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Mesenchymal Stem Cell-Derived Secretome-Based Therapy for Neurological Disorders: A Scoping Review

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Abstract

Stem cells are the foundation of cellular therapy. They are multipotent cells capable of self-renewing and differentiating into several cell lineages. They are being investigated and used for the treatment of a wide range of diseases. There are various stem cell types and sources, with mesenchymal stem cells standing out as one noteworthy example. With neurological disorders being a major cause of deaths and disabilities worldwide, ongoing studies are investigating the therapeutic potential of mesenchymal stem cells for treating neuropathies. This review comprehensively outlines various neurological diseases and explores the therapeutic potential of mesenchymal stem cells in ischemic stroke, multiple sclerosis, ALS, Alzheimer's, hypoxia, and glioblastoma. However, there are challenges and limitations in mesenchymal stem cell-based therapies, including concerns about immunocompatibility, maintenance of stemness and differentiation stability, and the potential risk of tumor formation.

Keywords

Neurological Disorders, Mesenchymal Stem Cells, Exosomes, Extracellular

Vesicles, Stem Cell Therapy

1. Background

1.1. Neurological Disorders

Neurological disorders such as multiple sclerosis, Epilepsy and neuromuscular disorders are a wide variety of problems affecting the organization, operation and communication in the nervous system, including both the central nervous system (CNS) and the peripheral nervous system (PNS) [1] [2] such as seizures and abnormal movements [3]. Infections, immune system deregulations, environmental factors, genetic predispositions, or a combination of these factors may cause these disorders [4]. The quality of life can be significantly affected by neurological illnesses since they frequently cause severe sensory, motor, cognitive, and behavioral deficits [2]. Early diagnosis and intervention are crucial for managing symptoms and improving outcomes. The treatment of neurological disorders typically involves a multi-faceted approach, including pharmacological therapies, physical and cognitive rehabilitation, surgical interventions, and lifestyle [5] [6]. While current treatment options can significantly alleviate symptoms and improve functionality, many neurological disorders, especially neurodegenerative diseases like Alzheimer's or amyotrophic lateral sclerosis (ALS), still lack definitive cures. Advances in stem cell research hold promise for more effective management in the future.

1.2. Mesenchymal Stem Cells (MSCs)

Mesenchymal stromal/stem cells (MSCs) are a subset of adult stem cells that have the capacity to differentiate into various cell types and undergo extensive self-renewal via multiple cell divisions [7] [8], and the ability to exert anti-inflammatory and immunosuppressive effects through interactions with a range of immune cells [9], making them a powerful tool in treating different pathologies. MSCs have the capacity to adhere to plastic in cell cultures [10], adopting a fibroblastic morphology that facilitates their expansion and manipulation *in vitro* [11]. Furthermore, MSCs express markers such as CD73, CD90, CD105 [6] and they lack the expression of hematopoietic stem cell markers such as CD14, CD34, CD45, and HLA-DR [11]. This unique profile aligns with their potential to differentiate along various lineages, including chondrogenic, osteogenic and adipogenic pathways when cultured under appropriate conditions [11]. Moreover, MSCs have the ability to express a collection of other markers such as α-actin (indicating their potential to contribute to smooth muscle development [11], nestin (Tuj-1), and myosin (muscle cell differentiation) [8] [9]. MSCs also have the potential to express key factors like the transforming growth factor-β (TGF-beta) receptor and integrins, which play pivotal roles in mediating cellular responses to their microenvironment [11] [12]. Recent studies highlighted the paracrine effects of MSCs, particularly the

