ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 04 | April - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EMERGING LEADER IN STEM CELL THERAPY: HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS-FUTURE THERAPEUTIC TRENDS

Clinical Research

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ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent adult stem cells widely distributed in the bone marrow, umbilical cord, fat, and other tissues and have high proliferation, multi-differentiation, and immunoregulatory abilities. They can inhibit the proliferation of immune cells and the secretion of inflammatory factors [26]. Compared with MSCs from other sources, human umbilical cord MSCs (hUCMSCs) have many advantages, such as a wide source, easy access to materials, strong proliferation ability, low immunogenicity, and great differentiation potential. They are most likely to become pluripotent stem cells with clinical application prospects. Wharton's jelly mesenchymal stem cells – WJMSC- provide three classic advantages – ease of collection with no legal or ethical issues, high differentiating potential and low immunogenicity. Shorter doubling time (21) and an extensive ex vivo expansion capacity provides yet another privileged status to these cells compared with embryonic stem cells. Therapeutic potential of these cells lie in their immuno-modulatory properties involving both innate and adaptive immunity. Graft vs Host disease (GvHD), Post transplant scenarios and autoimmune disorders could witness a revolution in treatment approach with greater understanding of the mechanism action of these cells. Regenerative medicine should get an immense benefit from proper understanding and utilization of these cells.

KEYWORDS

WJ-MSCs Wharton's Jelly Mesenchymal Stem Cells, GvHD Graft Vs Host Disease, MSCs -Mesenchymal stem cells, hUCMSCs Human umbilical cord blood stem cells, POF Premature ovarian failure

INTRODUCTION

Wharton's Jelly (WJ) was discovered by Thomas Wharton in 1656. It is a mucous connective tissue of the umbilical cord located between the amniotic epithelium and the umbilical vessels. McElreavey et al. in 1991,is credited with isolation of MSCs from the WJ portion of the umbilical cord (8).MSCs can be divided into two classes: adult and fetal/perinatal MSCs.Proliferative capacity of MSCs from adult cell sources is limited. MSCs originate in cellular types such as adipocytes, chondrocytes, osteocytes, smooth muscle cells, fibroblasts and hematopoietic supportive stroma (2). It would be interesting to note that they do not display the peculiar markers that hematopoietic and endothelial cells express, like Cluster of Differentiation (CD)34, CD45, CD11b, CD11c, CD14, CD19, CD79α, CD86, and HLA class II molecules and they do express surface markers, in accordance with the commonly accepted minimal criteria of the International Society for Cellular Therapy (ISCT), such as CD90, CD105, CD44, CD73, CD9, and very low levels of CD80 Mesenchymal stem cells are multipotent, demonstrate potential for self renewal and differentiation is possible into multiple mesenchymal lineages (1).Different tissues, such as skeletal muscle, adipose tissue, umbilical cord, synovium, dental pulp, amniotic fluid, as well as fetal blood, liver, bone marrow, lung and heart can serve as sources for MSCs(3).

MSCs derived from extra embryonic tissues, represent ideal choice for therapeutic use as there are no ethical issues with correction and teratoma formation is not observed (5,6). Fetal/perinatal tissues, from the embryo/foetus and cells obtained from extra-embryonic tissues like placenta umbilical cord, Wharton's jelly mesenchymal stem cells (WJ-MSCs) and amniotic membrane are excellent sources of these cells. Fetal MSCs possess an immune-privileged status which makes them a favourable choice for regenerative medical applications (7). WJ-MSCs finds extensive applications in diverse areas such as neurological disorders, kidney injury, lung injury, orthopedic injury, liver injury and cancer therapy (9,10,11,12,13,14).

The therapeutic efficacy of WJ-MSCs relates to its regenerative and immuno-modulatory potential. WJ-MSCs are capable both immune suppression and immune avoidance. This dual mechanism makes them very potent weapons for cellular therapies in allogenic transplantation. Low expression of Human Leukocyte Antigen (HLA) class I and an

absence of HLA-DR (15, 16) is another useful adjuvant when applying it as a therapeutic modality. Expansion of regulatory T cells (Treg) contributes to the suppression of the effectors responses to alloantigen and they are not capable of generating in vitro immune responses from allogenic T cells, suggesting that WJ-MSCs possess a specific low immunogenicity (17, 18). Large amounts of Interleukin (IL)-10, Transforming Growth Factor-β (TGF-β) ,IL-6 and vascular endothelial growth factor (VEGF) explains the immunosuppressive capability of MSCs (19).Soluble factors, such as hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), TGF-β1 and indoleamine 2 3-dioxygenase (IDO) may also mediate the immuno-modulatory effects of MSCs on T cells as detailed in Figure 1. These are also capable of inhibiting B cell proliferation, differentiation and antibody production without influencing the activation of B cells (20). Further investigation is needed. The most peculiar characteristic of WJ-MSCs is their ability to express the HLA-G6 isoform, implicated, as previously mentioned, in immune-modulation, an essential feature for promoting the use of WJ-MSCs in a cell-based therapy.

