ARTICLE

ADIPOSE TISSUE DERIVED MESENCHYMAL STEM CELLS

Elaheh Jalali[1], Mina Rabiee[2*]

[1]*MSc Biomedical Genetics, Department of Genetics, Madras University, Chennai, INDIA*

[2]*Researcher of Bandar Abbas Medical Genetics Center, Bandar Abbas, IRAN*

ABSTRACT

Stem cells are unspecialized cells in living bodies which have high potential of division,and can be differentiated under special physiological circumstances or in the presence of special factors to yield a variety of matured cells or specialized tissues. Mesenchymal stem cells (abbreviated as MSC) possess the property of heterogeneities and fibrolastosis, and are self-renewal and can be differentiated. Over the years, many initial and most flourished studies were performed on MSc which were separated from bone marrow; but in the recent years the use of adipose tissues have become common due to few special characteristics such as easy access, great texture and high reproduction power. The mesodermal cells have certain surface markers namely CD73, CD44, and CD90 but lack hypotonic surface markers such as CD11c, CD31, CD34, CD45, CD80 and CD86. In addition, mesodermal cells have the power to differentiate into a variety of tissues; either into other mesodermal cell types or into non-mesodermal tissues. These cells can also be used in tissue engineering and cell therapy to repair or replace damaged tissues with healthy tissues, as well as in the manufacture of vital drugs. Thus, this study aims to express few specific characteristics of MSCsisolated from adipose tissues.

KEY WORDS
Adipose tissue, Mesenchymal stem cell, Stem cell, Differentiation

Received: 16 Aug 2016
Accepted: 26 Sep 2016
Published: 30 Oct 2016

***Corresponding Author**
Email:
mina.rabiee1368@gmail.com

INTRODUCTION

A few cells in the body are the responsible for survival and a classic example of such cells are the stem cells. The stem cells can be differentiated and transformed to adult stem cells under specific circumstances. The evolution of 'Stem cell' studies and research in the biological sciences domain drives to a major academic field that focuses on technologies used for emerging a complete organism from a single cell. The substitution of damaged cells with the healthy cells is primarily studied.This improvises knowledge on embryology, developmental biology, grafting mechanisms and transplantation and can be used to treat cancer. The stem cells are self-renewal and can be transformed into osteoblasts, chondrocytes and adipocytes with high competence of division,which can create a regenerative cell population. One of the most important stem cell that attracts the attention of scholars is the MSCs that are categorized in the adult stem cells.

The MSc are known as pluripotent and fibroblastic cells, which can be separated from bone marrow, adipose tissue, umbilical cord blood, lungs [1-3], skin [4] and spleen [5]. The MSc count a valuable resource with the high productivity for repairing the tissues due their immunological characters, and high potency to proliferate and differentiate. Having this prominent specialty, the stem cells are used as a critical treatment tool to cure several diseases. According to several research results, treatment with MSCsexhabitgreater immunity in a short term.

The application of such cells in surgeries, stress, and different infectious conditions, decrease the probability of a transplant rejection and the usage of sub receptor drugs. The unique potential of stem cells, including the ability to differentiate and transform into specific cells in vivo, gives evidence that these cells can be used in transplantation to treat tissue-damaging diseases as a faithful method in the future. Considering the feasibility of cell isolation, the adipose tissues remain as good and suitable resourceas umbilical cord stem cell and bone marrow cells are more complicated. Moreover, many stem cells can be separated from a single adipose tissue. Based on the recent investigation, the adipose tissue stem cells are able to cure the liver injuries, muscular dystrophy, allergy, and myocardial infarction.

STEM CELLS

These are self-renewable cells that possess varying potency to differentiate into multiline ages and the ability to form clones (clonogenic) [6]. Ideally, the stem cell used for regenerative medicinal applications should meet the following criteria [7]:

- Found in abundant quantities (millions to billions of cells).
- Harvested by a minimally invasive procedure.
- Differentiate along multiple cell lineage pathways in a regulative and reproducible manner.
- Safely and effectively transplant into either an autologous or allogeneic host.
- Manufactured in accordance with current Good Manufacturing Practice guidelines [2, 8].

