Review

Exosomes and Stem Cells in Degenerative Disease Diagnosis and Therapy

Cell Transplantation
2018, Vol. 27(3) 349–363

DOI: 10.1177/0963689717723636
journals.sagepub.com/home/cll
SAGE

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Abstract

Stroke can cause death and disability, resulting in a huge burden on society. Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by motor dysfunction. Osteoarthritis (OA) is a progressive degenerative joint disease characterized by cartilage destruction and osteophyte formation in the joints. Stem cell therapy may provide a biological treatment alternative to traditional pharmacological therapy. Mesenchymal stem cells (MSCs) are preferred because of their differentiation ability and possible derivation from many adult tissues. In addition, the paracrine effects of MSCs play crucial anti-inflammatory and immunosuppressive roles in immune cells. Extracellular vesicles (EVs) are vital mediators of cell-to-cell communication. Exosomes contain various molecules such as microRNA (miRNA), which mediates biological functions through gene regulation. Therefore, exosomes carrying miRNA or other molecules can enhance the therapeutic effects of MSC transplantation. MSC-derived exosomes have been investigated in various animal models representing stroke, PD, and OA. Exosomes are a subtype of EVs. This review article focuses on the mechanism and therapeutic potential of MSC-derived exosomes in stroke, PD, and OA in basic and clinical aspects.

Keywords

stroke, Parkinson's disease, osteoarthritis, mesenchymal stem cells, exosomes, miRNA

Introduction

Stroke, Parkinson's disease (PD), and osteoarthritis (OA) are degenerative diseases associated with aging. Stroke is the leading cause of death and disability worldwide[1]. The standard treatment for stroke is tissue plasminogen activator (tPA) infusion within 4.5 h of onset[2–4]. Treatment with endovascular thrombectomy could extend the therapeutic window to 12 h after a stroke[5–8]. However, patients with stroke can develop long-term disability if cerebral blood flow is not recovered at a critical time point[8]. Therefore, the development of a novel therapy to restore brain function after an acute stroke is urgently necessary.

PD is the second most common neurodegenerative disease, with a prevalence of 1% to 2% among aging people[9]. The cause of PD is unknown but may involve genetic and environmental factors. Patients with PD have clinical features with progressive deterioration of motor functions, including bradykinesia, rigidity, resting tremors, and unstable gait. PD is associated with a pathological decrease in dopamine concentration, neuronal cell loss in the substantia nigra (SN), and Lewy body accumulation in other brain tissues[10,11]. A specific diagnostic test for PD is not available, and therefore its diagnosis mainly depends on clinical judgment. Functional connectivity measured through Positron emission tomography (PET) scan and functional MRI is helpful for making a clinical judgment[9].

Pharmacological agents for dopamine replacement include L-3,4-dihydroxyphenylalanine (L-DOPA), carbidopa,

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Submitted: December 14, 2016. Revised: June 06, 2017. Accepted: July 03, 2017.

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and monoamine oxidase-B inhibitors. These agents are useful in the early stages of PD; however, their long-term use may reduce efficacy and cause side effects involving involuntary motor action that may have an impact on patients' quality of life. Deep brain stimulation of the globus pallidus and subthalamic nuclei is another therapeutic modality. Although PD has several therapeutic modalities, no complete treatment can stop its degenerative process.

OA is a chronic degenerative joint disease occurring in older adults that is becoming a crucial health concern worldwide[12,13]. OA involves not only the knees but also the hands, hips, and spine and is characterized by the degeneration and destruction of the articular cartilage and changes in the subchondral bone with osteophyte formation[14]. Patients experience increasing pain and disability, resulting in decreased quality of life and a high economic burden[15]. OA is a multifactorial disease[16]. Its progression involves the interaction of personal factors (old age, female sex, obesity, genetics, and diet) and common factors (injury, misalignment, and abnormal loading of the joints), which increases the risk of comobility and mortality[17]. Current medical treatments for OA involve pain relief and joint mobility improvement. Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, topical analgesics, corticosteroid injections, and hyaluronic acid injections are commonly prescribed pharmacological treatments. Physical therapy also results in functional improvement. However, these treatments cannot restore articular cartilage regeneration or modify degenerative processes[18]. By contrast, surgical arthroplasty is an optimal treatment for patients with symptomatic OA whose condition is not controlled by conservative therapies[19]. Surgical arthroplasty results in long-term functional improvement and improves quality of life. However, instability and infection are the most common limitations, necessitating further joint revision surgery, particularly in overweight patients[20,21].

