Mesenchymal stem cells (MSC): Identification, Proliferation and Differentiation – A Review Article

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ABSTRACT: Stem cells have the remarkable potential to develop into many different specialized cells in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to repletion other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential to either endure a stem cell or become another type of cell with a more specialized function, such as a muscle cell, or a red blood cell, or a brain cell. Mesenchymal stem cells (MSC) are a group of cells present in bone-marrow stroma and the stroma of various organs with the capacity for mesoderm-like cell differentiation into, many types like osteoblasts, adipocytes, and chondrocytes. MSC are being use in the clinic for the treatment of a variety of clinical conditions. Cell-based therapies (CBTs) are quickly taking hold as a revolutionary new approach to treat many human diseases. Among the cells used for therapeutic functions, multipotent mesenchymal stromal cells, also often and imprecisely termed (MSC), are widely used because they are considered clinically safe, unique in their immune-capabilities, easily obtained from adult tissues, and easily developed and restore.

KEY WORDS: Stem Cell, Mesenchymal stem cells (MSC), MSC proliferation and Differentiation

INTRODUCTION

In the past decade, the field of stem cell biology has undergone a remarkable evolution sparked by report demonstrating that adult stem cells possess greater plasticity than dictated by established paradigms of embryonic development. Subsequently, much efforts have been devoted to deciphering the molecular mechanisms that regulate adult stem cells plasticity and developing ways to exploit it for a therapeutic intent. An orderly chain of highly regulated processes involving cell proliferation, migration, differentiation and maturation leads to the production and sustenance of most cell lineage in adult organism. The earliest cell type on this chain has been called a stem cell.

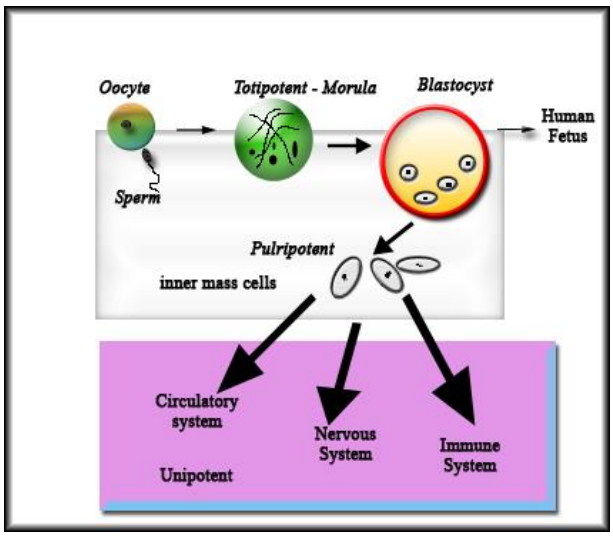

Figure 1 potency of stem cells

BASICS OF STEM CELLS

Stem cells have the remarkable potential to develop into many different cell different specialized cells in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to repletion other cells as long as the person or animal is still alive When a stem cell divides, each new cell has the potential to either endure a stem cell or become

another type of cell with a more specialized function, such as a muscle cell, or a red blood cell, or a brain cell. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease which is often referred to as "regenerative or reparative medicine."

HAEMATOPOEITIC STEM CELLS AND ITS EXPRESSION

Haematopoeitic stem cells are population of cells capable both of self-renewal and of differentiation into a variety of haematopoeitic lineages. Enrichment techniques in human haematopoeitic stem cells have used the expression of CD34, present on bone marrow progenitor cells. But most CD34 bone marrow cells are committed to their lineage, and more present studies have focused on the precise characterization of the pluripotent subset of CD34+ cells. Here, we report the characterization of two distinct subset of pluripotent stem cells from human fetal bone marrow, a CD34+ HLA-DR+ subset that can differentiate into all haematopoietic lineages, and a specialize more primitive subset, that is CD34+, HLA-DR-, that can differentiate into haematopoietic precursors and stromal cells capable of supporting the differentiation of these precursors. These information represent, to our knowledge, the first identification of a single cell capable of reconstituting the haematopoietic cells and their associated bone marrow microenvironment. (Shianghuang and Leon *et al*., 1992)

Based on historical radiation experiments in rodents, the haematopoeitic stem cell was defined by its biological properties and later by the expression of certain surface antigens (e.g. CD34), as well as the absence of lineage specific markers (e.g. DR). Quite recently, it was shown that haematopoeitic reconstruction can also be achieved by CD34+ stem cells, it can be isolated from the bone marrow, peripheral blood and cord blood cells. Due to novel techniques, CD34+ stem cells can be expanded on the level of a true stem cell but also directed towards their differentiation into specified tissues or organ systems. This requires the stability of primary fibroblast-like CD34 stem cells in vitro and their possible reversible and transient immortalization with optimized vector system. (Ralf Huss, *et al*., 2000).

