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Therapeutic Potential of Mesenchymal Stem Cells on Major Depressive Disorder

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Abstract: Major depressive disorder (MDD) has emerged as an escalating global health challenge in recent years, underscoring the urgent need for effective intervention strategies. Regenerative therapy employing stem cells has garnered significant attention as a potential therapeutic avenue for depression. Extensive research has highlighted the promising roles of various stem cell types, including mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and circulating stem cells (CSCs), in offering innovative approaches to address depression pathogenesis and facilitate disease modeling. Of particular interest, MSCs have emerged as a frontrunner in depression therapy due to several notable advantages over other stem cell types. Notably, MSCs are readily accessible, ethically unproblematic, and possess low immunogenicity risk, rendering them highly attractive to researchers. Accumulating evidence suggests that MSCs possess the capacity to home in on damaged brain regions, stimulate endogenous neurogenesis and neuroprotection, and modulate immune and inflammatory responses, thus positioning them as a promising candidate for cell-based depression therapy. This review primarily focuses on elucidating the current advancements and potential applications of MSCs in depression treatment. Additionally, we discuss prevailing obstacles and challenges associated with MSC therapy, aiming to provide a comprehensive overview of the landscape of MSC-based interventions for depression.

1. Introduction

Major depressive disorder (MDD) is characterized by enduring and profound feelings of sadness, diminished interest, and motivation. The incidence and mortality rates of MDD have shown a consistent rise over recent decades. According to data from the World Health Organization (WHO), approximately 350 million individuals worldwide suffer from MDD, with an estimated 800,000 MDD-related suicides occurring annually. It is projected that by 2030, MDD will ascend to the foremost position as the leading global cause of disease burden. Following the onset of the novel

coronavirus pandemic in 2019, there was a marked surge in the total number of depression cases. Statistics indicate a projected increase of 53.2 million additional depression cases worldwide in 2020, reflecting a growth rate of 27.6%, thereby introducing new complexities to the diagnosis and management of MDD. MDD frequently co-occurs with other psychiatric conditions such as anxiety disorders, attention deficit hyperactivity disorder, eating disorders, and substance abuse, as well as various physical ailments including diabetes, obesity, and autoimmune diseases. The profound impact of MDD on patients' daily functioning, interpersonal relationships, and vocational pursuits imposes a substantial burden not only on affected individuals but also on their families and society at large [1].

Currently, conventional treatments for Major Depressive Disorder (MDD) encompass pharmacotherapy, psychotherapy, and physical interventions5. Despite the proven efficacy of these modalities for a subset of patients, approximately 30 to 50% exhibit inadequate response and notable adverse effects. Furthermore, a significant proportion of MDD patients fail to fully regain premorbid social functioning post-clinical remission, often presenting with residual symptoms. This phenomenon diminishes their quality of life, engenders poor treatment adherence, and escalates the risk of disability, suicide, and heightened disease burden [2].

Hence, there exists an imperative to elucidate the pathophysiological mechanisms underlying MDD, facilitating early recognition and precise diagnosis, and enabling the development of efficacious therapeutic interventions characterized by minimal side effects and high remission rates. This endeavor aims to mitigate the incidence of comorbidities and diminish the risk of disability.

In recent years, stem cells, characterized by their capacity for self-renewal and differentiation, have garnered widespread attention and application in cellular therapy. Mesenchymal stromal cells (MSCs) represent multipotent progenitor cells capable of differentiating into various cell lineages including neurons, osteocytes, chondrocytes, and adipocytes. Numerous investigations have demonstrated the successful isolation of MSCs from diverse mammalian tissues, encompassing peripheral blood, endometrial polyps, placenta, umbilical cord, menstrual blood, bone marrow, cardiac tissue, and adipose depots. With the expanded utilization of stem cell transplantation in cellular therapy, research has elucidated the involvement of MSCs in modulating the pathogenesis of depression via multiple pathways, thereby highlighting their potential therapeutic efficacy in depression. MSCs exert their neuroprotective effects through both direct and indirect mechanisms, notably through the secretion of neurotrophic factors and extracellular matrix molecules such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1). These factors facilitate neurogenesis of primary neural progenitor cells, enhance nerve cell survival, and foster neuronal growth16. Furthermore, MSCs exhibit robust immunomodulatory properties, capable of attenuating inflammatory responses and diminishing levels of pro-inflammatory cytokines, thereby mitigating the association between excessive immune activation and depression pathogenesis. Additionally, central nervous system transplantation of MSCs serves to forestall cell apoptosis, bolster the growth and differentiation of host nerve cells and stem cells at the site of implantation, augment synaptic connections among neurons, thereby enhancing neuronal plasticity and promoting neurological recovery in patients afflicted with depression [1]. Consequently, MSC-based intervention therapy holds promise as a novel treatment modality for Major Depressive Disorder [3].