Stem cell therapy has been rapidly advancing in research and regenerative medicine for OA in recent years[22]. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can differentiate into chondrocytes[23–25]. However, the clinical applications of ESCs or iPSCs have raised considerable concerns about the tumorigenicity, low efficiency, and genomic insertion of transgenic sequences[26,27]. By contrast, mesenchymal stem cells (MSCs) can be isolated from various adult tissues, including the bone marrow and adipose tissues, which can provide abundant stem cells for regenerative therapy. In addition to the ability to differentiate into chondrocytes, MSCs can modulate immune responses with immunosuppressive and anti-inflammatory properties through their paracrine effects. However, MSC therapy has a dose-dependent effect that requires many cells[28].

Emerging evidence in recent years has shown that the paracrine effects of MSCs are mediated by the secretion of extracellular vesicles (EVs)[29]. Exosomes are a subtype of EVs, approximately 30 to 100 nm in diameter, and are released by cells in all living systems[30,31]. Exosomes are present in body fluids such as blood and cerebrospinal fluid[31] and harbor proteins, lipids, microRNA (miRNA), and RNA. Intercellular communication has been observed in exosomes under various physiological and pathological conditions[30,31]. MSC exosomes have been studied in various disease models and have shown therapeutic potential in managing stroke, PD, and OA. This review article focuses on the therapeutic potential of MSC exosomes and future directions for their use in research on these degenerative diseases.

Pathophysiology of Stroke, PD, and OA

Pathophysiology of Stroke

A thromboembolic event of a major artery that supplies the brain causes ischemic stroke[8]. Platelets combined with fibrin and thrombin cause thrombus formation at the site of the occluded artery[32,33]. The occlusion of the main artery results in the obstruction of downstream small vessels and subsequently leads to the disruption of the blood–brain barrier (BBB) as a result of the dysfunction of endothelial cells, pericytes, and astrocytes[34,35]. The progression of ischemic neuronal death can be observed hours after the occlusion of an artery[34,35]. Therefore, thrombolytic treatment using tPA infusion for stroke involves the rapid recanalization of occluded blood vessels and minimization of neuronal death[36]. After a stroke, the ischemic brain proceeds with a series of remodeling events to enable limited spontaneous functional recovery[37]. According to past studies in experimental models and the human ischemic brain, endothelial cells residing in preexisting brain vessels are then activated and angiogenesis begins[38–40]. However, endothelial cells in the brain, which circulate endothelial progenitor cells, are also partially involved in angiogenesis[41]. Newly formed vessels are permeable in the early stages of recovery but become less leaky when they mature[38,42]. A past study found that improved neurological outcomes also accompanied increased angiogenesis[43]. Neural stem cells (NSCs) are harbored in the subventricular zone (SVZ) and subgranular zone of the brain[36,44]. These NSCs can generate new neurons throughout their lives[44]. Neurogenesis increased after stroke in experimental animals[45,46] and has been found to couple with angiogenesis after stroke onset[46,47]. The newly generated neuroblasts in the SVZ migrate to the peri-infarct region along cerebral blood vessels[46,47]. Thus, neuroblasts have a vital functional role in brain repair after stroke[48]. NSC-derived oligodendrocyte progenitor cells (OPCs) can differentiate into mature oligodendrocytes through myelination[49,50]. Mature oligodendrocytes are vulnerable to cerebral ischemia. Therefore, OPCs generate new oligodendrocytes during brain repair processes, forming myelin sheaths around the newly generated axons in peri-infarct brain tissues[51,52]. After stroke, endothelial cells in the brain interact actively and mutually with oligodendrocytes to promote the growth of vessels and oligodendrocytes[53].

