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MINIREVIEWS

Is there a place for cellular therapy in depression?

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Abstract

Although efforts have been made to improve the pharmacological treatment of depression, approximately one-third of patients with depression do not respond to conventional therapy using antidepressants. Other potential non-pharmacological therapies have been studied in the last years, including the use of mesenchymal stem cell therapies to treat depression. These therapies are reviewed here since it is clinically relevant to develop innovative therapeutics to treat psychiatric patients. Experimental data corroborate that mesenchymal stem cell therapy could be considered a potential treatment for depression based on its anti-inflammatory and neurotrophic properties. However, some clinical trials involving treatment of depression with stem cells are in progress, but with no published results. These studies and other future clinical investigations will be crucial to define how much mesenchymal stem cells can effectively be used in psychiatric clinics as a strategy for supporting depression treatment.

Key Words: Mood disorders; Stem cells transplant; Mesenchymal stem-cells transplant; Inflammation; Immunomodulation; Depression

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INTRODUCTION

Depression is a highly prevalent disorder that affects the entire life span. In adults, the 12-mo prevalence of the major depressive disorder is approximately 6%[1], and the lifetime risk is 15%-18%[2]. It is one of the leading causes of disability worldwide[3]. In clinical terms, depression is a complex disorder with devastating consequences for patients and their families, provoking psychological suffering due to sadness, anxiety, anguish, and guilt; diminished cognitive performance; and impaired attention, memory, and reasoning. Moreover, depression has negative influences on decision-making and interpretation of facts, leading to wrong decisions. Depression is also a risk factor for the development and outcome of many chronic non-transmissible diseases, such as cardiovascular diseases and diabetes[4-6]. Evidence also suggests a small and positive association between depression and the overall risk of cancer, including liver and lung cancer[7].

Pharmacological treatment for depression has been available since 1957, when imipramine, a tricyclic antidepressant, and iproniazid, a monoamine oxidase inhibitor, were released[8,9]. In more than six decades, many drugs have been released commercially, improving the tolerability and safety of antidepressant treatment. However, with few exceptions, these medications' intended mechanism was to increase serotonin, noradrenaline, and dopamine availability. Although efforts have been made to improve pharmacological treatment of depression, approximately one-third of patients fail to respond to conventional antidepressants[10]. This limitation in the antidepressive efficiency is possibly related to the mechanism of action of the available antidepressants. Therefore, it is clinically relevant to develop innovative therapeutic strategies based on the pathophysiological aspects of depression.

Several lines of evidence suggest that chronic inflammatory states may be related to depression etiopathogenesis in recent years. This evidence made way for researchers to develop new anti-inflammatory therapies that could alleviate symptoms and the progression of depression[11,12]. In a previous study, our group investigated the possible use of stem cell therapy. Our hypothesis was based on the anti-inflammatory and neurodegenerative properties of stem cells, which could treat the pathogenic state that maintains depression.

Here, we performed a narrative review regarding the role of inflammation in depression and investigated the evidence suggesting that the use of stem cell therapies could be a realistic, safe, and effective strategy for treating depression.

INFLAMMATION PROVOKING DEPRESSION

A colossal research effort has been made in the last 60 years to unravel and understand the neurobiological processes underlying depression. This process started since tricyclic and monoamine-oxidase effectiveness in depression treatment was proven in 1957[13], and pharmacological drugs have been introduced in clinical practice. The attempt to identify the neurobiological processes and causes of depression started with understanding the antidepressant mechanisms of action. This strategy led to the identification of monoamines and their role in depression. Further, the development of almost all antidepressant medications was based on these discoveries.

In 1968, Carrol *et al*[14] postulated the role of the hypothalamus-hypophysis-adrenal axis (HPA axis) in depression etiopathogenesis, subsidizing the HPA axis hypothesis. The role of glucocorticoid hippocampal receptors in HPA-axis modulation in

depression has been extensively studied. Chronic stress modulates the inflammatory process that plays a crucial role in the neurobiological aspects underlying depression [15]. However, this research strategy has not led to the development of antidepressant medications.

The interest in the role of immunological and inflammatory mechanisms in depression is a natural consequence of HPA axis studies since cortisol can modulate these responses. Furthermore, consistent data on the role of psychological stress on depression development involves alterations in immune functions, mainly due to chronic inflammatory states[16,17].

The link between emotional stress, depression, and inflammation seems to involve evolutionary issues. Several lines of evidence suggest that metabolic, endocrine, and immune responses co-evolved, helping animal surveillance since animals need to actively seek food by exposing themselves to injury or predation and also need to defend themselves from pathogens[18].