bioactive molecules secreted collectively named "Secretome" [13]. Secretome is rich in bioactive substances, such as growth factors, cytokines, and microRNA that have been characterized for their neuro-regenerative, neuro-protective, and immunomodulatory attributes [12] [14]. Such properties underpin the rationale for considering MSCs as potential therapeutic agents in the area of neurological disorders, where their mechanisms of action offer potential avenues for ameliorating neurodegenerative processes and fostering neural tissue repair [1] [13]. The capacity of MSCs to mediate cell repair within the central nervous system (CNS) is essential for the possibility of applying MSC-based therapies in neurological disorders [12]. This involves the ability of MSCs to migrate toward sites of tissue damage, where they can subsequently differentiate into diverse cell lineages, thereby contributing to tissue regeneration and repair [9]. This immunomodulatory role involves the secretion of factors that can both suppress and stimulate immune processes, presenting a finely tuned system that can influence autophagy and affect neuromuscular function [4] [12]. In the context of neurological disorders, these immunomodulatory attributes may play a pivotal role in mitigating inflammation-driven neuronal damage [11] [15]. The efficacy of MSCs in therapeutic contexts is underscored by their abundant availability, as they can be obtained from diverse sources, including fat, bone marrow, cord blood, muscle tissue, and the placenta [11]. The ease of isolation from adipose tissue via lipoaspiration or abdominoplasty has positioned ADMSCs as particularly practical candidates for various therapeutic applications [14]. The differentiation processes of MSCs have various distinct pathways that are divided into three types: ectodermal, mesodermal, and endodermal [11]. Ectodermal differentiation into the neurogenic line involves the Notch-1 pathway as well as protein kinase A (PKA) pathway. Substances used to induce differentiation include hydrocortisone, dimethyl sulfoxide (DMSO), butylated hydroxyanisole (BHA), and potassium chloride (KCl), as well as basic fibroblast growth factor (bFGF), neurotrophin-3 (NT-3), β-mercaptoethanol (β-ME), brain-derived neurotrophic factors (BDNF), and nerve growth factor (NGF) [11] [12]. Meanwhile, differentiation to mesodermal, which includes the osteogenic, chondrogenic, and adipogenic linages, is done through pathways concerning TGF-β, PPAR-γ, Smad3, and SOX9 [11]. Osteogenic differentiation is stimulated with dexamethasone (Dex), β-glycerophosphate (β-GP), and ascorbic acid phosphate (aP) [8]. Furthermore, alkaline activity and the accumulation of calcium are analyzed to conform the process [8]. TGF-β2 and TGF-β1 are used for chondrogenesis, and finally dexamethasone (Dex), 3-isobutyl-1-methylxanthine (IBMX), and indomethacin and methylisobutylxanthine (IM) are used for Adipogenesis [8]. Finally, endodermal differentiation is achieved through signaling pathways involving TGF-β, fibroblast growth factor (FGF), and bone morphogenetic protein (BMP). Apart from the secretome, MSCs are recognized for paracrine factors such as exosomes and extracellular vesicles (EVs). EVs are small vesicles [16], containing a phospholipid bilayer that has a wide variety of proteins, DNA, mRNA, and miRNA molecules [17]. EVs are released after merging with the plasma membrane of a multivesicular

endosome.

