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Stem cells role in regenerative medicine

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Abstract

Stem cells are precursor cells capable of self-renew and of generating numerous mature cell types. As the field of human embryonic stem cells harvesting has been put under questionable ethic issues, other sources are under investigation and present tremendous potential: tissue specific progenitor stem cells, mesenchymal stem cells, umbilical cord cells, bone marrow stem cells, and induced pluripotent stem cells. Stem cells interest different departments of regenerative medicine as well as conservative wildlife. Stem cells might be a viable option for the treatment of pathologies such as spinal injuries, cardiovascular disease, diabetes, liver injuries or even osteoarthritis. Scientists are looking forward to developing molecules that can activate tissue specific stem cells, promote stem cells to migrate to the side of tissue injury, and promote their differentiation to tissue specific cells, so that many health issues could have an alternative and efficient treatment and or even be cured.

Keywords: stem cells, induced pluripotent stem cell, bone marrow stem cells, umbilical cord cells

INTRODUCTION

Stem cells are defined as precursor cells that have the capacity to self-renew and to generate multiple mature cell types (1). During embryogenesis, cells are initially proliferative and pluripotent and then they gradually become restricted to different cell paths. In adults, tissue stem cells are normally quiescent, but become proliferative upon injury. Knowledge from developmental biology and insights into the properties of stem cells are keys to further understanding and successful manipulation (2).

Pluripotency refers to the capacity of an individual cell to transform to all other cell types of the body and of the germline. This property is normally restricted to a brief window in the early development. Self-renewal is the production of identical daughter cells while retaining the ability for differentiation, being the defining characteristic of a stem cell. Stem cells are divided into 2 main forms: the embryonic stem cells and adult stem cells.

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Embryonic stem cells are derived from the inner cell mass of a blastocyst, an early-stage pre-implantation embryo. Human embryos reach the blastocyst stage 4-5 days post fertilization, at which time they consist of 50 to 150 cells. This process starts with the differentiation into the three germ layers, the ectoderm, mesoderm and endoderm, at the gastrulation stage. However, when they are isolated and cultured in vitro, they can be preserved in the stem-cell stage and are known as embryonic stem cells. Recent research leads to the development of regenerative medicine using embryonic stem cells. These cells present a great differentiate potential, having a great rate of in vitro culture growth, they have a great capacity of surviving in low oxygen medium and have a great potential to produce high levels of angiogenic and trophic factors (3,4).

Adult stem cells are undifferentiated cells found during the course of life. There are 2 types of adult stem cells: limited cells originated in the fully developed tissues such as the brain, skin, and bone marrow with the aim to generate only certain types of cells and pluripotent stem cells which are adult stem cells that have been artificially processed to be similar to the embryonic ones. Scientists first reported that human stem cells could be transformed in 2006, with no differences between induced pluripotent and embryonic stem cells, but scientists have not yet found one induced pluripotent stem cell that could develop every kind of cell and tissue (5).

Stem cells represent the base for all tissue and organs system of the body and mediate diverse roles in disease progression, development and tissue repair processes (6).

On the basis of trans differentiation, potential stem cells are four types: unipotent, multipotent, pluripotent and totipotent (7). The zygote cell represents the only totipotent stem cell in human body. This cell can give rise to whole organism through the process of trans differentiation. Cells from the inner cell mass of embryo are naturally pluripotent and can differentiate into cell representing three germs layer but do not differentiate into cells of extraembryonic tissue (8). The transdifferentiation potential of the embryonic, extraembryonic, fetal or adult stem cells depend on functional status of pluripotency factors such as OCT4, cMYC, KLF44, NANOG, SOX2 (9).

Scientists have successfully transformed regular adult cells into stem cells using genetic reprogramming. By altering the genes in the adult cells, researchers can reprogram the cells to act similarly to embryonic stem cells (10). Another candidate for cell therapy is considered to be the perinatal tissue, which possesses numerous types of stem (stromal) cells, having common characteristics of both embryonic and adult stem cells which are beginning to present interest in the treatment of several diseases. Perinatal stem cell sources are represented by cord blood hematopoietic stem cells, umbilical cord mesenchymal stem cells, amniotic membrane stem cells, amniotic fluid stem cells, amniotic epithelial cells and chorionic mesenchymal stem cells (11).

