Multipotent Stem Cell and Current Application

Aligholi Sobhani[1], Neda Khanlarkhani[1], Maryam Baazm[2], Farzaneh Mohammadzadeh[1], Atefeh Najafi[1], Shayesteh Mehdinejadiani[1], and Fereydoon Sargolzaei Aval[3]

[1] *Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Department of Anatomy, School of Medicine, Arak University of Medical Sciences, Arak, Iran*

[3] *Department of Anatomy, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran*

Abstract- Stem cells are self-renewing and undifferentiated cell types that can be differentiate into functional cells. Stem cells can be classified into two main types based on their source of origin: Embryonic and Adult stem cells. Stem cells also classified based on the range of differentiation potentials into Totipotent, Pluripotent, Multipotent, and Unipotent. Multipotent stem cells have the ability to differentiate into all cell types within one particular lineage. There are plentiful advantages and usages for multipotent stem cells. Multipotent Stem cells act as a significant key in procedure of development, tissue repair, and protection. Multipotent Stem cells have been applying in treatment of different disorders such as spinal cord injury, bone fracture, autoimmune diseases, rheumatoid arthritis, hematopoietic defects, and fertility preservation.

Introduction

How to define stem cells?

Stem cells are self-renewing and undifferentiated cell types that can be differentiate into functional cells (1-5). Self-renewal is the process by which stem cells generate unfirentiated daughter cells. It is required for preserve stem cell populations in different tissues (3,6).

Classification of stem cells

Stem cells can be classified into two main types based on their source of origin: (1) Embryonic stem cell, which derived from the inner cell mass of preimplantation embryos and has the ability to form all three embryonic germ layers (i.e., ectoderm, endoderm and mesoderm); (2) Adult stem cells, which scattered in various tissues and organs, and has the capability to produce at least one type of differentiated functional progeny (4,7-10). Although the later type is thought to have limited differentiation capability previously, recent evidence have shown the capacity of differentiation into the 3 embryonic layers (11). Such as induced pluripotent stem cells that can be able to generate from a variety of somatic cells and give rise into endodermal-, mesodermal-, and ectodermal-lineage cells (12,13).

Stem cells also classified based on the range of differentiation potentials (3): Totipotent, Pluripotent, Multipotent, and Unipotent. Totipotent cells such as Zygote and early Blastomeres (1-3 d from oocyte fertilization) have the ability to produce all types of cells while pluripotent cells such as inner cell mass of blastocysts (days 4-14 after oocyte fertilization) could generate all cell types excluding extra embryonic trophoblast lineage (3,9,14,15). Telomerase (Tert) catalytic subunit which is a landmark of pluripotent and germ cells, is express extensively in mouse and human oogonial stem cells (16). Also multilineage-differentiating stress-enduring (Muse) cells are one of the other Pluripotent stem cells examples that have capacity to generate cell types from all three germ layers (17). Multipotent stem cells have the ability to differentiate into all cell types within one particular lineage (14,15) and unipotent stem cells, are defined as cells that have the competency of differentiating into only one lineage (Figure 1) (3).

Corresponding Author: A. Sobhani

Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Tel: +98 21 64053308, Fax: +98 21 66419072, E-mail address: sobhania@tums.ac.ir
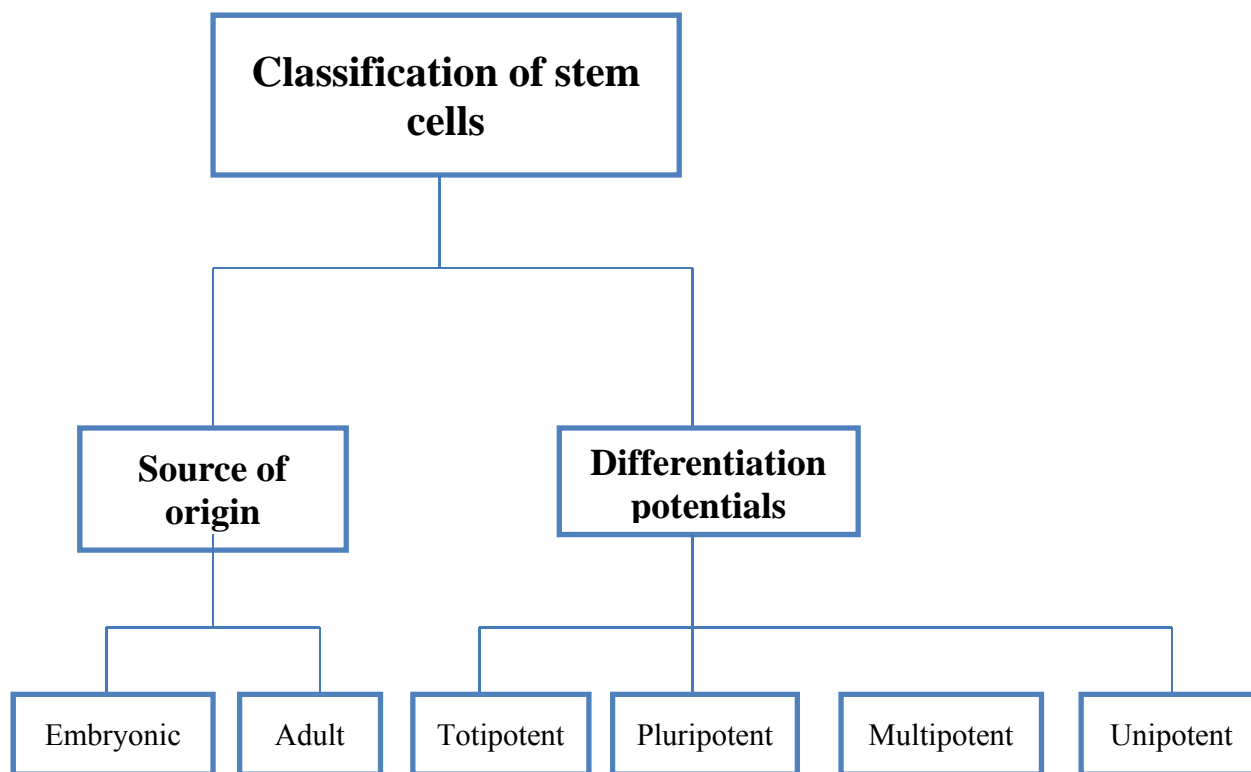
Figure 1. Classification of stem cells

Multipotent stem cells

Multipotent stem cells (MSCs) have the similar main characters of other stem cells. Like other stem cells, multipotent stem cells are undifferentiated cells that have the ability of self-renewing for extended time and give rise into specific cells with particular action. A MSC has the ability of differentiation into multiple lineages and self-renewing. MSCs act as a significant key in procedure of development, tissue healing, and defense. Recently, the application of stem cell for treatment of numerous disorders like neural and cardiac disorders has become a familiar subject with enormous guarantee in the upcoming of medical sciences (18,19).

This kind of stem cell can produce other line of cells although it has some limitation in its capacity of differentiation. For Example, brain's MSCs can generate dissimilar neural cells and glia or haematopoietic stem cells which can differentiate into most of the blood cells, but they do not have the ability of production of the brain cells. Bone marrow furthermore consists of MSCs which can differentiate to all blood cell forms (19).

MSCs are considered as adult stem cells due to their limited ability in differentiation into one or more cell lines. However one of the most famous MSC known as the mesenchymal stem cell can create a number of cell forms. Numerous researches has established that this specific stem cell can differentiate in to different tissue such as bone, muscle, cartilage, fat, and other related tissues (20,21).

MSCs can fundamentally create particular cell types. These kinds of stem cells are different from pluripotent stem cells which can produce nearly all cell type, or totipotent stem cells which can differentiate in to any cell (22). Pluripotent stem cells essentially specialize into MSCs, and formerly MSCs produce cells with a definite target and role (18,20).

MSCs are participated in different clinical trials for treatment of disorders. also, there are powerful researches to realize in what way stem cells can be used in order to management of different disorders (23). MSCs can move in the direction of the area of tissue damage, partially because of the expression of chemokine receptors in respond of the increasing amount of chemokines at the region of tissue injury (24).

MSCs have been applying in treatment of different disorders such as spinal cord injury, bone fracture, autoimmune disorder, rheumatoid arthritis, and hematopoietic defects in animal models (25-27). This area of research makes extra aspect of stem cell therapy. In this field the cells are transplanted to another caserepresenting a different allogeneic host instead of "self". Even though this way of management of diseases

still continuing, it is important in regenerative medicine to protect tissues before transplantation of the organ. Mesenchymal stem cells not only are used in tissue regeneration, but also be used for monitoring of the drugs (28).

MSCs have been considered as a patient-specific drugstores for injured tissue (29). What was initially supposed to have effortless ability of differentiation or stem commitment of mesenchymal tissue cells has established this issue to be a more noticeable and compound topic. These days MSCs are recognized to derive as pericytes, that have the ability of surveying of their domain, act as responder to limited stimulants with many useful interventions (30). The accessibility and adaptability of these amazing cells create them a great therapeutic choice for different part of medical approaches, and it becomes interesting topic in the scientific researches to found obvious method for the most advantageous use of MSC-based therapies (31).

An important form of MSC that recently researches are concentrated on is neural cells. Neural cells differentiate to nerve cells, that they don't have the similar revenue level as do other cells such as blood. These cells have been isolated from the adult and fetal brain tissues, which mean that these cells can differentiate into new nerve cells. The suggestions for remedy of brain and spinal cord injuries are vast and could basically offer a way for treatment of these conditions (28,32,33).

Characterization of MSC

MSCs are originated from different organs of adult beings. It is believed that they exist in the most body tissues, which they can back up dysfunctional or old cells. Therefore, their role is refilling the body's cells through a person's lifetime (28).