IDENTIFICATIONS OF STEM CELLS

Stem cells have an extensive capacity to proliferate, differentiate & self-renewal, enabling them to repopulate recipients after transplantation. Stem cells subpopulations have been defined in many mammals including humans by using the fluorescent dyes, rhodamine 123 & Hoechst 33342. Adult stem cells subpopulations have been identified that can rapidly efflux the Hoechst dye to produce a characteristic SP profile based on fluorescence-activated flow cytomeric analysis. SP cells obtained from normal marrow are characterized by a CD34 low/neg phenotype and capacity to reproduce lethally irradiated mice. A similar SP has been described in monkey and will regenerate CD34+ cells ex vivo. (Wulf *et al.*, 2009) deleted a malignant CD45+CD34 low/neg SP cells subset in > 80% of the acute myeloid leukaemia patients they studied. These cells generated CD45+CD34+ malignant haematopoeitic stem cells as well as committed myeloid progenitor (Hirschmann. *et al*., 2004).

MESENCHYMAL STEM CELLS (MSCS)

The mesenchymal stem cells (MSCs) in the adult bone marrow are necessary for the body to generate tissues such as bone, cartilage, muscle, ligament, tendon, adipose, and bone marrow.. Reproducible differentiation of human embryonic stem cells (hESCs) into MSCs does not require the use of any feeder layer. MSC stem cells can be grown for many generations in the laboratory and still retain a stable morphology and normal chromosome complement. MSCs, are contact inhibited, can be grown in culture for about 20 to 25 passages, have an immunophenotype same to bone marrow MSCs positive (CD34, CD45, CD44, CD13, CD73, CD90, CD105) human leukocyte antigen [HLA]-ABC, and stage-specific embryonic antigen [SSEA]-4), can differentiate into osteocytes and adipocytes, and can be used as fibroblast is a type of cell to support the growth of undifferentiated hESCs. The able to developed MSCs from hESCs should prove useful to produce large amounts of genetically identical and genetically modifiable MSCs that can be used to study the biology of MSCs and for therapeutic applications (Emmaneul. *et al*., 2006).

MSCs are non-haematopoeitic stromal cells that are capable of differentiating into and contribute to the regeneration of mesenchymal tissues like bone, cartilage, muscle, ligament, tendon, and adipose. MSCs are very less in bone marrow, representing 1 in 10,000 nucleated cells. And there is no immortal, they have the ability to expand many fold in culture while retaining their growth and multilineage potential. MSCs are can be identified by the expression of many molecules including CD105 (SH2) CD73 and CD34, CD45. The properties of MSCs make these cells potentially ideal candidates for tissue technology. It has been prove that MSCs, when transplanted systemically, are ability to transport to sites of physical harm or damage in animals, suggesting that MSCs have migratory capacity. The mechanism of migration of MSCs remain unclear. Chemokine receptors and their ligands and adhesion molecules play an important role in tissue specific homing of leukocytes and have also been implicated in trafficking of hematopoietic precursors into and through tissue. Many research have reported the functional expression of various chemokine receptors and adhesion molecules on human MSCs. Harnessing the migratory potential of MSCs by modulating their chemokine-chemokine receptor interactions may be a powerful way to increase their ability to correct inherited disorders of mesenchymal tissues or facilitate tissue repair in vivo. MSCs and their capacity to home to tissues together with the associated molecular mechanisms involve chemokine receptors and adhesion molecules. (Giselle chamberlain. *et al*., 2007).