2. Pathogenesis of MDD

The etiology of depression is multifaceted and intricate, stemming from the intricate interplay of genetic, biological, psychosocial, and environmental determinants. Individual differences contribute to the variability in responses to environmental stimuli, leading to disparate effects among various

populations. Consequently, the pathogenesis of depression manifests as a complex and heterogeneous phenomenon, eluding comprehensive explication by any singular mechanism. Presently, prevailing hypotheses concerning the inflammatory immune system, neurotransmitter imbalances, disruptions in neuronal and synaptic plasticity, environmental stressors and life events, as well as genetic predispositions among other contributory factors [4].

2.1 Hypothesis of Monoaminergic System

The monoaminergic system hypothesis posits that depression primarily arises from dysregulation of monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine. According to this framework, individuals with depression exhibit disruptions in neurotransmitter levels or functional and structural irregularities within monoamine-associated pathways, culminating in disturbances in emotional regulation and psychological well-bein. Beyond alterations in neurotransmitter levels, individuals with depression also manifest adaptive changes in neurotransmitter receptor function, influencing receptor number, density, post-receptor signaling pathways, and even gene transcription processes. Notably, antidepressants targeting monoamines have demonstrated significant efficacy in ameliorating mood and cognitive symptoms in depression patients. Functional magnetic resonance imaging studies have revealed that treatment with monoamine-targeted antidepressants partially restores functional abnormalities within the limbic-cortical-striatal-pallidal-thalamic circuitry. Nonetheless, not all depression patients experience symptom alleviation with monoamine-based pharmacotherapy or adjunctive interventions. Approximately one-third of depression patients fail to respond to antidepressants solely targeting monoamine reuptake, underscoring the multifactorial nature of depression etiology beyond aberrations in individual neurotransmitter levels [5].

2.2 Hypothesis of Inflammation

In recent years, mounting evidence has underscored the interplay between depression and systemic immune system activation. Numerous investigations have elucidated elevated levels of pro-inflammatory factors such as IL-1β, IL-2, IL-6, TNF-α, and CRP in individuals with depression, juxtaposed with decreased levels of anti-inflammatory cytokines like IL-10 and TGF-β, thereby engendering immune system dysregulation. The inflammation hypothesis posits that these pro-inflammatory mediators traverse the blood-brain barrier, activating microglia within the central nervous system, and subsequently influencing the onset and progression of depression through diverse pathways, including modulation of neurotransmitter synthesis and release, neuroendocrine function, and neuroplasticity, ultimately precipitating alterations in mood and behavior. Intriguingly, bidirectional interactions have been observed between depressive symptoms and inflammatory activation, wherein individuals with depression exhibit heightened susceptibility to autoimmune diseases, while those afflicted with inflammatory conditions exhibit a markedly elevated incidence of depression. Moreover, studies have demonstrated a positive correlation between pro-inflammatory factor levels and the severity of depressive symptoms, with depressed patients harboring elevated inflammatory biomarkers exhibiting a greater propensity for treatment resistance. Thus, elucidating the immune system's role in depression offers promising therapeutic avenues aimed at counteracting the deleterious effects of pro-inflammatory factors on mood and behavior [6].

2.3 The Neurotrophic Factor Hypothesis

The neurotrophic factor hypothesis posits that disruption of neurotrophic support constitutes a

pivotal mechanism underlying depression-related alterations in synaptic and brain-related functions. Neurotrophic factors, a class of proteins facilitating the survival, growth, and functional upkeep of neurons, include growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophic factor 3 (NT-3).