Two kinds of stem cells can be defined based on tissue source: embryonic stem cells and adult stem cells. Embryonic stem cells are pluripotent and can give rise to various cell types present in the body. Generally, adult stem cells are limited by number and the type of cell into which it can differentiate. For cell-based tissue regeneration, a potential advantage of using stem cells from an adult is that the patient's own cells could be expanded in culture and then re-introduced into the patient without the problem of tissue

rejection by the immune system.The biology of adult stem cells and their potential use in gene therapy have provided opportunities for therapeutic use in tissue regeneration [9].

There are some characteristics for adult stem cells, which make them suitable for clinical uses:like ease of harvest, high expansion rate in vitro and multiline age differentiation capacity [10]. Though the application of cellular therapy and regenerative medicine is rapidly growing, for regenerative medicinal purposes, stem cells should meet the above mentionedcriteria. Cell therapy using stem cells and their progeny is a promising approach that is capable of addressing many unmet medical needs. Recently, stem cell research has quickly progressed, allowing researchers to isolate and purify stem/progenitor cell populations from various tissues (i.e. hematopoietic, vascular endothelial and neural stem cells, as well as hepatic oval cells) [11]. In addition, several studies have shown that stem cells also benefit from immune modulatory capabilities [12].

MESENCHYMAL STEM CELLS

The self-renewable multipotent MSCs are found in many adult tissues,including the bone marrow, trabecular bone, adipose tissues, and muscles. According to some specific culture conditions, these cells can give rise to multiple mesenchyme-derived cell types, such as osteoblasts, chondrocytes, adipocytes, and myoblasts [13]. In addition tophenotypic characterization, the above mentioned are other minimal criteria that were proposed by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy to define MSCs [14]. Cells which exhibit characteristics of MSCs were isolated from adipose tissue, amniotic fluid, amniotic membrane, dental tissues, endometrium, limb bud, menstrual blood, peripheral blood, placenta and fetal membrane, salivary gland, skin and foreskin, sub-amniotic umbilical cord lining membrane, synovial fluid and Wharton's jelly [6, 15]. These days the MSCs have gained some attractiveness for clinical applications; example transplantation of bone, liver, cardiac,skeletal muscle and CNS at various stages, including clinical trials. The cause of this attention is the relative ease of expansion by well-described protocols, and the ability for induced-differentiation into a host of cell lines in vitro without ethical concerns attributed to embryonic stem cells [16].

It is known that progenitor cells from different sources exhibit similar lineage differentiation properties in the same environment. There are some evidences which say that the precise location of stem cells within native tissue is of significant interest that aids in processing and culture within the laboratory. MSCs may be derived from a common perivascular origin. Culture of perivascular cells from multiple tissues results in products expressing CD surface markers typically like MSCs (CD44, CD73, CD90 and CD105) that exhibit anticipated clonal proliferation and multi-lineage potential in suitable inductive conditions.These cells (a) should exhibits plastic adherence (b) possess specific set of cell surface markers, i.e. cluster of differentiation (CD)73, D90, CD105 and lack expression of CD14, CD34, CD45 and human leucocyte antigen-DR (HLA-DR) and (c) have the ability to differentiate in vitro into adipocyte, chondrocyte and osteoblast. These properties can be traced in all MSCs, although few differences exist in MSCs isolated from various tissue origins [6,15,16].

Moreover, MSCs being able to become mesodermal linage can also be able to become into a variety of cell lines which is originating from the ectoderm and endoderm for instance hepatocytes, neurons, and cardiomyocytes. The multi-linage differential potential of MSCsis investigated in vitro culture functional assays using specific differentiation media. This feature makes MSCsto be considered as a suitable source for tissue repair [17]. Although in most cases the isolated MSCs are heterogeneous in proliferation and differentiation, the expression of the characteristic MSC markers stand prominent. Cultivation of MSCs in vitro has three biological properties that qualify them for use in cellular therapy: (a) broad potential of differentiation, (b) secretion of trophic factors that favor tissue remodeling, and (c) immune regulatory properties [15]. Performance of MSCs is depended on a series of mechanisms in vivo including: (A) differentiation potential, (B) release of paracrine factors influencing the microenvironment, (C) scavenging of reactive oxygen species, (D) immune modulatory function and (E) fusion and rejuvenation of resident committed progenitor cells [5,18,19]. MSCs are an excellent candidate for cell therapy because (a) human MSCs are easily accessible; (b) the isolation of MSCs is straightforward and the cells can expand to clinical scales in a relatively short period of time; (c) MSCs can be bio-preserved with minimal loss of potency and stored for point of care delivery; and (d) human trials of MSCs thus far have shown no adverse reactions to allogeneic versus autologous MSC transplants, enabling creation of an inventory of third-party donor MSCs to widen the number of patients treated by a single isolation.