Only after collecting and culturing tissues it is possible to classify cells according to this operational concept. This difficulty in identifying stem cells in situ, without any manipulation, limits the understanding of their true nature (12,13). Boveri and Häcker were the pioneers who named the term of stem cell to describe cells committed to develop the germline (14). Stem cells have fascinated both biologists and clinicians for over a century. The origin of the term “stem cell” can be traced back to the late 19th century. The term stem cell originated in the context of two major embryological questions of that time: the continuity of the germplasm and the origin of the hematopoietic system.

HISTORY

The founder of bone marrow transplantation is considered to be Mathé in 1958. He performed the first marrow transplantation in former Yugoslavia with the aim to save six Yugoslavian nuclear researchers. Another hematologist who worked briefly with Mathé in the 1970s is Barrett of the US National Heart, Lung and Blood Institute (15). In the 1960s it was shown that a rare type of tumor called a teratocarcinoma contains cells that are both pluripotent and self-renewing (Kleinsmith & Pierce, 1964) (16).

In 1961, McCulloch and Till from Toronto University study the sensitivity of mammalian cells to radiation (17). They published a paper showing that a single cell taken from bone marrow can generate colony-making units containing cells that are needed to produce red and white blood cells, and platelets.

In 1963, an article published by Siminovitch (18) proved that stem cells do not just differentiate themselves into new cells, but also have the ability of self-renewal, thereby perpetuating the process throughout an individual’s lifetime. Becker and Siminovitch in an article published in 1963 (19) demonstrated possibility of transplanting marrow cells in mice. Taken together, these two important papers explained the future aim of the stem cells and provided the fundament for regenerative medicine.

In 1981, English biologists Evans and Kaufman isolated mouse embryonic stem cells that become commonly used animal model in stem cell and developmental biology research. In 1995 at the University of Wisconsin-Madison Wisconsin Regional Primate Center, Thomson began his exceptional work in deriving embryonic stem cells from isolated embryos; he

derived the first human embryonic stem cell line in 1998 and human induced pluripotent stem cells in 2007.

Fetal stem cells were first isolated and cultured by Gearhart and his team at the Johns Hopkins University School of Medicine in 1998.

In 2006, Shinya Yamanaka and his team generated induced pluripotent stem cells from adult mouse fibroblasts; they converted fibroblasts into pluripotent stem cells by modifying the expression of only four genes.

All cells are implicated in regenerative medicine and are implicated in miscellaneous cell therapy. Embryonic stem cells is an ideal model for regenerative therapeutics of disease and tissue anomalies.

EMBRYONIC STEM CELLS IN REGENERATIVE MEDICINE

Embryonic stem cells (ESCs) are pluripotent in their nature and can give rise to more than 200 types of cells and promise the treatment of any kinds of disease (20). The most important source of embryonic stem cells is in placental tissue, amnion, and umbilical cord. Fragments are usually obtained from amniocentesis, chorial villosity biopsy and at delivery moment from umbilical cord (20).

Human embryonic stem cells (hESC) have tremendous potential for cell therapy of human diseases such as neurodegenerative disorders, and in regenerative medicine. Since the first derivation of human embryonic stem cell lines from IVF blastocysts 3, the field of hESC research has generated substantial interest, although certain obstacles still remain including limited sources of oocytes and controversial ethical issues that have delayed further advancement (4) . Parthenogenetic stem cells are regarded as a substitute for ESCs lines derived from somatic cell nuclear transfer (SCNT), with higher efficiency and less ethical controversy and proven results in mouse and non-human primate models (21).

Ethical concerns limit the applications of ESCs, where set guidelines need to be followed; in that case tissue specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), umbilical cord cells (UCSCs), bone marrow stem cell (BMSCs), and induced pluripotent stem cells (iPSCs) can be explored as alternatives.

TISSUE SPECIFIC PROGENITOR STEM CELLS IN REGENERATIVE MEDICINE

Tissue specific progenitor stem cells (TSPSCs) maintain tissue homeostasis by continuous cell division, but, unlike ESCs, TSPSCs retain stem cells plasticity and differentiation in tissue specific manner, giving rise to few types of cells (Table 1). The number of TSPSCs population to total cells population is too low (22,23).