Mesenchymal stem cells (MSCs) and Mesenchymal progenitor cells (MPCs) are studied for their potential in regenerative medicine. MSCs have great potential, because various reports have shown that they can differentiate into many different cells types. However, the difference between Mesenchymal stem/progenitor cells and so-called fibroblasts is unclear. In this study, it was found that most of the distinct populations of primary fibroblast-like cells derived from various human tissues, including lung, skin, umbilical cord and amniotic membrane, contained cells that were ability to differentiate into at least one mesenchymal lineage, including osteoblasts, chondrocytes, and adipocytes. It was therefore proposed that primary fibroblast-like cell populations obtained from various human tissues do not comprise solely fibroblasts, but rather that they also include at least MPCs and possibly MSCs, to some extent. (Kozuhiro Sudo & Megumi Kanno. *et al*., 2007).

Mesenchymal stem cells (MSC) are a specialized cells present in bone-marrow stroma and the stroma of various organs with the capacity for mesoderm-like cell differentiation into, osteoblasts, adipocytes, and chondrocytes. MSC are being introduced in the clinic for the treatment of a variety of clinical conditions. The aim of the review is to provide an update regarding the characteristics of the MSC, their identification and culture, and mechanisms controlling their proliferation and differentiation. The current status of their clinical use is also reviewed. Areas in which research is needed to enhance the clinical use of bone-marrow stromal cells, mesenchymal stem cells (MSC), or skeletal stem cells. The stem cell characteristics of MSC are based on their ability to differentiate into multiple mesoderm-type cells, including osteoblasts, chondrocytes, and adipocytes and, under certain in vitro culture condition, into ectoderm-type cells, e.g., neuron-like cells (Dezawa et al. 2004), and ectoderm-like cells, e.g., hepatocytes (Lee et al. 2004). However, the differentiation capacity of MSC into non-mesoderm-like cells is still highly controversial and needs further confirmation. (Moustapha kassem, and Basem, *et al*., 2007).

Peripheral blood-derived multipotent mesenchymal stromal cells circulate in low number. They share, most though not at all, of the surface markers with bone marrow-derived multipotent mesenchymal stromal cells, possess diverse and complicated gene expression characteristics, and are capable of differentiating along and even beyond mesenchymal cells lineages. Although their origin and physio-pathological functions are still unclear, it presence in the adult peripheral blood might relate to some interesting but controversial subjects in the field of adult stem cell biology, such as systemic migration of bone marrow-derived multipotent mesenchymal stromal cells and the existence of common haematopoeitic mesenchymal cells (Qiling He & Chao Wan. *.et al.*, 2007).

BONE MARROW-DERIVED MESENCHYMAL STEM CELLS (BMSCS)

Isolation of adult stem cells (ASC) has proven difficult due to the lack of clearly defined ASC markers. Goodell et al demonstrated that hematopoietic stem cells (HSC) could be isolated by the ability of SCs to efflux Hoescht 33342 and forms a side population (SP) on FACS analysis. This method of SC isolation has been adapted for solid tissue such as the prostate and presently, unfractionated normal human kidney tissue (Goodell & Inowa. *et al*., 2008).

Bone marrow-derived mesenchymal stem cells (BMSCs) are a mostly researched adult stem cell population capable to differentiation into various lineages. Because many promising applications of tissue engineering wants cell expansion following harvest and involve the treatment of diseases and conditions of old age population, the effect of donor age and ex vivo should be understood to develop clinical techniques and therapeutics based on these cells. Furthermore, there currently exist little understandings as to how these two factors may be influenced by each other. Differences in adipogenic, chondrogenic, and oestrogenic differentiation capacity of murine MSCs harvested from donor animals of various age and number of passage of these cells were observed. Cells from younger donors adhered to tissue culture polystyrene better and proliferated in greater number than those from older animals. Chondrogenic and osteogenic potential decreased with each and every age group, and adipogenic differentiation decreased only in cells from the oldest donors. Both increasing age and the number of passages have lineage dependent effects on BMSCs differentiation potential. Furthermore, there is an obvious interplay between donor and cell passage

that in the future must be accounted for when developing cell-based therapies for clinical use (James and Kretlow, *et al*., 2008).