MSC transplantation is considered safe and has been widely tested in clinical trials of cardiovascular, neurological, and immunological disease with encouraging results [20]. Due of their great ability to treat many hazardous diseases in animal, recently MSCs are being explored for use in humans. Although the primary mechanisms of action have not been fully elucidated, studies indicate that MSCs can act on several levels of endogenous repair to bring resolution of diseases. MSCs have been shown to protect cells from injury and directly promote tissue repairwhen administered to treat animals undergoing acute renal failure, MSCs prevent apoptosis and elicit proliferation of renal-tubule epithelial cells in a differentiation-independent manner. When injected into the myocardium after an infarction, MSCs can reduce the incidence of scar formation. When administered to prevent the onset of IDDM, MSCs protect β-islets from autoimmune attack; and when administered after onset of the disease, they promote temporary restoration of glucose regulation, suggesting protection and repair of damaged islet tissues.

Many in vivo transplantation studies recently illustrated that adult MSCs have the ability todifferentiate into mesoderm-derived cell types as well as into cells with neuro-ectodermal and endodermal characteristics, proposingthat trans-differentiation occurs in mammalian systems [13]. MSCs have also been shown to modulate the immune system and attenuate tissue damage caused by excessive inflammation moreover they are able to promoting tissue repair directly [20]. Gene delivery by non-viral methods, including native DNA, liposomes, cationic polymers, and electroporation, is less efficient than virus-mediated DNA delivery. Typically, transfection efficiency by non-viral methods is limited to 20–25%. Furthermore, adult MSCs tend to resist trans-gene delivery by classic non-viral methods, as primary cultured cells do [18,21]. Despite these features, non-viral methods have several advantages, such as lower manufacturing costs, no (or weak) immunogenic responses with repeated administration, and are generally safe. Therefore, improving the transfection efficiency of non-viral methods for adult MSCswould prove to be beneficial in cell therapy [9].

ADIPOSE TISSUE DERIVED MESENCHYMAL STEM CELLS (ADSCS)

Adipose tissue

Bone Marrow (BM) was the original reference source for MSCs isolation, but now they are being isolated from a multitude of adult tissues, including muscle, adipose tissue, connective tissue, trabecular bone, synovial fluid, and perinatal tissues, such as umbilicalcord, amniotic fluid, and placenta. In particular, ubiquity, ease of retrieval and the minimally invasive procedure required for harvesting the adipose tissue (AT), makes it an ideal source for high yield MSCs isolation.Moreover, adipose tissue-derived MSCs (ADSCs) can be maintained longer in culture and possess a higher proliferation capacity compared to BM-derived MSCs.Though they are beneficiary, low number of harvested cells, limited amount of harvested tissues and donor site morbidity or patient discomfort are included the limitations with BM-MSCs in providing a sample. Hence, there was a need for ex vivo expansion or further manipulation of these cells before their preclinical or clinical use to satisfy the safety and efficacy requirements [8]. Therefore, AT was considered an attractive and alternative source which can be provided in large quantities from AT fragments [22].

Adipose tissue, similar to BM, is a mesodermal derived organ which includes a population of stem cells. These can be enzymatically derived fromAT anda homogenous population can be made in culture under suitable conditions, in order to express mesenchymalgrowth and exhibit stable growth and proliferation kinetics [10]. Adipose contains more multipotent cells per cc than BM, so it is apparently a good source of stem cells i.e.one gram of adiposetissueyields~5×103 stemcells,whichis100-foldhigher than the number of MSCs in one gram of BM(14). Adipose is a highly complex tissue and organ with a big role in energy metabolism, endocrinology, immunity, comprising mature adipocytes (>90%) and a stromal vascular fraction (SVF), which includes pre-adipocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, monocytes/macrophages, lymphocytes, and ASCs (14-16). The density of the AT stem cell reservoir varies as a function of location, type, and species [21]. It is now appreciated that AT contains a heterogeneous cell population that can change a function of obesity and diabetes [23].

