IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

" Review on Umbilical Cord Stem Cell Therapy"

[1]Priyanka Dnyaneshwar Pawar, [2]Kaveri T. Vaditake

Abstract:

The blood present in the vessels of the umbilical cord and placenta is known as umbilical cord blood. This blood has at least three distinct populations of stem cells, each with its own set of characteristics and properties. The second most popular source of stem cells for cell therapy is umbilical cord blood (UCB). As a result, regenerative medicine and the use of umbilical cord mesenchymal stem cell (UC-MSC) treatments have lately emerged as viable alternatives. UC-MSCs are multifunctional stem cells found in newborn umbilical cord tissue that can develop into a variety of cells with a wide range of therapeutic applications.

Key words :

Umbilical cord (UC), Mesenchymal stem cells (UC-MSC), Regenerative medicine, Umbilical cord stem cells therapy, Multifunctional stem cells.

1.Introduction:

The umbilical cord serves as a key link between the foetus and the placenta. The development of the umbilical cord begins in the embryologic stage around week 3 with the production of the connecting stalk. By week 7, the umbilical cord, which consists of the connecting stalk, vitelline duct, and umbilical veins encircling the amniotic membrane, has fully developed. The umbilical vessels transmit foetal blood back and forth to the placenta, with the umbilical vein bringing oxygenated blood containing nutrients from the placenta to the foetus and the umbilical arteries sending deoxygenated blood containing waste materials from the foetus to the placenta.

At the conclusion of the first trimester, embryonic tissues regress, leaving the umbilical cord, which is made up of two umbilical arteries and one umbilical vein, surrounded by Wharton's jelly, an extracellular matrix that resembles gelatin. The second trimester is when the umbilical chord elongates the most often. The typical umbilical chord has up to 40 helical twists and measures 50 to 60 centimeters in length and 2 cm in diameter. Increased foetal morbidity and mortality have been linked to abnormalities of the umbilical cord. (1, 2,3)

2.Umbilical cord stem cells

A kind of cell known as stem cells may self-renew and go through lineage differentiation. Developmental plasticity is the capacity of stem cells to generate one or more differentiated cell types. The three primary sources of stem cells in the human body are umbilical, adult, and embryonic. (4)

The umbilical cord, often thought to be a waste product, was discovered in 1974 to be a source of hematopoietic stem and progenitor cells. Aside from hematopoietic stem cells (HSCs), several scientists have identified mesenchymal stem cells (MSCs) from umbilical cord blood, while other investigations have failed to confirm their existence in significant proportions. (5)

Stem cells are simple cells that satisfy three essential characteristics. To begin, stem cells replenish themselves throughout life, dividing to make identical daughter cells and therefore maintaining the stem cell population. Second, stem cells have the ability to differentiate into specialized progeny cells. As stem cells develop, they may divide asymmetrically to produce an identical cell and a daughter cell that acquires specialized shape, phenotypic, and physiological features that identify it as a cell belonging to a given tissue.

"Pluripotent" cells are those that can develop into tissues derived from all three germ layers, such as ectoderm, Stem endoderm, and mesoderm. The embryonic stem cells (ESCs) produced from the inner cell mass of early embryos are the

greatest example of pluripotent stem cells. Most well-characterized stem cells are multipotent, meaning they can develop into derivatives of two of the three germ layers. The third quality of stem cells is that they may regenerate the tissues in which they reside. All tissue compartments include "stem cells," and the pace at which stem cells contribute to replacement cells varies across the body. Blood-forming stem cells, gut epithelial stem cells, and skin-forming stem cells, for example, must be regularly regenerated for good health.In contrast, the stem cells in the nervous system that replace neurons are relatively quiescent and do not participate in tissue renewal or replace neurons lost to injury or diseases.(6, 7,8)

2.1Types of umbilical cord stem cells:

1.Mesenchymal stem cells

2.Haematopoietic stem cells

3.Neural stem cells

4.Epithelial stem cells

5.Skin stem cells

3.Umbilical cord Mesenchymal stem cells:

A prospective source of mesenchymal stem cells is the human umbilical cord (UC) (MSCs). (8)

HUC-MSCs are multipotent and self-renewing. Under particular circumstances, they are able to constantly divide and differentiate into one or more cell types that make up human tissues and organs. They can be quickly extracted, separated, cultivated, enlarged, and purified, and they have an impact on immunological responses.

After several passes and growth, HUC-MSCs maintain their stemness. HUC-MSCs' lack of noticeable surface antigens, low transplant cell rejection rates, and lax matching standards make it easier to employ them in allografts..