Pathophysiology of PD

PD is a degenerative disease characterized by the progressive deterioration of motor function, affecting 0.3% of the entire population[54]. Abnormal accumulation of misfolded proteins in the brain, such as α-synuclein[55], causes PD, PD dementia, dementia with Lewy bodies, and multiple system atrophy. Progressive degeneration and loss of dopamine neurons in the SN and nerve terminals in the striatum are the pathological mechanisms of PD[56]. α-synuclein acts in synaptic transmission and vesicle release[57]. Lewy bodies are the pathological aggregates of α-synuclein within neurons and glial cells[55]. The toxic conformations of α-synuclein, oligomers and protofibrils[58], can propagate from cell to cell in a prion-like pattern[59]. This explains the progression of PD and its spread from the basal brain to neocortical areas[60]. In addition to the accumulation of α-synuclein, a co-aggregate of α-synuclein with amyloid β and τ has been found[61–63]. Furthermore, genome-wide association studies have found mitochondrial and lysosomal components including leucine-rich repeat kinase 2 (LRRK2)[64], Parkin/PARK2[65], PTEN-induced putative kinase 1 (PINK1)[66], and Parkinson disease protein 7 (DJ-1/PARK7)[67] in PD and Coenzyme Q2 (COQ2) in MSA[68]. Cell metabolism and protein clearance together play a role in PD pathophysiology. Locus coeruleus noradrenergic neuron degeneration may result in dementia and depression[69]. Degeneration of serotonergic neurons in the raphe obscurus and medial raphe may likewise cause depression[70]. However, the cause of selective degeneration and the loss of specific neurons in PD remain elusive. Infectious agents[71], pesticides[72], heavy metals[73], and living in rural environments[74] have been identified as risk factors for PD.

Pathophysiology of OA

Inflammation plays a substantial role in the progression of OA. Advanced OA has shown considerable synovial histological reactions (proliferation or inflammation) and roentgenographic evidence of calcification[75]. Arthroscopy revealed changes in the cartilage with superficial fibrillation, deep fissures, erosions, and synovial inflammation[76]. Histologically, B lymphocytes, T lymphocytes, plasma cells, T-helper cells, and Human Leukocyte Antigen - antigen D Related (HLA-DR)-positive dendritic-like cell infiltrations can be found in the intensely inflamed synovium[76]. However, the severity of cartilage lesions is unrelated to the severity of synovitis in early OA[77]. Recent studies have reported that low-grade inflammatory processes can not only promote disease symptoms but also accelerate disease progression. Activated macrophages and other innate immune cells release inflammatory cytokines, which promote cartilage damage[78]. The synovial tissue obtained from a patient with OA showed an increased number of immune cells associated with pro-inflammatory cytokine expression, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, and IL-22[79]. Matrix metalloproteinase (MMP) 1, 3, and 13 are directly responsible for extracellular matrix remodeling[80–82]. Physicians prescribe either nonselective NSAIDs (ibuprofen, naproxen, and diclofenac), which act as cyclooxygenase (COX)-1 and -2 inhibitors, or selective NSAIDs (celecoxib and rofecoxib), which act as COX-2 inhibitors, for controlling pain in patients with OA. However, nonselective NSAIDs are associated with considerable gastrointestinal (GI) complications. Although selective NSAIDs cause substantially lower GI complications, they result in a considerably higher risk of cardiovascular events, including myocardial infarction and stroke[83,84]. New anti-inflammatory therapeutics for OA are under development, and some of these are being studied in randomized controlled trials. Successful treatment requires appropriate patient selection based on synovial inflammatory biomarker measurements[85].

Stem Cell Therapy in Stroke, PD, and OA

In our previous article, we comprehensively reviewed the characteristics of MSCs[86]. In brief, stem cells can differentiate along different lineages and are capable of self-renewal. Adult MSCs are less problematic than ESCs in terms of tumorigenesis and ethical concerns. MSCs are stromal cells that can self-renew and exhibit multilineage differentiation. MSCs can be isolated from various tissues, such as the umbilical cord, endometrial polyps, menstrual blood, bone marrow, and adipose tissue. The ease of harvesting and the quantity of MSCs that can be obtained make them most practical for experimental and possible clinical applications. Other sources of MSCs may be discovered in the future. A major challenge is to elucidate the highly sophisticated mechanisms of differentiation, mobilization, and homing in MSCs. The multipotent properties of these cells make them an attractive choice for the development of clinical applications.

Stem Cell Therapy in Stroke

The aim of cell therapy is to replace, repair, or enhance the biological function of damaged cells and thereby restore brain integrity. Differentiated neuronal progenitors from stem cells can restore functional neuronal circuitry. We have previously reported that stem cell transplantation can repair the damage in animal[87–90] and human[91,92] stroke models. Moreover, stem cell therapy may secrete paracrine factors to promote the survival, migration, and differentiation of the endogenous precursor cells of the penumbra[93]. The clinical trials on stroke referred to in this study are drawn from 11 MSC records (searched on November 11, 2016, in clinicaltrials.gov, Table 1). Most relevant studies have used cultured and expanded autologous MSCs from bone marrow, adipose tissue, and umbilical cord. Technical

Table 1. Clinical Trials of MSCs in Stroke.