2. Therapeutic Potential of MSC

MSC can be used in diabetic pathologies such as: diabetic cardiomyopathy (DCM), diabetic neuropathy (DN), diabetic wounds, diabetic retinopathy (DR), and diabetic foot [13]. DCM is caused by extended hyperglycemia resulting in ventricular dysfunction [1]; studies showed that MSCs using their growth factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1) and hepatocyte growth factor (HGF) could promote angiogenesis and myogenesis, thus assisting in regeneration of vascular tissue [18] [19]. DN is characterized by the excess supply of glucose to the nephron in the kidneys, resulting in angiopathy of capillaries and blood vessels, which supply the glomeruli and release protein into urine [15] [20]. It is also characterized by neuron damage, decreased sensation, hyperalgesia, and lowered blood supply to the nerves [18] [21]. Studies have shown that DN MSCs lead to the re-establishment of muscles and blood capillaries by the production of FGF and VEGF [22], improvement in hyperalgesia, and better functioning of nerve fiber while also delaying the nerve conduction velocity [23]. In the case of DR, the MSCs promoted regeneration of retinal tissue by differentiating into neurons, photoreceptors, glial cells, and retinal pigment cells [15]. In addition, they improved the blood-retinal barrier and photoreceptor cells in the retina. Furthermore, Diabetes mellitus (DM) causes delayed wound healing and tissue necrosis due to a lack of growth factors, angiogenic factors, and unstable collagen matrix formation [15] [18]. The wound undergoes severe pathogenesis, necrotic tissue entrapment, and reduced function. Transplanting MSCs by circulation improves collagen production, strength, and integrity, leading to wound healing. Salidroside-pretreated MSCs promote paracrine function and neoangiogenesis, reducing hyperglycemia-induced reactive oxygen species generation [7] [23]. MSCs, with their immunomodulatory and immunosuppressive properties, promote the formation of regulatory T-cells (Treg) and support β-cells survival [12]. They release IL-6, which inhibits monocyte differentiation to dendritic cells (DCs) and delay apoptosis. MSCs suppress T-cell proliferation and cytotoxicity [9]. Furthermore, CB-MSCs have been reported to restore Th1/Th2 cytokine balance, promote Treg proliferation, and induce apoptosis in pancreatic islets [18]. Rheumatoid arthritis (RA) is a chronic autoimmune condition that targets the connective tissues and joints, causing chronic inflammation, pain, stiffness, and loss of mobility [24] [25]. MSC-based therapy is reported to provide comfort to patients who did not respond to standard-of-care drug-based treatments [21]. The collagen-induced arthritis (CIA) model in DBA/1 mice and Brown-Norway rats is an authenticated study for studying disease resolution with drugs and MSCs [26] [27]. Stem cells injected intravenously or parenterally migrate into inflamed arthritic tissues, reducing pathogenic cytokines and disease severity scores [18]. The CIA shares similarities with RA, such as Th1 and Th17 cell involvement and autoantibodies, thus can be considered to represent systemic immune responses

in human RA [14] [15]. As a matter of fact, Augello *et al.* injected allogeneic bone-marrow MSCs intraperitoneally in DBA/1 mice, showing significant reductions in inflammatory cytokines, Tregs, and disease severity [28]. Similarly, Lui *et al.* reviewed a single intravenous infusion of human umbilical cord MSCs (hUC-MSCs) on CIA in DBA/1 mice. Their research revealed an association between decreased proinflammatory cytokines and alleviation of RA symptoms [29]. In another study, Shandil *et al.* also injected human adipose-derived MSCs (hA-MSCs) intravenously in a mouse model of CIA, causing inhibition of inflammatory mediators and decreased Th1/Th17 cell expansion and induced the production of the anti-inflammatory cytokine IL-10 [4] [24]. Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread tissue inflammation and organ damage [30]. MSCs have proved the ability to regulate the immune system and control inflammation by inhibiting the activation of NF-κB, JACK/STAT, and Akt/GSK3β signaling pathways to replenish SLE lesions [14]. In fact, MSCs apply immunosuppressive effects through proinflammatory cytokine secretion and inhibition of lymphocyte activation and proliferation [24]. SLE is associated with the activation and proliferation of auto reactive B-cells and other T-cells' subtypes [31]. Additionally, the deficiency in anti-inflammatory subsets (Treg, Th2) and proinflammatory subsets (Th17, Th1) represent the crucial elements in SLE's pathogenesis. These factors lead to tissue inflammation, immune dysfunction and multiorgan failure [24] [32]. In this context, the most adapted animal model used is the Fas mutated MRL/lpr and NZB/W F1 mice which develop lupus-like symptoms similar to humans and are used to study the mechanism of MSC therapy [33]. Jang *et al.* studied the effect of human bone marrow-derived MSCs (hBM-MSCs) on female NZB/W mice, and found a reduction in autoantibodies, follicular T helper (Tfh) cells, proteinuria and humoral immune components [34]. According to a subsequent study by Lee *et al.*, umbilical cord MSCs (hUMSCs) used in the setting of NZB/W F1 mice reduced levels of proinflammatory (TNF-, IL-6, and IL-12) cytokines and inhibited the pathogenic and inflammatory immune response associated with SLE [35]. Furthermore, it seemed to postpone the onset of lupus autoimmunity [30]. Additionally, a study by Admou *et al.* showed that levels of the Anti-double-stranded deoxyribonucleic acid antibodies anti-dsDNA antibodies that are specific markers of systemic lupus erythematosus (SLE) [36], the NF-κB signaling pathway, the expression of TNF-alpha, ICAM-1, and plasminogen activator inhibitor-1 (PAI-1), and proteinuria were reduced after xenogeneic transplantation of human placenta-derived MSCs (hP-MSCs) into MRL/lpr mice [24]. Similar findings were reported by Zang *et al.*, who found that intravenous injection of hBM-MSC in MRL/lpr mice decreased proteinuria, T-cells proliferation, and serum levels of anti-dsDNA antibodies [21]. These investigations concluded that MSCs had an immunoregulatory influence on T-cell populations [21]. In addition, Zang *et al.* showed that injection of allogeneic BM-MSCs to MRL/lpr mice decreased B-cell maturation and differentiation in mice [21].

