Multipotent Stem Cell and Current Application

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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.

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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).

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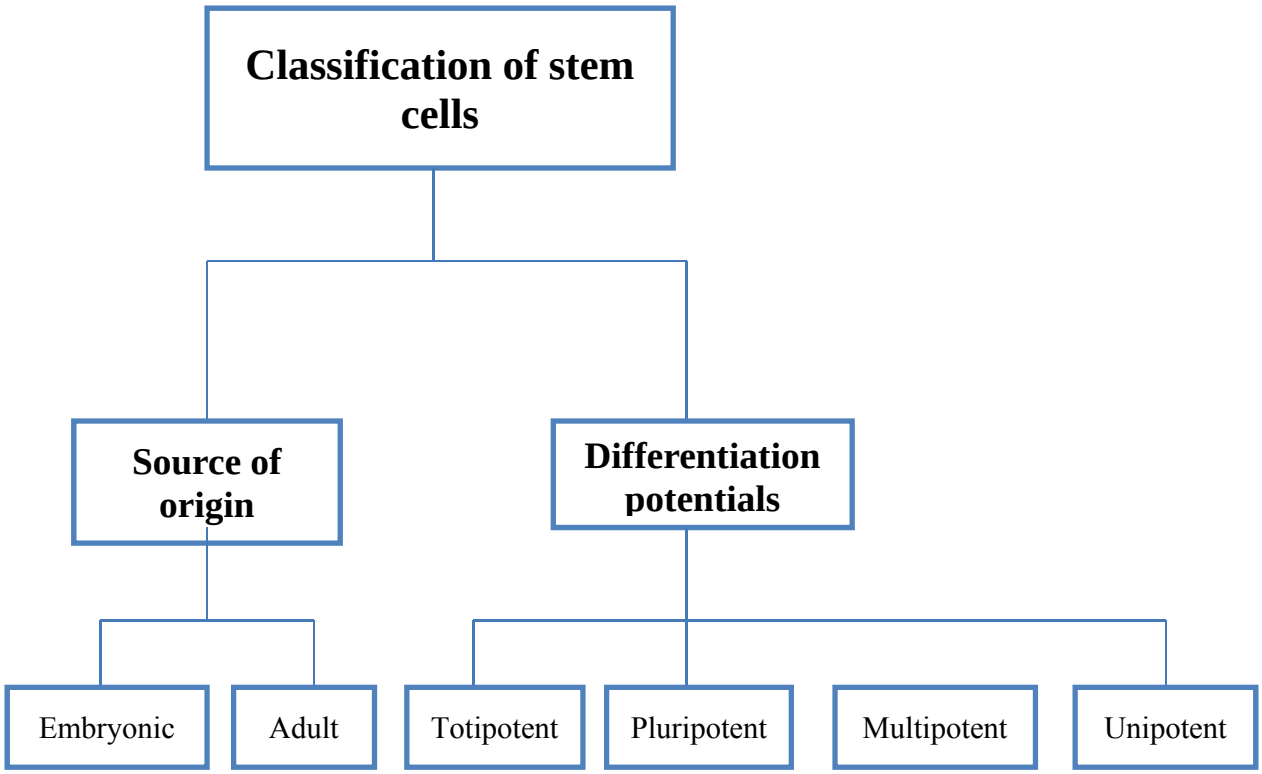

Figure 1. Classification of stem cells

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 releavedMvh 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?

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