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Current Perspectives of Therapeutic Applications of Umbilical Cord-Derived Mesenchymal Stem Cells in Various Diseases

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Abstract

The mesenchymal stem cells (MSCs) are the major focus of attention in regenerative medicine because of their intrinsic properties such as differentiation potential (can differentiate into various specialized cell types such as osteoblasts, chondrocytes, myocytes, and adipocytes), high self-renewal capacity, low immunogenicity and having immunomodulatory abilities. These cells can facilitate tissue repair by releasing biologically active molecules such as cytokines, growth factors, etc. Umbilical cord tissue is the rich and potential source of stem cells; especially MSCs. Isolation of MSCs from the umbilical cord is promising because of several advantages such as ease of availability, non-invasive procedure, and minimal ethical limitations, and also high proliferation capacity, plasticity, self-renewal capacity, and immunomodulatory activity than the MSCs from various origins. In this review, we summarized the latest progress in the applications of Umbilical cord mesenchymal stem cells (UC-MSCs) as regenerative medicine in various diseases.

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INTRODUCTION

Regenerative medicine involves the process of repairing or replacing (regenerating) the injured cells, or tissues and restoring the normal cellular functions. The interest in stem cell research and its therapeutic applications as regenerative medicine has been raised in recent years due to their distinctive curative properties. Mesenchymal stem cells (MSCs) are undifferentiated, multipotent stromal cells. The MSCs can be isolated from bone marrow, adipose tissue, peripheral blood, umbilical cord blood, umbilical cord tissue, placenta, amniotic fluid, dental pulp, and menstrual blood, etc. [1]. The MSCs are the major focus of attention in regenerative medicine because of their intrinsic properties such as differentiation potential (can differentiate into various specialized cell types such as bone cells (osteoblasts), cartilage cells (chondrocytes), muscle cells (myocytes), and fat cells (adipocytes)), high self-renewal capacity, low immunogenicity and having immunomodulatory abilities [2]. These cells can facilitate tissue repair by releasing biologically active molecules such as cytokines, growth factors, etc. [3]. Isolation of MSCs from the umbilical cord is promising because of several advantages such as ease of availability, non-invasive procedure, and minimal ethical limitations and also because of their high proliferation capacity, plasticity, self-renewal capacity, and immunomodulatory activity than the

MSCs from various origins. The UC-MSCs is the best source for allogeneic transplantation [4].

Thus, in the 21^{st} century, the regenerative medicine field holds the promise of revolutionizing treatment for various diseases.

In this review, we summarized the latest progress in the applications of UC-MSCs as regenerative medicine in various diseases to update the researchers and clinicians.

Isolation and Characterization of MSCs from Umbilical Cord

Umbilical cord tissue is the rich and potential source of stem cells; especially MSCs. MSCs can be isolated from various compartments such as umbilical amnion (AM-MSCs), subamnion (SA-MSCs), perivascular (PV-MSCs), Wharton's jelly (WJ-MSCs), and mixed umbilical cord (MC-MSCs) in the cord tissue. However, their maximum concentration (88%) was found in the perivascular space surrounding the three blood vessels and only in small quantity present in the cord tissue membrane [5]. UC-MSCs from these different compartments possess different biological properties. UC-MSCs from Wharton's jelly have fewer non-stem cell contaminants and exhibited more stemness characteristics and differentiation potential than UC-MSCs from other compartments. MSCs can be isolated from umbilical cord tissue by two methods – tissue expansion or tissue explant method and single-cell culture by enzymatic digestion method [6]. To isolate the MSCs, the cord tissue is cut into small pieces, vascular tissues are removed, and cord tissue is then washed with PBS or wash buffer then cut into small pieces of 1-2 mm^2. These pieces are then used to isolate MSCs by tissue expansion/ tissue explant method or digest with enzyme (collagenase) to get the single cells which are then cultured in a tissue culture dish or flask [7]. In the enzymatic digestion method, the collagenase enzyme disrupts the collagen matrix of the umbilical cord Wharton's jelly tissue and releases cells into the solution. The cells were then separated by centrifugation and plated on a tissue culture dish or flask with a stem cell culture medium. Various enzymes are used to dissociate WJ-MSCs from the matrix such as collagenase, hyaluronidase, trypsin, and dispase, etc. In explant method, Whorton's jelly umbilical cord tissue has adhered to the surface of the culture dish or flask which allows MSCs to migrate from cord tissue to the surrounding surface of the culture dish or flask and adhered to the surface and grow. Once the cells adhered to the surface, generally within the first week, the tissue can be removed [8].

