MESENCHYMAL STEM CELLS: A POSSIBLE SOURCE OF MULTIPLE SCLEROSIS TREATMENT

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ABSTRACT

There are high hopes for stem cell therapies for tissue repair because there are currently no treatments that promote the remyelination and regeneration of the neuronal network that has been damaged by the autoimmune onslaught that is present in multiple sclerosis (MS). Because of their alleged aptitude to transdifferentiate into brain cells and their power to modulate immunological responses, It has been proposed that mesenchymal stem cells (MSCs) could be used to treat MS. In the present review we highlighted the possible use of MSCs in MS patients as an alternate novel option. The small number of MS patients in research and the lack of positive benefits of MSC transplantation in cells treatments have been examined. Furthermore, the primary challenges and hazards associated with MSC therapy for MS patients have been elucidated. In conclusion, the MS treatment with MSC-based stem cell therapy showed lot of promise. However, a multitude of issues and restrictions that need to be fixed. Further research and quantification are required regarding the precise the cell stage to be transplanted, the precise description of the cell type to be given, the transplanted cells' in vivo destiny in different inflammatory models, the dosage, the mode of administration, the length of the therapeutic effect, and the stem cells' genomic stability.

KEYWORDS: Nchymal Stem Cells, Multiple Sclerosis, Homing, Immunomodulation.

INTRODUCTION

For young individuals with disabilities, multiple sclerosis (MS) is the most prevalent non-traumatic cause (<50 years old) in Europe, affecting over 2 million individuals globally (1). MS is a neuroinflammatory demyelinated condition of the central nervous system (CNS) that leaves sufferers physically disabled (2). Thirty out of one lac people have MS, and the ratio of males to females is 1:3. (2). So, females are twice as likely as males to have MS, which often manifests between the ages of 20 and 40 (9). Myelin sheath injury, which disrupts normal nerve impulse conduction, is one of its defining characteristics. Myelin sheaths are the protective substance that surrounds the nerve fibres in the brain and spinal cord (9). Increased neuron and oligodendrocyte mortality in MS, along with myelin loss, necessitates the use of neuroprotective or cell replacement therapy (8). To increase the survival of MS patients, several experimental therapies have been created.

It's interesting to note that stem cell therapy has emerged as a viable MS treatment approach. The first justification for using stem cells to treat MS came from the notion that they could differentiate into neural lineage cells to restore the CNS that had been damaged (6). Recently, numerous disease conditions, particularly neurodegenerative and neurological illnesses, have been believed to be effectively treated by stem cell transplantation or somatic cell reprogramming toward target cells (3).

ETIOLOGY OF MS

Although the exact cause of this condition is still unknown, it is generally accepted that it is related to T and B lymphocytes' attacks on myelin in the CNS (1). It has been proposed that a viral infection during infancy may be the initial event in the development of MS (4). Such an infection results in activated T-lymphocytes that are sensitive to myelin antigens and can pass through the blood-brain barrier (BBB). Another theory is that lymphocytes are more susceptible to viral proteins because they mimic myelin proteins. Some auto-reactive T cells may, after years of dormancy, re-enter the central nervous system (CNS) via the impaired blood-brain barrier and initiate an immune

response against myelin. Acute plaques sensitise B cells and cause them to produce antibodies specific to the myelin antigen. The following substances damage myelin: glutamate, nitric oxide (NO), inflammatory cytokines, and oligodendron glial cells, and other harmful byproducts that are created by microglia and macrophages. Although the CNS-damaging chemicals are the same, distinct kinds of MS may have diverse immune responses that start and spread the illness. Epstein-Barr virus (EBV) infection, UV light exposure, vitamin D deficiency, and individual genetic susceptibility are believed to be linked with one another and play a role in the aetiology of MS (4).

The four main subtypes of MS are relapsing-remitting, progressive-relapsing, secondary progressive, and primary progressive, depending on how the disease progresses (1, 3, 9). Relapsing-remitting is the most prevalent type of MS (80% of all MS cases are due to this condition), is characterised by partial remission between relapses (1, 3, 6). More than 50% of cases may advance to "secondary progressive" MS, which has progressively worsened neurological symptoms between episodes without any discernible remission phase (1, 6). About 20% of cases have primary progressive MS, that progresses from the outset and has no relapses (1, 3, 6). Patients with progressive-relapsing MS, which accounts for 5% of all MS cases, experience intermittent attacks as their condition worsens (1, 6).