As a principal member of the neurotrophic factor family, BDNF exhibits widespread distribution in brain regions such as the hippocampus, amygdala, and frontal cortex. Numerous studies have underscored BDNF's regulatory roles in modulating monoamine neurotransmitter levels, neuronal survival, growth, repair mechanisms, and synaptic plasticity. In the context of depression, BDNF emerges as a key player, with the severity of depressive symptoms correlating with BDNF expression levels. Notably, reductions in BDNF mRNA and protein expression in the brain are evident in depression patients, animal depression models, and in response to acute and chronic stressors. Experimental studies further elucidate the antidepressant effects achievable through hippocampal or midbrain BDNF administration, with implications for intracellular signaling within the mitogen-activated protein (MAP) kinase and cyclic adenosine monophosphate (cAMP) cascades. Research indicates that BDNF plays a crucial role in promoting hippocampal adult neurogenesis. Autopsies conducted on patients diagnosed with depression have revealed a correlation between reduced hippocampal size, diminished numbers of neurons and glial cells, and impaired hippocampal neurogenesis. Consequently, augmenting BDNF levels in the brain holds the potential to enhance neuroplasticity and mitigate hippocampal atrophy.

NGF, another prominent neurotrophic factor, predominantly originates from the hypothalamus, hippocampus, and cortex. It exerts its neuroprotective effects by fostering the development and survival of cholinergic neurons within the striatum and nucleus basalis of Meynert, thereby modulating acetylcholine production and metabolism through regulation of choline acetyltransferase and acetylcholinesterase. Notably, antidepressant treatment in depression patients correlates with elevated NGF levels, implicating NGF regulation as a viable avenue for antidepressant therapy.

NT-3, extensively expressed in the dentate gyrus of the hippocampus, emerges as a promising therapeutic target for mood disorders. Its multifaceted roles encompass regulation of monoamine neurotransmitters, synaptic plasticity, axonal and dendritic growth, neuronal proliferation, differentiation, survival, and modulation of BDNF signaling and the hypothalamic-pituitary-adrenal (HPA) axis. By binding to Trk-C receptors, NT-3 modulates neurogenesis and augments hippocampal plasticity, thus potentially restoring neuronal function and enhancing mood regulation and cognitive function [7].

2.4 The Neurogenesis and Synaptic Plasticity Hypothesis

Neurogenesis entails the continual process of generating new neurons within regions such as the dentate gyrus of the hippocampus and the subventricular zone adjacent to the lateral ventricles. Recent research has progressively unveiled the association between impaired neurogenesis in the hippocampus and dentate gyrus and the onset and progression of depression. Chronic exposure to various stressors, including restraint, social isolation, social defeat, sleep deprivation, and mild stress, can all precipitate diminished generation of new neurons. In humans, morphological alterations indicative of hippocampal atrophy have also been documented. Magnetic resonance imaging studies of depressed individuals have demonstrated reduced hippocampal volume compared to healthy counterparts. Similarly, autopsies of depressed patients have revealed decreased density of glial cells and granule cell neurons in the hippocampus. Consistent with observations in animal models, impaired neurogenesis manifests as diminished survival, proliferation, and differentiation of neural lineages within the dentate gyrus. Molecular analyses

have further correlated these findings with decreased expression of neurotrophic factor. Collectively, these findings provide compelling evidence linking depression to impaired neurogenesis in the hippocampus and dentate gyrus [8].

3. Mesenchymal Stem Cells and Depression: A Therapeutic Mechanism

Although MSCs have demonstrated the capacity to differentiate into neural lineage cells in vitro and express neuronal markers in animal models of depression, the in vivo survival rate of transplanted and differentiated cells remains notably low. Several studies have investigated the function of MSC-derived neuronal cells, proposing that differentiation and cell replacement in vivo may not be the primary mechanism underlying MSC-mediated alleviation of depression symptom. Instead, it is suggested that MSCs exert their therapeutic effects through the direct or indirect secretion of various neurotrophic factors, chemokines, extracellular matrix proteins, and other bioactive molecules. These substances play crucial roles in neuroprotection, synaptogenesis, endogenous neurogenesis, inflammation modulation, and immune response modulation, thereby contributing to the amelioration of depression symptoms. Figure 1 presents a schematic diagram outlining the mechanism by which MSCs exert therapeutic effects in depression.