In addition to triggering a fight or flight response, stress is characterized by increases in heart rate, blood pressure, cortisol, and catecholamines. It also activates inflammatory pathways in peripheral blood mononuclear cells[9]. However, when stress exposure occurs continuously without being resolved, metabolic and physiological responses are triggered that contribute to the formation of chronic inflammatory states[19]. Figure 1 shows the association between stress and neuroinflammation in depression etiopathogenesis based on several previous reviews[14,18,20].

HOW CHRONIC STRESS, THROUGH INFLAMMATION, CAN TRIGGER DEPRESSION?

Although acute stress induces an immunosuppressed state, chronic stress exposure has an antagonistic pro-inflammatory effect. As a result, the anti-inflammatory state develops to a chronic inflammatory condition due to the factors produced by exposure to chronic stress, such as catecholamines[19].

Catecholamines released by psychological stress can promote damage-associated molecular patterns (DAMPs), including high mobility group box 1 (HMGB1), ATP, and heat shock proteins. DAMPs are inflammatory signaling proteins released by different stress levels, including psychological factors[21,22]. For example, HMGB1 is a nuclear protein that is present in all cell types.

Once released, it activates through TLR4 and RAGE receptor inflammatory cascades, including the pyrin domain-containing protein 3 (NLRP3) inflammasome[20,23]. Inflammasomes are cytosolic protein complexes formed in myeloid cells, such as monocytes, in response to pathogenic microorganisms or sterile stressors, such as psychological stress. Activation of the NLRP3 inflammasome subsequently leads to caspase-1 activation, which in turn provokes cleavage of the pro-inflammatory cytokines interleukine-1β (IL-1β) and IL-18[20], and nuclear factor-κB (NF-κB) pathway activation with subsequent IL-6 release[21].

All events occurring outside the brain must change the brain physiology to trigger depression. There are three mechanisms by which inflammation in peripheral tissues reaches the brain, overcoming the blood-brain barrier (BBB). In the humoral pathway, pro-inflammatory cytokines, such as IL-1β, IL-18, IL-6, and TNFa, enter the brain through the leaky region of the BBB, such as circumventricular organs, or the binding of these cytokines to saturable transport molecules in the BBB[9]. In the neural pathway, the same cytokines bind peripheral afferent nerve fibers, such as the vagus nerve, which stimulates catecholaminergic fibers in the brain and translates into central cytokine signals. Moreover, activated immune cells, such as monocytes, reach the brain vasculature and parenchyma through trafficking mechanisms[9]. These different mechanisms act in coordination to trigger inflammation in the brain. For example, peripheral TNFa can stimulate microglia to produce CC-chemokine ligand 2 (CCL2), a chemokine that attracts monocytes to the brain[24]. Cytokines such as IL-1β and TNFa can also stimulate astrocytes to produce chemokines such as CCL2 or CXC chemokine ligand 1, thus attracting immune cells to the brain[25].

Peripheral inflammatory molecules induce astrocytes and microglia activation into the brain, triggering a complex inflammatory cascade. This cascade interferes with neurotransmission, the HPA axis, and neurotrophin balance synapses. An example of the peripheral effects on neuroinflammation is the expression of IL-1β and TNFa. These cytokines can induce the overexpression of some molecules, such as p38 mitogen-activated protein kinase, which alters the serotonin transporter, leading to a