The adipose-derived SVF cells and ASCsprovide a special and influential advantage for tissue engineering and regenerative medical applications [19]. ADSCs are ubiquitous and easily obtained in large quantities with little donor site morbidity or patient discomfort making the use of autologous ADSCs an appropriate research tool and cellular therapy [22]. At a cellular level, AT consists of mature adipocytes surrounded by fibroblasts, nerves, endothelial cells, and immune cells and pre-adipocytes cells contained within a stromo-vascular cell network [24]. Enzymatic digestion of AT, specifically lipoaspirate, generates a heterogeneous population of adipocyte precursors within a pellet of cells termed the stromal vascular fraction (SVF). Recently the capacity of such adipose-resident cells rise increasing attention in order to undergo multi-lineage differentiation in a manner we have learned to recognize as typical of stem cells [16].

Today, a customary method of AT aspiration is a surgical procedure which is relatively easy to harvest a large volume of tissue, obtaining an abundance of isolated stem and therapeutically active cells without the requirement of cell expansion in tissue culture facilities [14]. It is believed that a new era in regenerative medicine and clinical reconstruction has begun. Investigation and clinical use of BMSC is now standard; however, concerns over acceptability of harvesting techniques and potentially low cell yields (1 in 105 MSCs in culture adhere after initial plating) have driven the search for alternative autologous MSC sources. The identification of multipotent precursor cells within processed lip aspirates (PLAs) from human AT, building from well-established lessons in stem cell biology, has offered an alternative source.Characterization of such populations has revealed remarkable phenotypic similarities to BMSCs, while being accessed by a considerably more tolerated harvesting procedure. Other features include expression of specific markers of MSCs and un-expression of some markers such as hematopoietic markers for instance CD106, which make them unique.
BM derived MSCs have been the subject of many academic researches, but a big problem in this way was that the donor site morbidity that limited the amount of marrow that could be obtained [10]. Morphologically, ADSC are fibroblast-like cells and preserve their shape after in vitro expansion. Average doubling time of tissue cultured ADSC is between 4 to 5 days, and are similar to BMSC [14]. Stromal cells that have pre-adipocyte characteristics can be isolated from AT of adult subjects, propagated in vitro and induced to differentiate in vitro towards the osteogenic, adipogenic, myogenic and chondrogenic lineages

when treated with established lineage specific factors. A variety of names have been used to describe the plastic adherent cell population isolated from collagenase digests of AT. Among them, the international Fat Applied Technology Society reached consensus to adopt the term "adipose- derived stem cells" (ADSCs) to identify the isolated, plastic adherent, multipotent cell population [10].
The ADSCs have many advantages in tissue repair. For example, considering its mesodermal origin, ADSCs can be a valuable tool for repairing bone and cartilage defects. However, the use of ADSCs is expanding to both ectodermal and endodermal lineages such as: simulation of peripheral nerve repair, functional recovery in spinal cord damage, and liver injury repair. Besides, in the field of surgery, ADSCs can be used widely as fillers in plastic and cosmetic surgery.

In conclusion, it is evident that, besides other sources of MSCs, adipose derived MSCs are one of the best and influential sources being easily accessible and available through non-invasive method. It can be easily expanded to millions of cells without significant changes in phenotype and genotype, as well as the potential for being used in autologous transplantation in a wide variety of disorders from nerve to cardiac injuries and musculoskeletal problem [10].