FATE OF MESENCHYMAL STEM CELLS (MSCS

In spite of the advances in the knowledge on adult stem cells (ASC's) during the past few decade, their natural activities in vivo are still poorly understood. Mesenchymal Stem Cells (MSCs), one of the most promising types of ASCs for cell based therapies, are defined mainly functional assays using cultured cells. Introducing MSCs in vitro adds complexity to their study because the artificial conditions may introduce experimental artefacts. Inserting these results in the context of the organisms is difficult because the exact location and functions of MSCs in vivo remain elusive; the identification of the MSC niche is necessary to validate results observed in vitro, and to further the knowledge of the physiological functions of this ASC. An analysis of the evidence suggests a perivascular location for MSCs, correlating these cells with pericytes, and presents a model in which the perivascular zone is the MSC niche in vivo, where local cues coordinate the transition to progenitor and mature cells phenotypes. This model proposes that MSCs stabilize blood vessels and contribute to tissue and immune system homeostasis under physiological conditions, and assume a more active role in the repair of focal tissue damage. The establishment of the perivascular compartment as the MSC niche provides a basis for the rational design of additional in vivo therapeutic approaches. This view connects the MSC to the immune and vascular systems, emphasizing its role as a physiological integrator and its importance in tissue repair/regeneration (Lindolfo da Silva Meirelles *et al*., 2008).

Mesenchymal stem cells (MSCs) have been investigated as promising candidates for use in new cell-based therapeutic strategies such as mesenchyme-derived tissue repair. MSCs are easily isolated from adult tissues and are not ethically restricted .MSC-related literature, however, are conflicting in relation to MSC differentiation potential and molecular markers. Here, a comparison is made among MSCs isolated from the bone marrow (BM), umbilical cord blood (UCB), and adipose tissue (AT). The isolation efficiency for the both BM and AT was 100% but that from UCB was only 30%. MSCs from these tissues are morphologically and immunophenotyphically similar although their differentiation diverge. Differentiation to osteoblasts and chondroblasts was similar among MSCs from all sources, an analysed by cytochemistry. Adipogenic differentiation showed that UCB-derived MSCs produced few and small lipid vacuoles in contrast to those of BM-derived MSCs and AT-derived stem cells (ADSCs) (arbitrary differentiation values of 245.576 943 and 243.896 145.52 1m2 per nucleus, respectively). The mean area occupied by each lipid droplets was 7.37 1m2 for BM-derived MSCs and 2.36 1m2 for ADSCs, a finding indicating more mature adipocytes in BM-derives MSCs than in treated cultures of ADSCs. Analysis of FAPB4, ALP, and type II collagen gene expression by quantitative polymerase chain reaction confirmed adipogenic, ostrogenic and chondrogenic differentiation, respectively. Results showed that all three sources presented a similar capacity for chondrogenic and osteogenic differentiation, and they differed in their adipogenic potential. Therefore, it may be crucial to predetermine the most appropriate MSC source for future clinical applications. (Rebelatto, *et al*., 2008).

Mesenchymal stem cells (MSCs) have been isolated from a variety of human tissues, like bone marrow, adipose tissue, dermis, hair follicles, heart, liver, spleen, dental pulp. According to

their immunomodulatory and regenerative potential MSCs have shown impressive results in preclinical and clinical studies for a variety of conditions, such as graft versus host disease (GvHD), Crohn's disease, osteogenesis imperfect, cartilage damage and myocardial infarction. MSC cultures are composed of heterogeneous cell populations. Complications in defining MSC arise from the fact that different laboratories have employed different tissue sources, extraction, and cultivation technics. Although cells surface antigens of MSCs have been extensively explored, there is no conclusive evidence that unique stem cells markers are associated with these adult cells. Therefore the aim of this study was to examine expression of embryonic stem cell markers Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4 in adult mesenchymal stem cell populations derived from bone marrow, adipose tissue, dermis and heart. Furthermore, we tested whether human mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions. We found that bone marrow MSCs express embryonic stem cell markers Oct4, Nanog, alkaline phosphatase and SSEA-4, adipose tissue and dermis MSCs express Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4, whereas heart MSCs express Oct4, Nanog, SOX2 and SSEA-4. Our results also indicate that human adult mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions during early passages, as shown by distinct germ layer and embryonic stem cell marker expression patterns. Studies are now needed to determine the functional role of embryonic stem cell markers Oct4, Nanog and SOX2 in adult human MSCs. (Una Riekstina, *et al*., 2009).