Year	Phase	Current Status	Area	MSCs	Trial	Intervention	Comparator
2009	2	Active, not recruiting	Europe	Autologous MSCs	Intravenous stem cells after ischemic stroke	Autologous mesenchymal stem cells	No intervention
2012	1	Recruiting	USA	BM-MSCs	Autologous bone marrow mesenchymal stem cell transplantation for chronic stroke	intracerebral stem cell transplantation	No
2015	1	Recruiting	China	BM-MSCs	Autologous bone marrow mesenchymal stem cell transplantation for chronic ischemic stroke	intracerebral stem cell transplantation	No
2015	2	Not yet recruiting	China	UC-MSCs	Umbilical cord–derived mesenchymal stem cells treatment in ischemic stroke	Human umbilical cord mesenchymal stem cells	No intervention
2012	3	Recruiting	Korea	Autologous MSCs	The stem cell application researches and trials In NeuroloGy-2 (STARTING-2) Study (STARTING-2)	MSC treatment	Standard treatment
2010	2	Recruiting	Spain	Adipose stem cell	Reparative therapy in acute ischemic stroke with allogenic mesenchymal stem cells from adipose tissue, safety assessment, a randomized, double blind placebo controlled single center pilot clinical trial (AMASCIS-01)	ASC treatment	Placebo: IV fluids
2011	2	Recruiting	Malaysia	BM-MSCs	Intravenous autologous mesenchymal stem cells transplantation to treat middle cerebral artery infarct	IV infusion of BM-MSC	Standard treatment
2013	1/2	Not yet recruiting	USA	Allogenic BM-MSCs	Mesenchymal stromal cells for ischemic stroke	IV infusion of BM-MSC	IV normal saline
2013	1	Unknown status	China	UC-MSCs	Umbilical cord–derived mesenchymal stem cells therapy in hypoxic ischemic encephalopathy	IV infusion of UC-MSC	No
2011	1/2	Recruiting	China	Autologous BM-MSCs, EPCs	Autologous bone marrow stromal cell and endothelial progenitor cell transplantation in ischemic stroke	IV infusion of BM-MSC	IV normal saline with 5% serum
2016	2/3	Recruiting	Europe	Adipose stem cell	Regenerative stem cell therapy for stroke in Europe	IV infusion of ASC	IV cell excipients

Abbreviations: AMETIS, Autologous bone marrow stromal cell and endothelial progenitor cell transplantation in ischemic stroke; MSCs, mesenchymal stem cells; RESTORE, regenerative stem cell therapy for stroke in Europe; SAMCLS, mesenchymal stromal cells for ischemic stroke; UCMSC, umbilical cord mesenchymal stem cells; BMSCs, bone marrow stem cells; EPC, endothelial progenitor cells; ASC, adipose stem cells.

approaches generally use an intravenous injection to deliver the cells directly into the vein without using a scaffold. Most studies are in stage I or II and have worldwide testing area distributions. Currently, the most common approach is intravenous (IV) injection, which is simpler than multicomponent interventions in terms of technical delivery and regulatory approval.

Stem Cell Therapy in PD

Bone marrow-derived MSCs (BM-MSCs) have been examined for their therapeutic effect in a PD model; these studies have demonstrated the survival of grafted cells, tyrosine hydroxylase (TH) expression, and behavioral improvement[94–98]. Other stem cells, such as adipose-derived and umbilical cord-derived (ADSCs and UC-MSCs, respectively) MSCs, also improve PD symptoms[99,100]. Moreover, genetically modified MSCs with neurotrophic proteins, such as glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), or neurturin, have been indicated to have therapeutic potential in PD treatment. [101,102] In patients with PD, proliferation of activated microglia was noted in the SN[103]. TNF-α, IL-1β, and interferon-γ were elevated in the brains of patients with PD[104]. Immunosuppression therapy slowed PD progression[105]. Additionally, MSCs exhibited crucial anti-inflammatory and immunomodulatory effects on PD pathology. Only 3 clinical trials to date have adopted MSCs for PD therapy (Table 2). One trial is active but not yet recruiting, whereas the status of two other trials is unknown.

Stem Cell Therapy in OA

MSC therapy for OA may be a permanent biological treatment[106,107]. Stem cells from all sources, such as embryonic,

Table 2. Clinical Trials of MSCs in Parkinson's Disease.

