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Effects of Gestational Diabetes and Other Metabolic Syndromes on Stemness Properties of Adult Mesenchymal Stem Cells

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ABSTRACT

Stem cells are an auspicious contrivance for different therapeutic intermediation. Their inimitable properties include self-renewal, multilineage differentiation, and immunomodulation. These properties have enticed the attention and consideration of researchers and worldwide physicians to use these properties in treatment of different diseases. Stem cells can be classified as embryonic stem cells, fetal stem cells and adult stem cells, Mesenchymal stem cells (MSCs) and hematopoietic stem cells. Mesenchymal stem cells (MSCs) or mesenchymal stromal cells are myofibroblast-like cells, can be derived from different sources like bone marrow, adipose tissue, dental pulp, amniotic fluid, Wharton's jelly, umbilical cord blood, and cord tissue. Literature reports that Gestational diabetes mellitus (GDM) and other metabolic syndromes have an effect on cellular and transcriptomic processes of stem cells derived from different sources. The effect can be in the form of alteration in proliferation, differentiation and many other properties of MSCs. Current investigation shows metabolic disorders are not only responsible for genetic problems and certain disease risk factors in adult life but also have adverse effects on perinatal environment. Keeping all these factors in mind the purpose of this review would be beneficial to all those who would like to explore how the stem cells are affected from perinatal environment problems, like gestational diabetes, Type 2 diabetes preeclampsia and many more. The most important factor is that this can provide insight on utilization of stem cells after conditioning and later can be used in regenerative medicine.

Keywords: Adult mesenchymal stem cells, Metabolic syndromes, Gestational diabetes mellitus, Oxidative stress, Cellular senescence, Regenerative medicine

INTRODUCTION

Regenerative medicine is an evolving and hastily progressing field of research and therapeutics. Novelty and exploration in tissue engineering, bio-imaging, cells and on different types of stem cells are crucial for the progression of regenerative medicine, as revealed in current case studies and experimental trials [1,2].

Stemness Potentials

Stem cells are considered as an endogenous system of regeneration and repair within the human body, present in almost every type of tissue. Becker, et al., discovered stem cells for the first time. By definition two unique properties are attributed to stem cells i.e. self-renewal, and differentiation ability into several cell pedigrees under suitable conditions [3]. The potential of these cells is to differentiate in to one or more cell types, and this phenomenon is known as developmental plasticity uses of stem cells are centered on, such as cell replacement therapy, paracrine activity (in which different stem cells which are transplanted, produce trophic growth factors that help local tissue to reinstate and multiply), also fusion of potent stem cells with surviving dysfunctional cells to restore function [1,4]. The inbuilt ability of stem cells has promptly established the center stage of stem cell-based therapies in a new direction for novel therapies of human diseases [5].

Types of Stem Cells

According to potency of stem cells and differentiation into various cell lineages, they can be classified as totipotent (for example the zygote, the only mammalian cell which has ability to produce all cells and tissues of an organism), pluripotent (with ability to produce cells and tissues from all three germ layers-ectoderm, mesoderm and endoderm), multipotent (ability to produce more than one cell lineage) or unipotent (differentiate into a single cell phenotype) [2,6].

Sources of Stem Cells

Broadly stem cell sources are classified as, embryonic and non-embryonic; Embryonic stem cells (ESCs) are pluripotent, self-restoring cells, sequestered from the inner cell mass of the blastocyst and have ability to divide into all three germ cell layers. Non-embryonic stem cells generally adult stem cells are specific and have narrow potential of distinction. These cells can be sequestered from several sources and are considered as important and most widely used cells in regenerative medicine [7].