As ADSCs have mesodermal origin, they have the potential to differentiate into several lineages of osteogenic, chondrogenic, adipogenic, cardiomyogenic, myogenic, and neurogenic cells [16]. They can differentiate into tissues of endodermal and ectodermal lineages such as hepatocytes, pancreatic islet cells, endothelial cells, neural cells, and epithelial cells [22]. There are so many factors such as donor's age, donor's BMI, type of AT (white or brown) and localization of AT (subcutaneous or visceral), type of surgical procedure, culturing conditions, exposure to plastic, plating density, and media formulations that influence both proliferation rate and differentiation capacity of ADSCs. A detailed comparison of five different subcutaneous depots was determined. For example, ADSCs isolated from the arm and thigh maintained best adipogenic potential as a function of advancing age [14]. ADSC therapy in regenerative laboratories and clinical settings was used in treatment of wound beds with poor blood supply and for healing of radiation injuries. The safety and efficacy of ADSCs in reconstructive medicine was evaluated in many clinical trials [22].

History

The initial methods to isolate cells from AT were pioneered by Rodbelland colleagues in the 1960s [25]. In 2009, Sun and colleagues generated induced pluripotent stem (iPS) cells (see Glossary) by viral transduction of human ADSCs under feeder-free conditions, finding this to be fast and more efficient than induction of pluripotency in human fibroblasts [26]. In 2008, Yoshimura et al. expanded on their earlier work characterizing surface markers in lipoaspirate samples and adherent-ADSCs to release a 40-patient series of fat transfer procedures for breast augmentation, incorporating fat grafts supplemented with simultaneously extracted SVF cells in a process termed cell-assisted lipotransfer (CAL) [16].

Surgical strategies for tissue loss replacement initially laid on the historical maxim "replace tissue with like-tissue": fatty tissue has been transplanted since 1893, but literature has always shown only controversial results in the degree of lasting of corrections, due to fat reabsorption. SVF provides a rich source of pluripotent ADSCs, which were first identified by Zuk and named processed lipoaspirate (PLA) cells [14]. In 2007, Kucerova et al. showed that ADSCs can indeed facilitate anti-cancer therapy through expression of prodrug converting enzymes. In 2008, Yu et al. found that ADSCs promote tumor growth by enhancing tumor cell proliferation and suppressing apoptosis [26]. Yoshimura et al. used adipose-derived SVF cells in augmentation of soft tissues by cell- assisted lipotransfer (CAL) 51 in treatment of breast augmentation and facial lipoatrophy. In facial lipoatrophy, no complications or adverse side effects were noticed [22].

In 2001, for the first time, there was a great scientific effort for the discovery of accessible resources in order to separate stem cells from the fat tissues, and the efforts were completely successful [27]. Zak et al. (2002) separated the MSCs from the fatty tissues [28]. The research investigations by the Ivone Perce proved that separating stem cells from a patient's fat tissue change these cells by the molecular methods is feasible and can be used in improving the tissue [29]. Min showed that the synchronic linkage between fat tissue and undiscovered stem cells obtained from animal fat tissue lead to stability. Following this process, the density of the veins increased six times than normal and the increase in size of tissue and its stability was observed, as a result of secretion of vein-producing factor from the stem cells which were derived from the fat tissue [30].

Differentiation of adipose derived stem cells

The stem cells have three main specialties:

- Differentiation [31]
- Auto renewalcapacity [32]
- Plasticity [33]

Differentiation is a process where unspecific cells under given conditions can be transformed to specific cells. ADSCs have this ability to differentiate intomesenchymal lineages and non- mesenchymal lineages.

Adipogenesis

Adipogenesis can be used in human soft tissue reconstruction as fat grafting is not limited to mature adipocytes transplant. However, in the case of using the ADSCs they have the ability to differentiate and support new blood vessel growth [34]. Fat tissue isolation and re-injection of cells in accordance with adipogenesis and angiogenesis can improve the long-term survival of fat grafts. In reconstructive plastic surgery, the fat tissue is the main damaged tissue, which can be amended by overcoming problems that are related to angiogenesis and long-term survival [35]. On the other hand, the diagnosis of the molecules which were expressed in the differentiation of the fat tissue-derived stem cells (ADSCs) can be feasibletouse them as target drugs in order to prevent adipogenesis in obesity, diabetes mellitus and cardiovascular disorders [25]. Adipocyte differentiation takes about 14 days' time and after this periodthe intracellular lipid can be observed through staining with oil red, however, the gene of factor of adipocyte differentiation signaling in vivo remains unknown. It is presumed that most important stimuli could be insulin and glucocorticoid. In vitro the first stage of adipogenesis is stimulated by the IGF-1, which is the quasi-insulin growth factor. Glucocorticoide, insulin, fatty acids and growth hormones have equal leading roles in adipocyte differentiation [26].
When cultured in an adipogenic medium,ADSCs express several adipocytic genes, including lipoprotein lipase, Ap2, PPAR(gamma)2, leptin, glut4, and develop lipidladen intracellular vacuoles, which stand as the definitive markers of adipogenesis [36, 37].