3. Therapeutic Potential of MSC-Derived Exosomes

MSC-derived exosomes retain the therapeutic effects of MSC. These exosomes bear exosome-associated plasma membranes composed of lipids such as hexosylceramides, cholesterol, phosphatidylserine, sphingomyelin, and saturated fatty acids, coupled with proteins serving diverse roles [7] [12]. These encompass fusion proteins (e.g. ESCRT complex, ALIX, TSG101, and syntenin), membrane transporter proteins (Rab GTPases and annexins) [35], as well as evolutionarily conserved proteins like tetraspanins (e.g. CD9, CD63, CD81, and CD82), integrins, major histocompatibility complex (MHC) class II proteins, and heat shock proteins, all packaged into exosomes during their formation [4]. Exosomes play a critical role in cell activity determination. MSC-derived exosomes present MSC-specific markers (CD73, CD44, CD90) and surface markers (CD81, CD9) [7] [23]. Analysis of BMSC-derived exosomes' proteomics-based content showcased 730 functional proteins, regulating MSC growth, proliferation, adhesion, migration, and morphogenesis [7] [36]. These exosomes surpass their parent cells in extracellular-associated proteins. Also, exosomal contents encompass crucial RNA cargoes for immune system regulation, cell differentiation, and survival [37]. Prominent miRNAs within these exosomes stimulate angiogenesis, tissue remodeling, and cardiomyocyte increase [4]. While BMSC and adipose-MSC (AMSC) exosomes share RNA compositions, their tRNA species differ based on MSC differentiation status [4] [20]. Significantly, exosomes from both BMSCs and HLSCs carry cellular mRNA that regulates processes such as cell differentiation, transcription, and proliferation. Particularly, exosomes derived from HLSCs express mRNAs that influence metabolism and growth of liver cells [38]. Exosomes, encompassing DNA, RNA, and protein species, exhibit several functions. Large dsDNA fragments aid in identifying mutations like KRAS and p53, enabling pancreatic cancer prediction [39]. Recipient cells respond to exosomal DNA transfer with diverse biological effects [40]. MSC-derived exosomes serve a multitude of functions across various areas as shown in. In terms of tumor growth, they can either stimulate or hinder cancer cell growth by transferring tumor-associated miRNAs. BMSC-derived exosomes are found to target IRF2, inhibiting tumor formation in adult acute myeloid leukemia AML cells which is a type of cancer in where the bone marrow makes a large number of abnormal blood cells [41] and additionally, these exosomes carry miR101-3p, inhibiting oral cancer spread by targeting COL10A1, and suppress human lymphoma cells while inducing antioxidant enzyme activities [4] [20]. Exosomes from AMSCs induce apoptosis in prostate cancer through miR-145 and inhibit human ovarian cancer through cell cycle arrest and apoptosis [7] [42]. Exosomes are also implicated in promoting tumor growth, as seen with BMSC-derived exosomes stimulating tumor growth via ERK1/2 signaling in gastric cancer and expediting multiple myeloma development [4]. Furthermore, exosomes from HUCMSCs exhibit a protective effect and reduce tumor cell apoptosis, suggesting a potential role in chemotherapy protection [43]. Exosomes have demonstrated involvement in angiogenesis, promoting

