HHS Public Access

Author manuscript

Ageing Res Rev. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Ageing Res Rev. 2017 March ; 34: 39–50. doi:10.1016/j.arr.2016.11.002.

Stem cell therapies in age-related neurodegenerative diseases and stroke

Yuan Wang[1,*], **Xunming Ji**[2,*], **Rehana K. Leak**[3], **Fenghua Chen**[4], and **Guodong Cao**[4,5]

[1]Department of Neurology, Xuanwu Hospital, Capital University of Medicine, Beijing 100053

[2]Department of Neurosurgery, Xuanwu Hospital, Capital University of Medicine, Beijing 100053

[3]Division of Pharmaceutical Sciences, Duquesne University, Pittsburgh PA 15282

[4]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15260

[5]Geriatric Research Education and Clinical Centers, VA Pittsburgh Healthcare System, Pittsburgh, PA 15240

Abstract

Aging, a complex process associated with various structural, functional and metabolic changes in the brain, is an important risk factor for neurodegenerative diseases and stroke. These diseases share similar neuropathological changes, such as the formation of misfolded proteins, oxidative stress, loss of neurons and synapses, dysfunction of the neurovascular unit (NVU), reduction of self-repair capacity, and motor and/or cognitive deficiencies. In addition to gray matter dysfunction, the plasticity and repair capacity of white matter also decrease with aging and contribute to neurodegenerative diseases. Aging not only renders patients more susceptible to these disorders, but also attenuates their self-repair capabilities. In addition, low drug responsiveness and intolerable side effects are major challenges in the prevention and treatment of senile diseases. Thus, stem cell therapies—characterized by cellular plasticity and the ability to self-renew—may be a promising strategy for aging-related brain disorders. Here, we review the common pathophysiological changes, treatments, and the promises and limitations of stem cell therapies in age-related neurodegenerative diseases and stroke.

Keywords

Aging; stem cell; neurodegenerative diseases; stroke; plasticity; self-renew

Corresponding Author: Guodong Cao, Ph.D. VA Pittsburgh Healthcare System University Drive Pittsburgh, PA 15240 Fax: (412) 648-1239 Tel: (412) 383-4108, caog@upmc.edu.

*Yuan Wang and Xunming Ji contributed equally to this project

Conflict of interest

All authors have no actual or potential conflicts of interest, including any financial, personal or other relationships with other people or organizations within three years of beginning of the submitted work.

1. Introduction

Aging is a complex process associated with various structural, functional and metabolic changes in the brain, leading to an increase in vulnerability to diseases and eventually to organismal death (He et al., 2013). For example, aging is a critical factor in the development of neurodegenerative diseases and stroke. As human populations become progressively older worldwide, large numbers of patients are in urgent need of curative therapies for these intractable diseases (Isobe et al., 2014). In recent years, stem cell therapies have emerged as a promising therapeutic approach for age-related central nervous system (CNS) diseases.

2. Age-related changes in the CNS

It is well accepted that advancing age is accompanied by multiple alterations in brain structure, cellular and metabolic changes, increases in oxidative stress, decreased self-repair capacities, reduced sensorimotor and cognitive functions, and significantly increased susceptibility to neurodegenerative diseases.

Age-related alterations in brain structure, including decreases in neocortical and archicortical volume, surface area, brain weight, and a concomitant enlargement in the ventricular system (Pakkenberg et al., 2003), are associated with declined neural functions in elderly humans. For example, there is a negative linear relationship between cortical thickness and advancing age in most telencephalic areas (Fjell et al., 2014), and the rate of grey matter loss with age has been shown to range from 3.2 to 5.3 cm^3 or 0.5% each year (Good et al., 2001). The age-related loss in neuron numbers is approximately 9.5% over a 70 year age-span (from 20–90 years of age), with an average loss of nearly 85,000 cells per day, or 1 per second. Furthermore, the number of proliferating cells is negatively correlated with age, which suggests that neuronal regeneration capacity is also reduced as a function of age. In addition, decreases in receptors and neurotransmitters and decline in synapse numbers also contribute to age-related disturbances in neuronal function (Lanni et al., 2010).