MESENCHYMAL STEM CELLS / STROMAL CELLS IN REGENERATIVE MEDICINE

Mesenchymal stem cells (MSCs), the multilineage stem cells, differentiate only to mesodermal origin tissue, which includes tendons, bone, cartilage, ligaments, muscles, and neurons. MSCs are the cells which express combination of markers: $CD73^{+}$, $CD90^{+}$, $CD105^{+}$, $CD11b^{-}$, $CD14^{-}$, $CD19^{-}$, $CD34^{-}$, $CD45^{-}$, $CD79a^{-}$, and HLA-DR, reviewed elsewhere. The application of MSCs in regenerative medicine can be generalized from ongo-

TABLE 1. *Tissue specific progenitor stem cells in regenerative medicine*

Tissue specific stem and progenitor cells	Modalities / Conditions	Regenerative tissue effect	Use / Target
Intestinal progenitor	3D culture M/bacteria Myofibroblasts	Intestinal tissue	Regeneration of intestinal tissue
Dental pulp stem cells	Neuronal culture	Serotonin neuron	Neurogenesis
Mesoangioblasts	3D culture and transplantation to mice tibials	Tibials anterior muscles	Myopathies treatment
Pancreatic progenitors	3D culture	Pancreatic organoid beta-cell	Insulin therapy
Epithelial stem cell	R-spondin I (RSPO I) medium WNT3A medium 3D Matrigel	Fallopian tube organoid	Regeneration of fallopian tube
Limbal stem cell	Transplantation in mice eye	Corneal occupancy	Restoration of vision
Adipose derived stem cell (AdSCs)	Infusion to myocardial infarction	Regeneration of cardiac tissue	Treatment of ischemic heart disease
Inner ear stem cell	LY411575	Auditory hair cells	Restoration of acoustic function
Scheletal stem cell	+ Mesenchyma of skin/ prostate/ intestine	Skin epitelium Prostate epitelium Intestin epitelium	Stem cells factors based transdifferentiation
Skin-derived precursors		Vascular smooth muscle cells	Vascular regenerativ therapy

TABLE 2. *Stem cells applications in regenerative medicine and in disease therapeutics (31)*

Stem cells	Disease	Effects
Embryonic stem cells (ESCs)	Spinal cord injuries	Regeneration of spinal tissue and improved balance and sensation (32)
	Macular degeneration	Recovery from macular degeneration and macular defects and restoration of vision (33)
	Cardiovascular disease	Suppresses heart arrhythmias. Cardiomyocytes electrophysiologically integrate to heart as pacemaker (34)
	Liver injuries	Regeneration of liver tissue can be used as model for screening of drugs (35)
	Diabetes	Improvement in glucose level and obesity can be used for treatment of type 1 diabetes mellitus and type 2 diabetes mellitus
	Osteoarthritis	Regeneration of cartilage tissue can be used for treatment of injuries faced by athletes
Tissue specific progenitor stem cells TSPSCs	Diabetes	Pancreatic occupancy as β-cell can treat type 1 diabetes mellitus and type 2 diabetes mellitus
	Neuro dental problems	Possible application in treatment of neuro dental abnormalities (23)
	Acoustic problems	Cochlear regeneration leads to restoration of acoustic functions
	Intestinal degeneration	Regeneration of goblet mucosa can treat intestinal defects
	Corneal diseases	Regeneration of corneal tissue might treat multiple eye disease
	Muscular deformities	Muscle fiber regeneration; skeletal muscle defects treatment
	Eye diseases and retinopathy	Restoration of vascularization, diabetic retinopathy treatment
	Cardiac dysfunctions	Regeneration of ischemic myocardium
Mesenchymal stem cells MSCs	Bladder deformities	Bladder regeneration from different origins MSCs
	Dental problems	Regeneration of oral tissue and application in periodontics
	Bone degeneration	Regeneration of bones, reduction in injury pain (36)
	Muscle degeneration	Regeneration of heart scar and muscle tissue in controlled way
	Alopecia	Regeneration of hair follicle for treatment of alopecia
Umbilical cord stem cells UCSCs	Congenital heart defects	Regeneration of tissue repair for treatment of heart defects
	Diabetes	Improvement in function of β-cells leads to treatment of diabetes
	Systemic lupus erythematous	Improvement in renal functions & stopping degeneration of tissues
	LSD & neurodegenerative diseases	Treatment of Krabbe's disease, hurler syndrome, metachromatic leukodystrophy, Tay-Sachs Disease and Sandhoff, Parkinson's, stroke, and so forth (37,38)
	Cartilage and tendon injuries	Recovery from tendons and cartilage injuries
	Hodgkin's lymphoma	Treatment of Hodgkin's lymphoma and other cancers
	Peritoneal fibrosis	Effective in treatment of encapsulating peritoneal fibrosis
Bone marrow stem cells BMSCs	Anemia and blood cancer	Treatment of aplastic anemia, hematological malignancies
	AIDS	Treatment of AIDS as an alternative to antiretroviral drugs
	Blood clotting disorders	Therapeutics of burns and blood clotting diseases
	Neurodegenerative diseases	Treatment of neuronal damage disorders and cognitive restoration
	Oro-dental deformities	Regeneration of defects in oral bone, skin, and gum
	Diaphragm abnormalities	Replacement therapy by donor derived niched diaphragm
Induced pluripotent stem cells iPSCs	Neurodegenerative disorders	Autism Spectrum Disorders, Alzheimer's, seizer, and obstinate epilepsies treatment
	Liver & lung diseases	Treatment of chronic obstructive pulmonary diseases causing lungs and liver degeneration
	Diabetes	Treatment of diabetes mellitus and insulin production
	Lung degeneration	Lung degeneration
	AIDS	Immunotherapy of AIDS, HIV1, and other immune diseases