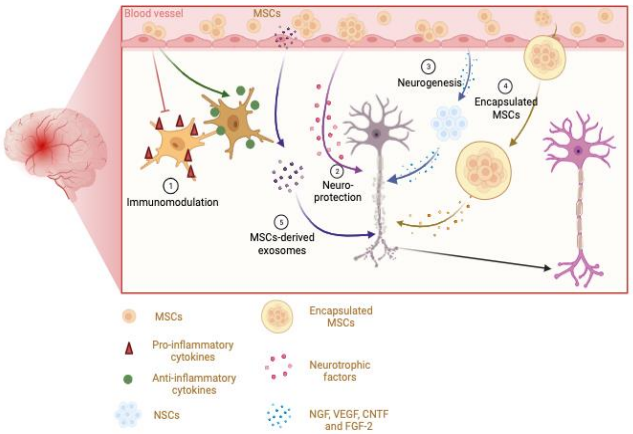

Figure 1: Illustrates the involvement of Mesenchymal Stem Cells (MSCs) in the therapeutic of depression.

3.1 Increasing of Neuroprotection

The neuroprotective effects of MSCs are believed to be mediated, at least in part, by their secretion of neurotrophic factors, which exert direct or indirect actions on host nerve cells. Studies have indicated that following transplantation into the central nervous system, MSCs respond to inflammation-inducing chemokines by migrating to damaged brain regions and expressing neurotrophic factors such as brain-derived neurotrophic factor (BDNF), β-nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1). These neurotrophic factors promote synaptic connectivity among damaged neurons, modulate inflammation to facilitate endogenous nerve cell growth, stimulate neurogenesis in both host nerve cells and stem cells at the implantation site—thereby enhancing proliferation and differentiation—reduce levels of free radicals, promote nerve cell survival, and mitigate apoptosis. Consequently, this cascade of events fosters the survival and regeneration of host neurons, thereby facilitating functional recovery.

Moreover, in addition to their direct effects on nerve cells, extracellular matrix molecules produced by MSCs have been demonstrated to enhance the damaged tissue microenvironment, promoting nerve cell attachment, growth, and axon extension, thereby further bolstering nerve

regeneration and neuroprotection. Notably, experiments conducted by Joyce et al. revealed that neurons cultured on extracellular matrix derived from MSCs exhibited a more intricate and extended neurite network compared to neurons cultured on poly-D-lysine.

Furthermore, studies by Koch et al. confirmed that MSCs express neural cell adhesion molecules, including netrin 4 from the family of soluble proteins homologous to laminin, which actively mediate axon guidance. Additionally, Gil et al. identified neurotrimin, a member of the IgLON family of nerve cell adhesion molecules, which promotes neuronal growth in dorsal root ganglion neurons through heterophilic and homophilic interactions. These neural cell adhesion molecules have the potential to further augment the endogenous neurogenic response to injury [9].

3.2 Promotion of Endogenous Neurogenesis

Notably, increased endogenous neurogenesis might be another mechanism by which MSCs improve the neurological function in depression. Neurogenesis is an ongoing process of the development of new neurons, which occurs in the dentate gyrus of the hippocampus. A growing body of evidence suggests that depression is linked to impaired neurogenesis in the hippocampus and dentate gyrus. MSCs contribute to neurogenesis by promoting the survival and differentiation of neural progenitor cells through differentiation into neural lineages as well as expression of neurotrophic factors.