Year	Phase	Current Status	Area	MSCs	Trial	Intervention	Comparator
2011	1/2	Recruiting, unknown status	China	Autologous BM-MSCs	Mesenchymal stem cells transplantation to patients with Parkinson's disease	IV BM-MSCs	No
2015	1/2	Active, not yet recruiting	USA	Allogenic BM-MSCs	Allogeneic bone marrow–derived mesenchymal stem cell therapy for idiopathic Parkinson's disease	IV BM-MSCs	No
2013	1/2	Unknown status	Italy	Autologous BM-MSCs	Clinical trial to evaluate bone marrow stem cell therapy for PSP, a rare form of Parkinsonism	Intra-artery infusion of BM-MSCs	No

Abbreviations: MSC, mesenchymal stem cells; PSP, progressive supranuclear palsy; BMSCs, bone marrow stem cells.

induced pluripotent, fetal, and adult stem cells, can be used in this therapy. Among these, MSCs are the first choice because they can not only differentiate into a chondrogenic lineage under defined culture conditions but also modulate the immune responses of individuals through anti-inflammatory effects[108,109]. In addition to direct chondrocyte differentiation that repairs damaged OA joints, the paracrine effect of MSCs plays a crucial immunosuppressive and anti-inflammatory role in immune cells[110]. MSCs can inhibit the proliferation and differentiation of naive T lymphocytes into the T-helper type 1 (Th1) or IL-17-producing effector T (Th17) phenotype[111]. Increasing evidence has indicated that MSCs participate in tissue repair and regeneration through their secretome, which includes exosomes. The downregulation of inflammatory cytokines and the induction of chondrocyte regeneration are essential for repairing diseased joints[112]. Both soluble and contact-dependent signals from the environment trigger the therapeutic effect of MSCs. Therefore, various mediators and EVs secreted from MSCs in the surrounding extracellular environment play vital roles in achieving the therapeutic effect of MSCs for OA.

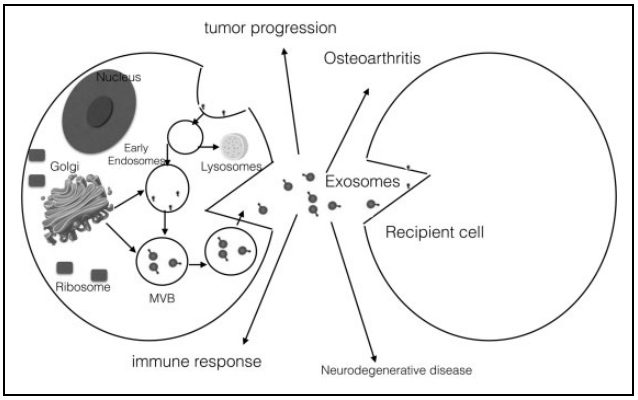

Fig. 1. Exosome synthesis and action. A cell membrane is an inward budding and formed multivesicular body (MVB). Exosomes are released after the MVB fuses with the membrane. Exosomes can carry lipids, proteins, and nucleic acids to recipient cells; they act as intercellular communicators and play crucial roles in immune response, neurodegenerative disease, osteoarthritis, and tumor progression.

Exosome Introduction

In past decades, transplanted stem cells were believed to heal damaged tissue by directly differentiating into cells at the damaged site. However, recent evidence has attributed the beneficial effects of stem cell transplantation not to their direct differentiation abilities, but rather their ability to secrete bioactive molecules, which provide a regenerative microenvironment for various injured tissues to limit the area of damage and mount a self-regulated regenerative response[113,114]. EVs are crucial mediators of cell-to-cell communication, which is involved in normal physiological processes and additionally plays a role in the development and progression of diseases. Therefore, current studies are increasingly focusing on the role of EVs in MSC transplantation and their therapeutic potential (Fig. 1). The major subtypes of EVs are exosomes, microvesicles, and apoptotic bodies[115]. Exosomes are 40 to 100 nm in diameter and can be isolated from all bodily fluids including blood, urine, bronchoalveolar lavage fluid, breast milk, amniotic fluid, synovial fluid, pleural effusions, and ascites through centrifugation[116]. Exosomes are endocytic materials that contain a particular set of protein families from intracellular compartments including the plasma membrane, endocytic pathway, and cytosol[117]. Exosomes contain CD63 and CD81 (tetraspanin proteins), Alix (the regulator of endosomal trafficking), and HSP70 (the chaperone protein)[31,118]. Exosomes also include messenger RNA (mRNA) and miRNA, which can transfer genetic information to target cells[119]. These exosomes, which contain proteins, mRNA, and miRNA, function as messengers from donor cells to recipient cells and induce physiological changes in recipient cells. The mRNA packed within exosomes can be translated after entering into the recipient cells. By contrast, miRNA is involved in RNA silencing and posttranscriptional regulation of gene expression in recipient cells[119].