Mesenchymal cells contribute to the 'stroma' of most normal and malignant tissues, with specific mesenchymal cells participating in their regulatory niches of stem cells. By examining how mesenchymal osteolineage cells modulate haematopoiesis, here we show that deletion of Dicer1 specifically in mouse osteoprogenitors, but not in mature osteoblasts, disrupts the integrity of haematopoiesis. Myelodysplasia resulted and acute myelogenous leukaemia emerged that had acquired several genetic abnormalities while having intact Dicer1. Examining gene expression altered in osteoprogenitors as a result of Dicer1 deletion showed reduced expression of Sbds, the gene mutated in Schawchman Bodian-Diamond syndrome-a human bone marrow failure and leukaemia pre-disposition condition. Deletion of Sbds in mouse osteoprogenitors induced bone marrow dysfunction with myelodysplasia. Therefore perturbation of specific mesenchymal subsets of stromal cells can disorder differentiation, proliferation & apoptosis of heterologous cells, and disrupt tissue homeostasis. Furthermore, primary stromal dysfunction can result in secondary neoplastic diseases, supporting the concept of niche-induced oncogenesis. (Marc, Raaijimakers et al., 2010).

MESENCHYMAL STEM CELLS (MSCS AND TISSUE ENGINEERING)

Our understanding of the role of bone marrow (BM)-derived cells in cutaneous homeostasis and would healing had long been limited to the contribution of inflammatory cells. Present studies, however suggest that the bone marrow contributes of significant proportion of non-inflammatory cells to the skin, which are have primarily in the dermis in fibroblast-like morphology in the epidermis in a keratinocyte phenotype; and the number of these BM-derived cells increases markedly after wounding. In the present, several studies indicate that MSCs derived from the BM could significantly impact would healing in diabetic and non-diabetic animals,

through cell differentiation and the release of paracrine factors, implying a profound therapeutic potential. This review discusses the most recent understanding of the contribution of BM-derived non inflammatory cells to cutaneous homeostasis and wound healing. (Yaojion & Robert, et al., 2010).

In recent years, the potential of cartilage tissue engineering techniques employing mesenchymal stem cells (MSCs) to repair damaged human cartilage and defects has generated much interest. Traditionally, sources of MSCs included patient's own bone marrow. However, little have been reported on adult peripheral blood (PB) as a source of MSCs, which has been a subject of much debate amongst scientists owing to its extremely low density in PB and the difficulties associated with extracting MSCs from PB. The objectives of this study were to isolate MSCs derived from bone marrow and peripheral blood as a source and to assess their potential to undergo in vitro chondrogenesis using a biocompatible three-dimensional scaffold. In defining MSCs, the cells isolated from its source must meet these 3 criteria: (i) adherence to plastic when maintained in culture; (ii) positive expression of several antigens such as CD90, CD105, CD73; (iii) ability to differentiate into osteoblasts, adipocytes & chondrocytes under in vitro inductive conditions. PB samples (2 ml) were collected and mononuclear cells extracted and separated using Ficoll-Paque PLUS thorough centrifugation. Subsequently, suspended cells were removed after 5 days of culture, and adherent cells left to grow. Cells were detached upon reaching 80-90% confluence and subcultures to 4 passages prior to further experiments. MSC antigens were recognized by monoclonal antibodies CD90, CD105 and CD73. To distinguish MSCs from haematopoeitic stem cells, CD34 surface markers were used as negative controls. The characterized human blood derived progenitor cells were cultured in three-dimensional alginate scaffolds using chondrogenic induction medium to promote chondrogenesis. Chondrogenesis was quantitated by sulphated glycosaminoglycan (S-GAG) production measured by 1, 9-dimethylmethylene blue (DMMB) assay. Furthermore, chondrogenic-MSCs were examined and histologically compared using Safranin O staining to that of human chondrocytes as a means to determine chondrogenic transformation. Gene expression analysis was carried out by reverse transcriptase-polymerase chain reaction (RTPCR) of differentiated human blood-derived progenitor cells using chondrocyte (cartilage cell)-specific phenotypic markers. The results showed that the cell derived in our processing technique share similar characteristics with adult MSCs and chondrocytes. Induction of chondrogenesis has been demonstrated in human blood-derived progenitor cells, which could give a ready source of chondrocytes for engineering biological therapies. In the practical sense, PB isolation would prove to be less invasive, less expensive and less traumatic for patients to undergo therapy as compared to the 2-stage procedure of current available tissue engineering technique.(Pan-Pan Chong, et al.,2011).