Tfilin et al. demonstrated that the depressive behavior of FSL rats (Flinders sensitive line, an animal model of hereditary depression) was ameliorated following bone marrow-derived MSCs transplantation via cerebroventricular injection. The MSCs primarily migrated to the ipsilateral hippocampal dentate gyrus, CA1 and CA3 regions of the hippocampus, and to a lesser extent to the thalamus, hypothalamus, cortex and contralateral hippocampus. The ipsilateral dentate gyrus and hippocampus of engrafted rats exhibit active neurogenesis, as evidenced by an increase in DCX-expressing cells in the granular cell layer, BDNF-expressing cells in the subgranular zone, and GFAP-expressing cells in the dentate hilus.

Research has also shown that most engrafted MSCs failed to show DCX and GFAP, two markers common to freshly produced cells. The findings suggest that endogenous cells were primarily responsible for maintaining neurogenesis, and that MSCs, rather than developing into neural offspring, interact with local neuroprogenitors to modulate their therapeutic action in the nervous system.

Following the implantation of human MSCs into the dentate gyrus of the hippocampus of immunodeficient mice, Monuz et al. found identical findings suggesting markedly increased the proliferation of endogenous neural stem cells that expressed the stem cell marker Sox2. Furthermore, in apolipoprotein E knockout animals and prenatal heroin exposure, respectively, the transplantation of neural stem cells, or MSCs, in the hippocampus and dentate gyrus led to increased neurogenesis and an improved behavioral phenotype.

Studies have shown that the promotion of endogenous neurogenesis by MSCS may be related to the chemokines secreted by MSCs. The expressions of NGF, VEGF, CNTF and FGF-2 in the hippocampus of rats were generally increased after transplantation. It is possible that chemokines secreted by MSCs act directly on NSCs, or it is possible that MSCs-secreted factors activate astrocytes adjacent to hippocampal NSCs, and that activated astrocytes express some factors that independently promote neurogenesis, ultimately leading to increased neurogenesis [10].

MSCs have also been found to secrete several canonical Wnts such as Wnt1, 2, and 7b, or to stimulate the synthesis of Wnt3a by other cells after contact with MSCs, which can modulate the Wnt/β-catenin pathway. The Wnt/β-catenin signaling plays an important role in balancing NSCs self-renewal and neuronal differentiation in the adult DG, and it regulates hippocampal network

plasticity. The activation of the Wnt/β-catenin signaling pathway by MSCs contributes to the increase of hippocampal neurogenesis and the recovery of hippocampal structure and function, so as to play an antidepressant role.

Transplantation of MSCs into the central nervous system can modulate hippocampus neurogenesis, enhance the expression of neurotrophins by endogenous cells, and reduce depressive-like behaviors. Thus, we suggest that MSCs can be used as a new model for the treatment of depression.

3.3 Regulation of Immunity

MSCs have demonstrated potent immunomodulatory capabilities in the context of chronic inflammatory disease and injury. Interestingly, hyperactivation of innate immunity has been implicated in the etiology of depression. Excessive proinflammatory cytokines release such as IL-1, IL-6, and TNF-alpha leads to behaviors comparable to depression, and MSCs have the ability to downregulate the expression of these proinflammatory cytokines. Activation of NLRP3 inflammasome is implicated in the pathogenesis of depression by mediating caspase-1 activation, which hence promotes the division and release of pro-inflammatory factors IL-1b and IL-18. Studies have shown that after transplantation of human umbilical cord mesenchymal stem cells (hUC-MSCs) in a mice model of chronic unpredictable mild stress (CUMS), behavioral assessments revealed amelioration in depressive-like behaviors, and they were also able to modulate intracellular signaling of NLRP3 inflammasome /caspase-1 in vivo to counteract proinflammatory cytokine secretion and elevated levels of thermal cell death. This may be due to blockade of the neuronal complement C3a receptor in the mouse hippocampus which brings important benefits to patients with depression.

Furthermore, Huang et al.'s findings demonstrated that adipose-derived mesenchymal stem cells (ADSC), which are extracted and cultured from adipose tissue, could significantly ameliorate the depression-like behavior of CMS mice in the forced swimming test (FST), tail suspension test (TST), and sucrose preference test (SPT). Moreover, it suppressed the production of pro-inflammatory factors such as MCP-1, TNF-α, IL-1β, and IL-6 as well as the activation of microglia. Additionally, ADSC may enhance TrkB and BDNF expression as well as Nrf2/HO-1 signaling while suppressing TLR4/NF-κB signaling in brain tissue, which is in line with previous research on inflammation and depression [11].