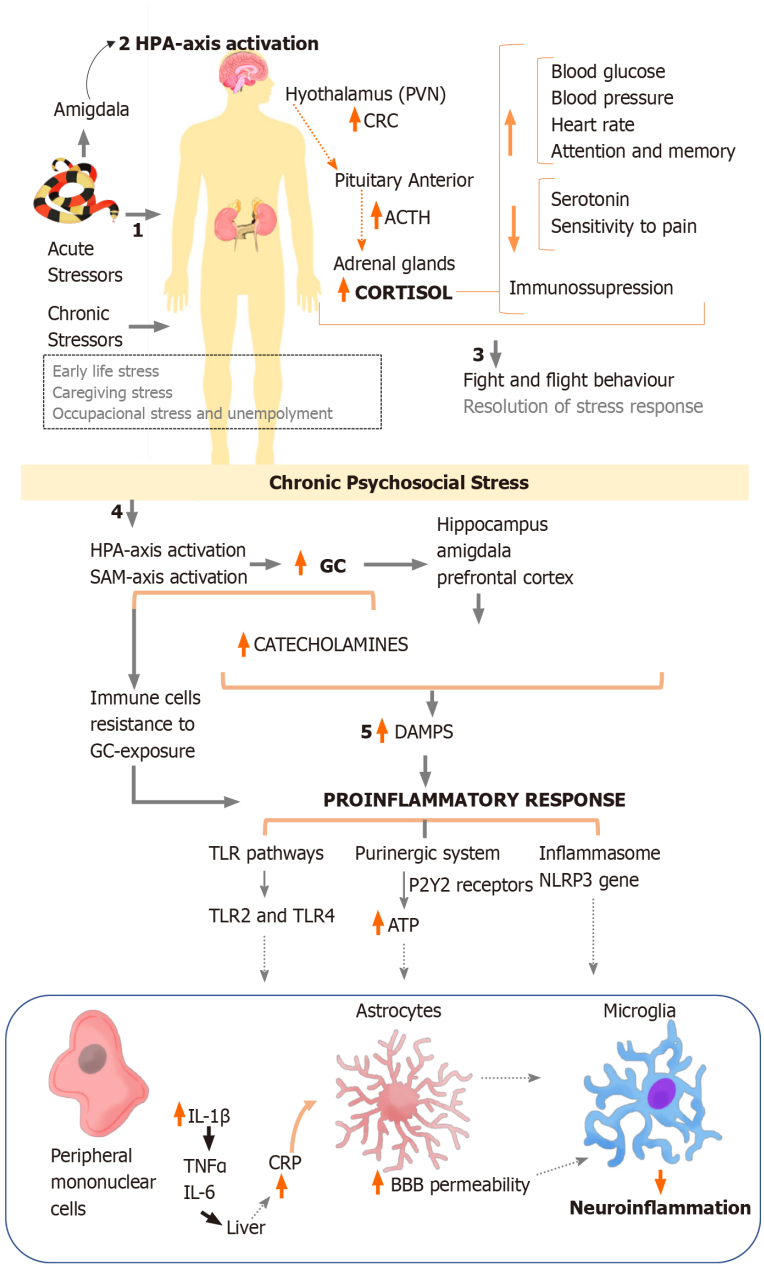

Figure 1 Synthesis of stress acute and chronic response on the inflammatory pathway. (1-2) Stressors trigger a primary neuroendocrine response from the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic Parvocellular neurons from the paraventricular nucleus secrete a corticotrophin-releasing hormone (CRH) and vasopressin. CRC induces, subsequently, the anterior hypophysis to release the adrenocorticotropic hormone, leading to a glucocorticoid secretion (cortisol in humans and corticosterone in rodents) by the adrenal cortex; (3) Acute physiological alterations prepare the human to fight or flight from stressors. These are evolutionary adaptive behaviors related to surveillance. Therefore, stress induces transient activation of HPA- axis activity paralleled by temporary increases in CRH transcription. Sympathetic-Adreno-Medullar axis is also activated in the stress response causing several physiological systemic changes. Acute stress also leads to an immunosuppressive state; (4) On the contrary, the exposure to chronic stress leads to excessive sustained elevated levels of stress hormones, including CRH and corticosterone, can be harmful and predispose to risk of several chronic non-transmissible diseases, including psychiatric disturbs; (5) And mechanisms involving an increase in neural apoptosis an in the levels of some molecules associated to stress response, especially catecholamines. These processes induce the production of immunogenic Damage-associated molecular patterns (DAMPs) molecules. (6) DAMPs can activate at least three inflammatory pathways that contribute to the increase of brain-blood barrier permeability, promoting ingress of some systemic peripheral inflammatory cells into the brain contributing to the neuroinflammatory states cause dysfunction and increase the risk of depression. HPA: Hypothalamic-pituitary-adrenal; PVN: Paraventricular nucleus; CRH: Corticotrophin-releasing hormone; VP: Vasopressin; ACTH: Adrenocorticotropic hormone; GC: Glucocorticoid; SAM: Sympathetic-Adreno-Medullar; DAMPs: Damage-associated molecular patterns; BBB: Brain-blood barrier.

decrease in the availability of serotonin in the synaptic cleft[9].

IL-6, another pro-inflammatory cytokine, contributes to the generation of high levels of reactive oxygen and nitrogen species, which cause oxidative stress. This reaction decreases tetrahydrobiopterin (BH4) availability, a cofactor enzyme in monoamine synthesis, diminishing serotonin, noradrenaline, and dopamine availability. The cytokines, particularly IL-1β and TNFa molecules, alter the kynurenine pathway by

increasing quinolinic acid levels (QA). The elevation of QA levels occurs by the activity of the indoleamine 2,3-dioxygenase enzyme, which catalyzes tryptophan into kynurenine. As QA synthesis involves tryptophan, depletion of this amino acid directly affects serotonin production. Furthermore, QA has a dangerous effect on the brain by increasing oxidative stress, astrocyte degeneration, and neuronal apoptosis. Therefore, inflammatory activation generates metabolic alterations that can contribute to the risk of depression and suicide[9,16,26-28].