Although neurogenesis persists throughout life, the ability of the adult brain to repair itself is limited and the rate of cell renewal slows down with age. The proliferation and number of neuroblasts in the subventricular zone (SVZ)—one of two regions in adult brain that have neurogenesis capacity—show an age-dependent decline (Arslan-Ergul et al., 2013), due to the decrease in neural precursors and enhancement of apoptosis of newborn cells (Chen and Sun, 2007). Increased expression of the senescence regulator, decreased growth factor concentrations, and decline in metabolic functions all contribute to impairments in neural stem cell (NSC) maintenance and neuronal differentiation (Rafalski and Brunet, 2011). In short, adult neurogenesis wanes exponentially as a function of age (Jinno, 2015).

In addition to age-related impairments in neurogenesis, there is a 30% decline in white matter volume with aging (Marner et al., 2003). Axon numbers decrease 10% per decade (Marner et al., 2003), and total myelinated nerve fiber lengths exhibit 40–50% reduction with age (Pakkenberg et al., 2003). The age-dependent white matter alterations encompass Wallerian degeneration, axonal damage, demyelination, gliosis, and fiber loss (Burzynska et al., 2010). However, white matter plasticity/restoration also continues through adulthood

(Wang and Young, 2014). Oligodendrocyte progenitor cells (OPCs) are activated by many chemical signals during axonal inflammation and demyelination and migrate from the ventricular zone to the appropriate destination and differentiate into mature, myelinating oligodendrocytes. Compared with young brains, the aged brain had fewer OPCs, with lower proliferation and differentiation potential (Ohta et al., 2003). Furthermore, the number of oligodendrocytes decreases in an age-dependent manner (Jinno, 2015). As a result, the efficiency of remyelination is significantly reduced in the aged brain (Yang et al., 2012). In addition, a decline in axonal regeneration and functional recovery in injured older animals is associated with loss of extracellular matrix components, neurotrophic factors, and intrinsic feedback mechanisms (Roozbehi et al., 2015). Thus, the capacity of white matter for plasticity and repair is greatly diminished during aging.

The neurovascular unit (NVU) is composed of neurons, glial cells (oligodendroglia, astrocytes, and microglia), and vascular elements (endothelium, pericytes, and vascular smooth muscle cells), and these components are known to communicate and interact with each other (Bell and Zlokovic, 2009). Oxidative stress, protein and DNA modifications and damage, and mitochondrial dysfunction are key mechanisms linked with aging (Sahin and Depinho, 2010). Other age-related pathophysiological alterations in the CNS include cell senescence and apoptosis, caloric restriction and metabolic dysfunctions, neuroinflammation, and microglia activation. All these factors contribute to NVU damage, leading to neurovascular uncoupling, basement membrane rupture, pericyte loss, and blood-brain barrier (BBB) compromise. The role of the neurovasculature and BBB in the development and progression of neurological diseases is well accepted. Thus, neuronal injury is not the only contributor to disease initiation and development, and rectifying disruption in glial and vascular cells may offer new methods to ameliorate neuronal degeneration (Zlokovic, 2011).

3. Common features of neurodegenerative diseases and stroke in aging

Neurodegenerative diseases, the most common disorders of the brain, are characterized by the formation of disease-specific misfolded proteins, loss of neurons and synapses, and eventually cause cognitive and/or sensorimotor malfunctions (Bredesen et al., 2006). Stroke is one of the major causes of disability and mortality worldwide and is characterized by ischemia-induced disruption of neuronal networks and disturbances in the BBB, both of which contribute to significant neurological dysfunction (Ding et al., 2013; Corbett et al., 2014). Aging, an important risk factor for both neurodegenerative disease and stroke, not only renders patients more susceptible to these disorders, but also attenuates self-repair capabilities (Hung et al., 2010; Donnellan et al., 2012). In addition, lowered drug responsiveness and intolerable side effects remain key challenges in the prevention and treatment of senile diseases. Cell-based therapies, which offer both cell replacement and neuroprotection, have emerged as a new research tool and therapeutic approach in neurodegenerative diseases and stroke field.