MSCs are adult stem cells that are created in human in a number of mature and embryonic organs, consist of adipose (fat), dermis (skin), synovial fluid, periosteum, umbilical cord blood, placenta and amniotic fluid (20,34-36). In adults, though, the main organs of consisting MSCs are bone marrow, adipose tissue , dental pulp, and hair follicle (20,36).

The universal society of stem cell research recognized a standard collection of criterion for identifying MSCs included (1) plastic-adherent cells; (2) the ability of differentiation into tri-lineage including bone, cartilage and fat; (3) expression of specific markers such as CD105, CD73 and CD90; and (4) negative expression for CD45, CD34,CD11b, CD14, CD79a and HLA-DR (37).

Benefits of MSCs

Meanwhile MSCs are separated from pluripotent stem cells; by now these stem cells have incompletely differentiated and they endure specifying during they are growing. They haven't been recognized in whole adult organs until now. Nevertheless new investigations are often demonstrating a detection of MSCs in novel body organs (38). Multipotent adult stem cells seem mainly beneficial in transplantation. They may be harvested, while regularly with trouble, from an individual's tissues and then directed to progress into a definite sort of cells, before injected into the identic case. This way prevents the immunological problems of pluripotent fetal stem cell applications, that immune system of a patient's could possibly refuse a "foreign" tissue. Extra advantage of these stem cells is that the ethical problems and disagreement related to isolating of fetal stem cells is evaded, since fetal tissues or an aborted embryo are not required for stem cell therapy (39).

Some of the MSCs have trophic properties. The main trophic possessions of MSCs are the expression of growth factors and chemokines to induce cell proliferation and angiogenesis. MSCs produce mitogenic proteins such as transforming growth factor-alpha (TGF-a), TGF-b, hepatocyte growth factor, epithelial growth factor (EGF), basic fibroblast growth factor and insulin-like growth factor-1 (IGF-1) to enhance the division of fibroblast, epithelial and endothelial cells (40-42). MSCs are secreting Vascular endothelial growth factor, IGF-1, EGF andangiopoietin-1 to strengthen endothelial cell line and set off angiogenesis (43).

An anti-inflammatory and immunomodulatory action is one of the other benefits of MSC. MSCs produce a selection of growth factors and anti-inflammatory proteins in reaction to inflammatory molecules including interleukin-1 (IL-1), IL-2, IL-12, TNF-a and interferon-gamma (INF-g), that have compound response mechanisms amongst the different immune cells (44).

In addition to properties that mentioned above, these cells have anti-apoptotic properties. The anti-apoptotic actions of MSCs are not completely identified, but a number of important anti-apoptotic proteins have been known. IGF-1 and IL-6 production up regulate the generation of Akt (protein kinase B) and nuclear factor kappa-light-chain-enhancer of activated B cells (18,45).

Isolation and identification of MSCs

MSCs derived from different tissue including: bone marrow, adipose tissue, umbilical cord blood, olfactory bulb, deciduous dental pulp and adult tissue such as

muscle, testis, etc. (46).

All these cells do not have the capability to reconstruct a complete organ and characterized by quick adherence, colony formation, extended proliferation and differentiation to all three germ layer. These cells are characterized by using a long list of indeterminate markers (Table 1) constantly changing in response to their microenvironment, both in vitro and in vivo (47).

Table 1. Multipotent stem cells and their markers

Cell Type		Markers
Human marrow stromal cells	**Negative for**	CD45, 34, 14, 11, 80, 86, 40 , 31, 18 , and 56
	Positive for	CD105 (SH2), 73 (SH3/4), 44, 90 (Thy-1), 71$^+$, 106, 166, 29, Stro-1 and intercellular adhesion molecule-1$^+$
	High expression	integrins α1, α5 and α1
	Low expression	integrins α2, α3, α6, αV, β2 and β4
	No expression	integrins α4, αL and β2
VSELs	**Negative for**	CD45
	Positive for	SSEA-1, Oct-4, Nanog, Rex-1, Sca-1, CXCR4, Stella and Fragilis
Adipose stem cells	**Negative for**	CD31 and Stro-1
	Positive for	P75NTR,CD9, 10, 13, 29, 34, 44, 49$_d$, 49$_e$, 54, 55, 59, 105, 106, 146, and 166
Dental pulp stem cells	**Negative for**	CD14, 45, 34
	Positive for	Stro-1, SH2, 3 and 4, CD29, 44, 166
Keratinocyte stem cells	**Negative for**	CD24 and 34
	Positive for	CD73, 44 and 90

One of the most important sources for MSCs is bone marrow (BM). Bone marrow contains a heterogeneous population of cells: hematopoietic stem cells, marrow stromal cells, endothelial progenitor cells and very small embryonic-like stem cells (VSELs) (48). Among them marrow stromal cells and VSELs are multipotent stem cells. There are some differences between these two cells. Marrow stromal cells have small cell body and few process (fibroblast like cells), but VSELs are very small in size and formed sphere-like colonies in vitro (49).

For a long time the adherent nature of marrow stromal cells has been used to isolate these cells from total bone marrow cells (47). By this method a population of fibroblastic cells will isolate, but these cells are heterogeneous by different biological properties. Some studies have been focused on isolating a purified population of marrow stromal cells from bone marrow. In this regard, some antibodies have been used to isolate this subpopulation including: SB-10, STRO-1, SH-2, and HOP-26. These antibodies react with non-

hematopoietic progenitor bone marrow stromal cells. Unfortunately, there are no specific markers for these cells (50). It is believed that adult human marrow stromal cells do not show the hematopoietic markers such as CD45, CD34, CD14, or CD11. In addition the co-stimulatory molecules like CD80, CD86, or CD40 do not exist on these cells. Among the adhesion molecules studied, CD31 (platelet/endothelial cell adhesion molecule-1), CD18 (leukocyte function-associated antigen-1), and CD56 (neuronal cell adhesion molecule-1) do not express on the human marrow stromal cells but CD106 (vascular cell adhesion molecule-1), CD166 (activated leukocyte cell adhesion molecule), intercellular adhesion molecule-1, and CD29 were found on these cells. Another markers expressed on these cells are CD105 (SH2), CD73 (SH3/4), CD44, CD90 (Thy-1), CD71, and Stro-1 (51). Waller *et al.*, (52) isolated a population of CD34-, CD38-, HLA-DR-, and CD50- from fetal bone marrow by fluorescence-activated cell sorting. This fraction showed marrow stromal cells characteristics. Marrow stromal cells exhibit high

expression of integrins α1, α5 and α1, low expression of α2, α3, α6, αV, β2 and β4, and no expression of α4, αL and β2. Human MSCs also express HLA-ABC and not HLA-DR but the latter is upregulated following treatment with interferon (50). It has been claimed that for isolating a purified marrow stromal cell more than one marker should be used.

VSELs are other multipotent cells in bone marrow. These cells could mobilize in peripheral blood in response to injury. VSELs are SSEA-1+, Oct-4+, Nanog+, Rex-1+, Sca-1+, CD45- (49). In addition these cells express some features of primordial germ cells such as CXCR4, Stella and Fragilis, so, it seems that VSEL stem cells are the progeny of epiblast cells (48).

Adipose tissue, like bone marrow contains a supportive stroma that is easily isolated from human lipoaspirates. Like the other multipotent stem cells, adipose stem cells (ASCs) don't have specific cell marker. After lipoaspiration, and enzymatic digestion, it is possible to use different antibody by FACS or magnetis activated cell sorting methods. Previous studies showed that human ASCs could be isolated as CD34-positive cells/CD31-negative cells by using magnetic beads. Another study suggests that the cell membrane protein p75NTR is a useful indicator of ASCs (53). Human adipose stem cells were analyzed by flowcytometry and immunocytochemistry and these data showed that ASCs have a protein expression phenotype similar to bone marrow stromal cells except one difference. They express CD9, CD10, CD13, CD29, CD34, CD44, CD 49d, CD 49e, CD54, CD55, CD59, CD105, CD106, CD146, and CD166. STRO-1 has not been detected on human ASCs (54,55).

Another source of multipotent cells is dental pulp. The stem cells derived of dental pulp could be isolated from the pulp chamber of each tooth. Different types of antibodies were used for characterization of these cells. After primary culture, data analysis revealed that these cells do not express not only the hematopoietic markers such as CD14, CD45 and CD34 but also some of the smooth muscle, neuronal, cartilage and fat markers. These cells show expression level of vascular cell adhesion molecule 1, MUC-18 (CD146), a-smooth muscle actin, alkaline phosphatase, type I collagen, osteonectin, osteopontin, and osteocalcin, type III collagen and fibroblast growth factor 2 (56). Some evidences showed that these cells also express STRO-1 (like marrow stromal cells), CD29 and CD44 (57). Flow cytometric analysis showed that dental pulp stem cells and bone marrow stem cells were equally SH2, SH3, SH4, CD29 and CD 166 positive (58).

Hair follicles contain keratinocyte stem cells (KSCs) and capable to reconstitute themselves throughout life. These cells localize in the outer root sheath (ORS). The expression levels of WNT inhibitors, WIF1 and DKK3 increase in ORS. The activin/ bone morphogenetic protein (BMP) signaling antagonist FST was selectively overrepresented in the bulge ORS. The blockade of activin signaling by FST may also promote maintenance of KSC quiescence. Another upregulated transcript, angiogenic factor ANGPTL2, may also support development of vasculature and nutrition of bulge ORS cells. These cells do not express CD24; it could be used for KSCs enrichment (59). KSCs similar to marrow stromal cells areCD44+, CD73+, CD90+, and CD34–, and have a population doubling time of 27 h (60).