Sources of Adult Stem Cells

Adult stem cells (ASCs) are multipotent stem cells, less differentiated cells present in different organs. The key role of ASCs is to retain cell turnover and helps in repairing the tissue in which they exist. According to the different sources of origin ASCs have been classified, as Hematopoietic stem cells (HSCs) and Mesenchymal stem cells (MSCs). HSCs are derived from Bone marrow (BM) or Umbilical cord blood (UCB) and peripheral blood. Mesenchymal stem cells (MSCs) are myofibroblast-like cells which are multipotent, present in many tissues. MSCs considered as clonogenic cells have self-renewal properties together with differential ability into various mesodermal cell lineages, including adipocytes, chondrocytes, osteocytes, smooth muscle cells, fibroblast cells, and hematopoietic supportive "stromal" cells [7,8]. Adult mesenchymal stem cells (MSCs) are one of the most promising source for cell and cell-based gene therapy in bone repair, because they can be derived from different sources like Bone marrow (BM) compartment, adipose tissue, dermal tissue, intervertebral disc, various dental tissues, human placenta, cord tissue and blood, and peripheral blood, etc. [9].

Bone Marrow-Derived Mesenchymal Stem Cells

Bone marrow (BM) has been extensively explored as adult-type mesenchymal stem cell source. These cells are readily expandable *in vitro*, have been used for different clinical conditions and studies, like in myocardial infarction, osteogenesis imperfecta, and graft versus host disease treatment. BM mesenchymal stem cells have shown higher capability of osteogenic distinction but lower ability to adipogenic distinction [10,11].

Adipose Tissue-Derived Mesenchymal Stem Cells

Adipose-derived stem cells (ASCs) also considered as multipotent stem cells sequestered from fatty tissues. These cells are similar to fibroblasts morphologically and differentiate into various cell lineages as like other MSCs. Due to this property; these cells are potentially used in regenerative medicine. Another similarity of ASCs like MSCs is their promising immunomodulatory capacity as they release variety of cytokines and certain trophic growth factors like TNF-α, IFN-γ, PGE-2, and IL-17, etc. Anna, et al., indicated that these stem cells can be used *in-vivo*, in spinal cord damage and neurodegenerative problems, in allergic and autoimmune conditions, etc. [12,13].

Umbilical Cord Derived Mesenchymal Stem Cells

The Umbilical cord which acts as connecting structure between the developing fetus and the placenta helps in exchange of blood between fetus and mother [3]. Within the umbilical cord stroma, a gelatinous substance, Wharton's jelly is present. Functionally this jelly-like structure provides protection to umbilical vasculature within umbilical cord from clumping and maintains cord flexibility [14]. Blood within the Umbilical Cord and Wharton's jelly contains abundant amount of MSCs, have superior differential capacity and is easy to isolate [15].

Comparison of Stemness Properties of Adult Mesenchymal Stem Cells

Mesenchymal stem cells derived from the Umbilical cord, have greater stemness potential comparative to many other

sources of adult type mesenchymal stem cells. These cells have outstanding propagation and disparity characteristics and easily accessible in huge numbers from readily available umbilical cord sources which were previously not in use and discarded. Mesenchymal stem cells derived from umbilical cord can be sequestered and cultivated quickly and reasonably *in vitro* [5]. Literature reports that UCMSCs can also be stored easily in "cord blood banks" in both settings like in private banking as well as for public setups, so that individuals can utilize their own personal cells' bank for future translational therapies [16]. UCMSCs have differentiating capabilities into several cell kinds like adipose tissue, bone marrow, skeletal muscle, and cartilage, etc. These cells have a plasticity specialty and confer to those tissue injury places where these cells distinguish into several cell categories according to precise micro conservational conditions. Compared to other sources, the proliferative and differential potential of UCMSCs does not reduce with age as compared to other sources [17]. A low risk of graft versus host reaction has been reported in patients receiving UCMSCs, compared to those who received bone marrow transplants [18].

