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REVIEW ARTICLE

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Umbilical Cord Wharton's jelly and Aiponse Tissue derived Mesenchymal Stem Clls

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ABSTRACT

Introduction: 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. Some of the most crucial stem cells are mesenchymal stem cells (abbreviated as MSC). MSCs have the property of heterogenisis 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 mesenchymal stem cells in addition to bone marrow also gained from tissue such as umbilical cord and adipose tissue and so in recent years have attracted attention of many researchers. Adipose tissue derived mesenchymal stem 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. The aim of this study is to evaluate the Features of adipose tissue and umbilical cord Wharton's jelly that makes these tissues more remarkable than other tissues.

Key words: Mesenchymal Stem Cell, Adipose tissue, Umbilical cord, Wharton's jelly

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Introduction:

A few cells in the body are 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 (1). The evolution of 'Stem cell' studies and researches 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 primary goal of this scientific field. This process 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 (2,3).

The MSc are known as pluripotent and fibroblastic cells which can be separated from bone marrow, adipose tissue, umbilical cord blood, lungs (4-6), skin (7) and spleen (8). The MSc count a valuable resource with the high productivity for repairing the tissues due to 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 MSs exhibits greater immunity in a short term (3). 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 a good and suitable resource as umbilical cord stem cell. Moreover, many stem cells can be separated from a single adipose tissue. Based on the recent investigations, the adipose tissue stem cells are able to cure the liver injuries, muscular dystrophy, allergy, and myocardial infarction. Wharton's jelly is also a rich tissue in cells with mesenchymal tissue morphology that surrounds the umbilical cord vessels, protects it against impact and pressure. The first isolated and cultured fibroblast-like cells from human Wharton's jelly was reported by Mac Alryvry (9). From that time until now, the use of Wharton's jelly has been shown in various clinical studies which differentiate these cells into neural cells, insulin-secreting cells of the pancreas, liver-like cells and cardiovascular tissue (10,11).

Stem Cells:

These are self-renewable cells that have varying potency to differentiate into multiline ages and the ability to form clones (clonogenic) (12). Ideally, the stem cell used for regenerative medicinal applications should meet the following criteria (2):

- 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 (13).

Stem cells are classified into four types based on their origin, including embryonic stem cells, fetal stem cells, umbilical cord blood stem cells and adult stem cells. There are some characteristics for adult stem cells which make them suitable for clinical uses: ease of harvest, high expansion rate in vitro and multiline age differentiation capacity (14). The application of cellular therapy and regenerative medicine is rapidly growing, however for regenerative medicinal purposes, stem cells should meet the above mentioned criteria. Cell therapy which 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) (15). In addition, several studies (16) have shown that stem cells also benefit from immunomodulatory capabilities.

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 (17). In addition to phenotypic characterization, the above mentioned are another minimal criterion that were proposed by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy to define MSCs (18).

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 (12,19). 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 (20). 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 producing of 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 (28). These cells: (a) should exhibit plastic adherence, (b) posse specific set of cell surface markers, i.e. cluster of differentiation (CD)73, D90, CD105, lack expression of CD14, CD34, CD45, 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 (12,19,20).

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 MSCs is investigated in vitro culture functional assays using specific differentiation media. This feature makes MSCs to be considered as a suitable source for tissue repair (21). Although in most cases the isolated MSCs are heterogeneous in proliferation and differentiation, and the expression of the characteristic MSC markers stand prominent. Cultivation of MSCs in vitro has three biological properties that qualify them for using in cellular therapy: (a) broad potential of differentiation, (b) secretion of trophic factors that favor tissue remodeling, and (c) immunoregulatory properties (19). 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) immunomodulatory function, and (e) fusion and rejuvenation of resident committed progenitor cells (8,22,23).

MSCs are an excellent candidate for cell therapy because: (a) human MSCs are easily accessible; (b) the isolation of MSCs is straight forward 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 (24). 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 repair when 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 to differentiate into mesoderm-derived cell types as well as into cells with neuro-ectodermal and endodermal characteristics, proposing that trans-differentiation occurs in mammalian systems (17). 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 (24). 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 (23, 25). 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 MSCs would prove to be beneficial in cell therapy (26).