Application of MSC

One of the challenging contentions that scientists should determine is whether or not a MSC has essentially the ability of specialization into a cell kind different from the tissue which is derived. Present studies on MSCs, though, is now denying the acceptance that MSCs have the limitation in differentiation into the cell types consistent to their original tissues. These stem cells seem to have the potency which surpass the formerly supposed restrictions for generating different cell types, although they perform uncommonly and only under the constricted situations (37).

To recognize this process, the topic of stem cell plasticity has to be purposed. Plasticity of stem cells is a phrase that explains the fact of adult stem cells derived from one organ producing the particular cells of another organ. Extensively, it has been supposed that adult stem cells are tissue-specific, thus they only differentiate to cell kinds in the tissues they are locating (34,37). This potential result of plasticity can be applied in stem cell therapy. It means that if researchers can arrange this differentiation, for example, a blood stem cell could be applied as a substitute for other tissues. Though, there are plentiful debates that must be overwhelmed before this belief can be used in clinic. Nowadays, it seems more reasonable that MSCs will have applied usage in their originating tissues (37,39).

MSCs can be able to differentiate into several cell lines, including osteoblasts, chondrocytes, adipocytes, and myocytes. The highly multipotent cell populations are a respected origin of cells that can be developed as an option in the clinic. In this part we present recent clinical and preclinical use of MSCs (61).

Cardiovascular diseases

Cardiovascular diseases cause death of heart tissue, and the capacity of replacement of these affected myocardial tissue is a vital aim in tissue engineering (62). MSCs transplantation has been revealed to significantly recover cardiac function (end systolic and diastolic volumes, and left ventricular ejection fraction) in several animal models (63,64) and a reduced mortality rate (63). The cell transplantation has a lot of practical advantages such as reduction of the development of heart failure, improvement of the overall action, and rise of the local wall movement.

The mechanisms of these beneficial effects are not exclusively clear, but it is considered as the result of improved myocardial perfusion, recovery of scar, regeneration of cardiomyocytes, and enrolment and activation of endogenous progenitor cells (65,66). Bollini *et al*., (67) was established the therapeutic potential of amniotic fluid stem cell (AFSCs) as a multipotent stem cell for severe heart attack. In this investigation, ischemia in Wistar rats has been induced by 30 min left anterior descending coronary artery ligation, and then AFSCs were administrated. As a result, AFSCs could prevent myocardial cell death and decrease the necrosis extent. Further researches have been recognized AFSCs which are labeled with iron oxide particle in the mouse heart 28 d after transplantation (62). Lee *et al*., (68) applied AFSCs to produce cell bodies that were arranged spherically symmetrical, and were transferred in the periinfarct region of myocardium directly in an immune-suppressed rat.

Medical experiments have been applied in acute heart tissue infarction (MI), ischemic cardiomyopathy, and heart dysfunction. Experimental procedure have been performed via intravenous stem cell therapy (69), intracoronary cell infusion (70), and intramyocardial injection (71). The other clinical usages of MSCs are in the field of cardiovascular disorders. In 2012, Traverse *et al*., (72) studied on 87 cases with acute left ventricle (LV) defection. They have shown that there are no meaningful variances in LV ejection fraction or extent of tissue death between placebo and autologous bone marrow stem cells infusion. Lately, direct myocardial injection of autologous cultured bone marrow mesenchymal stem cells resulted in constant recovery in exercise capacity, beneficial tissue remodeling, angina attack frequency and nitroglycerin consumption at one year after transplantation (71,73).

In a randomized, double-blind, placebo-controlled study, intravenous allogeneic MSCs transplantation examined in 53 cases with severe MI. MSCs were injected in peripheral intravenous path during 10 d of percutaneous intervention for MI. The allogeneic cells was carefully tolerated (74). Advantages were informed for left ventricular ejection fraction and converse renovation in patients with anterior infarcts and, furthermore, there was sign of a decrease in arrhythmic problems in six month fallow-up (69). Chen and colleagues studied the consequences of autologous BM-MSCs therapy in patients with subacute MI. They reported that the perfusion defects improved 3 mo after BM-MSCs transplantation by positron emission tomographic imaging, and left ventriculography proved improvement of ejection fraction (EF) and LV cavity sizes between MSCs-treated cases and placebo group. Prominently, this investigation presented that intracoronary MSCs infusion in patients with acute MI was harmless, and there were no deaths and no arrhythmias through the follow-up (70). In a clicical trial study, eight ischemic cardiomyopathy patients received transendocardial injection of autologous BM-MSCs in LV scar and border zone. There are no serious adverse events in the procedure (71). In a multicenter, randomized MSCs study has been shown that left ventricular end-systolic volume reduce in patients with ischemic heart desease who received intramyocardially autologous BM-MSCs. Furthermore, cell therapy improved the 6-min walk distance, quality of life, physical performance in these patients (75,76).

Liver disease

In some liver diseases such as fulminant hepatic failure (FHF), the only effective treatment option is orthotopic liver transplantation but this treatment needs long term immunosuppressive therapy, suitable organ donor and high costs. Stem cell therapy might be an appropriate treatment for this disease. Previous studies transplanted MSCs-derived hepatocytes and undifferentiated MSCs into immunodeficient mice with liver failure. This treatment could decrease oxidative stress and promote repopulation of hepatocytes (77). In a rat model of acute liver injury, systemic infusion of MSCs had following advantages: prevent the release of liver injury biomarkers, reduce the apoptotic cell number, and increase the hepatocytes proliferation (78). It seems that the peri-portal area is the desired region for the transplanted MSCs (79). In response to partial hepatectomy, adult liver MSCs proliferated and participated in liver regeneration of recipient mouse. MSCs infusion could improve the liver function and the quality of life of patients with liver cirrhosis, hepatitis B,

hepatitis C, alcoholic liver disease, and cryptogenic fibrosis without severe adverse effects (80-82). In liver failure MSCs transplantation have short-term efficacy, although long term outcomes were not affected (76,83).

Inflammatory bowel diseases

Crohn disease, a type of inflammatory bowel disease, is caused by a combination of immune and bacterial factors. There are no treatment options for patients with Crohn disease (62). Because of immunomodulatory properties of placental MSCs, stem cell therapy has developed as a new treatment for patients with resistant Crohn disease (62). Recently, stem cell therapy in patients with Crohn disease could become effective on reducing the signs of disease and this treatment did not show any side effects and toxicities (62).

One phase I trial was conducted to treat Crohn's fistulas with autologous adipose-derived MSCs. Eight fistulas in four patients were injected with MSCs.

In numbre of these fistulas, external openings were enclosed with epithelium at the end of week 8, and other fistulas were healed with a decrease in output flow (84). Also this group was confirmed the therapeutic achievement of MSCs therapy in a phase II trial of this study. Patients with complex perianal fistulas were randomly assigned to treatment with fibrin glue or fibrin glue plus adipose-derived MSCs. This study proved a significant superiority on fistula occlusion of 71% vs 16% in fibrin glue alone (85). In one study, BM-MSCs were isolated from patients with Crohn's disease exhibited morphology, phenotype and proliferation ability similar to MSCs from healthy peoples. Three patients showed clinical responses with CDAI decrease conversely 3 patients required surgery because of disease worsening (86). Ciccocioppo *et al*., (87) documented the efficacy of intrafistular injections of autologous BM MSCs every 4 wk (in 10 Crohn's disease patients). Sustained complete closure was observed in 7 patients and an incomplete closure in 3 patients (76,87).

Osteoarticular diseases

There are numerous clinical trials in the field of multipotent stem cell therapy. One of the most usable stem cells is MSC. A number research groups have established the use of MSCs in orthopedics therapies (88, 89).

Preclinical studies on mice have shown that the scaffolds coated with AFSC could accelerate bone mineralization (90). Micro computed tomography

scanning analysis of constructs confirmed the formation of the hard tissue within the scaffold and an increasing in thickness of new bone appeared at the implantation place. Scaffolds are useful to promote bone regeneration after major injuries. These studies confirmed that AFSCs could contribute in improvement of bone generation after injury (62,91). Micro-CT and histomorphometry results in mouse model of segmental bone fractures proved that mobilization of BM-MSCs caused significant augmentation of bone growth (92).

Because of the unique properties of MSCs, these cells are a valuable tool for cartilage regeneration. Among the various sources for MSCs, BMSc is the best choice for this purpose. The chondrogenic capability of stem cells derived from adipose tissue is lower than BMSCs because the cartilage derived from these cells has low content of collagen type II (46). For in vitro differentiation of BMSCs to chondroblasts some growth factors such as TGF and BMP should be added to the culture medium. The differentiated MSCs expressed chondroblast markers and could be used for treatment of OA and rheumatoid arthritis (93,94). In one study, MSCs and hyaluronic acid injected into the article could accelerate cartilage regeneration (95). Also BMSCs in combination with synthetic extracellular matrix could completely repair the defect in rabbits with osteochondral disease (96). In other study using BMSCs transplantation in patients with osteochondral disease could improve their cartilage condition (97,98).

A study showed stem cells combined with platelet rich plasma (PRP) accelerate bone regeneration in oral implantology surgeries. This combination has shown higher capacity than PRP alone to promote bone regeneration (99).

Autoimmune disease

Ditadi and colleagues established that AFSCs have the ability to differentiate into hematopoietic line cells consist of erythroid, myeloid, and lymphoid cells in vitro. This issue suggest that AFSCs can be a practical origin of cells to restore the hematopoietic system (100). They have found AFSC-derived macrophages, NK, B, and T cells (both CD4 and CD8) 4 mo after AFSC transplantation into immunodeficient RAG1_/_ C57BL/6 (Ly5.1) mice. Subordinate AFSC transplantation was partly effective, which are commending the existence of a little amount of hematopoietic progenitor cells in the population of multipotent AFSC. These transplantation trials showed that AFSCs have longterm ability of the hematopoietic regeneration in vivo and potential therapeutic uses for

the management of blood and immune diseases (100).