QA and cytokines also have a critical synergistic effect on glutamate metabolism. QA directly stimulates N-methyl-D-aspartate receptors (NMDA), decreasing glutamate re-uptake and stimulating glutamate release by astrocytes[9]. In astrocytes, pro-inflammatory cytokines decrease the expression of glutamate re-uptake pumps, increasing glutamate release. This combined action triggers high glutamate levels inside and outside the synapses, allowing the activation of extra-synaptic NMDA receptors. Alterations in the glutamatergic pathway induce a decrease in molecules with neurogenic functions, particularly brain-derived neurotrophic factor (BDNF)[9,29,30]. It should be noted that conventional antidepressant medication acts by increasing monoamine availability in the synapse, thereby increasing BDNF and consequently promoting neurogenesis through BDNF action on its receptor TrkB[31,32].

The effect of neuroinflammation has an impact on neurocircuit function. Inflammation has been associated with a decrease in responsiveness to reward stimuli, particularly in the ventral striatum. For example, in healthy volunteers, the administration of low doses of endotoxin, which can increase pro-inflammatory cytokine levels more safely, is associated with the development of depressive mood. This effect was related to the diminished activity of the ventral striatum to the anticipated reward measured by functional magnetic resonance imaging (fMRI)[33]. Interferon-a administration to treat chronic hepatitis virus C infection-induced depression, anhedonia, and fatigue. This administration reduced ventral striatum activation with reward-anticipatory stimuli during fMRI. In the same study, positron emission tomography demonstrated an association between the behavior and fMRI results with 18F-dopa turnover in the ventral striatum; changing presynaptic dopamine function was consistent with decreased dopamine synthesis or release[34]. Evidence also described that typhoid immunization could produce inflammation by IL-6 augmentation and activation of the subgenual anterior cingulate cortex (sgACC), a region implicated in depression and depressive symptoms. Moreover, the elevation in IL-6 concentrations decreases the connectivity between the sgACC and amygdala, medial prefrontal cortex, superior temporal sulcus, and ventral striatum[35].

Many of these brain changes induced by peripheral inflammation and neuroinflammation have been described in experimental and epidemiological studies that involve chronic exposure to social stress. Exposure to social stress can increase soluble TNFa receptors and IL-6 molecules. The elevation of soluble TNFa receptor can increase the dorsal ACC and anterior insula activity, two brain regions that process rejection-related distress and negative affect[36,37]. Experimental protocols where stress was induced in the laboratory conditions described the increased feelings of social and rejection behaviors associated with inflammatory activation by increasing IL-6 Levels and high left amygdala activity, a brain area directly related to detection and response threats[38].

Child abuse is one of the main risk factors for chronic stress and inflammation in the etiopathogenesis of depression. Early adversity is considered a risk factor for developing depression, and emotional abuse shows the strongest association, followed by neglect[39]. A growing body of literature showed that early adversity could shape immune cells and inflammatory cascades. A meta-analysis performed by Baumeister *et al*[40] showed that adult individuals exposed to childhood trauma had elevated baseline blood levels of C-reactive protein, IL-6, and TNFa.

Therefore, the pieces of evidence commented here can support the hypothesis that depression is an inflammatory disease. A meta-analysis showed higher peripheral levels of IL-6, TNFa, IL-10, IL-12, IL-13, IL-18, CCL2, IL-1b receptor antagonist, soluble IL-2 receptor, and soluble TNF receptor 2 in depressive patients. In comparison, the INFγ blood levels were lower in these individuals. Moreover, the concentrations of IL-1b, IL-2, IL-4, IL-8, IL-5, CCL3, IL-17, the soluble IL-6 receptor, and the transforming growth factor-beta one did not present differences associated with depression[41].

ANTIDEPRESSANTS AND ANTI-INFLAMMATORY DRUGS ON DEPRESSION

As inflammation could trigger depression, the logical question is that anti-inflammatory drugs could positively affect depression. A recent meta-analysis on this issue included studies involving the impact of anti-depressive drugs on different pro and anti-inflammatory cytokines (IL-1b, IL-2, IL-4, IL5, IL-6, IL-8, IL-10, IL-12, TNFa, INFy, and others)[42]. Moreover, the meta-analysis found that antidepressant responders had lower levels of IL-8 than non-responders. Antidepressant treatment only decreased TNFa levels, IL-5, and granulocyte-macrophage colony-stimulating factor in responsive patients. However, when treatment-resistant patients were compared to non-depressed controls, IL-6, IL-8, TNFa, C-reactive protein (CRP), and macrophage inflammatory protein-1 were associated with poor treatment outcomes[43].