Clinical Application of Adult Mesenchymal Stem Cells

Adult MSCs are using in treating the patients of myeloid disorders successfully. Different studies have shown the scientific tribunals for assessing the effectiveness of MSCs in the treatment of different disorders like Alzheimer's disease, stroke, cerebral palsy, autism, cartilage injury, osteoarthritis, and in some metabolic disorders like Diabetes [19]. Umbilical cord-derived mesenchymal stem cells are also accomplished of founding a stratified epithelial layer that scattered on non-natural mediums like collagen gels colonized with fibroblasts cells known as feeder cells. Different scientists have investigated the viability of cultivated cells for the corneal epithelial reconstruction [20]. The usage of umbilical cord-derived Mesenchymal stem cells (MSCs) as stroke therapy is interesting. Immune reactions will not be occurred by the use of autologous umbilical cord MSCs, After injecting peripherally, these stem cells passes through the blood-brain barrier especially in brain damage parts. Intravenous use of these mesenchymal stem cells also diminished apoptosis and fortified the cellular propagation endogenously subsequently in stroke patients [21]. Several finalized clinical trials have verified the use of MSCs in diseases like acute myocardial ischemia (AMI), liver cirrhosis, amyotrophic lateral sclerosis (ALS) and GVHD, etc. [7].

Effects of Different Metabolic Conditions on the Properties of Mesenchymal Stem Cells

The striking stemness potential and varied clinical uses of mesenchymal stem cells have sparked interest in the possible effects of various diseases on these cells. Literature reports that MSCs' properties are altered by several metabolic conditions like diabetes etc. Self-renewal and distinction abilities of mesenchymal stem cells are strongly affected by metabolic conditions [22]. Many studies showed the aged MSCs accrue extreme volume of reactive oxidative stress elements and instantaneously have reduced ant oxidative protection. These affected cells also showed diminished propagation rate, increased vulnerability to apoptosis plus reduced multiline age distinction potential, which sturdily confines their beneficial worth [23,24]. MSCs sequestered from metabolic disorders individuals acquired the following problems like reduced propagation ability, clonogenic budding and diminished population expanding time [25,26]. Moreover, different studies stated that metabolic syndrome affected the surface antigens expressions of mesenchymal stem cells, like lowered intensities of CD90, CD105 and CD73 were observed. Another study showed that these reduced countenance of CD90 in patients suffering from T2DM, causes augmented susceptibility of apoptosis and senescence in stem cells [27,28]. Literature reports that basically the extreme amassing of β-galactosidase protein levels, which is basically linked with cellular senescence, large quantity of deceased stem cells and lessened Ki67 countenance leads to additional dropping the stemness potential of mesenchymal stem cells. Diminished multipotency of MSCs due to metabolic syndrome and specially type 2 diabetes, occurs due to the different products of advance glycation, oxidative pressure and inflammation, are responsible to overwhelm the propagation rate, persuade apoptosis and surge the fabrication of ROS intracellularly which may be liable for the reduced differentiation potential metabolic syndrome patients stem cells [29,30]. Another study reported the lesser the differentiation capacity of mesenchymal stem cells into adipogenic and osteogenic cells in obese persons. Also, mesenchymal stem cells remote from diabetic individuals exhibited decreased osteogenic distinction and the regulation of CXCL12 (a chemokine), was down [31] (Figure 1).

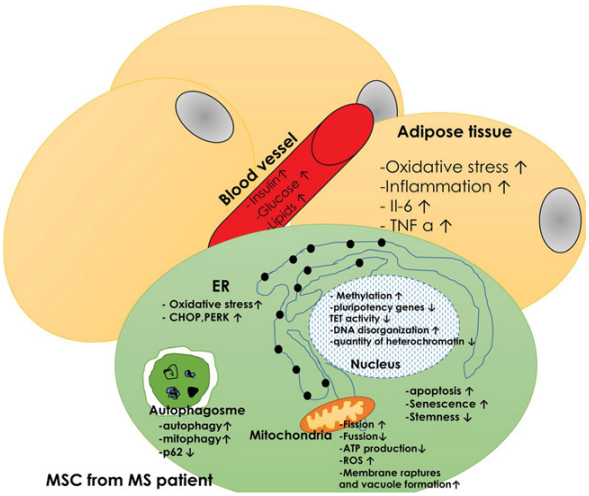

Figure 1 Alteration in MSCs properties due to metabolic syndrome [22]