NONIMMORTALIZED FIBROBLAST CELL LINES

New human nonimmortalized fibroblast cell lines were derived from many sources: from embryonic stem cells (ESCs) (the SC5 MSC and SC3a MSC lines), from bone marrow of a 5 to 6 week old fetus (the FetMSC line), and from foreskin of a 3 year old child (the FRSN line). All the lines are successfully used as feeders during cultivation of human ESCs. The mean doubling time of the cell populations fluctuates depending on the line from 25.5 h in the SC5 MSC line to 38.8 h

in the SC3a MSC line. The growth curves indicate active cell proliferation of all lines. Numerical and structural karyotypical analysis has shown these lines to have a normal karyotype: 46, XX (SC5 MSC and SC3a MSC) and 46, XY (FetMSC and FRSN). To determine the status of these lines, comparative analysis of surface markers was performed with the aid of flow cytofluorimetry, and expression of the c antigens characteristic of human mesenchymal stem cells (MSCs) was revealed: CD44, CD73, CD90, CD105, and HLA ABC and the absence of expression of CD34 and HLA DR. Interlinear differences in the expression level of the marker CD13 (c kit) were revealed. Immunofluorescent and cytofluorimetric analysis of expression of surface markers and transcription factor Oct 4 that are characteristic of human ESCs has shown that, in all four lines, expression of TRA 160 and Oct 4 is absent, whereas in expression of SSEA 4 there are observed the interlinear differences not depending on the origin of cells. At present it is not yet clear whether the revealed interlinear differences affect essentially the functional status of mesenchymal stem cells. Immunofluorescent analysis in cells of all lines showed expression of markers of early differentiation into derivatives of three germ layers characterizing ESCs, which might possibly provide wide MSC possibilities during reparation of different tissue damages, depending on the corresponding microenvironment. The capability of cells of all lines for directed differentiation into the adipogenic and osteogenic directions was revealed (T. A. Krylova, et al- 2011). The objective of the study is to evaluate efficiency of in vitro isolation and myogenic differentiation of mesenchymal stem cells (MSCs) derived from adipose connective tissue (AD-MSCs), bone marrow (BM-MSCs), and skeletal muscle tissue (MC-MSCs). MSCs were isolated from adipose connective tissue, bone marrow, and skeletal muscle tissue of two adult 6 week old rats. Cultured MSCs were treated with 5-azacytidine (AZA) to induce myogenic differentiation. Isolated MSCs and differentiated cells were evaluated by immunocytochemistry (ICC), fluorescence-activated cell sorting (FACS), PCR, and RT-PCR. AD-MSCs showed the highest proliferation rate while BM-MSCs had the lowest one. In ICC, isolated MSCs had strong CD90- and CD44-positive expression and negative expression of CD45, CD13, and CD34, while AZA-treated MSCs had strong positive desmin expression. In FACS analysis, AD-MSCs had the highest percentage of CD90- and CD44-positive-expressing cells (99% and 96%) followed by BM-MSCs (97% and 94%) and MC-MSCs (92% and 91%).At 1 week after incubation with AZA treatment, the peak of myogenin expression reached 93% in differentiated MC-MSCs, 83.3% in BM-MSCs, and 77% in AD-MSCs. MSCs isolated from adipose connective tissue, bone marrow, and skeletal muscle tissue have the same morphology and phenotype, but AD-MSCs were the most easily accessible and had the highest rate of growth on cultivation and the highest percentage of stem cell marker expression. Moreover, although MC-MSCs showed the highest rate of myogenic differentiation potential and expression of myoblast markers, AD-MSCs and BM-MSCs still can be valuable alternatives. The differentiated myoblastic cells could be an available new choice for myoblastic auto-transplantation in regeneration medicine. (Fatma Meligy, *et al*., 2012).