The primary treatment for both aGvHD and cGvHD involves immunosuppression by glucocorticoids, with a response rate ranging from 30 to 50%. On the contrary, many immunosuppressive strategies have been studied for steroid-resistant aGvHD (such as mycophenolate, mofetil, pentostatin, monoclonal antibodies directed against T lymphocytes, cytokines and their receptors, mTOR inhibitors and extracorporeal photopheresis) but none have proven to have a consistent effectiveness and safety level .Seriousness of the event necessitates measures to explore alternative forms of treatment as treatment mortality may exceed 50% with conventional therapies (22). Kang-Hsi Wu et al. in 2011 reported the first case of Wharton's Jelly derived MSCs used in a human clinical application, in two pediatric patients with severe steroid-resistant aGvHD(23) followed by 2016, Boruczkowski et al in 10 cases (24).

Intracoronary Human Wharton's Jelly-Derived Mesenchymal Stem Cells (WJ-MSCs) Transfer in patients with acute myocardial infarction (AMI)" (25) is a completed trial held by the Navy General Hospital of Beijing. The purpose of the trial was to investigate the efficacy and safety of the intracoronary transfer of WJMSCs in patients with ST-segment elevation myocardial infarction. The Navy General Hospital of Beijing is also the sponsor of the "Intracoronary or intravenous infusion human Wharton' Jelly-derived Mesenchymal Stem Cells in patients with ischemic cardiomyopathy (NCT-02368587) study.

There is a proposed plan by the same research team to improve endometrial receptivity before transferring good embryos, taking advantage of the regenerative properties of MSCs after confirming immuno-modulatory potential of these cells. Both placenta-derived MSCs and WJ-MSCs can be induced to differentiate in endometrium. Due to neurocrine and paracrine effect of WJ-MSCs, are being investigated in terms of their capacity to influence the neurodegeneration present in ALS. Intracavernous WJ-MSCs injection in diabetic patients with erectile dysfunction has also shown benefits.Intrathecal injections are being evaluated in treatment of chronic traumatic spinal disorders also- (NCT03003364) by Banc de Sang i Teixits. (NCT0296-3727) is a trial that evaluates the efficacy of intra-articular WJ-MSCs injection in patients with knee osteoarthrosis. "NEOX CORD 1K "is being tried for non-healing diabetic foot ulcers (CONDUCT I)" trial (NCT0216-6294). Mesenchymal stem cells (MSCs) can be used for RA treatment due to their immunoregulatory effects.Infact this exact effect could be same in offering this modality of treatment to other autoimmune disorders too. In fact it is shown that hUCMSCs regulated T cell proliferation, apoptosis, and differentiation at the transcriptional level and T lymphocyte associated inflammatory factors in vivo and vitro to play an immunoregulatory role, ultimately providing a theoretical foundation for the clinical transformation and application of hUCMSCs in the treatment of RA. MSCs, which are able to alter the frequency and function of memory lymphocytes including Th17, follicular helper T (Tfh) cells and gamma delta (γδ) T cells while promoting Treg cell generation, have been proposed as a candidate of choice for RA cell therapy.

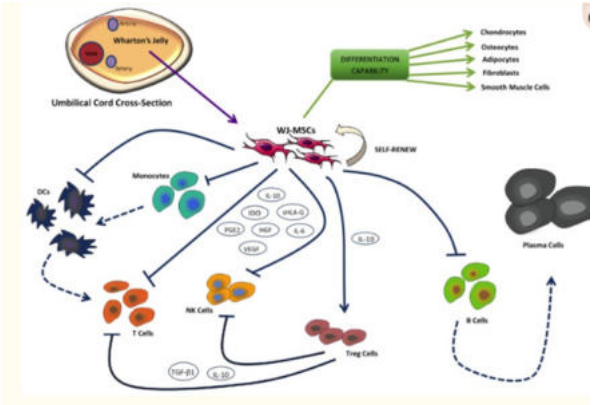
For cardiac conditions cardiac regeneration should (1) be autologous, in order to reduce severe complications of the immune system and disease transmission; (2) exhibit a controlled cell division capacity; (3) differentiate towards both cardiomyogenic and endothelial cell lineages; and (4) integrate efficiently and functionally into injured myocardium after cell implantation(27,28).

Look into the following advantages too. Compared with other perinatal stem cell sources such as umbilical cord, establishment of primary UCBMSC cultures does not lead to a relatively high-cost and long procedure based in enzymatic digestion or explant methods. UCB is safe and painlessly extracted, long-term cryopreserved, and has a lower risk of transmitting viral infections or somatic mutations than adult tissues (i.e., bone marrow). UCBMSCs are useful cellular population to preclinically assess the immunoreactivity of prospective therapeutic cells also. Transplantation of human UCMSCs improved the ovarian dysfunction caused by autoimmunity in POF in animal models (29).

CONCLUSIONS

Spiraling interest, ease of procurement, potential of Immunomodulation and differentiation potential catapults this to the fulcrum of research with greatest stem cell therapeutic potential in the coming decades. The lower immunogenicity of hUCBMSCs is attributed to its immaturity; in contrast to alternative adult cell sources. There is a role of microRNAs (miRNAs) and exosomal miRNAs in controlling MSC gene expression and driving MSC therapeutic outcomes. The clinical application of MSCs holds great promise for the treatment of infertility or ovarian insufficiency, and to improve reproductive health for a significant number of women worldwide.

Figure 1



Mechanisms of MSC Immunomodulation

Soluble factors secreted by MSCs such as IDO, PGE2, sHLA-G5 can suppress T and NK cell functions. In addition, MSCs can indirectly mediate immunosuppression by inhibiting dendritic cells (DCs) and inducing the expansion of regulatory T cells (Tregs).

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