tumor growth by enhancing CXCR4 expression and angiogenesis in gastric carcinoma and colon cancer, and influencing Wnt signaling [40]. In the context of drug resistance, they play roles in communication during drug treatment, cell migration enhancement, and gene expression induction. Furthermore, these exosomes influence metastasis by affecting dormant cells, stimulating metastatic tumor formation and shuttling miR-205 and miR-31 to suppress metastatic potential, while assisting in tumor migration and dormancy [4] [20]. Moreover, exosomes favor invasiveness via purinergic signaling [4]. They facilitate immune cell subpopulation modulation, including T-cells, NK cells, macrophages, DC, and B-cells interactions [4] [20].

4. Therapeutic Potential of EVs

MSC-derived EVs are considered to be the most promising cell-free therapy for tissue repair and regeneration [44] [45]. EVs can induce anti-inflammatory, antifibrotic, and immunosuppressive effects via miRNA, mRNA, and proteins [46]. Research on animals has shown that EV-encapsulated mRNAs, which are involved in transcriptional regulation, proliferation and immune regulation, induced tissue regeneration against acute renal disease [47]. Moreover, EVs were used to block the signaling pathway that induced apoptosis and suppressed proliferation of renal epithelial cells *in vitro* [41]. Additionally, in a mouse model of hypoxia-induced pulmonary hypertension, EVs were reported to suppress inflammation, by inhibiting the signal transducer and activator of transcription 3 (STAT3) pathways. Also, these EVs suppressed the upregulation of the hypoxia-inducible miR-17 superfamily and the growth-inhibitory miR-204 [44] [48]. On the other hand, MSC EVs have been described to have opposing effects such as: tumor progression via tumor microenvironment remodeling and tumor suppression via immune response regulation and intercellular signaling [49]. Also, EVs have been deemed safe carriers for antitumor drugs, and they can inhibit the activation and proliferation of a variety of proinflammatory cells such as Th1, Th17, and M1 macrophages [50], leading to reduction in the secretion of proinflammatory cytokines. Simultaneously, they enhance the proliferation of anti-inflammatory cells [51], such as M2 macrophages and Tregs, and they play a role in immune regulation. EVs also exhibit immunomodulatory functions by increasing secretion of proinflammatory cytokines [44] [52]. Also, EVs show a balance between immune response and immune tolerance, due to the bioactive molecules they carry such as: mRNA, miRNA, cytokines chemokines, immunomodulators, and growth factors [49]. MSC-derived EVs control the proliferation and differentiation of T- and B-cells [41] [49]. When subjected to inflammatory stimulation, EVs carrying activated TGF-β can impede T-cell proliferation [53]. This inhibition affects CD4+ T-cells, involving several pathways including Smad. These EVs also harbor HLA-G5, which is capable of suppressing the proliferation of both CD4+ and CD8+ T-cells while decreasing the release of IFN-γ [49]. MSC-EVs have been found to down-regulate IL-2 signaling and to inhibit T-cell proliferation by targeting CD25.

Also, they promote the differentiation of naive T-cells into anti-inflammatory phenotypes, such as Tregs [49]. MSC-EVs mediate Treg differentiation *in vitro* and *in vivo* and reduce pathogenic Th17 amplification and proinflammatory factors. Additionally, they increase the number of regulatory B-cells (Bregs) and promote IL-10 secretion [41]. Furthermore, MSC-EVs can directly inhibit B-cell proliferation and activation [16] [38].