The immunomodulatory properties of MSCs make them an ideal tool for treating autoimmune diseases. In systemic lupus erythematosus (SLE) cases, there are contradictory outcomes on the therapeutic application of MSCs. In one study, two young lupus patients were received intravenously one dose of 1 million/kg autologous BM-MSCs (101). During 14 wk of follow-up, there were no opposing effects or changes in SLE disease activity. One case with preceding kidney involvement, 4 mo fallowing the cell transplantation, had a renal flare needing methylprednisolone and cyclophosphamide (101). Liang and colleagues have described intravenous injection of 1 million/kg MSCs into 15 patients including three children with insistently acute SLE. They have reported the improvement of all patients clinically after MSCs therapy (102). The similar group as well investigated whether double MSCs injection is more advantageous than single cell transplantation. In this study, 58 severe SLE patients consist of a number of children were registered, in which 30 cases accidentally received a single dose of MSCs, and remaining cases received two doses of MSCs. These cases were checking out for survival amounts, disease relief, and regeneration, in addition to the adverse events related to transplantation. The consequences revealed that there are not any significant differences between the single and double doses of MSCs transplantation after one year follow-up (103). The amount of mesenchymal progenitor cells which are exist in the synovial fluid in patients with rheumatoid arthritis is decreased (104). This fact can be described via the reduced enrolment of MSCs in the joint (105) or an inhibited proliferation ability of MSCs (106) related to reduced telomere size (76,107).

Type 1 diabetes

The World Health Organization estimates 347 million people worldwide have diabetes. As many as 3 million Americans may have type 1 diabetes (T1D), and each year, more than 15000-40000 children are diagnosed with T1D in the United States (108). Recent management for diabetes mellitus depend on regular several insulin injections, or use of insulin pump, or β-cell or whole pancreas transplantation (62). Wei *et al.*, (109) established that hAECs can be induced for expression of insulin and GLUT-2 mRNA, and they studied the capacity of hAEC for restoration of glucose levels in blood of diabetic mice. In the hAEC-treated mice, level of glucose in blood has been declined to standard range post transplantation. Also, the body

weights of transplanted animals return to normal in comparison with not hAEC-treated mice. Chang and coworkers proved that MSCs which were derived from placenta can be able to make insulin and glucagon (110). The use of MSCs for the cure of T1D due to their ability to differentiate into insulin producing cells and immunological characteristics (111). Hisanaga *et al.*, (112) reported that addition of activin A and betacellulin accelerated MSCs differentiation, and immunoreactive insulin was detected 14 d after the treatment. Another study (113) showed that MSCs, when cultured in well-defined circumstances, may be able to differentiate into cells with the capacity of producing insulin. Additionally, these insulin-secreting cells made masses which, after injection to mice, developed manner comparable to islets of Langerhans. These masses expressed endocrine gene of insulin (I and II), glucagon, somatostatin, and pancreatic polypeptide. Immunohistochemistry analysis as well proved that these masses expressed the insulin, somatostatin, pancreatic polypeptide and C-peptide (113). ELISA assays in the diabetic/severe combined immunodeficiency (NOD/SCID) mouse model verified that blood levels of mouse insulin increase in the human MSCs-treated in comparison to untreated diabetic mice. Moreover the numbre of pancreatic islets and β cells producing mouse insulin have been increased. Most of the β cells in the islets were mouse cells that secreted mouse insulin (114). Few clinical trials using MSCs for T1D are ongoing (76).

Lung diseases

Respiratory disease is an important reason of illness and death. The reasons of respiratory disorders are vary, but the conclusion of the subsequent organ damage is equivalent. These problems are consisting of chronic inflammation, fibrosis, and scarring which causes dysfunction of lung tissue. Amniotic epithelial cells have indicated that they have the potential of using in the treatment of different disorders like cystic fibrosis, pulmonary fibrosis, chronic obstructive lung disease, acute respiratory distress syndrome, pulmonary hypertension, and pulmonary edema (62). The transplantation of human amniotic epithelium cells (hAECs) in animal models of lung disease, has been exposed to decrease both inflammation and following fibrosis besides improving lung function (115). Transplantation of hAECs in mice with bleomycin-induced lung disease caused decrease in gene expression of proinflammatory cytokines tumor necrosis factor-α, transforming growth factor-β, interferon-γ, and

interleukin-6, reduced pulmonary collagen deposition, α-smooth muscle actin expression, and inflammatory cell infiltrate (116). Current researches have made hAECs to express lung-specific proteins consist of the ion channel cystic fibrosis transmembrane conductance regulator, proposing the noticeable use of hAECs for the treatment of patients with cystic fibrosis (62).

Ortiz *et al.,* (117) reported that exogenous administrated MSCs in a mouse bleomycin-induced lung injury model could be found in the injured lungs and these cells seemed to accept characteristics of epithelial cells. MSCs injection closely after exposure to bleomycin also meaningfully decreased the grade of bleomycin-induced inflammation and collagen precipitation in lung tissue. Conservation was related to the transformation of engrafted MSCs into particular and different lung cell phenotypes, with a surge in ranges of G-CSF and GM-CSF and a decline in inflammatory cytokines (118). In a mouse acute lung injury model (lipopolysaccharide (LPS)-induced), demonstrated that MSCs suppressed the LPS induced increase in circulating proinflammatory cytokines lacking of reduction in circulating stages of anti-inflammatory mediators. Histological analysis revealed that MSCs, but not fibroblasts, significantly reduced lung neutrophils at 6,24, and 48 h after LPS treatment (76). Mei *et al.,* (119) found that albumin, total protein, and immunoglobulin M in BAL were increased 3 d after intratracheal LPS and the phenomena were attenuated by MSCs infusion. MSCs transfected with angiopoietin-1 caused additional development in both alveolar inflammation and permeance. Krasnodembskaya *et al.,* (120) reported that MSCs have antibacterial action in a mouse model of pneumonia. They described that mice received live E. coli intratracheally had higher BAL lavage protein after 18 h, and BAL protein was expressively reduced by intratracheal injection of MSCs 4h later.

Numerous investigations evaluated the potential of MSCs as a treatment strategy for Cystic fibrosis (CF). Wang *et al.,* (121) recognized that MSCs have the capacity of differentiation into respiratory epithelia. MSCs therapy for CF patients caused CFTR gene modification, and expression of CFTR does not affect the multipotency of MSCs and are able to contribute to apical chloride secretion in response to cAMP agonist stimulation, signifying the option of emerging cell-based therapy for CF. Another study (122) found that MSCs from cord blood which cultured in specialized airway growth media or with specific growth factors can differentially expressed mRNA for Clara cell secretory protein, CFTR, surfactant protein C, and thyroid

transcription factor-1. Additionally, systemically administrated cord blood-MSCs can migrate to the airway and alveolar epithelium of immunotolerant (NOD/SCID) mice and gain CFTR expression (76).

Renal disease

Regenerative therapy of kidney disease and severe kidney damages can prevent the necessity of the dialysis and/or kidney transplantation in some patients. Perin *et al.,* (123,124) established that AFSCs can afford to development of kidney both ex vivo and in vivo. AFSCs have been injected into the injured tubules in a mouse model of acute tubular necrosis, and supply a protecting impact. Consequently in these animals, levels of creatinine and urea nitrogen in blood decreased and the number of damaged tubules decreased. This useful impact of AFSCs was also associated with meaningful rises in proliferative action of tubular epithelial cells, reduction cast creation, and decrease of apoptosis in tubular epithelial cells (62).

Neural regeneration

One of the main objectives of regenerative medicine is the permanent improvement of demolition of the brain tissue via exploiting of stem cells in order to regulate the procedure of neurogenesis (62). In the twitcher mouse model of neurologic disease the transplantation and continued existence of AFSCs in the rodent brain was confirmed (90). These mice have lack in the lysosomal enzyme named galactocerebrosidase so they are suffering from wide neurodegeneration and neurological destruction, beginning with the malfunction of the oligodendrocytes. AFSCs have been engrafted straightly into the lateral ventricles of the growing brain of a neonatal mouse and stay alive and take part into the fetal mouse brain. Rehni *et al.,* (125) emphasized the ability of AFSCs in Ischemic stroke induced in mice. In this study, ischemia is induced by middle cerebral artery occlusion and reperfusion and causes cerebral injury and makes behavioral disorders included distinctly reduced memory, motor coordination, sensorimotor skills, and somatosensory functions in mice. Current clinical researches recommend that AFSCs can play significant roles in the treatment of degenerative or behavioral brain disease such as stroke, Parkinson disease, Alzheimer disease, and spinal injuries (62,126).

MSCs and male infertility

There are few cells in the normal human testis, which are significant for spermatogenesis that is complex procedure. The key cells are consist of germ

cells with different developing steps, Sertoli cells placed in the seminiferous tubules, and interstitial Leydig cells secreting hormone named testosterone, which is essential for typical procedure of spermatogenesis (127).

These preserving stem cells are responsible for maintaining spermatogenesis. They have an unexpected ability in clinical applications for treatment of infertility. In the testis, stem cells are adjusted by special microenvironments recognized as niches. Spermatogonial stem cells (SSCs), which are male germ line stem cells, able to constantly create sperm through the adulthood (128). Recently, a small number of methods have been presented in order to maintaining reproduction in prepubertal boys and adults. In most of these strategies SSCs have been applied in the treatment of infertility (127).

Many couples encounter infertility and look for help for their unwanted childlessness. Stem cells able to differentiate into several practical cell types and their finding have created the fields of regenerative medicine and cloning. Researchers have required developing ways using stem cells to recover fertility. Stem cells have the ability of differentiation into the most of the cell type available in the body. During the differentiation, stem cells have lost this plasticity; however, some tissues. In fact, adult stem cells have been functionally identified in a wide range of tissues, and are believed to hold great promise for tissue regeneration. We focus here on the therapeutic potential of stem cells for the treatment of male fertility (129).