STEM CELLS

Stem cells are undifferentiated cells found in the body that can either stay in this state where they can continue to produce more of their own cells or grow into different types of cells with specialized roles. J. Xiao and associates, 2015). Neural stem cells (NSCs), hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) are among the different types of stem cells that are known to exist (Mansoor S. et al., 2019; Xiao. J. et al., 2015). HSCs were initially used to immunoablative treatment for MS patients in 1995. Mansoor S. and collaborators (2019). Since then, a variety of stem cell types have been used to halt progressive axonal atrophy and persistent demyelination. Despite the many benefits of lymphoma caused by the Epstein-Barr virus (EBV), thrombocytopenia, and subsequent malignant disease, the use of HSC in clinical therapy has been limited. Moreover, ESCs generated via in vitro fertilization are sensitive to epigenetic changes and susceptible to changes in culture or environment (3). To prevent the formation of teratocarcinomas, it is also necessary for iPSCs to undergo differentiation into the target cells before transplantation. Remarkably, research has demonstrated showing remyelination and immunomodulation are enhanced by autologous or allogenic MSC implantation in the central nervous system by producing immunoregulatory substances, replacing lost cells, and having neuroprotective benefits.

MESENCHYMAL STEM CELLS (MSCs)

MSCs, also known as mesenchymal progenitor cells, are adult stem cells that are not hematopoietic and can differentiate into many lineages and self-renew. (3, 7, 10). Friedenstein et al. first isolated, identified, and described MSCs from the bone marrow in 1967 (3). Subsequently, MSCs were extracted from peripheral blood, dental pulp, fetal liver, muscle, lung, adipose tissue, umbilical cord, and synovial membranes. (3, 4, 7). Roughly 0.01% to 0.001% of all nucleated cells in bone marrow are spindle-shaped fibroblastic cells (2, 4). Human mesenchymal stem cells (MSCs) can be classified into the following categories, according to the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy: the capacity to develop in vitro into chondroblasts, adipocytes, and osteoblasts. The surface molecules CD105, CD73, and CD90 expression; and the plastic adherence under conventional culture conditions (2, 4, 7). These standards are currently used to maintain the ability of MSCs to differentiate while allowing for their separation and in vitro growth. According to recent studies, MSCs can develop both in vitro and in vivo into non-mesenchymal cell lineages such as skeletal myocytes, neurons, and visceral mesoderm cells. J. Xiao and associates, 2015). Moreover, MSCs' low immunogenicity-especially when employed in an allogenic way-has allowed for their successful application in xenogeneic situations. According to Barati S. et al. (2020), autologous MSCs have demonstrated the highest success rate in clinical trials.

They make an excellent choice for clinical applications due to their feasibility for autologous transplantation as well as their capability for repopulation and differentiation (3) MSCs are a diverse and multipotent population of stem cells with trophic and neuroprotective properties. They can encourage neurogenesis, axonal regeneration, and synaptogenesis. (2). MSCs make an excellent choice for clinical applications due to their feasibility for autologous transplantation as well as their capability for repopulation and differentiation (3).

By expressing OPC markers such A2B5 and oligodendrocyte transcription factor (Olig2), MSCs have demonstrated the ability to develop into oligodendrocytes in the context of treating multiple sclerosis (MS) (7).

MSCs' THERAPEUTIC STRATEGIES FOR TREATING MS

MIGRATION

The term "homing" describes a cell's capacity to move into a tissue, cell niche, or damaged area. The MSC dosage, supply, and culture conditions, the distribution mechanism, and host injury are some of the parameters that affect migration and homing to the tissues that are harmed (Barati S. et al., 2020). Signals from the injured region are used to evaluate the migratory capacity of cells. It is unknown exactly how MSCs migrate and homing to tissues work, but it is consistent with the process by which injured tissues release proteins and ligands (or receptors) to help MSCs migrate to the damaged areas.

The semi-permeable blood brain barrier (BBB) blocks large molecules and cells. After a disturbance, MSCs can pass across regions where the BBB is inadequate. Numerous chemokines, growth factors, and receptor interactions have also been demonstrated to have an impact on migration and homing. These comprise the following: monocyte chemokine receptor type 4 (CXCR4), vascular endothelial growth factor (VEGF)/VEGF receptor, platelet-derived growth factor (PDGF)/PDGF receptor, stem cell factor/ckit, and stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4).Numerous chemokines, growth factors, and receptor interactions have also been demonstrated to have an impact on migration and homing. These comprise the following: monocyte chemokine receptor type 4 (CXCR4), vascular endothelial growth factor (VEGF)/VEGF receptor, platelet-derived growth factor (PDGF)/PDGF receptor, stem cell factor/ckit, and stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4).