5. Use of MSCs in Neurology

MSCs have emerged as promising remedy for neurological disorders along with ischemic stroke, Alzheimer, hypoxia, and many other brain-related diseases [45]. Hypoxia, a condition marked by low oxygen levels within the body tissues, can lead to severe and perilous range of illnesses which include tissue damage and disorders, stroke, coronary heart attack, and breathing failure [54]. MSCs have proven efficacy in treating the neurological complications induced by hypoxia. In preclinical studies, MSCs proved to enhance healing in animal models of hypoxia, including stroke and acute breathing misery syndrome [18]. Furthermore, different cellular reactions to decreased oxygen stress can be identified during *in vitro* cultures. This can aid in the proliferation, survival, and migration of MSCs under hypoxic conditions [10]. MSCs have reportedly proven potential as a therapeutic alternative for Alzheimer's disease, a neurodegenerative disorder characterized by means of cognitive decline and reminiscence loss [55] by decreasing inflammation, supporting neuronal survival, and enhancing cognitive function [17]. These effects can be attributed to the secretion of numerous increase factors and cytokines via MSCs, which could guide neuronal fitness and modulate the immune response [4] and promote neuronal survival not only by secreting neuroprotective and anti-inflammatory elements, but also by enhancing microglia clearance of accumulated protein aggregates and moving functional mitochondria and miRNAs to improve the bioenergetic profile of neurons [21]. MSC based therapies aim to slow down disease progression via reducing infections and therefore enhancing the quality of life for individuals, especially when detected in early stages [56]. MSC can replace damaged or misplaced neuron-like cells. Furthermore, studies have shown that MSCs have the capability to decrease the accumulation of amyloid beta protein, a significant marker of Alzheimer's disease. As a result, the progression of the disease is delayed, leading to enhanced cognitive abilities [26]. Ischemic stroke (IS) is a condition characterized by means of the blockage of blood drift to the brain, resulting in tissue damage and neurological deficits [57]. This leads to cell death and cerebral infarction which makes this condition one of the main causes of death and disability [58]. The effectiveness of MSC therapy is thought to rely on the homing capacity of MSCs to target lesions and their successful implantation [21]. However, the continuous passage of MSCs has been determined to decrease the expression of certain chemokines receptors (consisting of CCR2 and CXCR4), thereby affecting their homing ability. To enhance the homing potential of MSCs [59], it has been discovered that gene modification or

pretreatment of MSCs can increase the expression of chemokines (CCR1, CCR2, and CXCR4). This interplay, especially between CCL2/CCR2 and SDF-1/CXCR4, has been shown to seriously enhance the homing and migration of modified MSCs in the course of acute ischemic assault, main to super improvements in neurological [60]. Furthermore, in an experimental model of middle cerebral artery occlusion (MCAO), it was reported that only a small fraction of MSCs injected intravenously reached the ischemic brain tissue. Most of these cells were trapped in the lung and spleen, thereby impacting their homing ability [61]. On the other hand, another study observed that arterial injection of MSCs facilitated their migration to damaged brain tissue more efficiently [62]. Moreover, genetically modified MSCs exhibited prolonged survival in ischemic brain tissue and decreased vascular embolization [63]. Exosomes and microvesicles originating from MSCs, being small in size and capable of easily passing through lung tissue, carry various therapeutic molecules that have capacity benefits for stroke remedy [64]. However, acquiring enough quantities of extractable exosomes and microvesicles engaged a big variety of MSCs [65]. To address this, techniques for culturing MSCs can be enhanced by incorporating microcarriers and whole fiber bioreactors, creating a three-dimensional environment for MSC culture. This allows for substantial amplification of MSCs and facilitating their use in therapy [57]. Amyotrophic lateral sclerosis (ALS) is a rare, fatal, idiopathic neurological disease, affecting the neurons responsible for controlling voluntary muscle movements. As for the treatment of ALS, a definitive therapy remains to be discovered [66]. Yet, numerous ongoing studies have shown benefits using MSCs based therapy. It was reported that the transplant of MSCs found inside the bone marrow into the spinal canal extensively helped expand the quality of life of ALS patients [59]. They secrete neurotrophic elements and rework into useful cells like astrocytes and microglia [67]. Cutting-edge remedies for ALS are palliative, but stem cellular therapy offers hope by addressing disease progression through multiple mechanisms [68]. The premise is to improve the microenvironment of the disease through transplanting stem cells that generate a neuro-protective milieu, slowing motor neuron degeneration [24]. Conversely, glioblastoma (GBM) is a competitive and distinctly invasive and malignant brain tumor that grows rapidly and can severely impact health [69]. Studies have revealed that MSCs exhibit anti-tumor characteristics in the setting of GBM. Given that GBM is classified as grade IV within the central nervous system, studies have shown that MSCs potentially possess anti-GBM properties, mainly by regulating angiogenesis, controlling the cell cycle, and inducing apoptosis [69]. Moreover, MSCs have been used as sensitizing agents and carriers for delivering specific anti-cancer substances [70]. MSCs have confirmed healing ability in various clinical applications, as they are able to either differentiate into specified cell types or release numerous growth and trophic elements to exert their outcomes [71]. Although several studies were conducted, and the results indicated very promising outcome, further trials involving a larger population are required to validate the findings and enhance our understanding of the MSC-based therapy