Spermatogenesis is a multiparts and firmly regulated procedure in which a number of germ-line stem cells give rise in to finally form spermatozoa (130). These stem cells, known as SSCs are located in the basal section of the epithelium that covers the seminiferous, and they stay on the basement membrane. SSC self-renewal ensures the preservation of the large amount of stem cells, as their differentiation creates a large number of germ cells. Consequently, an equilibrium among the self-renewing and differentiating of the SSC in the mature testis is necessary to sustain normal spermatogenesis and fertility during life (131).

In vitro expansion of germ cells from stem cells to generate mature sperm which can be able to contribute in the standard embryo and fetal development has been tried in the last decade. These days, different investigations have indicated the differentiation of the embryonic or somatic stem cells of the mouse and human into male gametes. However, the exact function of these structures still needs to be confirmed (132).

Different researches have been shown MSCs can differentiate into either germ line stem cells or early germ cells in vitro and develop male gametes in vivo after transplantation (133-136).

In 2006, Nayernia *et al.,* (137) established that MSCs derived from bone marrow of mice are able to generate germ line stem cells in vitro. MSCs-derived germ line stem cells ,like germ line stem cells differentiated from teratocarcinoma and ESCs, stop at premeiotic levels leading transplantation into the testes of adult infertile mice (137). Newly, these researchers have published that human bone marrow stem cells may be able to differentiate into the male gamete from (135). Though, they are not able to study the functional capability of these cells (132).

One of the other approaches that recently have been used a lot is multipotent stem cell transplantation in the testes. In 2007, Lue *et al.,* (138) also published that transplantation of bone marrow stem cells into the testis can be useful implication for infertile men. However, different study demonstrated the useful consequences of transplantation of mesenchymal stem cells into the testes of sterile cases (139,140).

MSCs and female infertility

Nowadays stem cells, as new source in diseases treatment especially infertility, are notable for researches. Stem cells, as undifferentiated cells, are presented in different tissues including: the embryonic, fetal, and adult stages of life and play important role in renewal of tissues and organs.

Approximately 15% of couples are suffering infertility (141). Advances in stem cell science have created new hopes in the treatment of infertility.

Currently, this idea about ovary capacity for oocyte production has been challenged in during lifetime of female mammalian (142). Zuckerman *et al*., (143, 144) believed that the oocyte production by female reproductive system is stopped during the postnatal period.

In 2004, Johnson *et al.,* (145) suggest in fact oogenesis and follicugenesis continue over the life of female mammalians. These findings predicate new treatments for infertility caused by aging, ovary insufficiency, premature ovarian failure (145).

There are different source for obtaining stem cells included cleavage or blastocyst stages of embryo (embryonic stem cells, ESC), extra-embryonic tissues (umbilical cord) (146), the placenta (147), and also the amniotic fluid (90). In addition those can be found in adult tissues among bone marrow (148), blood (149), fat (39), skin (150), and also the testis (151).

In the past several years, many attempts have been made toward producing germ cells from stem cells. Currently, there are several reports in relation to this subject. At the beginning of the previous decade, several studies showed production oocyte and sperm from embryonic stem cells in vitro (152-155). Then Geijsen *et al.,* (155) showed that these gametes are able to develop to embryo. Also it is reported follicle production from germline stem cells obtained from mouse ovary by Johnson *et al.,* (145). Particularly, other studies have been demonstrated ovary surface epithelium as source of stem cells (156-158), so that Gene expression profiling confirmed that ovary surface epithelium is a possible foundation of cells with the markers of pluripotency/multipotency (159).

Not only neo-oogenesis is possible by mentioned pluripotent stem cells but also this that is by multipotent stem cells, specifically bone marrow and peripheral blood (160).

BM and peripheral blood as extragonadal sources of germ cells was introduced by Johnson *et al.,* (160). This group can show to recover oogenesis in infertile mice models using transplantation of BM cells and peripheral blood (160). It is demonstrated germline specific markers is expressed in BM of adult mice including Oct4, Mvh, Dazl, Stella, Fragilis (161). Also it was detected specific markers of female germ cell homeobox gene Nobox in BM of adult females (162). In parallel studies, quantitative assessment releaved Mvh expression level alters in BM during the female reproductive cycle (160).

Although BM is a major source of multipotent stem cells, but this procedure is invasive and also obtained cell numbers is low. Thus these problems caused to use other sources (163).

Induction of fetal porcine skin-derived stem cells revealed their capacity to differentiate into oocyte-like cells (OLCs). Confirmation of the differentiation was done by expressed markers such as Oct4, GDF9b, and DAZL. Indeed it is shown if the subsequent differentiation was continuing, they would become into follicle-like aggregates, so that secretion of estradiol and progesterone is detected in OLCs (164).

In 2011, Song S. H *et al.,* (165) in a study on porcine multipotent stem/stromal cells obtained from skin, adipose, and ovarian tissues presented that they can differentiate into putative oocyte-like cells. This researcher group was able to show skin stem/stromal cells (SSCs), adipose stem/stromal cells (ASCs), and ovary stem/stromal cells (OSCs) are similar in characteristics morphology, alkaline phosphatase (AP)

activity, cell cycle stage, the expression of cell surface and pluripotency related markers. In addition, capacity of them in forming of oocyte-like cells (OLCs) was proven using differentiation medium under experimental conditions (165).

Also Irma Virant-Klun *et al.,* (166) isolated cells with the characteristics of pluripotent/multipotent stem cells from adult human ovaries. This researcher team was able to show expressing markers of pluripotency (alkaline phosphatase, surface antigen SSEA-4, OCT4, SOX-2, NANOG, LIN28, STELLA), germinal lineage (DDX4/VASA) and multipotency (MCAM/CD146, Thy-1/CD90, STRO-1) using different methods (166).

As well in other study was demonstrated that ovarian theca-derived multipotent stem cells (TSCs) had high proliferative potential and these cells were able to differentiate into mesenchymal lineages and OLCs. Cell surface markers expression is detected (CD29, CD44 and CD90) on TSCs, while pluripotent markers were not express except SOX2. However under in vitro conditions, in order to differentiation into OLCs were detected that transcription factors consist of OCT4, NANOG and SOX2, specific marker of oocyte genes such as GDF9B, C-MOS, DAZL, VASA, ZPC, SCP3 and STELLA and the marker of folliculogenesis named follicular stimulating hormone receptor expressed. These results support the ability of ovarian theca-derived multipotent stem cells as new source in oogenesis (167).

Finely, fertility restoration by neo-oogenesis in during postnatal can be used in many cases among cancer patients, premature ovarian failure, and gonadal tissue cryopreservation options.

Obviously there are numerous debates about the overcoming of the safe use of multipotent stem cells, nevertheless the advantages of these cells are abundant so they have been considered as a potential for treatment of diseases. Also the use of these stem cells does not have the problems such as ethical issues which are considered for pluripotent and totipotent stem cells. Although support of these cells for research and therapeutic applications is expected to need more time?

Acknowledgement

References

1. Bongso A, Fong CY. Human embryonic stem cells: their

nature, properties, and uses, in Trends in Stem Cell Biology and Technology. Springer 2009:1-17.

2. Hosseinkhani H, Hosseinkhani M. Tissue engineered Scaffolds for stem cells and regenerative medicine, in Trends in Stem Cell Biology and Technology. Springer 2009;367-87.

3. Gargett CE. Adult stem cells in the human endometrium. In: Simon C, Pellicer A, eds. Stem Cells in Human Reproduction: Basic Science and Therapeutic Potential. 2nd ed. London: Informa Healthcare, 2009:160-76.

4. Alison MR, Poulsom R, Forbes S, Wright NA. An introduction to stem cells. J Pathol 2002;197:419-23.

5. Larijani B, Esfahani EN, Amini P, Nikbin B, Alimoghaddam K, Amiri S, et al. Stem cell therapy in treatment of different diseases. Acta Med Iran 2012;50:79-96.

6. Smith A. The battlefield of pluripotency. Cell 2005;123:757-60.

7. Fu RH, Wang YC, Liu SP, Huang CM, Kang YH, Tsai CH, et al. Differentiation of stem cells: strategies for modifying surface biomaterials. Cell Transplant 2010;20:37-47.

8. Board S. Stem cells--scientific, medical, and political issues. N Engl J Med 2002;346:1576-9.

9. Li L, Xie T. Stem cell niche: structure and function. Ann Rev Cell Dev Biol 2005;21:605-31.

10. Nandedkar T, Narkar M. Stem cell research: its relevance to reproductive biology. IJEB 2003;41:724-39.

11. Bunnell BA, Flaat M, Gagliardi C, Patel B, Ripoll C. Adipose-derived stem cells: isolation, expansion and differentiation. Methods 2008;45:115-20.

12. Yoshida Y, Yamanaka S. iPS cells: a source of cardiac regeneration. J Mol Cell Cardiol 2011;50:327-32.

13. Niibe K, Kawamura Y, Araki D, Morikawa S, Miura K, Suzuki S, et al. Purified mesenchymal stem cells are an efficient source for iPS cell induction. PLoS One 2011;6:e17610.

14. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell 2008;132:567-82.

15. Krampera M, Franchini M, Pizzolo G, Aprili G. Mesenchymal stem cells: from biology to clinical use. Blood Transfus 2007;5:120-9.

16. Woods DC, White YA, Tilly JL. Purification of oogonial stem cells from adult mouse and human ovaries: an assessment of the literature and a view toward the future. Reprod Sci 2013;20:7-15.