Chondrogene

ADSCs can be used in curing arthritic joints or in joint reconstruction. Scientists always look for suitable treatment of osteochondral defects. Meanwhile, in this process cell therapy with mesenchymal have been considered very special. These cells have high potential of reproduction and can easily differentiate to the osteochondral tissue, which is a cell resource [38]. In laboratory, the chondrogenic differentiation results when TGF-b, insulin and ascorbate are added to the medium culturing environment. The increase of extra cellular matrix proteins of cartilage will happen if suspension of cells is in the 3-d calum alginate gel. In this condition, collagen type II and aggrecan type IV can develop in a cell for several weeks. High-density cell culture techniques can ease the phenotypic changing of cells to dense chondrogenic nodules under the specific conditions. If the cells are monolayered then the chondrogenesis is not potential enough to culture ADSCs [39].

Researches show that smooth and skeletal muscle can be created in the absolute culture environment including 5% horse serum, glucocorticoid like hydrocortisone or dexamethasone, during ADSCs differentiation. The culturing of the ADSCs in presence of the 5-azacytidine, hydrocortisone, and dexamethasone, causes the expression of the genes which are related to the muscle in accordance with normal myogenesis. This process is accompanied with the early expression of the master regulatory factors like myf-5, myod-i, nyf-6, and myogenin followed by myosin heavy chain expression. This process can be done during two weeks, including increasing length of tissue and multi-nucleating the cells [37].

Osteogenesis

In the recent decades, several cell groups separated fat tissues of human and other species have the potential to differentiate in toosteoblast in vitro. Under the osteogenic conditions, ADSCs make stimulate expression of genes and proteins related to the flotypeosteoblast including alkaline phosphatase, cojen type I, osteopontin, osteocalcin, bone sialo protein, RanX1, BMP-2, BMP-4, PMP receptor and PTHreceptor. The ADSC differentiation can help in bone grafting and joint break reconstruction. Primarily, Lee et al. (2003) showed that in vitro the differentiation of ADSC to osteoblast lineages was similar to bone forming in vivo. Through their work, ADSC were separated from epididymal adipose tissue in rat, and then were moved into the Sub-Q; and after 8 weeks reasonable evidences of bone forming was observed [40]. Many works showed that dexamethasone was required for stimulating osteogenesis in vitro; however, its exact mechanism remains unclear. The experiment also showed that b-glycerophosphateis necessary for calcification and mineralization. The study explained that for stimulating osteogenesis, the environment should contain ascorbate and b-glycerophosphate derivations with vitamin D or dexamethasone [37].

CONCLUSION

Adipose-derived stem cells are able to differentiate to the several types of cells and thus are very profitable in reconstructive medicine. In reconstructive medicine, researches and preclinical investigations are trying to overcome the problems faced with the usage of mesenchymal stem cells in order to cure diseases. Mesenchymal stem cells can be separated from fat tissue and bone marrow. For many years, the bone marrow was an important resource for providing the mesenchymal stem cells using in tissue engineering, but in recent years, fat tissue has replaced bone marrow tissues as the separation of mesenchymal stem cells from fat tissue is easier and has minimal side effects. It can also differentiate into several types of tissues. This research aims to investigate adipose-derived stem cells, have better privilege when compared with other stem cells.