THERAPEUTIC INTEREST ON MSCS

There is an increasing interest in adult stem cells, especially mesenchymal stem/stromal cell (MSCs), in hematology and regenerative medicine because of the simplicity of isolation and ex vivo expansion of these cells. Periodically, MSCs are functionally isolated from tissue based on their capacity to adhere to the surface of culture flasks. This isolation procedure is hampered

by the unpredictable influence of secreted molecules and interactions with co-cultured hematopoietic and other tow different cells, as well as by the arbitrarily selected removal time of non-adherent cells prior to the expansion of MSCs. Finally, functionally isolated cells do not provide biological information about the starting population. To circumvent these limitations, several steps have been developed to facilitate the prospective isolation of MSCs based on the selective expression or absence of surface markers. The isolation and ex vivo expansion of these cells require an adequate quality control of the source and product. Here we summarize the most frequently used markers and introduce new targets for anti-body-based isolation and characterization of bone marrow-derived MSCs. (Hariciandan, *et al*., 2012).

Cell-based therapies (CBTs) are quickly taking hold as a revolutionary new approach to treat many human diseases. These specialize cells used in these treatments, multiptent mesenchymal stromal cells, also often and imprecisely termed (MSC), are widely used because they are considered clinically safe, unique in their immune-capabilities, easily obtained from adult tissues, and quickly expanded as well as stored. However, despite these established advantages, there are limiting factors to employing MSCs in there therapeutic strategies. Foremost is the lack of a general consensus on a definition of these cells, marring efforts to prepare homogeneous lots and more importantly complicating there in vitro and in vivo investigation. Furthermore, although one of the most profound clinical effects of MSC intravenous administration is the modulation of host immune responses, no adequate ex vivo assays exist to consistently predict the therapeutic effect of each MSC lot in the treated patient. Until these issues are addressed, this very promising and safe new therapeutic approach cannot be used to its full advantage. However, these confounding issues do present exciting opportunities. The first is an opportunity to discover unknown aspects of host immune responses because the unique effect driven by MSC infusion on a patient's immunity has not yet been identified. In addition, there is an opportunity to develop methods, tests, and tools to better define MSCs and MSC-based therapy and provide consistency in preparation and effect. To this end. There laboratory recently developed a new approach to induce uniform pro-inflammatory MSC1 and anti-inflammatory MSC2 phenotypes from bone marrow-derived MSC preparations. I anticipate that MSC1 and MSC2 provide convenient tools with which to address some of these limitations and will help advance safe and effective CBTs for human disease. (Aline et al., 2012).

Although stem cells are present in various adult tissues and body fluids, bone marrow has been the most impressive source of stem cells for treatment of a wide range of diseases. Present results for stem cells from adipose tissue have put it in a position to compete for being the leading therapeutic source. The major advantage of these stem cells over their counterparts is their amazing proliferative and differentiation potency. However, their pancreatic lineage Tran’s differentiation competence was not compared to that for bone marrow- derived stem cells. This Review aims to identify an efficient source for trans differentiation into pancreatic islet-like clusters, which would increase potential application in curative diabetic therapy. The results reveal that mesenchymal stem cells (MSC) derived from bone marrow and subcutaneous adipose tissue can differentiate into pancreatic islet-like clusters, as evidenced by their islet-like morphology, positive dithizone staining and expression of genes such as Nestin, PDX1, Isl 1, Ngn 3, Pax 4 and Insulin. The pancreatic lineage differentiation was further corroborated by positive results in the glucose

challenge assay. However, the results indicate that bone marrow-derived MSCs are superior to those from subcutaneous adipose tissue in terms of differentiation into pancreatic islet-like clusters. In conclusion, bone marrow-derived MSC might serve as a better alternative in the treatment of diabetes mellitus than those from adipose tissue. (Dhanasekaran. *el al*., 2013).

CONCLUSION

Stem cells have been in the news in recent year because they can grow and differentiate into many cell types, with much promise for treating a variety of diseases and injuries.

Scientists are now utilizing stem cells of different origin; opening up the research and treatment options for humans. Differing from embryonic stem cells, adult stem cells are procured form a variety of tissues, including skin, fat (adipose) and bone marrow, among other tissues. Adult stem cells are less controversial because the samples are easily obtained and the "host" is not destroyed, as with an embryo.

Stem cells can differentiate into many cell types as they develop, including bone, cartilage, nerves, muscles, and so on. Thus, treatment using stem cells is treatment using stem cells is termed "regenerative medicine" and has many potential uses for a wide variety of diseases and injuries. Stem cells medicine holds much promise for a variety of diseases, including liver, kidney, heart, neurologic and immune-mediated diseases.

In future, stem cells may be able to treat and possibly cure diseases for which there is no adequate therapy today.

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