17. Wakao S, Kitada M, Kuroda Y, Shigemoto T, Matsuse D, Akashi H, et al. Multilineage-differentiating stress-enduring (Muse) cells are a primary source of induced pluripotent stem cells in human fibroblasts. Proc Natl Acad Sci U. S. A. 2011;108:9875-80.

18. Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 2013;45):e54.

19. Mundra V, Gerling IC, Mahato RI. Mesenchymal stem cell-based therapy. Mol Pharm 2012;10:77-89.

20. Bibber B, Sinha G, Lobba AR, Greco SJ, Rameshwar P. A Review of Stem Cell Translation and Potential Confounds by Cancer Stem Cells. Stem Cells Int 2013;2013:241048.

21. Campagnoli C, Roberts IA, Kumar S, Bennett PR, Bellantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. Blood 2001;98:2396-402.

22. Chen FM, Wu LA, Zhang M, Zhang R, Sun HH. Homing of endogenous stem/progenitor cells for <i> in situ </i> tissue regeneration: Promises, strategies, and translational perspectives. Biomaterials 2011;32:3189-209.

23. He Q, Wan C, Li G. Concise review: multipotent mesenchymal stromal cells in blood. Stem Cell 2007;25:69-77.

24. Friedenstein AJ, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues: cloning in vitro and retransplantation in vivo. Transplant 1974;17:331-40.

25. Weiss DJ, Bertoncello I, Borok Z, Kim C, Panoskaltsis-Mortari A, Reynolds S, et al. Stem cells and cell therapies in lung biology and lung diseases. Proc Am Thoracic Soc 2011;8:223-72.

26. Yagi H, Soto-Gutierrez A, Kitagawa Y, Tilles AW, Tompkins AG, Yarmush ML. Bone marrow mesenchymal stromal cells attenuate organ injury induced by LPS and burn. Cell Transplant 2010;19:823-30.

27. Guan XJ, Song L, Han FF, Cui ZL, Chen X, Guo XJ, et al. Mesenchymal stem cells protect cigarette smoke-damaged lung and pulmonary function partly via VEGF–VEGF receptors. J Cell Biochem 2013;114:323-35.

28. Khanlarkhani N, Atlasi MA, Kashani R, Naderian H, Taherian AA, Nikzad H. The effects of progestrone on the in-vitro expression of P0, S100 and Krox20 genes in adipose-derived stem cells. Tehran Univ Med J 2011;69:67-74.

29. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell 2011;9:11-5.

30. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J Cell Physiol 2007;213:341-7.

31. Haynesworth S, Barer M, Caplan A. Cell surface antigens on human marrow-derived mesenchymal cells are detected by monoclonal antibodies. Bone 1992;13:69-80.

32. Butti E, Cusimano M, Bacigaluppi M, Martino G. Neurogenic and non-neurogenic functions of endogenous neural stem cells. Frontiers Neurosci 2014;8:92.

33. Kennea NL, Mehmet H. Neural stem cells. J Pathol 2002;197:536-50.

34. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell 2008;3:301-13.

35. Traktuev DO, Merfeld-Clauss S, Li J, Kolonin M, Arap W, Pasqualini R, et al. A population of multipotent CD34-positive adipose stromal cells share pericyte and mesenchymal surface markers, reside in a periendothelial location, and stabilize endothelial networks. Circ Res 2008;102:77-85.

36. Zimmerlin L, Donnenberg VS, Rubin JP, Donnenberg AD. Mesenchymal markers on human adipose stem/progenitor cells. Cytometry Part A 2013;83:134-40.

37. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7.

38. Tsao CW, Chiang MZ, Cheng YC. Effects of Chemical and Physical Shear-Stress Stimulation of Human Placenta-Derived Multipotent Stem Cells in Microchannel. Proceedings of the ASME 2013 11th International Conference on Nanochannels, Microchannels, and Minichannels, 2013.

39. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell 2002;13:4279-95.

40. Haynesworth SE, Baber MA, Caplan AI. Cytokine expression by human marrow-derived mesenchymal progenitor cells in vitro: Effects of dexamethasone and IL-1α. J Cell Physiol 1996;166:585-92.

41. Haynesworth SE, Baber MA, Caplan AI. Pro-osteogenic trophic effects by PKA activation in human mesenchymal stromal cells. Biomaterials 2011;32:6089-98.

42. Caplan AI, Bruder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. Trends Mol Med 2001;7:259-64.

43. Chen L, Tredget EE, Wu PY, Wu Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PloS One 2008;3:e1886.

44. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815-22.

45. Gnecchi M, He H, Noiseux N, Liang OD, Zhang L, Morello F, et al. Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. FASEB J 2006;20:661-9.

46. Yoshimura H, Muneta T, Nimura A, Yokoyama A, Koga H, Sekiya I. Comparison of rat mesenchymal stem cells derived from bone marrow, synovium, periosteum, adipose tissue, and muscle. Cell Tissue Res 2007;327:449-62.

47. Bianco P, Riminucci M, Gronthos S, Robey PG. Bone marrow stromal stem cells: nature, biology, and potential applications. Stem Cell 2001;19:180-92.

48. Kucia M, Wysoczynski M, Ratajczak J, Ratajczak M. Identification of very small embryonic like (VSEL) stem cells in bone marrow. Cell Tissue Res 2008;331:125-34.

49. Kucia, M., R. Reca, F. Campbell, E. Zuba-Surma, M. Majka, J. Ratajczak, et al., A population of very small embryonic-like (VSEL) CXCR4+ SSEA-1+ Oct-4+ stem cells identified in adult bone marrow. Leukemia, 2006. 20(5): p. 857-869.

50. Barry FP, Murphy JM. Mesenchymal stem cells: clinical applications and biological characterization. Int. J. Biochem. Cell Biol 2004;36:568-84.

51. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cell 2007;25:2739-49.

52. Waller EK, Olweus J, Lund-Johansen F, Huang S, Nguyen M, Guo G, et al. The common stem cell" hypothesis reevaluated: human fetal bone marrow contains separate populations of hematopoietic and stromal progenitors. Blood 1995;85:2422-35.

53. Yamamoto N, Akamatsu H, Hasegawa S, Yamada T, Nakata S, Ohkuma M, et al. Isolation of multipotent stem cells from mouse adipose tissue. J Dermatol Sci 2007;48:43-52.

54. Gronthos S, Franklin DM, Leddy HA, Robey PG, Storms RW, Gimble JM. Surface protein characterization of human adipose tissue-derived stromal cells. J Cell Physiol 2001;189:54-63.

55. Schäffler A, Büchler C. Concise Review: Adipose Tissue-Derived Stromal Cells—Basic and Clinical Implications for Novel Cell-Based Therapies. Stem Cell 2007;25:818-27.

56. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U.S.A. 2000;97:13625-30.

57. Jo YY, Lee HJ, Kook SY, Choung SW, Park JY, Chung JH, et al. Isolation and characterization of postnatal stem cells from human dental tissues. Tissue Eng 2007;13:767-73.

58. Pierdomenico L, Bonsi L, Calvitti M, Rondelli D, Arpinati M, Chirumbolo G, et al. Multipotent mesenchymal stem cells with immunosuppressive activity can be easily isolated from dental pulp. Transplant 2005;80:836-42.

59. Ohyama M, Terunuma A, Tock CL, Radonovich MF, Pise-Masison CA, Hopping SB, et al. Characterization and isolation of stem cell–enriched human hair follicle bulge cells. J Clin Invest 2006;116:249-60.

60. Varma MJO, Breuls RG, Schouten TE, Jurgens WJ, Bontkes HJ, Schuurhuis GJ, et al. Phenotypical and functional characterization of freshly isolated adipose tissue-derived stem cells. Stem Cell Dev 2007;16:91-104.

61. Tuan RS. Stemming cartilage degeneration: adult mesenchymal stem cells as a cell source for articular cartilage tissue engineering. Arthrit Rheum 2006;54:3075-8.

62. Murphy SV, Atala A. Amniotic fluid and placental membranes: unexpected sources of highly multipotent cells. Semin Reprod Med 2013;31:62-8.

63. Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, et al. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. Nat Med 2006;12:459-65.

64. Dai W, Hale SL, Martin BJ, Kuang JQ, Dow KS, Wold LE, et al. Allogeneic mesenchymal stem cell transplantation in postinfarcted rat myocardium short-and long-term effects. Circulation 2005;112:214-23.

65. Hatzistergos KE, Quevedo H, Oskouei BN, Hu Q, Feigenbaum GS, Margitich IS, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. Circ Res 2010;107:913-22.

66. Kuraitis D, Ruel M, Suuronen EJ. Mesenchymal stem cells for cardiovascular regeneration. Cardiovasc Drugs Ther 2011;25:349-62.

67. Bollini S, Cheung KK, Riegler J, Dong X, Smart N, Ghionzoli M, et al. Amniotic fluid stem cells are cardioprotective following acute myocardial infarction. Stem Cell Dev 2011;20:1985-94.

68. Lee WY, Wei HJ, Lin WW, Yeh YC, Hwang SM, Wang JJ, et al. Enhancement of cell retention and functional benefits in myocardial infarction using human amniotic-fluid stem-cell bodies enriched with endogenous ECM. Biomaterials 2011;32:5558-67.

69. Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. J Am Coll Cardiol 2009;54:2277-86.

70. Chen Sl, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. J Am Coll Cardiol 2004;94:92-5.

71. Williams AR, Trachtenberg B, Velazquez DL, McNiece L, Altman P, Rouy D, et al. Intramyocardial Stem Cell Injection in Patients With Ischemic Cardiomyopathy Functional Recovery and Reverse Remodeling. Circ Res 2011;108:792-6.

72. Traverse JH, Henry TD, Pepine CJ, Willerson JT, Zhao DX, Ellis SG, et al. Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. JAMA 2012;308:2380-9.