CONFLICT OF INTEREST
There is no conflict of interest

ACKNOWLEDGEMENTS
None

FINANCIAL DISCLOSURE
None

REFERENCES

[1] Roemeling-van Rhijn M, Reinders ME, de Klein A, Douben H, Korevaar SS, Mensah FK. [2012] Mesenchymal stem cells derived from adipose tissue are not affected by renal disease. Kidney Int, 82(7): 748- 758.
[2] Wang YH, Ho ML, Chang JK, Chu HC, Lai SC, Wang GJ. [2009] Microporation is a valuable transfection method for gene expression in human adipose tissue-derived stem cells. Mol Ther, 17(2): 302 -308.
[3] Cavarretta IT, Altanerova V, Matuskova M, Kucerova L, Culig Z, Altaner C. [2010] Adipose tissue-derived mesenchymal stem cells expressing prodrug-converting enzyme inhibit human prostate tumor growth. Mol Ther, 18(1): 223-231.
[4] Pournasr Khakbaz B, Baharvand H. [2007] Human mesenchymal stem cells and there, clinical aapplication. Iran J Anatomy Sci, 5: 167- 215.
[5] Bunnell BA, Betancourt AM, Sullivan DE. [2010] New concepts on the immune modulation mediated by mesenchymal stem cells. Stem Cell Res Ther, 11;1(5): 34.
[6] Gimble JM, Katz AJ, Bunnell BA. [2007] Adipose-derived stem cells for regenerativemedicine. Circ Res, 11;100(9): 1249-60.
[7] Bitrer RE, Schofer C, Weipotishammer K. [1999] Recrulment of bone marrow drived cells by skeletal and cardiac muscle in adult distrophic mdx mioe. Anat Embryol, 199(5): 391-396.
[8] Pournasr Khakbaz B, Baharvand H. [2007] Human mesenchymal stem cells and their clinical application. J Iran Anat Sci, 5(19): 157-206.
[9] Sharifi AM, Ghazanfari R, Tekiyehmaroof N, Sharifi MA. [2012] Isolation, cultivation, characterization and expansion of human Adipose-Derived mesenchymal stem cell for use in regenerative medicine. Int J Hematol Oncol Stem Cell Res, 6(1): 1-5.
[10] Mehrabani D, Mehrabani G, Zare S, Manafi A. [2013] Adipose-Derived stem cells (ADSC) and aesthetic surgery: A mini review. World J Plast Surg, 2(2): 65–70.
[11] Larocca RA, Moraes-Vieira PM, Bassi EJ, Semedo P, de Almeida DC, da Silva MB, Thornley T, Pacheco-Silva A, Câmara NO. [2013] Adipose tissue-derived mesenchymal stem cells increase skin allograft survival and inhibit Th-17 immune response. PLoS One, 4;8(10): e76396.
[12] Song L, Tuan RS. [2004] Transdifferentiation potential of human mesenchymal stem cells derived from bone marrow. FASEB J, 18(9): 980-2.
[13] Casadei A, Epis R, Ferroni L, Tocco I, Gardin C, Bressan E, Zavan B. [2012] Adipose tissue regeneration: A state of the art. J Biomed Biotechnol, 2012(5110): 462543.
[14] Castro-Manrreza ME, Montesinos JJ. [2015] Immunoregulation by mesenchymal stem cells: Biological aspects and clinical applications. J Immunol Res, 2015: 394917.
[15] Johal KS, Lees VC, Reid AJ. [2015] Adipose-derived stem cells: Selecting for translational success. Regen Med, 10(1): 79-96.
[16] Kim N, Cho S.-G. [2013] Clinical applications of mesenchymal stem cells. Kor J Intern Med, 28(4): 387–402.
[17] Gimble JM, Bunnell BA, Frazier T, Rowan B, Shah F, Thomas-Porch C, Wu X. [2013] Adipose-derived stromal/stem cells: A primer. Organogenesis, 9(1): 3-10.
[18] Lin F. [2012] Adipose tissue-derived mesenchymal stem cells: A fat chance of curing kidney disease? Kidney Int, 82(7): 731- 733.
[19] Parekkadan B, Milwid JM. [2010] Mesenchymal stem cells as therapeutics. Ann Rev Biomed Eng, 15;12: 87-117.
[20] Adipose-derived mesenchymal cells for bone regereneration: State of the art. [2013] Biomed Res Int, 416391.
[21] Baek SJ, Kang SK, Ra JC. [2011] In vitro migration capacity of human adipose tissue-derived mesenchymal stem cells reflects their expression of receptors for chemokines and growth factors. Exp Mol Med, 43(10): 596- 603.