Adipose tissue derived mesenchymal stem cells (ADSCs)

Nowadays, MSCs are isolated from different tissue for instance from adipose tissue, umbilical cord, multitude of adult tissues including muscle, etc. AT is a strong source of MSCs isolation because of some special characteristic like, ubiquity, ease of retrieval and the noninvasive procedure needed for harvesting the adipose tissue (AT). ATs posse a higher proliferation capacity but BM-MSCs have some limitations in providing a sample which are the result of low number of harvested cells, limited amount of harvested tissues and donor site morbidity or patient discomfort. 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 (26, 28). Adipose tissue, is a mesodermal-derived organ which includes a bulk of stem cells. These tissues can be enzymatically derived from AT and following this, it is possible to make a homogenous population in culture under suitable conditions. A variety of names have been used to describe the plastic adherent cell population isolated from collagenase digests of AT. For example, the International Fat Applied Technology Society adopts the term “adipose-derived stem cells” (ADSCs) to identify the isolated, plastic adherent, multipotent cell population (14). ATs mesodermal origin, i.e., ADSCs can be a valuable tool for repairing bone and cartilage defects and also it can be expanded to both ectodermal and endodermal lineages.

ADSCs are ubiquitous and easily obtained in large quantities with a very rare case of morbidity of donors cases, or low numbers of patient discomfort, which is making the use of autologous ADSCs an appropriate research tool and cellular therapy (27). At a cellular level, ATs consists the mature adipocytes surrounded by fibroblasts, nerves, endothelial cells, and immune cells and pre-adipocytes cells containing a stroma-vascular cell network (1).

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 rises more attention to undergo multi-lineage differentiation in a manner we have learned to recognize as typical of stem cells (20). ATs have remarkable phenotypic similarities to BMSCs, meanwhile they have offered an alternative source instead of BM for MSC. 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. In conclusion, adipose derived MSCs are one of the best and available among 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 (14). The safety and efficacy of ADSCs in reconstructive medicine was evaluated in many clinical trials (27).

Wharton's jelly stem cells

Adding to the mesenchymal stem cells, bone marrow and adipose are obtained from sources such as umbilical cord tissue. The umbilical cord contains two arteries and a vein, which are surrounded by mucoid connective tissue is called Wharton's jelly. Surrounding Umbilical cord is covered with epithelium tissue. In its matrix, there are rich texture of proteoglycans and mucopolysaccharides which that is the most abundant amino glycosoaminoglycans in this context of hyaluronic acid. This substance is contained the hydrated gel around fibroblasts cells and the collagen fibers which is protected the umbilical cord against pressure (29).

Recently, Umbilical Cord has been proposed as a source of mesenchymal stem cells (MSC) instead of bone marrow (BM). The adult stem cells potential for proliferation and differentiation decreases with aging of the donor person, so, Umbilical cord stem cells are multipotent cells which have higher priority compared with adult stem cells. Moreover, MSC Umbilical Cord have more advantages such as offering for reducing the immune response and for rapidly dividing. Mesenchymal stem cells in umbilical cord tissue, are obtained from different segment including blood vessels segment (30), amniotic membrane (31) and Wharton's jelly (32).

Wharton's jelly superior features:

Umbilical cord tissue mesenchymal stem cells have several features that distinguish it from other sources including of: 1) separated in large volumes, 2) As adipose cells on their surface have mesenchymal markers and non-hematopoietic markers, 3) Fast-growing and can be frozen and stored in the freezer and melting out again, 4) to extend as the colony, 5) host proteins are expressed Easily (33), 6) Wharton's jelly stem cells are not carcinogenic, but embryonic stem cells because of telomerase activity after renal transplantation turn to tumors (34), 7) These cells have the ability to differentiate into a variety of tissues, 8) The cells are not recognized by HLA that provides possibility to use these cells in allogeneic transplants (35). These cells have been used in various clinical studies. Also, it has been found that the Wharton's jelly stem cells inhibit the growth of breast cancer, ovarian cancer and osteosarcoma involved (10,11). These cells are important in the sense that they have greater differentiation potential rather than other mesenchymal stem cells from other adult tissues. In addition, for the purposes of cell therapy in clinical scale, cell separation steps, including propagation and cultivation method, take advantages from more affordable and less time consuming and methods, more intensive work, easily disassembled and stored in a laboratory environment, no difference between fresh frozen isolated mesenchymal stem cells in cell viability, and durability of the situation their Proteins (37).

Conclusion:

In this study, Superior properties and characteristics of mesenchymal stem cells and adipose tissue was investigated. Stem cells isolated from adipose tissue are adult ones, while Wharton's jelly mesenchymal stem cells are extracted from umbilical cord of embryonic fetus, so this recent one is more useful for extracting the mesenchymal stem cells. Both of these cells with unique features, are a good source of mesenchymal stem cells. These two category of tissues would be a good candidate cells for using in tissue engineering, cell therapy and tissue regeneration. Mesenchymal stem cells can be isolated from different tissues

including bone marrow, adipose, and umbilical cord.

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