MSCs can be characterized by three criteria according to the International Society of Cellular Therapy (ISCT). These are (1) adherence to the plastic surface during standard culture conditions, (2) expression of cell surface markers such as CD73, CD90, and CD105, and NO expression of other markers such as CD11b, or CD14, CD34, and CD45 (3) *in vitro* differentiation capacity into mesenchymal lineages (chondroblasts, osteoblasts, and adipocytes) [9].

Therapeutic Applications of UC-MSCs

MSCs have already marked their importance in the regenerative medicine field, as they showed proliferative capacity and differentiated into the mesenchymal lineage, can secrete a variety of cytokines and growth factors, also have the profound immunosuppressive ability *in vitro*. The UC-MSCs derived from cord blood and Wharton's jelly possesses similarity in immunophenotype, morphology (fibroblast-like spindle-shaped cells), and expressing the same surface marker when cultured *in vitro.* UC-MSCs played a crucial role in regulating inflammation and tissue regeneration. UC-MSCs exert numerous paracrine and immunomodulatory functions to control the inflammation process and initiate subsequent steps of tissue repair. External signals from the microenvironment influence the expression and secretion profiles of UC-MSCs which causes UC-MSCs to perform a regulatory function corresponding to immune cells at the inflammation site. During the regeneration stage, UC-MSCs synthesize and modify the extracellular matrix, stimulating angiogenesis and re-epithelialisation. The UCMSCs have therapeutic applications in various diseases such as orthopaedic conditions, neurologic conditions, autoimmune conditions, diabetes, respiratory conditions, infectious diseases, cancer, etc. [10].

Orthopedic Conditions

Orthopedic conditions such as bone fractures due to trauma, osteoporosis or tumors, etc. have a tremendous impact on health, social and economic conditions. Regeneration of bone fractures due to these conditions in old-aged patients is a major concern. Stem cells due to their self-renewal and differentiation capacity can be effectively employed to treat these conditions. Stem cells application can effectively and rapidly improve the bone regeneration process. Application of stem cells along with biomaterials/scaffolds and growth factors can accelerate bone healing at the fracture site [11].

The treatment for osteoporosis is based on the application of drugs for osteogenesis stimulation or bone resorption inhibition. However, drug treatment has several drawbacks such as existing bone loss cannot be reversed, causing serious side

effects such as osteonecrosis, cancer, thromboembolic events, and strokes. In osteoporosis, UCMSCs treatment improved osteoblast activity and reduced osteoclast differentiation, maturation, and functionality [12].

Animal studies (osteoporosis rat models) showed that UCMSCs transplantation results in an increase in the production of TGF-β1 and runt-related transcription factor 2 (Runx2) which helps in mobilization of MSCs to the affected site, osteoblast differentiation, enhancing osteocalcin expression, increasing bone mass, collagen content and bone formation [13, 14].

Like chondrocytes and cartilage, UCMSCs also express type II collagen, aggrecan, SOX-9, cell growth factors, cytokines, and chemokines. Thus, UCMSCs treatment would be the effective treatment for osteoarthritis [15].