[22] Oh SH, Muzzonigro TM, Bae SH, LaPlante JM, Hatch HM, Petersen BE. [2004] Adult bone marrow-derived cells trans-differentiating into insulin-producing cells for thetreatment of type I diabetes. Lab Invest, 84(5): 607-17.
[23] Mohammadi Z, Afshari JT, Keramati MR, Alamdari DH, Ganjibakhsh M, Zarmehri AM, Jangjoo A, Sadeghian MH, Ameri MA, Moinzadeh L. [2015] Differentiation of adipocytes and osteocytes from human adipose and placental mesenchymal stem cells. Iran J Basic Med Sci, 18(3): 259-66.
[24] Grove JE, Bruscia E, Krause DS. [2004] Plasticity of bone marrow-derived stem cells. Stem Cells, 22(4): 487- 500.
[25] Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ. [2001] Multilineage cells from human adipose tissue: Implications for cell-based therapies. 7(2): 211-28.
[26] Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. [2002] Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell, 13(12): 4279-95.
[27] Hsu VM, Stransky CA, Bucky LP, Percec I. [2012] Fat grafting's past, pre- sent, and future: Why adipose tissue is emerging as a critical link to the advancement of regenerative medicine. Aesthet Surg, 32(7): 892-9.
[28] Zhu M, Zhou Z, Chen Y, Schreiber R, Ransom JT, Fraser JK. [2010] Supplementation of fat grafts with adipose-derived regenerative cells improves long-term graft retention. Ann Plast Surg, 64(2): 222-8.
[29] Lacaud G, Robertson S, Palis J, Kennedy M, Keller G. [2001] Regulation of hemangioblast development. Ann N Y Acad Sci, 938: 96-107.
[30] Zech N. [2004] Adult stem cells manipulation and possible clinical perspective. Reprod Med Endocrinol, 1(2): 91- 99.
[31] Baharvand H, Matthaei KI. [2004] Culture condition difference for establishment of new embryonic stem cell lines from the C57BL/6 and BALB/c mouse strains. In Vitro Cell Dev Biol Anim, 40(3-4): 76-81.
[32] Tholpady SS, Llull R, Ogle RC, Rubin JP, Futrell JW, Katz AJ. [2006] Adipose tissue: Stem cells and beyond. Clin Plast Surg, 33(1): 55–62.
[33] Stosich MS, Mao JJ. [2007] Adipose tissue engineering from human adult stem cells: Clinical implications in plastic and reconstructive surgery. Plast Reconstr Surg, 119(1): 71–83; discussion 4–5.
[34] Rodriguez AM, Elabd C, Delteil F, Astier J, Vernochet C, Saint-Marc P, Guesnet J, Guezennec A, Amri EZ, Dani C, Ailhaud G. [2004] Adipocyte differentiation of multipotent cells established from human adipose tissue. Biochem Biophys Res Commun, 5;315(2): 255-63.
[35] Boone C, Mourot J, Gregoire F, Remacle C. [2000] The adipose conversion process: Regulation by extracellular and intracellular factors. Reprod Nutr Dev, 40(4): 325–58.
[36] Winter A, Breit S, Parsch D. [2003] Cartilage-like gene expression in differentiated human stem cell spheroids: A comparison of bone marrow-derived and adipose tissue-derived stromal cells. Arthritis Rheum, 48(2): 418–29.
[37] Bieback K, Kern S, Kluter H, Eichler H. [2004] Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood. Stem Cells, 22(4): 624- 634.

[38] Cowan CM, Shi Y-Y, Aalami OO. [2004] Adipose-derived adult stromal cells heal critical-size mouse calvarial defects. Nat Biotechnol, 22(5): 560–7.
[39] Lee JA, Parrett BM, Conejero JA. [2003] Biological alchemy: Engineering bone and fat from fat-derived stem cells. Ann Plast Surg, 50(6): 610–17.
[40] Duplomb L, Dagouassat M, Jourdon P, Heymann D. [2007] Differentiation of osteoblasts from mouse embryonic stem cells without generation of embryoid body. In Vitro Cell Dev Biol Anim, 43(1): 21–4.