Among these, the interaction between CXCR4 and SDF-1 is important for MSC migration into the tissue in response to specific chemotactic stimuli. (3). It has been demonstrated that transplanted MSCs are more precisely targeted when SDF-1 is overexpressed. Furthermore, past studies have indicated that MSCs move across the BBB by rolling and adhering to endothelium in a way like leukocytes. According to studies, in mice with experimental autoimmune encephalomyelitis, VLA-4 regulates the interactions between MSCs and BBB-endothelial cells. (11). The MSCs' place of origin is also essential for these cells to move. According to research, MSCs extracted from bone marrow (BM-MSCs) express fewer migratory factors than MSCs produced from adipose tissue (Ad-MSCs) and umbilical cord Wharton's jelly (UC-MSCs). It has been demonstrated that only Ad-MSCs express CCR-1 and that UC-MSCs and Ad-MSCs express integrin-4 at higher levels than BM-MSCs (3).

In conclusion, studies have demonstrated that the efficiency of MSC rolling, transmigration, and invasion in many organs is determined by the expression patterns of integrins and adhesion molecules in the MSC membrane. These expression patterns differ according to the type of surrounding tissues and arteries.

MMPs are a type of endoproteinases that break down every component of the extracellular matrix to allow cells to more easily pass through it. A unique family of MSC surface molecules called integrins is involved in multiple cell types migrating (3).

IMMUNOMODULATION

MSCs are categorized as immunomodulator cells when they communicate with immune cells either directly or indirectly. MSCs suppress the production of pro-inflammatory cytokines, control the Th1/Th2 ratio, and slow down the growth of T cells. Additionally, MSCs stop B cells from proliferating, ending their life cycle and stopping them from producing antibodies. Moreover, MSCs prevent dendritic cells and natural killer cells (NKCs) from proliferating and becoming activated. MSCs also affect the immune system by regulating Tregs, or regulatory T-cells, in terms of activity. Numerous soluble substances are produced by MSCs, such as prostaglandin E2 (PGE2), transforming growth factor-1 (TGF-1), nitric oxide (NO), interleukin-10 (IL-10), hepatocyte growth factor (HGF), and indoleamine-pyrrole. 2.

DIFFERENTIATION AND NEURODEGENERATION

The biggest challenge in treating CNS degeneration is that neural tissue cannot sufficiently repair itself. Patients with demyelinating multiple sclerosis experience long-term impairment due to neurodegenerative lesions. Recent research has suggested that using MSCs therapeutically to treat MS patients may be a good idea because they can develop into a range of cell types. In vitro and in vivo, MSCs can develop into oligodendrocyte neurons, and astrocytes, among other mesodermal and non-mesodermal cells. S. Mansoor and associates (2019). The neuroectodermal lineage is characterized by characteristics shared by a subgroup of MSCs called MSC-derived neural progenitor cells (MSC-NPs), which also have a lower propensity to develop into mesodermal cells. These characteristics make them a viable choice for lowering the risk of ectopic differentiation following MSC transplantation.

CLINICAL TRIALS IN MS USING MSCS

The safety and viability of MSC therapy have been demonstrated by numerous clinical studies carried out in the previous few years, with positive outcomes. Nine RRMS patients received intravenous BM-MSC infusions over a six-month period as part of a phase II study. The findings showed that individuals receiving MSC treatment tended to have less cumulative gadolinium-enhancing lesions (GELs) on MRI. Furthermore, a non-significant decrease in Th1 cell frequency was seen in the peripheral blood of patients receiving MSC treatment. In an open-label phase 2a trial, ten patients with visual pathway impairment caused by SPMS were administered an autologous BM-MSC injection via intravenous means. After six months, there were improvements in visual evoked response latency and sharpness.

The purpose of the experiment was to assess autologous MSCs' safety and effectiveness as a potential neuroprotective therapy for SPMS. These results are consistent with MSCs' capacity to provide neuroprotective effects and stimulate endogenous oligo-dendrogenesis and remyelination.

2015 saw the launch of a Phase I neural stem cell clinical trial including 20 patients with RRMS in order to examine the efficacy and safety of neural progenitor cells generated from autologous MSCs. Patients will receive intrathecal injections of grown MSC-neural precursor cells (NPC) for six months and be monitored for 27 months. This experiment's evaluation of effectiveness over 36 months is its secondary goal.