Furthermore, it has been tested for its potential anti-inflammatory use in the attenuation of depressive symptoms. A meta-analysis of randomized controlled trials showed an antidepressant effect of anti-cytokine drugs[44]. The anti-TNFa adalimumab and etanercept, except infliximab, showed an antidepressant effect. Previous studies have also described some antidepressant effects of dupilumab, an antagonist drug of the alpha subunit of the IL-4 receptor, and ustekinumab, which inactivates IL-12 and IL-23 cytokines[45]. Randomized controlled clinical trials have described the anti-depressive effect of some anti-inflammatory drugs such as (1) Glycyrrhizic acid, an HMGB1 inhibitor, was useful as an add-on with selective serotonin re-uptake inhibitor in the treatment[45]; (2) Minocycline, a tetracycline antibiotic, that lowers neuroinflammation by inhibiting microglial activation and inhibiting the release of HMGB1[46]. However, minocycline was effective only in patients with baseline levels of CRP > 2.8 mg/L[47]; and (3) Although bipolar disorder (BD) is not in the scope of this review, a clinical trial stands out here describing that coadministration of N-acetylcysteine and aspirin for 16 wk was associated with a reduction in depressive symptoms in BD-patients[48].

Despite the evidence suggesting that anti-inflammatory drugs could help treat depression, further investigations are needed to evaluate the safety of prolonged periods of anti-inflammatory co-treatments in patients with depression[49]. In this context, the search for non-pharmacological anti-inflammatory therapeutic strategies is of great interest to the psychiatric clinic, as in the case of stem cell treatments, which have been applied in other clinical areas, has been intensively investigated for more than 10 years[50,51].

CLINICAL USE OF ADULT STEM CELLS

Stem cells are defined as adult unspecialized cells with self-renewal ability and high regenerative potential[52,53]. Adult stem cells can differentiate into several cell lines and activate or inhibit a sequence of molecules involved in anti-inflammatory and anti-apoptotic pathways[52,53]. Mesenchymal stem cells (MSCs) were first detected in the bone marrow. However, they can also be isolated from the umbilical cord tissue and adipose tissue, among other sources[52-57].

Stem cells were first described in the middle of the 20th century in mouse models [58,59], and stem cell transplantation was first applied in humans in 1957[60,61]. In the following decades, bone marrow stem cells-transplants have saved the lives of patients suffering from a great variety of diseases, mainly conditions affecting the hematopoietic or immunological system. Due to relatively low MSC-immunogenicity, the transplantation of these cells presents a low risk of tumorigenicity and less complicated ethical/regulatory issues compared to embryonic pluripotent stem cells [57,62].

Studies of therapeutic MSCs applications have expanded, showing that both allogeneic and autologous transplantation is possible due to the low immunogenicity of these cells and immunomodulatory effects[63]. These studies, including experimental investigations performed in several animal models of inflammatory and autoimmune-mediated disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and myasthenia gravis[64-66] and other conditions associated with inflammatory disturbances such as sepsis[67], lung fibrosis[68], diabetes[69], atherosclerosis [70], and osteoarthritis[71].

STEM CELLS-BASED THERAPIES FOR NEUROINFLAMMATORY DISORDERS

Stem cell therapies have emerged as a standard for the treatment of both subacute and chronic inflammatory processes and neurological disorders. Investigations have suggested the potential use of adult stem cells therapy to treat several neurological conditions, such as multiple sclerosis[72], autoimmune encephalomyelitis[73], Alzheimer's disease, and other dementia conditions[74], Parkinson's disease[75], and epilepsy[76]. Most studies emphasize the immunomodulatory nature of adult stem cells, with its therapeutic efficiency related to neurological diseases, particularly triggering anti-inflammatory states.

For example, in epilepsy, seizure activity can induce pro-inflammatory molecules, therefore affecting the severity and frequency of seizures[77]. Transplantation of bone marrow mononuclear cells (BMMCs) or human umbilical cord blood mononuclear cells in experimental epilepsy models induced significant improvements in neurological function[78,79]. After a seizure, brain injury induces a highly regulated cascade of biological events, characterized by the release of cytokines, chemokines, and protectins in the neuronal microenvironment[80,81], which was attenuated by adult stem cell transplantation, decreased the inflammatory states, and promoted tissue repair through cell-cell interactions and paracrine effects[80-83]. Furthermore, some evidence showed that adult stem cells stimulate angiogenesis and endothelial repair through paracrine actions[82,83]. In Alzheimer's disease, MSCs have been shown to reduce IL-1, IL-2, TNFa, and IFN-γ in the serum and oxidative stress, which showed an anti-inflammatory effect[84].