4. Therapeutic Effects of MSCs Exosomes on Depression

With a deeper understanding of mesenchymal stem cells (MSCs), research interest has increasingly shifted towards the therapeutic potential of MSC-released exosomes—membrane-bound vesicles ranging from 30 to 200 nm in diameter. Exosomes encapsulate various functional proteins, mRNA, microRNA, and lipids, rendering them an attractive option for efficient cell-free therapeutic applications in tissue repair strategies.

Studies indicate that MSC-derived exosomes possess tissue repair and regeneration capabilities akin to MSCs and demonstrate the ability to target damaged tissues. Moreover, their small size, extended circulation half-life, high permeability, and excellent biocompatibility contribute to their therapeutic potential. The nanoscale dimensions of exosomes enable facile traversal of the blood-brain barrier, thereby offering significant promise for nervous system healing. Furthermore, the risks of infection and immune rejection associated with MSC transplantation can be mitigated by utilizing exosomes. Additionally, MSC-derived exosomes can be subjected to gene editing to enhance their efficacy [12]. Consequently, exosomes produced by MSCs emerge as a promising avenue for future depression treatment.

Moreover, Kin et al.'s study introduced a novel approach wherein MSCs were encapsulated within polymer hollow fibers comprising semipermeable membranes to create encapsulated MSCs (eMSCs). Subsequent implantation of eMSCs into the ventricles of Wistar Kyoto (WKY) rats with congenital depression alleviated their depressive-like behavior and augmented the antidepressant effects of MSCs. This intervention not only promoted endogenous neurogenesis in the hippocampal subependymal zone and dentate gyrus but also stabilized the secretion of brain-derived neurotrophic factor and fibroblast growth factor-2, upregulated vascular endothelial growth factor, and enhanced the intrinsic expression of ciliary neurotrophic factors and their receptors. Encapsulation significantly improved the survival rate and duration of MSCs in vivo, thereby sustaining robust secretion of neurotrophic factors. Overall, encapsulation facilitated heightened antidepressant effects and positive regulation of neurogenesis by MSCs, underscoring the notion that transplanted MSCs may confer functional benefits primarily through the secretion of neurotrophic factors rather than integration into the host itself following graft survival and differentiation.

5. Clinical Trial

As of March 2024, the search terms "Mesenchymal Stem Cells" and "Depression" were used to search the clinical database NIH Clinical Trial. The results showed that there were a total of 4 trials on MSCs for depression interventions, mainly used in Phase I & II. Phase trials to evaluate efficacy and clinical safety (Table 1).

Table 1: Clinical trials of intervention with MSCs in depression

Ethics No. and Country	Target population	Means of intervention	Experimental phase	Objectives
NCT02675556 United States	Treatment-resistant depression (n=80)	Allogeneic MSCs, $1*10^8$ cells single i.v. infusion	Phase I, prospective, randomized, double-blind, placebo-controlled trial	An incidence of treatment-related serious adverse events and assessment of inflammation levels in the body
NCT03522545 United States	Treatment-resistant bipolar depression (n=30)	Allogeneic bone marrow- derived MSCs	Phase I, randomized, double-blind, placebo-controlled trial	Change in depression as assessed by the MADRS Scale.
NCT03265808 United States	Alcohol use disorder and major depression (n=80)	Allogeneic MSCs, $1*10^8$ cells single i.v. infusion	Phase I/II, prospective, randomized, double-blind, placebo-controlled trial	An incident of treatment emergent-serious adverse events
NCT04202770 United States	Refractory depression, anxiety disorders, neurodegenerative diseases (n=300)	Focused ultrasound and exosomes	Single group assignment	Change in depression as assessed by the Beck depression inventory.