HUC-MSCs are now employed to treat a number of illnesses. They possess a number of distinctive qualities that are necessary for their therapeutic uses. Differentiation: HUC-MSCs' ability to produce differentiated cells encourages tissue regeneration and enhances tissue function.. (9, 10)

3.1.Advantages Of UC-MSC:

From tissues taken from foetus, adults, and embryos, stem cell populations can be extracted. Because of their remarkable potential for self-renewal and pluripotency (ability to develop into all germ layers), embryonic stem cells (ESCs) are a leading possibility for tissue engineering both in vitro and in vivo. Nevertheless, in addition to ethical limitations, technological challenges with the removal of immature cells that may cause a teratoma severely restrict the practical uses of ESCs.

Adult stem cells, which are found in tissues including the skin, bone marrow (BM), and adipose tissue, may have broader therapeutic uses.. (9)

4.Impact of Human umbilical cord mesenchymal stem cells transplantation on clinical treatment ?

4.1. Rheumatoid Arthritis:

An inflammatory condition that affects the tissues around the joints called arthritis. Its complicated genesis is mostly attributed to an autoimmune response, infections, and trauma. Synovial hyperplasia and joint destruction are hallmarks of the prevalent systemic inflammatory illness known as rheumatoid arthritis (RA), which also causes clinically substantial functional impairment and lowers quality of life. Atherosclerosis, which causes cardiovascular issues and poses a major threat to human health and life, is more likely to develop in RA patients.(11)

Mesenchymal stem cells (MSCs) are cells that have the capacity to differentiate in a variety of ways and are derived from the early mesoderm. In 1970, Friedenstein and colleagues found that in vitro-grown fibroid cells from bone marrow could be implanted beneath the skin to create bone tissue and restore the blood microenvironment. MSCs can be found in a wide range of tissues, including bone marrow (BM), skin, adipose tissue (AD), umbilical cord (UC), and others, according to several research. Due to their paracrine effects, interactions with other immune cells, limited immunogenicity, and lack of HLA II and HLA I expression, MSCs also possess immunosuppressive properties in addition to their multi-lineage differentiation capability. Studies have revealed that BM-MSCs create regulatory T (Treg) cells, promote low reactivity in T lymphocytes, control the production of inflammatory mediators, considerably lower blood levels of tumors necrosis factor (TNF), and

prevent severe bone and cartilage damage. MSCs may be used to treat severe autoimmune illnesses that have failed to respond to therapy due to their capacity for tissue repair and immunomodulatory effects.(11, 12,13)

4.2.Type 1 Diabetes Mellitus:

A collection of metabolic illnesses known as diabetes are defined by hyperglycemia brought on by inadequate insulin production, a weakened sensitivity to insulin, or both. Type 1 insulin-dependent diabetes mellitus (T1DM) and type 2 insulin-independent diabetes mellitus are the two kinds of diabetes that are identified clinically (T2DM). Due to islet cell dysfunction, T1DM is often characterised by low levels of insulin and C-peptide, whereas T2DM is linked to a decline in insulin receptor sensitivity. It has been demonstrated that intravenously administered HUC-MSCs may locate pancreatic islets and develop into functional islet-like cells in diabetic rats. Although preventing the activation of the NLRP3 inflammasome and inflammatory factors, these cells influence macrophage polarization. The progression of diabetes is improved by these anti-inflammatory actions. Among diabetic patients, the metabolic index improved, the levels of insulin and C-peptide rose, the number of Treg cells increased, and glycosylated haemoglobin, fasting glucose, and daily insulin requirements reduced 6 months to 1 year after intravenous injection of HUC-MSCs. Diabetes can be treated using HUC-MSCs in a secure and efficient manner.

Diabetes mellitus type 1 is a kind of the condition where the pancreatic beta cells that produce insulin are destroyed by the immune system. Due to the lengthy waiting list of patients in need of transplants and the scarcity of donor pancreas, the current gold standard treatment for pancreatic transplantation has several drawbacks. In the nascent field of regenerative medicine, mesenchymal stem cells (MSCs), a relatively new potential treatment in several domains, have already made their impact. Current research has demonstrated that MSC implantation lowers glucose levels via paracrine effects rather than through direct transdifferentiation into cells that produce insulin. [20] As a result, after being transplanted with pancreatic islets, these cells may employ their pro-angiogenic and immunomodulatory properties to manage diabetes.(14, 15,16,17,18,19,20,21)

4.3. Cardiovascular Diseases:

Globally, heart disease is the leading cause of death, taking the lives of almost 20 million individuals between the ages of 30 and 70 each year. The condition now tends to afflict younger people. Heart transplants, surgical procedures, and drug therapy are among the possible treatments. Surgery is generally not advised until the problem is severe since it is frequently accompanied with complications. Even if the patients live and their condition becomes better, they still need a long-term maintenance treatment. A generally safe and efficient alternative treatment for cardiac disorders is provided by HUCMScs