CHALLENGES AND RISKS OF MSCS ADMINISTRATION IN CLINICAL THERAPY

Approaches to treating multiple sclerosis include cell therapy. While there are no conclusive therapeutic outcomes to yet, this strategy is appropriate for immune regulation and brain repair in MS patients. Cell therapy remains superior to other treatments, despite certain drawbacks similar to those of any other treatment. The capability of mesenchymal stem cells for immunomodulation, repair, and remyelination, along with their capacity to release cytokines, account for this. Extensive research on the mechanisms and constraints of this therapy is necessary in light of the ongoing challenges. While MS disease progression can be slowed down and immune system regulation achieved with MSCs, a number of problems remain.

The two primary techniques for transplanting MSCs were Intravenous (IV) injection (systemic delivery) and Intravenous therapy (IT) infusion (local administration), according to multiple therapy trials conducted on MS patients. IV infusion has been demonstrated to be one of the easiest and least invasive ways to help patients reach a systemic concentration of MSCs. However, only a tiny portion of stem cells penetrate the central nervous system (CNS) as damaged tissue in MS patients due to their ability to circulate across numerous tissues and become trapped in systemic organs.One of the main risks that might impact both donors and recipients is infection. Following the acquisition of donor MSCs, infection may occur. It is believed that microorganisms can move easily to injection sites in recipients. Moreover, immunosuppressive drugs increase the risk of infection (3). The other big issue with MSC therapy is paradoxical disease activation. Surprisingly, later studies revealed that MSCs also regulate Th1 and Th17. Earlier research had shown that MSCs inhibit Th1 and Th17 cell growth in addition to the production of the cytokines linked to them (3).

CONCLUSION

Multiple sclerosis therapy with MSC-based stem cells has a lot of promise. However, there are numerous issues and constraints that must be fixed. Further research and quantification are needed to determine the precise cell stage that must be transplanted, The exact type of cell that needs to be given, the in vivo outcomes of implanted cells in many kinds of models like inflammation, the dosage, the manner of administration, the length of time the therapeutic effect lasts, and the stem cells' genetic stability.

REFERENCES

1. Connick P., Kolappan M., Crawley C., et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. The Lancet Neurology, 11(2), 150–156; 2012.
2. Barati S., Tahmasebi F., Faghihi F. Effects of mesenchymal stem cells transplantation on multiple sclerosis patients. Neuropeptides, 84, 102095; 2020.
3. Mansoor S. R., Zabihi E., Ghasemi-Kasman M. The potential use of mesenchymal stem cells for the treatment of multiple sclerosis. Life Sciences, 116830; 2019.
4. Xiao J., Yang R., Biswas S. Mesenchymal Stem Cells and Induced Pluripotent Stem Cells as Therapies for Multiple Sclerosis. International Journal of Molecular Sciences, 16(12), 9283–9302; 2015
5. Uccelli A., Laroni A., Freedman M. S. Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological

diseases. The Lancet Neurology, 10(7), 649–656 2011. doi:10.1016/s1474-4422(11)70121-1

6. Uccelli A., Morando S., Bonanno S. Mesenchymal Stem Cells for Multiple Sclerosis: Does Neural Differentiation Really Matter? Current Stem Cell Research & Therapy, 6(1), 69–72; 2015
7. Gugliandolo A., Bramanti P., Mazzon E. Mesenchymal Stem Cells in Multiple Sclerosis: Recent Evidence from Pre-Clinical to Clinical Studies. International Journal of Molecular Sciences, 21(22), 8662; 2020.
8. Odinak M. M., Bisaga G. N., Novitskii A. V. et al. Transplantation of Mesenchymal Stem Cells in Multiple Sclerosis. Neuroscience and Behavioral Physiology, 42(5), 516–520; 2012.
9. Li J.-F., Zhang D.J., Geng Tet al. The Potential of Human Umbilical Cord-Derived Mesenchymal Stem Cells as a Novel Cellular Therapy for Multiple Sclerosis. Cell Transplantation, 23(1_suppl), 113–122; 2014.
10. Liang J., Zhang H., Hua et al. Allogeneic mesenchymal stem cells transplantation in treatment of multiple sclerosis. Multiple Sclerosis Journal, 15(5), 644–646; 2009.
11. B. Rüster, S. Göttig, R.J. Ludwig, R. Bistrian, S. Müller, E. Seifried, et al., Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells, Blood 108 (2006) 3938–3944.

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