73. Haack-Sorensen M, Friis T, Mathiasen AB, Jorgensen E, Hansen L, Dickmeiss E, et al. Direct intramyocardial mesenchymal stromal cell injections in patients with severe refractory angina: one-year follow-up. Cell Transplant 2013;22:521-8.

74. Fischer UM, Harting MT, Jimenez F, Monzon-Posadas WO, Xue H, Savitz SI, et al. Pulmonary passage is a major obstacle for intravenous stem cell delivery: the pulmonary first-pass effect. Stem Cell Dev 2009;18:683-92.

75. Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, et al. Cardiopoietic Stem Cell Therapy in Heart FailureThe C-CURE (Cardiopoietic stem Cell therapy in heart failURE) Multicenter Randomized Trial With Lineage-Specified Biologics. J Am Coll Cardiol 2013;61:2329-38.

76. Zheng GP, Ge MH, Shu Q, Rojas M, Xu J. Mesenchymal stem cells in the treatment of pediatric diseases. World J Pediatr 2013;9:197-211.

77. Kuo TK, Hung SP, Chuang CH, Chen CT, Shih YRV, Fang SCY, et al. Stem cell therapy for liver disease: parameters governing the success of using bone marrow mesenchymal stem cells. Gastroenterology 2008;134:2111-21.

78. van Poll D, Parekkadan B, Cho CH, Berthiaume F, Nahmias Y, Tilles AW, et al. Mesenchymal stem cell–derived molecules directly modulate hepatocellular death and regeneration in vitro and in vivo. Hepatology 2008;47:1634-43.

79. Khuu DN, Nyabi O, Maerckx C, Sokal E, Najimi M. Adult human liver mesenchymal stem/progenitor cells participate in mouse liver regeneration after hepatectomy. Cell Transplant 2013;22:1369-80.

80. Mohamadnejad M, Alimoghaddam K, Mohyeddin-Bonab M, Bagheri M, Bashtar M, Ghanaati H, et al. Phase 1 trial of autologous bone marrow mesenchymal stem cell

transplantation in patients with decompensated liver cirrhosis. Arch Iran Med 2007;10:459-66.

81. Kharaziha P, Hellström PM, Noorinayer B, Farzaneh F, Aghajani K, Jafari F, et al. Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I–II clinical trial. Eur J Gastroenterol Hepatol 2009;21:1199-205.

82. Zhang Z, Lin H, Shi M, Xu R, Fu J, Lv J, et al. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. J Gastroenterol Hepatol 2012;27:112-20.

83. Peng L, Xie DY, Lin BL, Liu J, Zhu HP, Xie C, et al. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: Short-term and long-term outcomes. Hepatology 2011;54:820-8.

84. García-Olmo D, García-Arranz M, Herreros D, Pascual I, Peiro C, Rodríguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis. Colon Rectum 2005;48:1416-23.

85. Garcia-Olmo D, Herreros D, Pascual I, Pascual JA, Del-Valle E, Zorrilla J, et al. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. Dis. Colon Rectum 2009;52:79-86.

86. Duijvestein M, Vos ACW, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW, et al. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. Gut 2010;59:1662-9.

87. Ciccocioppo R, Bernardo ME, Sgarella A, Maccario R, Avanzini MA, Ubezio C, et al. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut 2011;60:788-98.

88. Goel A, Sangwan S, Siwach R, Ali AM. Percutaneous bone marrow grafting for the treatment of tibial non-union. Injury 2005;36:203-6.

89. Hernigou P, Poignard A, Manicom O, Mathieu G, Rouard H. The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. J Bone Joint Surg Br 2005;87:896-902.

90. De Coppi P, Bartsch G, Siddiqui MM, Xu T, Santos CC, Perin L, et al. Isolation of amniotic stem cell lines with potential for therapy. Nat Biotechnol 2007;25:100-6.

91. Kashani IR, Zaminy A, Barbarestani M, Hedayatpour A, Mahmoudi R, Vardasbi S, et al. In vitro osteogenesis of rat adipose-derived stem cells: comparison with bone marrow stem cells. Arch Med Sci 2009;5:149-55.

92. Kumar S, Ponnazhagan S. Mobilization of bone marrow mesenchymal stem cells< i> in vivo</i> augments bone healing in a mouse model of segmental bone defect. Bone 2012;50:1012-8.

93. Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Res Ther 2008;10:223.

94. Tuan RS, Chen AF, Klatt BA. Cartilage regeneration. J Am Acad Orthop Surg 2013;21:303-11.

95. Lee KB, Hui JH, Song IC, Ardany L, Lee EH. Injectable mesenchymal stem cell therapy for large cartilage defects—a porcine model. Stem Cell 2007;25:2964-71.

96. Liu Y, Shu XZ, Prestwich GD. Osteochondral defect repair with autologous bone marrow-derived mesenchymal stem cells in an injectable, in situ, cross-linked synthetic extracellular matrix. Tissue Eng 2006;12:3405-16.

97. Wakitani S, Imoto K, Yamamoto T, Saito M, Murata N, Yoneda M. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthr Cartil 2002;10:199-206.

98. Guilak F, Estes BT, Diekman BO, Moutos FT, Gimble JM. 2010 Nicolas Andry Award: Multipotent adult stem cells from adipose tissue for musculoskeletal tissue engineering. Clin Orthop Relat Res 2010;468:2530-40.

99. Viña JA, El-Alami M, Gambini J, Borras C, Viña J, Peñarrocha MA. Application of mesenchymal stem cells in bone regenerative procedures in oral implantology. A literature review. J Clin Exp Dent 2014;6:e60-5.

100. Ditadi A, de Coppi P, Picone O, Gautreau L, Smati R, Six E, et al. Human and murine amniotic fluid c-Kit+ Lin− cells display hematopoietic activity. Blood 2009;113:3953-60.

101. Carrion F, Nova E, Ruiz C, Diaz F, Inostroza C, Rojo D, et al. Autologous mesenchymal stem cell treatment increased T regulatory cells with no effect on disease activity in two systemic lupus erythematosus patients. Lupus 2010;19:317-22.

102. Liang J, Zhang H, Hua B, Wang H, Lu L, Shi S, et al. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann Rheum Dis 2010;69:1423-9.

103. Wang D, Akiyama K, Zhang H, Yamaza T, Li X, Feng X, et al. Double allogenic mesenchymal stem cells transplantations could not enhance therapeutic effect compared with single transplantation in systemic lupus erythematosus. Clin Dev Immunol 2012;2012:273291.

104. Jones EA, English A, Henshaw K, Kinsey SE, Markham SF, Emery P, et al. Enumeration and phenotypic characterization of synovial fluid multipotential mesenchymal progenitor cells in inflammatory and degenerative arthritis. Arthritis Rheum 2004;50:817-27.

105. Endres M, Neumann K, Häupl T, Erggelet C, Ringe J, Sittinger M, et al. Synovial fluid recruits human

mesenchymal progenitors from subchondral spongious bone marrow. J Orthop Res 2007;25:1299-307.

106. Jones E, Churchman S, English A, Buch M, Horner E, Burgoyne C, et al. Mesenchymal stem cells in rheumatoid synovium: enumeration and functional assessment in relation to synovial inflammation level. Ann Rheum Dis 2010;69:450-7.

107. Kastrinaki MC, Sidiropoulos P, Roche S, Ringe J, Lehmann S, Kritikos H, et al. Functional, molecular and proteomic characterisation of bone marrow mesenchymal stem cells in rheumatoid arthritis. Ann Rheum Dis 2008;67:741-9.

108. Nir T, Melton DA, Dor Y. Recovery from diabetes in mice by β cell regeneration. J Clin Invest 2007;117:2553-61.

109. Wei, J.P., T.S. Zhang, S. Kawa, T. Aizawa, M. Ota, T. Akaike, et al., Human amnion-isolated cells normalize blood glucose in streptozotocin-induced diabetic mice. Cell transplant, 2003. 12(5): p. 545-552.

110. Chang CM, Kao CL, Chang YL, Yang MJ, Chen YC, Sung BL, et al. Placenta-derived multipotent stem cells induced to differentiate into insulin-positive cells. Biochem Biophys Res Commun 2007;357:414-20.

111. Fiorina P, Jurewicz M, Augello A, Vergani A, Dada S, La Rosa S, et al. Immunomodulatory function of bone marrow-derived mesenchymal stem cells in experimental autoimmune type 1 diabetes. J Immunol 2009;183:993-1004.

112. Hisanaga E, Park KY, Yamada S, Hashimoto H, Takeuchi T, Mori M, et al. A simple method to induce differentiation of murine bone marrow mesenchymal cells to insulin-producing cells using conophylline and betacellulin-delta4. Endocr J 2008;55:535-43.

113. Oh SH, Muzzonigro TM, Bae SH, LaPlante JM, Hatch HM, Petersen BE. Adult bone marrow-derived cells trans-differentiating into insulin-producing cells for the treatment of type I diabetes. Lab. Invest., 2004. 84(5): p. 607-617.

114. Lee RH, Seo MJ, Reger RL, Spees JL, Pulin AA, Olson SD, et al. Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proc Natl Acad Sci U.S.A. 2006;103:17438-43.

115. Murphy S, Lim R, Dickinson H, Acharya R, Rosli S, Jenkin G, et al. Human amnion epithelial cells prevent bleomycin-induced lung injury and preserve lung function. Cell Transplant 2011;20:909-23.

116. Murphy SV, Shiyun S, Tan JL, Chan S, Jenkin G, Wallace EJ, et al. Human amnion epithelial cells do not abrogate pulmonary fibrosis in mice with impaired macrophage function. Cell Transplant;2012:21:1477-92.

117. Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, et al. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. Proc Natl Acad Sci U.S.A. 2003;100:8407-11.

118. Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, et al. Bone marrow–derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol 2005;33:145-52.