ing clinical trials, phasing through different state of completions (24,25).

UMBILICAL CORD CELLS IN REGENERATIVE MEDICINE

Umbilical cord cells (UCSCs), generally harvested at the time of child birth, is the best-known source for stem cells, procured in noninvasive manner, having lesser ethical constraints than ESCs. The umbilical cord is a rich source of hematopoietic stem cells (HSCs) and MSCs, which possess enormous regeneration potential (26,27). Umbilical cord has emerged as futuristic source for personalized stem cell therapy. Transplantation of UCSCs to Krabbe's disease patients regenerates myelin tissue and recovers neuroblastoma patients through restoring tissue homeostasis. The UCSCs organoids are readily available tissue source for treatment of neurodegenerative disease. Peritoneal fibrosis caused by long term dialysis, tendon tissue degeneration, and defective hyaline cartilage can be regenerated by UCSCs. Intravenous injection of UCSCs enables diabetes, spinal myelitis, systemic lupus erythematosus, Hodgkin's lymphoma, and congenital neuropathies treatment. Cord blood stem cells banking offer a long-lasting source of stem cells for personalized therapy and regenerative medicine (27).

BONE MARROW STEM CELL IN REGENERATIVE MEDICINE

Bone marrow stem cell (BMSCs) in soft spongy bones is responsible for formation of all peripheral blood and comprises hematopoietic stem cells (producing blood cells) and stromal cells (producing fat, cartilage, and bones) (28).

INDUCED PLURIPOTENT STEM CELLS IN REGENERATIVE MEDICINE

The field of induced pluripotent stem cells (iPSCs) technology and research is new to all other stem cells research, emerging in 2006 when, for the first time, Takahashi and Yamanaka generated ESCs-like cells through genetic incorporation of four factors, Sox2, Oct3/4, Klf4, and c-Myc, into skin fibroblast (9). Technological advancement has enabled the achievement of iPSCs from various kinds of adult cells phasing through ESCs or direct trans differentiation.

STEM CELLS IN WILDLIFE CONSERVATION

The unstable growth of human population threatens the existence of wildlife, through overexploitation of natural habitats and illegal killing of wild animals, leading many species to face the fate of being endangered and extinct. For wildlife conservation, the concept of creation of frozen zoo involves preservation of gene pool and germ plasm from threatened and endangered species. The frozen zoo tissue samples collection from dead or live animal can be DNA, sperms, eggs, embryos, gonads, skin, or any other tissue of the body. Preserved tissue can be reprogrammed or transdifferentiated to become other types of tissues and cells, which offers the opportunity for conservation of endangered species and resurrection of life (29,30).

The main possible outcomes in using stem cells are presented in Table 2.

CONCLUSIONS

The spectacular progress in the field of stem cells research represents an important step in the stem cells regenerative therapeutics. We are looking forward for the day when we will be able to produce wide ranges of tissue, organoid, and organs from adult stem cells in order to introduce stem cells in the routine treatment of certain pathologies. Inductions of pluripotency phenotypes in terminally differentiated adult cells have better therapeutic future than ESCs, due to least ethical constraints with adult cells. In the near future, there might be new pharmaceutical compounds; those can activate tissue specific stem cells, promote stem cells to migrate to the side of tissue injury, and promote their differentiation to tissue specific cells.

There is high optimism for use of BMSCs, TSPSCs, and iPSCs for treatment of various diseases to overcome the contradictions associated with ESCs.

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