Among the most relevant stem cells' action mechanisms is the release of extracellular vesicles carrying soluble factors, microRNAs, and organelles[85]. Initially, the release of extracellular vesicles was thought to represent a disposal mechanism by which cells eliminate unwanted proteins and other molecules. Among the extracellular vesicle subtypes, significant attention has been given to exosomes. Exosomes are small membrane vesicles with a diameter between 40 and 100 nm[86], and different biological molecules, including proteins, lipids, and nucleic acids that may be captured and act in a biologically active manner on recipient cells. Various studies have described the beneficial actions of MSCs by delivering exosomes instead of cells[87, 88]. Therefore, MSC cells or exosome transplantation could offer an efficient and safe non-pharmacological therapy to treat neurological conditions.

POTENTIAL USE OF BMMCS AND MSCS IN DEPRESSION: EVIDENCE FROM PRECLINICAL STUDIES IN EXPERIMENTAL MODELS

The optimistic results obtained from experimental studies involving BMMCs and MSCs in the therapy of neurological conditions open the perspective of developing non-pharmacological cell treatments for psychiatric disorders. The main results of these studies are presented in Table 1. The potential therapeutic effects of adult cells-based therapies have been well characterized across *in vivo* studies of depression models, including an investigation performed by our research team[89]. This study evaluated the effect of BMMCs transplantation on the restoration of sucrose preference in rats subjected to chronic stress. This well-established model triggers depressive symptoms in animals. The study also evaluated the potential inflammatory modulation of BMMCs in stressed rats. The levels of pro-and anti-inflammatory cytokines in different brain areas, blood, and spleen were also quantified. In this protocol, escitalopram was used as a positive antidepressant control. The results demonstrated that BMMCs transplantation in stressed rats: (1) Restored spontaneous sucrose consumption in stressed rats; (2) Had a robust anti-inflammatory effect, increasing the levels of the anti-inflammatory cytokine IL-10 in the amygdala, hippocampus, frontal cortex, other brain areas, and in the spleen and blood; a lowering effect on pro-inflammatory cytokine levels (IL-1 β, IL-6, TNFa, and INF-γ) was also detected in the same brain and peripheral tissues; and (3) Decreased levels of oxidized DNA quantified by 8'2-deoxyguanosine. In summary, the therapeutic use of BMMCs presented a positive impact on symptoms of depressed rats, and possible mechanisms involved in this effect include immunomodulation of inflammatory states in both the peripheral and central nervous systems.

Another recent study performed by Huang *et al*[90] team verified the results involving potential therapeutic MSC-transplantation in depression by anti-inflam-

Table 1 Concise information of some studies on the effects of administration of mesenchymal stem cells with different sources and exosomes

Ref.	Type and characteristics of animal model used	Timing of intervention with cells after insult	Type of cells infused and route of administration	Major finding
do Prado-Lima *et al*[89], 2019	Wistar rats; depression, induced with CMS	30th day of the CMS protocol	BMMCs from mice. Single-dose (1 × 10^{7} cells). i.v.	Anti-inflammatory effects; Reduction of pro-inflammatory cytokines; increased expression of anti-inflammatory cytokines; BMMCs decreased 8'2-deoxyguanosine level
Huang *et al*[90], 2020	C57BL/6 mice; depression-induced with CMS	21th day of the CMS protocol	ADSCs from C57BL/6 mice; Repeated i.v. (3 times) 1 × 10^{6} cells/dose	ADSC treatment improved depressive-like behaviors. Reduced the expression of inflammatory factors in the serum Reduced microglial activation in the hippocampus
Kin *et al* [91], 2020	Wistar Kyoto rats model of treatment-resistant depression	Day zero	MSCs from the bone marrow of Wistar rats. Single-dose 3 × 10^{5} cells/5 µl i.v.	MSCs encapsulation enhanced the treatment effects of MSCs in an animal model of treatment-resistant depression
Li *et al* [92], 2020	Mice model depression induced by CUMS	14th to the 42nd day CUMS protocol	MSCs lines from human umbilical cords (hUC-MSCs); Repeated (4 times) 1 × 10^{6}/ dose i.v.	The hUC-MSCs treatment improved the anxiety-like behaviors of CUMS, decreased pro-inflammatory factor levels, and increased anti-inflammatory factor levels. The hUC-MSCs inhibit microglial M1 polarization and the level of inflammation factors. The hUC-MSCs can alter the polarization of microglia by inhibiting C3a-C3aR signaling from reducing neuroinflammation. The hUC-MSCsdecreased neuronal damage and synaptic deficits
Guo *et al* [93], 2020	Sprague Dawley rats; Depression model by corticosterone injection	Day zero	BMSCs-derived exosomes 1 mL exosomes (100 µg/ 1 mL PBS) i.v.	BMSCs-derived exosomes improved hippocampal neuron injury of rats with depression by upregulating miR-26a
Li *et al* [94], 2020	Male BALB/c mice depression, induced by CS	After 30 days of the CMS protocol	Exosomes from NK cells one time. Exosomes 66.42 µg i.v.	The exosomes miRNA-containing from NK cells could alleviate symptoms of chronic mild stress in mice. miRNA decreased the levels of pro-inflammatory cytokines (I L-1β, IL-6, and TNFα) released by astrocytes in vivo; Exosomes with low miR-207 levels showed decreased antidepressant activity in vivo experiments. Exosomes with low miR-207 levels showed decreased antidepressant activity MiR-207 could reduce the release of pro-inflammatory cytokines in vitro