Neurologic Disorders

Neurologic disorders such as stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease, etc. are growing concerns. Neurological impairments are generally irreparable due to inadequate regeneration in the central nervous system (CNS). The treatment options are also restricted for neurological diseases. MSCs because of their regenerative capacity, immunomodulatory properties, low immunogenicity, migration to the injured site, homing to brain areas at the affected site, paracrine, and antiapoptotic effect, etc. become promising approaches to treat neurologic disorders [16]. Also, the neurorestorative and neuroprotective effects of UCMSCs have been reported in terms of improvement in ischemic injury and differentiation of UCMSCs into neurons and astrocytes. UCMSCs secrete neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) which exerts a paracrine effect on Schwann cells to increase their viability and proliferation. UCMSCs reduce the behavioral impairment, slow the disease progression and promote neuroregeneration in animal models of amyotrophic lateral sclerosis, Alzheimer's disease (AD), Parkinson's disease, stroke, traumatic brain injury, and spinal cord injury [17].

UC-MSCs played a significant role in spinal cord injury (SCI) by alleviating neuropathic pain and promoting functional recovery likely by activating glial cells and regulating inflammatory factors. Animal studies showed that UCMSCs migrated to the injured site and speedily recovered motor function; reduce the secretion of IL-6, TNF-α, MIP3α, and up-regulated GDNF, IL10, and IL-13 expression and thus improve the repair mechanism of the injured spinal cord tissue. UCMSCs also induce genetic changes related to axonal regeneration, neurotrophy, and cell apoptosis in common and specific manners. UCMSCs promoted spinal neuron survival, axonal regeneration, decreased glial scared lesion cavity formation, reduced numbers of active macrophages, and thus significantly improved motor and sensory function. UCMSCs inhibited p38 mitogen-activated protein kinase (MAPK) pathway activated after SCI and reducing spinal cord neuronal apoptosis [18].

Regenerative properties and other characteristics of stem cells such as the paracrine effect and immunomodulation can be effective in Autism spectrum disorder (ASD). Also, preclinical and clinical studies showed that stem cell therapy can be a great therapeutic promise in neurologic disorders [19]. ASD patients showed an imbalance of innate and adaptive immune response such as alterations in NK cells, CD3+, CD4+, and CD8+ T cells, also abnormal monocyte and macrophage response which overproduced inflammatory cytokines. Stem cells inhibit over activation and proliferation of these cells and also inhibit proinflammatory cytokines (TNF-α and IFN-γ) and increase anti-inflammatory cytokines (IL-10). In phase 1 clinical trial, repeated infusions of UCMSCs in ASD children were reported to be safe and tolerable with no serious adverse events and an improvement in symptoms and inflammatory cytokine levels [20].

Autoimmune Diseases

Autoimmune diseases are characterized by the generation of immune response to self-antigens and chronic inflammation due to the over-activation of immune cells that can lead to dysfunction and damage of multiple organs. The conventional treatment used to treat autoimmune diseases is the medication (immunosuppressive agents, non-steroidal drugs, corticosteroids, antibodies against B lymphocytes, etc.) to control the overactive immune response, reduce inflammation, and relieve symptoms such as pain, fatigue, swelling, and skin rashes, etc. however, these medications have several side effects such as serious infection, malignancy, etc. which limit the use of these drugs [21]. Systemic Lupus Erythematosus (SLE) is characterized by anti-nuclear autoantibodies, dysfunctional cellular response, tissue injury, and multiple organ failure. Autophagy (by activated T cells) has an important role in SLE. UC-MSCs transplantation as a treatment in SLE showed downregulation of the autophagy by inhibiting respiratory mitochondrial

biogenesis in activated T cells, thus decreasing T cell apoptosis through mitochondrial transfer. Also, secretion of indoleamine 2, 3-dioxygenase (IDO) by UC-MSCs in large quantity inhibits T cell proliferation in SLE patients. UC-MSCs also reduce the proliferation and differentiation of B cells and therefore reduce the production of auto antibodies and regulate Treg/Th17 balance in SLE patients. Thus, transplantation of UC-MSCs is effective in SLE [22].