Despite advancements in the management of the condition by mechanical and surgical therapy techniques, heart failure continues to be the top cause of mortality globally. The standard curative treatment for end-stage heart failure is a heart transplant. The use of this method, which also necessitates lifelong immunosuppression, is nonetheless constrained by the lack of available donor hearts. Other surgical procedures, such implanting mechanical ventricular assist devices, can easily result in bleeding, infections, and other problems and come with substantial medical expenditures. Stem cell treatment has recently been created and thoroughly studied as an alternative therapeutic approach for heart failure. Because adult cardiac cells seldom divide and heart tissue cannot mend itself, it may be feasible to treat ischemic regions by grafting mesenchymal stem cells (MSCs) Because of their low immunogenicity, paracrine action, and immunosuppression, MSCs have been employed to heal injured hearts. In ischemic scar tissue, MSCs release growth factors and chemokines that promote angiogenesis, induce cardioprotection, and remodel the extracellular matrix. The use of MSCs increased cardiac function and the regeneration of heart tissue in injured hearts, according to several clinical investigations.(22, 23,24)

4.4. Acute Liver Failure:

Rapid liver cell death, a systemic inflammatory response, and severe liver malfunction are the hallmarks of acute liver failure (ALF), a clinical condition that poses a serious risk to life and can result in serious consequences such coagulation issues, hepatic encephalopathy, and jaundice. 1 The best treatment for this condition is liver transplantation, however it is not routinely used due to a scarcity of donors, immunological rejection, and other issues. 2 New ALF treatments are thus desperately needed. ALF can be treated with stem cells, according to growing body of research.

Mesenchymal stem cells (MSCs) may develop into a variety of cell lineages due to their multidirectional differentiation potential and capacity for self-renewal. MSCs also inhibit inflammation, control immune responses, and reduce metabolic and oxidative stress by secreting soluble substances, to name a few of their therapeutic benefits. 3 Most significantly, MSCs are less problematic ethically and easier to get than other forms of stem cells. 4 Moreover, they are less likely to develop tumors. They are more suited for clinical application because of these qualities. Recent research on MSCs in ALF patients and animal models has demonstrated that MSCs enhance liver functioning and regeneration. The therapeutic effects and mechanisms of MSCs from different sources in ALF are also different and summarized in this review to provide a basis for clinical application of MSCs for ALF treatment(26, 27,28,29,30)

4.5. Spinal Cord Injury:

Mesenchymal stem cells from the human umbilical cord (hUC-MSC) are a potential option for SCI treatment. Their usage has several advantages, including supporting revascularization, reducing inflammation, preventing cellular apoptosis, producing numerous trophic factors, and causing hUC-MSCs to differentiate into oligodendrocytes and neurons.

They are also a very good option for SCI treatment due to other benefits such their absence of contamination, ease of procurement, minimal immunogenicity, and quick proliferation.

While the early chronic phase of SCI is poorly understood, it is distinguished by a significant immune cell infiltration and a peak release of pro-inflammatory cytokines from the wounded tissuesThis research protocol outlines a proposed clinical trial to evaluate the safety and effectiveness of intrathecal transplantation of MSC to treat early chronic SCI since patients with this stage of SCI are often seen in clinics.(31, 32)

4.6.COVID-19 Acute Respiratory Distress Syndrome:

Beginning in early 2020, the coronavirus disease 2019 (COVID-19), a pneumonia-like illness brought on by the SARS-CoV-2 virus, reached pandemic levels. Some SARS-CoV-2 patients get severe COVID-19 that necessitates hospitalisation. Severe COVID-19 is thought to be caused by SARS-CoV-2 infection-induced hyperinflammation, an overactive immune response that sets off a cytokine storm, and a prothrombotic condition that is together known as immunothrombosis.

Acute respiratory distress syndrome (ARDS)-progressing patients need high-flow oxygen treatment, close monitoring, and usually mechanical ventilation.

According to reports, 52.4% of patients with COVID-19 and ARDS died. 10 Novel therapeutics that might lessen the excessive inflammatory response brought on by the immunopathological cytokine storm and immunothrombosis, hasten the recovery of functional lung tissue, and reduce death in patients with severe COVID-19 are urgently needed.

MSCs, often referred to as mesenchymal stromal cells or medicinal signalling cells, are mesenchymal stem cells that have been found to moderate hyperactive immunological and hyperinflammatory processes, support tissue healing, and release antimicrobial compounds. These cells have been investigated for the treatment of autoimmune illnesses (such as type 1 diabetes [T1D]), systemic lupus erythematous, inflammatory disorders, and steroid-refractory graft-versus-host disease due to their safety profile when injected intravenously (GvHD).have had mixed but encouraging outcomes in ARDS of viral and nonviral origin, and they have been observed to reduce lung fibrosis and inflammation. MSCs are currently being tested in many ongoing trials in patients with severe COVID-19, and preliminary uncontrolled studies have shown encouraging effects. (33, 34).

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