BMMCs: Bone marrow mononuclear cells; ADSCs: Adipose-derived mesenchymal stem cells; CMS: Chronic mild stress; CS: Chronic stress; BDNF: Brain-derived neurotrophic factor; TrkB: Tyrosine receptor kinase B; BV2: Microglial cells; eMSC: Capsules with MSCs; hUC-MSCs: Human umbilical cord mesenchymal stem cells; CUMS: Chronic unpredictable mild stress model; miR-26a: MicroRNA-26a; SOD: Superoxide dismutase; MDA: Malondialdehyde; LDH: Lactate dehydrogenase; TNFα: Tumor necrosis factor α; IL-1β: Interleukin-1β; NK: Natural killer cells; i.v.: Intravenously injected.

matory action. The experimental protocol used adipose-derived mesenchymal stem cells (ADSCs) injected into C57BL/6 mice on the 21st day of a protocol of 42 d of chronic mild stress (CMS). The animals were tested by three behavioral assays: sucrose preference, tail suspension, and forced swimming test. All tests are broadly recognized as behavioral assays to identify depressive and anti-depressive chemical and behavioral factors. ADSC transplantation remedied depressive-like behaviors. The authors also observed that ADSC treatment reversed and prevented the increase in the production of some pro-inflammatory cytokines (CCL2, TNFa, IL-1β, and IL-6) in the serum and promoted the expression of BDNF and its receptor TrkB in the brain tissue. ADSC treatment increased the nuclear factor-E2 related factor 2 (Nrf2), which in turn has an anti-inflammatory effect by inhibiting TLR4/NF-κB pathway activation. Immunofluorescence detection revealed that the number of ionized calcium-binding adaptor molecule 1 (Iba1+), a protein expressed only in microglia and involved in its activation, decreased after ADSC treatment. In the same study, Nrf2-modified ADSCs were co-cultured with microglia cells and then exposed to lipopolysaccharide (LPS). Nrf2 downregulation decreased the protective effects of ADSCs against LPS-induced microglial activation and M1 polarization; however, Nrf2 overexpression markedly suppressed LPS-induced TLR4/NF-κB expression in microglial cells[90].

Kin *et al*[91] implanted the encapsulated MSCs (eMSCs) into the lateral ventricle and observed antidepressant effects *via* neurogenic pathways in Wistar Kyoto rats. These rats exhibited congenitally higher depression-like behaviors and resistance to conventional antidepressant treatments. Therefore, Kyoto rats are considered a promising model for treatment-resistant depression. The implantation of eMSCs counteracted

depressive-like behavior on days 13 to 15 after implantation and enhanced endogenous neurogenesis in the subventricular zone and the dentate gyrus of the hippocampus. The eMSCs displayed a robust and stable secretion of vascular endothelial growth factor, BDNF, fibroblast growth factor 2, and ciliary neurotrophic factor. Implantation of eMSCs into the lateral ventricle activated relevant pathways associated with these growth factors.

Li *et al*[92] described the therapeutic action of human umbilical cord MSCs (hUC-MSCs) on chronic middle stress in mice. The animals were induced with hUC-MSCs once a week for four weeks for 42 d. The hUC-MSCs treatment induced downregulation of some pro-inflammatory genes (GFAP, Iba1, Il-1, TNF, IL-1b, and TNFa). Moreover, the treatment also downregulated IL-10, transforming growth factor-β and AMPA gene expression. The authors reported a modulation in the microglia M1/M2 polarization balance and a decrease in neuroinflammation involving complement C3 molecules, specifically in the C3a-C3aR pathway.

