy on blood cancer treatment, such as children's acute promyelocytic leukaemia (APL). A group of pioneer scientists in China used Arsenic and retinoic acid to induce children's APL and have achieved "a complete remission in 92 - 95% of patients with this disease" (Wang ZY, 2000). However in solid tumors, the differentiation inducers and chemotherapeutic agents are difficult to penetrate into the inside of solid tumors. How to improve this penetration is still a big challenge for pharmaceutical researchers.

3. Induced pluripotent stem cells

Induced pluripotent stem cells (Thomson, et al., 1998), commonly abbreviated as iPS cells or iPSCs are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of specific genes. Induced Pluripotent Stem Cells are similar to natural pluripotent stem cells, such as embryonic stem (ES) cells, in many respects, such as the expression of certain stem cell genes and proteins, chromatin methylation patterns, doubling time, embryoid body formation, teratoma formation, viable chimera formation, and potency and differentiability, but the full extent of their relation to natural pluripotent stem cells is still being assessed (Ying, et al., 2003).

iPSCs were first introduced in 2006 from mouse cells and in 2007 from human cells. This has been cited as an important advance in stem cell research, as it may allow researchers to obtain pluripotent stem cells, which are important in research and potentially have therapeutic uses, without the controversialuse of embryos. They also avoid the issue of graft-versus-host disease and immune rejection unlike embryonic stem cells because they are derived entirely from the patient.

Depending on the methods used, reprogramming of adult cells to obtain iPSCs may pose significant risks that could limit its use in humans. For example, if viruses are used to genomically alter the cells, the expression of cancer-causing genes or oncogenes may potentially be triggered. In February 2008, ground-breaking findings published in the journal Cell, scientists announced the discovery of a technique that could remove oncogenes after the induction of pluripotency, thereby increasing the potential use of iPS cells in human diseases (Evans & Kaufman, 1998). In April 2009, it was demonstrated that generation of iPS cells is possible without any genetic alteration of the adult cell: a repeated

treatment of the cells with certain proteins channeled into the cells via poly-arginine anchors was sufficient to induce pluripotency (Martin, 1981). The acronym given for those iPSCs is piPSCs (protein-induced pluripotent stem cells).

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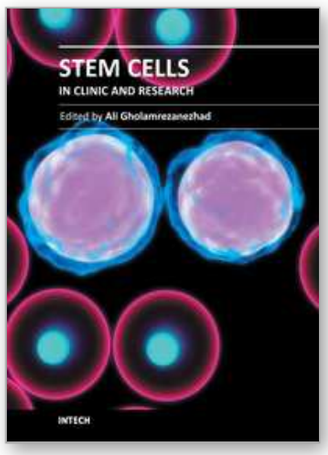

Stem Cells in Clinic and Research

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Based on our current understanding of cell biology and strong supporting evidence from previous experiences, different types of human stem cell populations are capable of undergoing differentiation or trans-differentiation into functionally and biologically active cells for use in therapeutic purposes. So far, progress regarding the use of both in vitro and in vivo regenerative medicine models already offers hope for the application of different types of stem cells as a powerful new therapeutic option to treat different diseases that were previously considered to be untreatable. Remarkable achievements in cell biology resulting in the isolation and characterization of various stem cells and progenitor cells has increased the expectation for the development of a new approach to the treatment of genetic and developmental human diseases. Due to the fact that currently stem cells and umbilical cord banks are so strictly defined and available, it seems that this mission is investigationally more practical than in the past. On the other hand, studies performed on stem cells, targeting their conversion into functionally mature tissue, are not necessarily seeking to result in the clinical application of the differentiated cells; In fact, still one of the important goals of these studies is to get acquainted with the natural process of development of mature cells from their immature progenitors during the embryonic period onwards, which can produce valuable results as knowledge of the developmental processes during embryogenesis. For example, the cellular and molecular mechanisms leading to mature and adult cells developmental abnormalities are relatively unknown. This lack of understanding stems from the lack of a good model system to study cell development and differentiation. Hence, the knowledge reached through these studies can prove to be a breakthrough in preventing developmental disorders. Meanwhile, many researchers conduct these studies to understand the molecular and cellular basis of cancer development. The fact that cancer is one of the leading causes of death throughout the world, highlights the importance of these researches in the fields of biology and medicine.

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