Stem Cells Actively Secrete Exosomes

MSC-derived exosomes can be steadily isolated from the MSC-conditioned medium. They are as effective as direct MSC transplantation, and their beneficial therapeutic effects have been demonstrated in various models, including those for cardiovascular disease, acute kidney injury, liver injury,

lung injury, and cutaneous wound healing[115,120]. The protective effects are specific to MSC-derived exosomes and are not exhibited by fibroblast-derived exosomes[121]. MSCs can secrete a higher amount of exosomes than other types of cells[122]. The morphology, isolation, and storage conditions of MSC-derived exosomes are the same as those of exosomes derived from other cells[122]. MSCs can produce many more exosomes than other cells can[122]. In a myocardial infarction model, the use of exosomes derived from myc-transformed MSCs was found to reduce the infarction size[123]. The proposed mechanism was that the myc transformation of MSCs caused them to infinitely produce a large amount of exosomes, which would exert therapeutic effects. Moreover, the myc transformation of MSCs increased the proliferation rate, which reduced the time required for cell production[123]. Thus, this method can effectively enable MSCs to produce a substantial amount of exosomes.

Role of Exosomes in Immune Responses

Exosomes are considered carriers of immune responses[124–128]. Immunomodulation mediated by exosomes remains controversial. The promotion or suppression of immune responses depends on the characteristics of the parent cell[129]. Antigen-presenting cells (APCs), including dendritic cells (DCs) and B lymphocytes, secrete exosomes that carry immunostimulatory molecules. These molecules, which participate in the development of antigen-specific immune responses, include MHC-I, MHC-II, and CD80/CD86 DC exosomes–activated T cells[130–135]. In addition, B lymphocyte-derived exosomes can facilitate antigen presentation and stimulate T cells in vitro. These actions indicate a role in T cell memory and tolerance[130,136]. Moreover, exosomes derived from B lymphocytes could be delivered to follicular DCs in vitro, suggesting that follicular DCs might passively obtain peptide-loaded major histocompatibility complex II (MHC-II) molecules for stimulating CD4 T cells[137]. miRNA is involved in immune regulation[138] and can be transferred by exosomes and affect immune activities[139]. Exosomes can be unidirectionally transferred between T cells and APCs[139]. Inhibition of exosome formation impaired APC exosome and miRNA transfer in T cells. However, the contribution of exosomes is difficult to determine because almost all cells can secrete exosomes, only one cell type can be studied in vitro, the in vivo setting is much more complicated, and exosome exchange may be bidirectional. Different organs may have different vesicle transfer mechanisms[140,141]. Therefore, exosomes can either activate or suppress the immune response depending on the donor cell type[142–144]. Exogenous miRNA delivery to target cells appears to be facilitated by exosomes. However, recipient uptake mechanisms should be explored further[145].

Effect of Exosomes on the Brain

The regulation of immune function by exosomes has been reported for microglia or macrophages in the brain. The proteomics of exosomes secreted from microglia has identified several known vesicle proteins already present in B cells and DC-secreting exosomes; microglia-secreted exosomes also express MHC-II molecules[146]. Upon activation, the microglia release both membrane vesicles and soluble inflammatory cytokines including IL-1β, IL-6, and TNF-α[147–149]. During central nervous system (CNS) inflammation, the number of microglia-secreted exosomes increases, and they enter into cerebral spinal fluid (CSF) circulation[150]. Therefore, circulating exosomes can be regarded as the markers of inflammation that locally or systemically affect the CNS[150]. Endothelial cells in the brain can also release small membrane vesicles—endothelial microparticles (EMPs)—which are considered useful indicators of the status of the disordered endothelium[151,152]. After stroke, EMPs released from the injured endothelium are linked with microcirculatory injuries, capillary blockage, inflammatory processes, and BBB disruption. The amount of circulating EMPs has been correlated with the severity of stroke, volume of brain lesions, and outcome. When inflammatory cytokines (IFN-γ and TNF-α) are stimulated, endothelial cells secrete EMPs[153].