Rheumatoid arthritis (RA) is a systemic and chronic autoimmune disease involving progressive deterioration of joints. The treatment includes antirheumatic drugs, non-steroidal anti-inflammatory drugs, Steroids, and newer biologic agents (abatacept, rituximab, adalimumab, etc.). However, not all patients get benefited from these current therapies. In RA patients, UC-MSCs transplant can enhance the immune modulation by decreasing the T-cell activation and proliferation markers, increasing Tregs cells population and homing potential, activating macrophages with reparative properties, increasing Th2 cell population secreting anti-inflammatory cytokines, reducing the level of proinflammatory cytokines, inhibiting joint swelling and cartilage erosion, thus reduce the symptoms of RA directly or indirectly [13].

Multiple sclerosis (MS) is characterized by progressive destruction of myelinated axons in the central nervous system (CNS) by the immune system that can cause serious complications of CNS such as devastating motor, sensory, balance, and cognitive problems and disability, etc. The conventional treatment includes the use of corticosteroids, plasma exchange (plasmapheresis), ocrelizumab, Interferon beta medications, etc. However, there are side effects of therapy such as insomnia, increased blood glucose level and blood pressure, flu-like symptoms, fluid retention, mood swings, liver damage, etc. The UC-MSCs treatment has slowed down the progression of neurodegeneration in MS patients. UC-MSCs treatment effectively reverses the suppressive function of Tregs which is impaired in MS, also increases the anti-inflammatory molecules such as TGF-β1, IL-10, and PGE2, and reduces the pro-inflammatory cytokines associated with inflammation of the central nervous system CNS [14].

Type 1 Diabetes (T1D)

Type 1 diabetes (T1D) is characterized by damage or loss of insulin-producing cells (pancreatic β cells) leading to insulin deficiency and hyperglycemic condition. Activated CD8 cells damage the pancreatic β cells and can alter the Treg population. The conventional treatment includes insulin administration, artificial pancreas, controlled diet, etc. However, T1D patient needs lifelong insulin treatment. The UCMSCs treatment in T1D patients resulted in the restoration of insulin to euglycemic levels by activation of Pdx-1 and differentiation into pancreatic β cells. UCMSCs also trigger expansion of Treg cells by releasing HLA-G that reduces effector Th1 cells and rebalance the Teff/ Treg ratio [23].

Type 2 Diabetes (T2D)

Type 2diabetes (T2D) is characterized by progressive and unavoidable pancreatic β-cell dysfunction that can lead to insulin deficiency. The conventional treatment includes medication Metformin (Fortamet, Glumetza, etc.), insulin therapy, healthy diet, and exercise, etc. Clinical data indicates that UCMSCs transplantation in T2D patients improved islet function, reduced insulin requirement, or free from insulin requirement, stable plasma glucose levels, and safe [24].

Respiratory Conditions

Respiratory infections such as SARS-COV-2 (COVID-19), chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, Influenza, etc. causes major health concern. COPD is a chronic inflammatory disease of the lungs characterized by tissue destruction, inflammation, and obstructed airflow from the lungs. The conventional treatment for COPD includes stopping smoking completely, bronchodilator drugs, steroids, antibiotics, lung therapy such as oxygen therapy, lung surgery, and transplant, etc. For the treatment of both acute and chronic lung diseases, stem cell therapy can be an attractive approach mainly because the stem cells can protect the lung function by simultaneously targeting multiple pathological processes [25].

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. Hyper inflammation, cytokine storm due to overactive immune response, and immunothrombosis are observed in severe cases. The presently approved treatments are only supportive and not curative. The UCMSCs therapy can be found effective because of their potential immunomodulatory ability and some natural immunity to the coronavirus. The anti-inflammatory factors secreted by UCMSCs prevent or attenuate cytokine storm and over-activation of the immune system. After transplantation, UCMSCs accumulate in the lungs and protect alveolar epithelial cells, prevent pulmonary fibrosis, potentially improve the pulmonary microenvironment, and lung function [26].