[24] [25].

6. Therapeutic Challenges

While MSCs show potential and promising results for therapeutic purposes in neurology, and despite several advancements made in the past decade, there are numerous challenges that remain to be addressed for any successful implementation [40]. A common misconception among individuals opting for MSC-based therapy is the belief that undergoing this treatment will provide a cure for their condition. However, the treatment will only slow down the advancement of the disease rather than treating it completely [72]. A second challenge is to ensure immune compatibility. MSCs may be transplanted as allogeneic cells with a low risk of rejection due to their low expression of MHC-I and HLA-I, and the absence of expression in HLA-II, CD40, CD80 and CD86 [73]. Generally, MSCs are believed to have a low immunogenicity, which means they have a reduced potential to trigger an undesirable physiological immune reaction [74]. However, it is reported that MSC immunogenicity may increase after extraction from donors due to inappropriate handling methods, environmental factors, and lifestyle conditions [75]. Even after injection, the *in vivo* inflammatory molecules can increase MSCs' immunogenicity and decrease their viability and differentiation potential. Consequently, an absence of efficacy is seen, leading to the rejection of the injected cells and potentially cause more serious infections. To prevent this, immunocompatibility is the primordial factor to consider [76]. Whilst MSCs are recognized for their significant differentiation, regeneration, regulation, and replacement capabilities; various laboratories have demonstrated that genes associated with "stemness" exhibit a high expression rate in both undifferentiated and de-differentiated MSCs [77]. Hence, it has been noticed that the differentiation of MSCs into osteoblasts, chondrocytes, adipocytes, and other stemness genes resulted in a decrease in the expression of these genes [23], as indicated in **Table 1**.

Table 1. Table showing different stemness genes of MSCs [78].

Abbreviation	Names	Functional Description
HMGB1	High mobility group box 1	Interacts with SDF-1 and CXCR4, required for tissue repairment
KLF2	Kruppel-like factor 2	Enhances MSC proliferation, required for maintenance of stemness
MCM2	Minichromosome maintenance marker 2	Required for cell division and DNA replication
CCNA2	Cyclin A2	Regulates cell cycle
PCNA	Proliferating cell nuclear antigen	Recruits and retains many enzymes required for DNA replication and repairment
POLA1	DNA polymerase alpha 1	Required for DNA replication
POLD1	DNA polymerase delta 1	Required for DNA replication
REC4	Replication factor C subunit 4	Required for DNA replication

Continued

MAD2L1	Mitotic arrest-deficient 2 like 1	Executes mitotic checkpoint
CDK1	Cyclin-dependent kinase 1	A catalytic subunit of protein kinase complex that induces cell entry into mitosis
CCNB1	Cyclin-B1	Predominantly expressed in the G2/M phase of cell division
CDC45	Cell Division cycle 45	An important component of the replication for, in DNA unwinding