119. Mei SH, McCarter SD, Deng Y, Parker CH, Liles WC, Stewart DJ. Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med 2007;4:e269.

120. Krasnodembskaya A, Song Y, Fang X, Gupta N, Serikov V, Lee JW, et al. Antibacterial Effect of Human Mesenchymal Stem Cells Is Mediated in Part from Secretion of the Antimicrobial Peptide LL-37. Stem Cell 2010;28:2229-38.

121. Wang G, Bunnell BA, Painter RG, Quiniones BC, Tom S, Lanson NA, et al. Adult stem cells from bone marrow stroma differentiate into airway epithelial cells: potential therapy for cystic fibrosis. Proc Natl Acad Sci U.S.A. 2005;102:186-91.

122. Sueblinvong V, Loi R, Eisenhauer PL, Bernstein IM, Suratt B, Spees JL, et al. Derivation of lung epithelium from human cord blood–derived mesenchymal stem cells. Am J Respir Crit Care Med 2008;177:701.

123. Perin L, Giuliani S, Jin D, Sedrakyan S, Carraro G, Habibian R, et al. Renal differentiation of amniotic fluid stem cells. Cell Prolif 2007;40:936-48.

124. Perin L, Sedrakyan S, Giuliani S, Da Sacco S, Carraro G, Shiri L, et al. Protective effect of human amniotic fluid stem cells in an immunodeficient mouse model of acute tubular necrosis. PloS One 2010;5:e9357.

125. Rehni AK, Singh N, Jaggi AS, Singh M. Amniotic fluid derived stem cells ameliorate focal cerebral ischaemia-reperfusion injury induced behavioural deficits in mice. Behav. Brain Res 2007;183:95-100.

126. Kashani IR, Golipoor Z, Akbari M, Mahmoudi R, Azari S, Shirazi R, et al. Schwann-like cell differentiation from rat bone marrow stem cells. Arch Med Sci 20117:45-52.

127. Aponte PM, Schlatt S, Franca LR. Biotechnological approaches to the treatment of aspermatogenic men. Clinics 2013;68:157-67.

128. Itman C, Mendis S, Barakat B. All in the family: TGF-β family action in testis development. Reproduction 2006;132:233-46.

129. Kobayashi H, Nagao K, Nakajima K. Focus issue on male infertility. Adv Urol 2011;2012:6.

130. Rooij DG, Russell LD. All you wanted to know about spermatogonia but were afraid to ask. J Androl

2000;21:776-98.

131. Kobayashi H, Nagao K, Nakajima K. Therapeutic Advances in the Field of Male Infertility. Stem Cell Res 2013;1:39-54.

132. Marques-Mari A, Lacham-Kaplan O, Medrano J, Pellicer A, Simón C. Differentiation of germ cells and gametes from stem cells. Hum Reprod Update 2009;15:379-90.

133. Hua J, Yu H, Dong W, Yang C, Gao Z, Lei A, et al. Characterization of mesenchymal stem cells (MSCs) from human fetal lung: potential differentiation of germ cells. Tissue Cell 2009;41:448-55.

134. Hua J, Pan S, Yang C, Dong W, Dou Z, Sidhu KS. Derivation of male germ cell-like lineage from human fetal bone marrow stem cells. Reprod. Biomed. Online 2009;19:99-105.

135. Drusenheimer N, Wulf G, Nolte J, Lee JH, Dev A, Dressel R, et al. Putative human male germ cells from bone marrow stem cells. Soc Reprod Fertil Suppl 2006;63:69-76.

136. Hosseinzadeh Shirzeily M, Pasbakhsh P, Amidi F, Mehrannia K. Comparison of differentiation potential of male mouse adipose tissue and bone marrow derived-mesenchymal stem cells into germ cells. Iran J Reprod Med 2013;11:965-76.

137. Nayernia K, Lee JH, Drusenheimer N, Nolte J, Wulf G, Dressel R, et al. Derivation of male germ cells from bone marrow stem cells. Lab Invest 2006;86:654-63.

138. Lue Y, Erkkila K, Liu PY, Ma K, Wang C, Hikim AS, et al. Fate of bone marrow stem cells transplanted into the testis: potential implication for men with testicular failure. Am J Pathol 2007;170:899-908.

139. Monsefi M, Fereydouni B, Rohani L, Talaei T. Mesenchymal stem cells repair germinal cells of seminiferous tubules of sterile rats. Iran J Reprod Med 2013;11:537-44.

140. Zhao XH, Qiu JH, Cai WQ, Li S, Li W. Preparation of infertile male rabbits by local electron beam irradiation for intratesticular transplantation of autologous bone marrow stem cells. Acta Cirurgica Brasileira 2013;28:148-53.

141. Boivin J, Bunting \L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 2007;22:1506-12.

142. Gong SP, Lee ST, Lee EJ, Kim DY, Lee G, Chi SG, et al. Embryonic stem cell-like cells established by culture of adult ovarian cells in mice. Fertil Steril 2010;93:2594-601.

143. Zuckerman S, Baker T. The development of the ovary and the process of oogenesis. Ovary 1977;1:41-67.

144. Zuckerman S. The number of oocytes in the mature ovary. Recent Prog Horm Res 1951;6:63-109.

145. Johnson J, Canning J, Kaneko T, Pru JK, Tilly JL. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 2004;428:145-50.

146. McGuckin C, Forraz N, Baradez MO, Navran S, Zhao J, Urban R, et al. Production of stem cells with embryonic characteristics from human umbilical cord blood. Cell Prolif 2005;38:245-55.

147. Miki T, Lehmann T, Cai H, Stolz DB. Stem cell characteristics of amniotic epithelial cells. Stem Cell 2005;23:1549-59.

148. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143-7.

149. Barnes D, Loutit J. Haemopoietic stem cells in the peripheral blood. Lancet 1967;290:1138-41.

150. Alonso L, Fuchs E. Stem cells of the skin epithelium. Proc. Natl Acad Sci U.S.A. 2003;100):11830-5.

151. Guan K, Nayernia K, Maier LS, Wagner S, Dressel R, Lee JH, et al. Pluripotency of spermatogonial stem cells from adult mouse testis. Nature 2006;440:1199-203.

152. Toyooka Y, Tsunekawa N, Akasu R, Noce T. Embryonic stem cells can form germ cells in vitro. Proc Natl Acad Sci 2003;100:11457-62.

153. Hübner K, Fuhrmann G, Christenson LK, Kehler J, Reinbold R, De La Fuente R, et al. Derivation of oocytes from mouse embryonic stem cells. Science 2003;300:1251-6.

154. Clark AT, Bodnar MS, Fox M, Rodriquez RT, Abeyta MJ, Firpo MT, et al. Spontaneous differentiation of germ cells from human embryonic stem cells in vitro. Hum Mol Genet 2004;13:727-39.

155. Geijsen N, Horoschak M, Kim K, Gribnau J, Eggan K, Daley GQ. Derivation of embryonic germ cells and male gametes from embryonic stem cells. Nature 2004;427:148-54.

156. Bukovsky A, Svetlikova M, Caudle MR. Oogenesis in cultures derived from adult human ovaries. Reprod Biol Endocrinol 2005;3:17.

157. Virant-Klun I, Zech N, Rožman P, Vogler A, Cvjetičanin B, Klemenc P, et al. Putative stem cells with an embryonic character isolated from the ovarian surface epithelium of women with no naturally present follicles and oocytes. Differentiation 2008;76:843-56.

158. Virant-Klun I, Rozman P, Cvjeticanin B, Vrtacnik-Bokal E, Novakovic S, Rülicke T, et al. Parthenogenetic embryo-like structures in the human ovarian surface epithelium cell culture in postmenopausal women with no naturally present follicles and oocytes. Stem Cell Dev 2009;18:137-50.

159. Virant-Klun I, Skutella T, Stimpfel M, Sinkovec J. Ovarian surface epithelium in patients with severe ovarian infertility: a potential source of cells expressing markers of pluripotent/multipotent stem cells. J Biomed Biotechnol 2011;2011:381928.

160. Johnson J, Bagley J, Skaznik-Wikiel M, Lee HJ, Adams GB, Niikura Y, et al. Oocyte generation in adult mammalian ovaries by putative germ cells in bone marrow and peripheral blood. Cell 2005;122:303-15.

161. Saitou M, Barton SC, Surani MA, A molecular programme for the specification of germ cell fate in mice. Nature 2002;418:293-300.

162. Suzumori N, Yan C, Matzuk MM, Rajkovic A. <i> Nobox </i> is a homeobox-encoding gene preferentially expressed in primordial and growing oocytes. Mech Dev 2002;111:137-41.

163. Peng L, Jia Z, Yin X, Zhang X, Liu Y, Chen P, et al. Comparative analysis of mesenchymal stem cells from bone marrow, cartilage, and adipose tissue. Stem Cell Dev 2008;17:761-74.

164. Dyce PW, Wen L, Li J, In vitro germline potential of stem cells derived from fetal porcine skin. Nat. Cell Biol 2006;8:384-90.

165. Song SH, Kumar BM, Kang EJ, Lee YM, Kim TH, Ock SA, et al. Characterization of porcine multipotent stem/stromal cells derived from skin, adipose, and ovarian tissues and their differentiation in vitro into putative oocyte-like cells. Stem Cell Dev 2011;20:1359-70.

166. Stimpfel M, Skutella T, Cvjeticanin B, Meznaric M, Dovc P, Novakovic S, et al. Isolation, characterization and differentiation of cells expressing pluripotent/multipotent markers from adult human ovaries. Cell Tissue Res 2013;354:593-607.

167. Lee YM, Kumar BM, Lee JH, Lee WJ, Kim TH, Lee SL, et al. Characterisation and differentiation of porcine ovarian theca-derived multipotent stem cells. Vet J 2013;197:761-8.