Acute lung injury (ALI) involves pulmonary edema and atelectasis caused by capillary membrane injury

due to multiple traumas, bacterial and viral infections, etc. Viruses such as influenza virus, adenovirus, coronavirus (CoV), respiratory syncytial virus (RSV) and cytomegalovirus (CMV), etc. cause ALI. Treatment includes medications, ventilators, etc. however, medications cannot repair the damaged lung cells. UCMSCs have a beneficial effect on influenza virus infection. UCMSCs secrete growth factors such as angiopoietin-1 (Ang1) and hepatocyte growth factor (HGF), decrease alveolar protein permeability (APP) levels, inflammation, and improve survival of lung injury mouse model. Basic fibroblast growth factor 2 (FGF2) expressing UCMSCs showed the enhanced therapeutic effect on lipopolysaccharide-induced ALI [27].

Organ Transplantation

Graft-versus-host disease (GVHD) is a serious and life-threatening condition resulting due to the presence of white blood cells remaining within donor's tissue/graft which recognize the recipient as a foreign/non-self and attack recipient's body cells causing a range of medical problems. The treatment includes the use of steroids and anti-inflammatory drugs, immunosuppressive drugs. The treatment needs to be taken for a longer period and depends on how patients respond to the therapy. UCMSCs possess immunosuppressive, immunomodulating, and low immunogenic properties; express HLA class I and not class II antigens, etc. UCMSCs modulated cellular and innate immune pathways. UCMSCs can suppress B cell and T cell proliferative, differentiation, and chemotactic properties by producing soluble factors. UCMSCs modify the dendritic cell's function by impairing antigen-presenting ability. UCMSCs induce more anti-inflammatory cytokines. These properties of UCMSCs make them a promising tool in graft failure management and graft-versus-host disease (GVHD) prevention or treatment. Repeated transfusions of UCMSCs in patients after allogeneic hematopoietic stem cell transplantation increased in Treg cells while a decrease in memory B lymphocytes and NK cells. The th1:Th2 ratio was also changed which lead to immune tolerance acquisition, inhibition of GVHD, and improvement in transplantation survival rate. UCMSCs treatment in chronic GVHD patients resulted in an increase in IL-10 producing CD5+ regulatory B cells (Bregs) and reduction in inflammatory cytokine production by T cells. UCMSCs balance the Treg/Th17/Th1 ratio. UCMSCs secrete HLA-G to promote the proliferation of myeloid-derived suppressor cells and reduce acute GVHD after HSCT. Co-transplantation of UCMSCs and HSCs in children with severe aplastic anemia resulted in faster hematopoietic engraftment without infusion-related toxicity. In severe steroid-resistant acute GVHD cases, UCMSCs transplantation resulted in dramatic improvement without additional immunosuppressive therapies in clinical manifestations of GVHD [28].

Cancer Therapy

MSCs have an important property of tumor tropism which can be used in cancer therapy. UCMSCs do not induce tumorigenesis and their anti-tumor effect was due to their secretome. UCMSCs exert their anti-tumor activity by arresting the tumor cell cycle in specific phases, by increasing apoptosis and attenuating the migration of tumor cells. *In vitro* studies of UCMSCs co-cultured with A375 melanoma cells exert antitumor effects by exhibiting proliferation inhibition, apoptosis induction, and suppression of invasion of A375 melanoma cells. A decrease in expression of several kinases (AKT, STAT3, and mTOR) and promotion of cytoskeletal rearrangement in A375 melanoma cells has been noted. UCMSCs and breast cancer cell line MCF-7 co-culture showed that UCMSCs as well as their secretome have a cytotoxic effect on MCF-7 cells which was mediated by induction of apoptosis. It has been shown that *in vitro* and *in vivo* naïve UCMSCs attenuate tumor cell growth of both human and animal origin. The mechanism suggested is the production of many secretory proteins/peptides and also overexpression of multiple tumor suppressor genes which induce cell death and cell cycle arrest of cancer cells. *In vivo* studies of humans and rats, UCMSCs transplant showed that both cells can effectively decrease tumor weight [29].