Moreover, prolonged culture through serial passaging has the ability to adversely affect the expression of genes related to stemness [79]. In an effort to conduct clinical trials with a sufficient quantity of MSCs, it is essential to expand cells' number on a large scale. However, this method frequently results in the issue of MSC senescence and subsequent adjustments in gene expressions [75]. Hence, long-term cultures of MSCs often results in decreased abilities for proliferation and differentiation, as well as a shorter lifespan [80]. Although specific molecules have been identified to influence the stemness of MSCs and regulate their differentiation, effectively controlling the fate of MSCs in a complex *in vivo* environment remains a challenge [81]. Another crucial challenge encountered during MSC-based treatment is the potential emergence of cancer-associated MSCs, or tumoral transformation [75]. Previous studies revealed that cultured MSCs during their growth display a decrease in the expression of CD13, CD29, CD44, CD73, CD90, CD105, and CD106 compared to MSCs in the stromal fraction. Additionally, the expression of senescence-related proteins such as p53, p21, and p16 varies under different conditions [38]. After short-term *in vitro* cultures, it was observed that wild-type MSCs underwent cellular senescence, whereas p21(-/-) p53(+/+) MSCs exhibited a higher rate of spontaneous apoptosis without any signs of tumoral transformation due to the absence of expression of c-myc protein, associated to this transformation [82]. Conversely, different studies have diagnosed cancers-related MSCs (CA-MSCs) characterized by the presence of specific markers CD44, CD73, and CD90 [34]. These CA-MSCs exhibited an upregulation of the TGF-β/BMP superfamily and demonstrated the capability to differentiate into cancer-associated fibroblasts (CAFs) during later passages [76]. While MSC-based treatment strategies have made significant strides, emerging as the preferred choice for numerous diseases, it is essential to acknowledge the existing challenges.

7. Conclusion and Future Perspective

Due to their immunomodulatory properties, their ability to migrate to damaged tissues, renew and differentiate into multiple cell lineage, MSCs and MSCs-derived exosome therapy holds tremendous promise for the future in addressing neurological diseases. Beyond their regenerative capacities, stem cells and exosomes are subjects of extensive research aiming to elucidate their role in mitigating inflammation. It is significant to investigate these elements for a comprehensive

understanding of their therapeutic potential. Research and clinical studies show that MSC-derived exosomes have promising advantages, including reduced immunogenicity and low risk of tumor development. They can also mediate intercellular communication, ultimately resulting in immunomodulation, angiogenesis, neurogenesis, and neuroprotection. In addition, various studies reported the repair of injured peripheral nerves and central nervous system by different MSC-EVs. However, the challenges faced by cell therapies arise from a dearth of theoretical understanding and the absence of uniform guidelines to appraise the therapeutic efficacy of stem cells. The investigation of MSCs-derived extracellular vesicles as a therapeutic approach is garnering increased attention within the scientific community, positioning MSCs as a novel and promising therapy for many diseases, including neurological disorders.

Authors' Contributions

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Data

Data is available upon request.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviations

ALS	Amyotrophic lateral sclerosis
CNS	Central nervous system
PNS	Peripheral nervous system
MSC	Mesenchymal stem cells
ADMSC	Adipose mesenchymal stem cells
PKA	Protein kinase A
DMSO	Dimethyl sulfoxide
BHA	Butylated hydroxyanisole
KCL	Potassium chloride
bFGF	Basic fibroblast growth factor
NT-3	Neurotrophin-3
B-ME	*β*-mercaptoethanol
BDNF	Brain-derived neurotrophic fac-tors
NGF	Nerve growth factor
Dex	Dexamethasone
B-GP	*β*-glycerophosphate
SOX9	SRY-box transcription factor 9
FGF	Fibroblast growth factor
CD	Cluster of differentiation
HLA	Human leukocyte antigen
EV	Extracellular vesicle
BMMSC	Bone marrow mesenchymal stem cells
TGF-*β*	Transforming growth factor *β*
VEGF	Vascular endothelial growth fac-tor
JACK/STAT	Janus kinase/signal trans-ducers and activators of transcription