In a clinical trial, 13 women with treatment-resistant depression received four infusions of concentrated cord blood cells at weekly intervals, with a single dose of 250 million cells. Patients' depression levels declined, they displayed a more positive attitude and more vivid facial expressions, and their average Beck questionnaire score dropped from 28.66 to 14.71. Furthermore, there was a notable improvement in their cognitive capacities, encompassing working memory, mental processing speed, verbal and visual learning, and executive function. The authors concluded that the

neurotrophins released from umbilical cord blood cells may participate in neuroimmune regulation in the central nervous system, repair damaged brain tissue, and ultimately improve depressive symptom.

Researchers also looked at the clinical effectiveness of combining MSCs transplantation with traditional depression treatment in another trial. Thirty cases each from the sixty depressed patients were randomly assigned to the observation and control groups. Conventional therapy plus the transplantation of human umbilical cord MSCs was administered to the observation group, while conventional therapy was administered to the control group. Eight weeks of treatment were given to each group. The patients were assessed both before and after the intervention using the Hamilton Depression Scale (HAMD). The serum levels of IL-1β, IL-6, TNF-α, 5-HT, NE, and BDNF were measured using ELISA. The observation group's total effective rate was significantly greater than the control group's eight weeks following transplantation. The HAMD score was significantly lower than the control groups, and the levels of serum TNF-α, IL-1β, and IL-6 were also significantly lower than the control groups, while the levels of 5-HT, NE, and BDNF were significantly greater. In both groups, the levels of 5-HT, NE, and BDNF were significantly greater after transplantation than they were before, whereas the HAMD scores and serum levels of TNF-α, IL-1β, and IL-6 were significantly lower. Following MSCs transplantation, a few individuals in the observation group experienced hot flushes, but their body temperatures remained normal. After three days, the hot flashes stopped, and no additional abnormalities were found. Nine incidents, including blurred vision, headaches, dizziness, elevated blood pressure, palpitations, appetite loss, dry mouth, nausea, and vomiting, were seen in the control group. In conclusion, the combination of traditional therapy and transplanting human umbilical cord MSCs has a positive impact on depression, offering a fresh approach to the treatment of depression. The mechanism might have to do with MSCs' ability to reduce inflammation, release more monoamine neurotransmitters, and encourage the brain's production of neurotrophins [13].

6. Barriers and Challenges in MSCs Therapy

While studies have highlighted the potential of mesenchymal stem cells (MSCs) in treating depression, there remains uncertainty regarding their precise therapeutic efficacy. Clinical trial outcomes may be influenced by various factors, including cell source, dosage, administration route, among others, necessitating further research to ascertain their therapeutic impact. MSCs can be sourced from diverse tissues such as bone marrow, adipose tissue, among others, with each source potentially yielding MSCs with distinct properties and effects. Hence, selecting the most suitable cell source is paramount for therapeutic effectiveness.

Despite MSCs generally being regarded as having a favorable safety profile, certain risks persist during clinical application. Although in vitro culture of bone marrow-derived MSCs is generally considered safe and devoid of malignant transformation risk, reports of tumor formation in humans following in vitro cultured cells have been documented. Additionally, the long-term tumorigenic risks of MSCs and their effects on the immune system remain unclear. Consequently, further research and vigilant monitoring are imperative to comprehensively understand the long-term safety profile and potential side effects of MSC-based therapies.

7. Conclusion

MSCs currently play a pivotal role in regenerative medicine. This article delves into the role and potential mechanisms of MSCs in depression treatment. Numerous studies have illustrated that MSCs offer multifaceted support for depression treatment through mechanisms such as neuroprotection, neurogenesis, immune regulation, and neurotrophic support. While most

preclinical studies have demonstrated significant improvements in emotional behavior and impaired neurological functions of depression following MSC intervention, several key issues remain unresolved before clinical application. These include determining the optimal source of MSCs, transplantation dosage and frequency, timing of transplantation, transplantation route, and monitoring and management of adverse events. With an in-depth understanding of the mechanisms underlying MSC therapy for depression and the execution of large-scale clinical trials, addressing these issues is expected to become more feasible. In the future, MSC intervention therapy is anticipated to play a crucial role in both experimental and clinical applications of depression, potentially ameliorating the high resistance rates observed with existing therapies and addressing the long-term residual symptoms experienced by many patients post-treatment.

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