Premature Ovarian Insufficiency (POI)

Premature ovarian insufficiency (POI) is a disorder of unknown etiology that causes infertility in young women before the age of 40 years and is characterized by amenorrhoea, hypoestrogenism, and hypergonadotropism. It is highly heterogeneous and causative factors such as genetic, infections, autoimmune and iatrogenic have been suggested. There is a greater risk for bone loss, cardiovascular disease, and premature death in POI patients. There is no effective therapy available. Hormone replacement therapy (HRT) is the commonly used therapy to overcome estrogen deficiency symptoms. However, long term use of this therapy can lead to an increased risk of endometrial, ovarian, and breast cancer. In a rat model of accelerated ovarian aging, intravenous UCMSCs treatment for 1 month increased anti-apoptotic and antioxidant enzymes, decrease apoptotic cells, and significant improvement in ovarian function and structural parameters. UCMSCs transplantation in nat-

urally aging rats as models of perimenopausal rats increases estradiol (E2), and anti-Mullerian hormone (AMH) and decrease in follicle-stimulating hormone (FSH), improvement in ovarian structure, increase in follicle number, and in the expression of HGF, VEGF and IGF-1 proteins which improves the ovarian reserve function and resisting ovarian senescence [30]. UCMSCs expressed heme oxygenase-1 (HO-1) is essential in restoring the ovarian function of POF mice. The studied effect of UC-MSCs treatment on the restoration of ovarian function and clinical outcomes in POI patients through follow-ups. They observed normal clinical behavior and no serious side effects of treatment in all patients. UC-MSCs transplantation resulted in the restoration of ovarian function, better outcome in POI patients experiencing shorter amenorrhoea durations (<1 year), and normal deliveries [31].

ABBREVIATIONS

ALI: Acute lung injury; ASD: Autism spectrum disorder; CD: a cluster of differentiation; CNS: central nervous system; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease-19; GDNF: Glial cell line-derived neurotrophic factor ; GVHD: Graft-versus-host disease; HGF: Hepatocyte growth factor; HLA-G: Human leukocyte antigen (HLA)-G; HSCs: Hematopoietic stem cells; HSCT: Hematopoietic stem cell transplantation; IFN-γ: Interferon gamma; IGF-1: Insulin-like growth factor 1; IL: Interleukin; MIP3α: Macrophage Inflammatory Protein-3 alpha; MS: Multiple sclerosis; MSCs: Mesenchymal stem cells; mTOR: mechanistic target of rapamycin; NK: Natural killer; PGE2: Prostaglandin E2; POI: Premature ovarian insufficiency; RA: Rheumatoid arthritis; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; SCI: spinal cord injury; SLE: Systemic Lupus Erythematosus; STAT: Signal transducer and activator of transcription; T1D: Type 1 diabetes; T2D: Type 2 diabetes; Teff: Effector T cells; TGF-β1: Transforming growth factor-beta 1; TNF-α: Tumour necrosis factor-alpha; Treg: Regulatory T cells; UC-MSCs: Umbilical cord mesenchymal stem cells; VEGF: Vascular endothelial growth factor.

CONCLUSION

In summary, UCMSCs have a potential role in various medical fields such as orthopedic conditions, neurological conditions, autoimmune conditions, diabetes, respiratory conditions, infectious diseases, organ transplantation, and cancer therapy, etc. due to their intrinsic properties such as differentiation potential (can differentiate into various specialized cell types such as bone cells (osteoblasts), cartilage cells (chondrocytes), muscle cells (myocytes), and fat cells (adipocytes)), high self-renewal capacity, immunosuppression capacity, low immunogenicity and having immunomodulatory abilities, etc. Also, ease of availability, non-invasive procedure, and minimal ethical limitations are some of the advantages of its use as regenerative medicine. Various clinical trials of UCMSCs for different disease conditions are in progress. Thus, in the 21^{st} century, the regenerative medicine field holds the promise of revolutionizing treatment for various diseases.

Conflict of Interest

The authors declare that they have no conflict of interest in this study.

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