Therapy efficacy using BMMCs-derived exosomes in rats with depression induced by corticosterone treatment was performed by Guo *et al*[93]. The exosome therapy upregulated miR-26a microRNA, increased hippocampal tissue proliferation, and suppressed apoptosis in depressive-like rats. Treatment decreased oxidative stress and inflammation by inducing high superoxide dismutase antioxidant enzyme levels and decreasing lipoperoxidation, TNFa, and IL-1β levels in both serum and hippocampus.

Another study administered natural killer (NK)-cell-derived exosomes carrying miR-207, capable of inhibiting the NF-κB signaling pathway in astrocytes. This exosome treatment was effective in diminishing depressive symptoms in mice submitted to CMS and decreased the levels of IL-1b, IL-6, and TNFa released by astrocytes. The critical element of the exosome effect was the presence of the miR-207 molecule. When NK-cells were transfected with miR-207 inhibitor and exosomes were produced by and injected in astrocytes, the impact on IL-1b, IL-6, and TNFa levels was no longer observed[94].

CLINICAL TRIALS IN DEPRESSIVE PATIENTS

The results from different experimental studies strongly support the potential therapeutic use of stem cells in treating depression. However, while data from experimental models have shown beneficial effects in depression, gaps remain to be explored. Further studies are needed to clarify whether any MSCs type could be as effective and safe as an antidepressant therapy. For example, MSCs from the bone marrow have the best potential to treat depression, considering the significant data regarding them. However, ethical problems are to be considered when it comes to autologous transplants that require surgical intervention to obtain these cells. Moreover, allogeneic cell transplantation could be an acceptable clinical strategy. However, further studies are needed to assess the safety of using these cells from donors with a different genetic background than the patient.

In addition, further studies are needed to establish the optimal dose, administration route, and fundamental mechanisms of action. The translation ability of such experimental models to the target human population, possibly composed of refractory and polypharmacy patients, merits further discussion. For instance, previous efforts with several compounds that passed through animal studies with promising results have failed in clinical trials, partially due to the poor validity of such models to represent the target patient population[95].

Due to these gaps, the first clinical trials involving cell-based products or exosomes to treat depression have been registered to international platforms. At Clintrial.gov, the keywords "depression," "depressive disorder," and "cell therapy" were used to perform the search. This research led us to find four registered clinical studies involving the use of MSCs as a treatment for patients with depression. Currently, four clinical studies (phases 1 and 2) are under evaluation for the safety, efficacy, and tolerability of the administration of MSCs and exosomes (Table 2). However, most of the results are not yet available, as these studies are still in the patient recruitment phase. Therefore, the results are anticipated to be published from these trials soon.

CONCLUSION

Cell therapy, through BMMCs or MSCs transplantation or the administration of cell products such as exosomes, may have a place in treatment-resistant depression. The

Table 2 List of registered cell-based clinical trials for treating depression

Study	Country	Target population	Product	Study design	Outcomes
NCT02675556	United States	Treatment-resistant depression; (n = 80)	Allogeneic MSCs; 10^8 cells single i.v. infusion; source not reported	Phase I, placebo-controlled 1:1	Incidence of any treatment-emergent serious adverse events; Reduction of Inflammation.
NCT03522545	United States	Treatment-resistant bipolar depression; (n = 30)	Allogeneic bone marrow-derived MSCs; dose not reported	Phase I, placebo-controlled	Change in depression as assessed by the MADRS Scale.
NCT03265808	United States	Alcohol use disorder and major depression; (n = 80)	Allogeneic MSCs; 10^8 cells single i.v. infusion; source not reported	Phase I/II	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	Beck depression inventory (BDI-II)

MSCs: Mesenchymal stem cells.

number of preclinical studies is still limited; therefore, further development of clinical trials is encouraged.

As technology and knowledge involving all aspects of cells or cell-based products develop, the easier it is to identify the best alternative (cells or exosomes) to try as an antidepressant treatment, the lower the costs and the more established the routines. A significant development should be expected to understand its potential and possible side effects better.

Despite the limited number of preclinical studies, many issues have not been identified, such as how long the antidepressant effect persists. It is a critical question that has consequences for the feasibility of these procedures as treatment. Because of the challenge that represents the treatment of resistant depression, the possibility of an effective treatment in this chronic, severe, and prevalent condition must be explored.

For this, a more significant number of clinical studies are needed to evaluate several open questions considering the variability of the effectiveness of the use of stem cells in the treatment of depression.

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