Recent research points to a link between Gestational diabetes, a communal metabolic condition during pregnancy, and the development of functional variations in stem cell properties [32]. Gestational DM (GDM) is a temporary metabolic condition resulting from glucose derangement and intolerance due to insulin insensitivity during pregnancy [32-34]. GDM affects on cellular and transcriptomic processes of umbilical cord-derived MSCs [35]. The effect occurs due to alteration of propagation ability and differentiation capacity of MSCs Alterations of p16Ink4a which inhibits cyclin-dependent kinase, arrest cell cycle, so the proliferation and capacity of regeneration of MSc decrease in certain organs [36,37]. GDM affected UC-MSCs also showed decreased multilineage differentiation potentials than normal UCMSCs. Furthermore, GDM affected UC-MSCs showed diminished mitochondrial activity which causes reduced proliferation capacity of MSCs and premature senescence [38]. Another study showed that Gestational diabetes may affect the development of embryo due to glucose concentration variation. This problem basically occurs due to the oxidative stress which causes decrease proliferation of cells and chances of cellular senescence and cell death rate increase [39]. In 2015, a study showed the role of gestational diabetes in endothelial dysfunction. Microarray data showed different genes like CDC20, CDC A2, CDCA8 participate in cell division cycle that was altered in GDM [40].

Stem cells present in perivascular areas are known as predecessor of mesenchymal stem cells having more proliferative ability and multi-lineage distinction potential, equated to mesenchymal stem cells isolated from bone marrow [41-45]. Literature showed that the progression and renewing ability of these stem cells present in perivascular areas can be altered due to maternal gestational diabetes [32]. Type 2 Diabetes Mellitus (T2D) has also been linked to changes in stem cells. This condition recognized as high Blood glucose levels (BG) due to insulin resistance [46]. The study showed that diabetes causes premature aging of stem cells and impaired proliferation, paracrine capability, myogenic differentiation of bone marrow and umbilical cord-derived MSCs. Diabetic MSCs also showed low differentiation capacity in culture conditions [47]. Due to Diabetes mellitus, Reactive oxygen species (ROS) production increases. Prior studies have shown that ROS reacts with lipids, protein, and DNA causing oxidative stress-induced cellular damage. These environment inhibit cell proliferation and initiate cell apoptosis and cell death, restraining the survival rate of transplanted stem cells in diabetic conditions [48].

Endothelial progenitor cells (EPC), a part of Mesenchymal stem cells, helps in repairing damaged endothelium, angiogenesis process, and neovascularization [49]. Preeclampsia, a hypertensive condition, is a communal reason for both maternal and fetus worldwide [50,51]. Literature reports decreased quantity and alteration in function of fetal Endothelial colony-forming cells (ECFC), a stem cell type, in preeclampsia patients [52]. Pre-eclamptic mother's fetuses show decreased hepatic hematopoiesis and lowered the number of stem cells in umbilical cord blood. A histomorphometric study showed the diminished quantity of erythroid predecessors and early granulopoietic cells in fetuses liver of preeclamptic mothers. Different studies also exposed that the altered levels of cytokines and growth factors in blood of fetus due to this preeclamptic problem [53].

CONCLUSION

In summary, metabolic syndrome strongly affects the self-renewal and differentiation capacities of MSCs. In the current scenario of increased interest and on-going researches on stemness potential and their impact on regenerative medicine, this review may prove beneficial for identifying the different adverse effects of GDM, type 2 diabetes mellitus and preeclampsia on MSCs derived from different adult sources for designing methods (genetic modification and preconditioning) to enhance survival rate of MSCs for therapeutics. The innovative approaches related to stem cells therapies can be fully beneficial only after the acquisition of in-depth knowledge of the complete spectrum encompassing alterations caused by common metabolic conditions. Knowledge of stem cells modifications by these diseases proved beneficial in both public and private stem cell banking, of which the later has a very important role in Autologous and Allogeneic stem cells therapy of diseases like cerebral palsy, Autism and in certain cardiac and orthopedic diseases. In future there is a need to find out ways and methods of utilization of disease affected mesenchymal stem cells, in different clinical trials, *in-vivo* and *in-vitro*.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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