The third exosome effect on the brain is derived from brain tumors. Tumor-derived exosomes can act like cancer vaccines due to their tumor-specific antigenicity and hereditary spastic paraplegia (HSP) that favor the activation of APCs[154,155]. Human gliomas can express a mutation of the epidermal growth factor receptor variant III (EGFRvIII). This variant can define clinically distinct glioblastoma subtypes[156] and serve as a biomarker[157]. Glioma-secreted exosomes can also promote the oncogenic transformation of neighboring cells through the transfer of EGFRvIII[158]. Tumor-derived exosomes can additionally intervene in immune suppression by augmenting the activities of regulatory T cells and myeloid-derived suppressor cells; they suppress activated T cells and natural killer (NK) cells by inhibiting DC maturation[159]. Therefore, tumor-derived exosomes appear to harbor both immune-promoting and immune-supressing functions.

Potential of Stem Cell–Derived Exosomes in Stroke, PD, and OA Treatment

Exosome Therapy in Stroke

Neurons, astrocytes, and glia can release various membranous vesicles into the extracellular space. These EVs may act as carriers of proteins associated with neurodegenerative diseases. EVs may be involved in the spreading of these misfolded proteins in the brain. Therefore, only exosomes can be adopted as a treatment modality. Intravenous injection of exosomes has been demonstrated to be more efficient than the use of cells in treating stroke. Exosomes can transfer their cargo miRNA to recipient cells[160,161]. More than 700 miRNAs are bound to argonaute2, a component of the RNA-induced silencing complex in MSC-derived exosomes[162].

Engineered exosomes with elevated miRNA levels have a beneficial effect on brain remodeling after stroke[163,164]. Immunosuppression induced by stroke in peripheral blood can exacerbate stroke outcomes[165,166]. MSC-derived exosomes can communicate with NK cells and lymphocytes to attenuate postischemic immunosuppression[167]. Exosomes of miR133b-overexpressed MSCs have recently been reported to improve neural plasticity and functional recovery in a stroke model[164,168]. miR133b was downregulated in the rat brain after cerebral artery occlusion; however, the miR133b level increased after MSC administration[164,168]. The transfer of miR33b from MSCs to astrocytes through exosome-downregulated connected tissue growth factor expression can reduce glial scarring and promote neurite growth[169]. In a stroke model, miR-133b also inhibited Ras homolog gene family, member A (RhoA) expression in neurons, which promoted the regrowth of the corticospinal tract[170]. Exosomes of hASCs-mediated PKCδ splicing and increased neuronal survival[171]. Intravenous injection of Adipose derived stem cells (ADSCs)-derived exosomes could reduce the brain infarct zone and improve neurological function in a stroke model[172]. BM-MSCs derived from diabetic mice reduced miR-145 expression and aided recovery from stroke[173]. Intravenous injection of MSC-derived exosomes could improve functional recovery and neurite remodeling, neurogenesis, and angiogenesis[163]. Exosome miR-9 and miR-124, brain-specific miRNA, are promising biomarkers for diagnosing stroke severity and as alternatives to therapy[174]. The direct use of exosomes from specific cell sources has considerable potential in stroke treatment.

Potential Benefits of Exosomes in PD

No reliable diagnostic tool is currently available for PD. Exosomes have two roles in PD: as a diagnostic biomarkers and for therapy. For diagnosis, increased mutation in LRRK2 in urine was recently reported to be associated with idiopathic PD and the severity of cognitive impairment[175–177]. Another study found that the Neural cell adhesion molecule L1 (L1-CAM) exosome τ level was significantly higher in patients with PD than in controls and was correlated with the CSF tau levels[178]. The level of α-synuclein was also higher in L1-CAM-positive EV isolated from the plasma of patients with PD than in control patients[179–181]. The expression profiles of miRNA and mRNA in exosomes of PD also served as diagnostic tools for PD. Neurotrophin signaling, mechanistic target of rapamycin (mTOR), ubiquitin-mediated proteolysis, and dopaminergic and glutamatergic synapse were the most significant pathways in PD miRNA patterns[182]. For therapy, exosomes derived from human dental pulp have recently been found to reduce 80% of 6-hydroxydopamine (OHDA)-induced dopamine neuron apoptosis[183]. Exosomes carrying catalase exerted substantial neuroprotective effects on in vitro and in vivo models of PD[184]. In summary, the use of exosomes to treat PD is in its early stages, being mostly incorporated in diagnosis and rarely in treatment.

Potential Benefits of Stem Cell–Derived Exosomes in OA

Inflammation plays a vital role in the pathogenesis of OA. Catabolic factors, such as IL-1α or TNF-α, present in OA joints inhibit the differentiation of stem cells that impair chondrogenesis[185]. MSC-derived exosomes can suppress the secretion of the pro-inflammatory cytokines TNF-α and IL-1β and can also increase the secretion of anti-inflammatory cytokines, thus increasing the level of transformation growth factor-β. Exosomes may induce the conversion of Th1 cells into Th2 cells and reduce the differentiation of T cells into Th17 cells[186]. Therefore, MSC-derived exosomes can suppress the inflammation of OA joints and introduce a trophic effect that stimulates tissue-intrinsic stem cells to repair damaged tissues, similar to MSCs[113]. Although MSC-derived exosomes have exhibited considerable advances in many disease models, they have only now been incorporated into OA therapy. Zhang et al. reported that exosomes derived from human embryonic MSCs promoted osteochondral regeneration in a surgical rat model of osteochondral defects[187]. The model showed complete restoration of the cartilage and subchondral bone 12 wks after a single intra-articular exosome injection. By contrast, the contralateral phosphate buffered saline (PBS)-treated defects only formed fibrous repair tissues. miRNAs are also involved in chondrogenesis and cartilage degeneration in OA[188]. For instance, miR-140 is related to chondrocyte differentiation[189]. miR-320 directly targets MMP-13 and produces the IL-1β-stimulated catabolic effect[190]. Both miR-140 and miR-320 are significantly decreased in OA cartilage. By contrast, miR-455 overexpression during the aging process exacerbates OA progression[191]. MiR-181b is significantly downregulated during chondrogenic differentiation and significantly overexpressed in OA cartilage[192]. Therefore, MSC-derived exosomes likely attenuate OA progression through the delivery of miRNA. Various MSC-origin exosomes may function differently in OA. Clinical trials have demonstrated the therapeutic effects of BM-MSCs, adipose-derived MSCs (ADSCs), and human UC-MSCs in OA. Some clinical trials are ongoing[22]. However, the low RNA content in exosomes appears to be considerably influenced by donors, cell types, environments, and cell differentiation status. Baglio et al. concluded that adipose and bone marrow MSC subtypes secrete different transfer RNA species that may have clinical applications[193]. Furthermore, Salomon et al. demonstrated that under hypoxic conditions, placental MSCs released exosomes in a dose-dependent manner that stimulated placental microvascular endothelial cell migration and tube formation[194].

Conclusion and Prospects

Stem cell–derived exosomes carried and transferred their cargo (similar to miRNA) to parenchymal cells in the brain

or cartilage. Thus, exosomes mediate plasticity and functional recovery from stroke or OA. Because of the requirements of complex paracrine factors, exosomes may be used as a treatment modality for complicated diseases such as stroke and OA. Different miRNA contents of stem cell–derived exosomes can be used to modulate the therapeutic response to stroke and may increase their therapeutic potential. Moreover, exosomes can be used as a diagnostic marker for PD.

Exosomes have many benefits aside from the cell-based therapy reported in clinical trials for stroke[195,196]. In contrast to injecting cells into the vein systemically, exosomes, which have diameters measured in nanometers, may easily enter the brain by passing through the BBB[197,198]. Direct injection of MSCs may result in the obstruction of small vessels in organs[199]. Because of their small size, exosomes have no apparent obstructive effect on small vessels.

Research is ongoing on the benefits of the stem cell–derived exosome therapy for degenerative diseases such as stroke, PD, and OA. Stem cell–derived exosomes, whether naturally occurring or engineered, can provide therapeutic benefits. Although exosome therapies have shown positive results, most studies have focused on acute injury disease models. Stroke, PD, and OA are multifactorial chronic degenerative diseases with chronic inflammation. Additional studies are required to elucidate the pathogenesis of these degenerative diseases and the potential benefits of exosomes derived from different MSC sources, preconditioning statuses, doses, and therapeutic regimens.

The purity of exosomes should be further examined. Differential centrifugation and a sucrose gradient can yield a mixed gradient product[200]. Mass exosome production is expensive and time consuming. Thus, future studies should focus on reducing the cost and time required for exosome production. Regarding the modification of exosomes for therapy, exosome products should be thoroughly characterized to prevent adverse events.

Authors' Note

This article was edited by Wallace Academic Editing.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Paul R. Sanberg (PRS) is the coeditor in chief of Cell Transplantation. Neither PRS nor any of his colleagues were involved in the peer-review process or decision for this manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: The authors were supported by the following intramural grants from Buddhist Tzu Chi General Hospital: TCRD 104-07 (to Chang Y. H.) and TCRDI-104-01-03 (to Ding D. C.).

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