4. Stem cells at the forefront of basic research

Stem cells are characterized by the ability to self-renew and to differentiate into mature cells (Henningson et al., 2003). There are two therapeutic strategies employing stem cells: stimulation/boosting of the endogenous neural progenitor cells and implantation of exogenous stem cells. The potential mechanisms underlying stem cell therapies including direct replacement of damaged or lost cells, facilitation of tissue repair, secretion of trophic factors and growth molecules, mobilization of endogenous stem cells, and immunomodulation (Chiu and Rao, 2011). Engrafted stem cells have been shown to integrate into the resident neural and synaptic networks to promote neurological reconstruction in animal models of neurodegeneration (Chan et al., 2014a). Stem cell therapies have also been tested in neurodegenerative diseases and stroke clinical trials. Although stem cell research is still in its infancy, it has become evident that stem cell therapy is safe and beneficial (Karussis et al., 2013). Here we summarized the type and general aspects of stem cells used in basic research and clinical trials as well as the routes of stem cell delivery.

4.1. Embryonic stem cells (ESCs)

ESCs have potent self-renewal and differentiation capacities and can further divide into multilineage adult cells including mesenchymal stem cells (MSCs), neural stem cells (NSCs), and other cell types. Thus, ESCs can be used as a limitless cell resource for regenerative medicine (Wobus and Boheler, 2005), and their differentiation into specific neurons has great clinical utility in regenerative therapies for CNS disorders (Drouin-Ouellet and Barker, 2014). However, ethical considerations have prompted research into alternative stem cell sources. Furthermore, the equivalent capabilities to differentiate into various somatic cell types may be problematic for stem cell-based therapies (Kazmerova et al., 2013). Multiple experiments have demonstrated that ESCs engrafted into animals present with poor differentiation and inappropriate migration properties, and, in some cases, the formation of teratomas or tumors (Carson et al., 2006). In addition, allogeneic transplantation of ESCs might lead to rejection of implanted cells by the host tissue (Spits et al., 2008). These problems have hindered the application of ESCs in translational medicine.

4.2. Induced pluripotent stem cells (iPSCs)

In 2006, Takahashi and Yamanaka successfully reprogrammed mature cells into iPSCs by forced expression of a set of transcription factors (Takahashi and Yamanaka, 2006). This process is now called reprogramming and refers to the induction of a pluripotent state in a previously differentiated cell type. iPSCs can originate from a wide variety of cells, such as fibroblasts, hepatocytes, circulating T cells and keratinocytes, despite varying efficiencies (de Lazaro et al., 2014). Cells from the same individual can be reprogrammed by specific manipulations to achieve entirely different cell states. For example, in a patient with a degenerative brain disorder, a pluripotent cell can be taken from the skin or blood, and the resulting iPSCs can become a reliable source for generating those neural cells that are affected by the neurological disorder. Transplantation of iPSCs into a syngeneic recipient overcomes the negative side-effects of immunogenicity (Isobe et al., 2014). As iPSCs can be produced without oocytes or embryos, ethical concerns that restrict the application of ESCs

do not apply (Hanley et al., 2010). iPSCs provide a valuable avenue for autologous cell transplantation with no risk of graft rejection (Behari and Singhal, 2011). Using an optimized differentiation method, iPSCs can be converted into mature functional neural lineages, such as motor neurons, dopaminergic, gamma aminobutyric acid (GABA)-ergic, and glutamatergic subtypes, as well as oligodendrocytes, greatly widening the scope of potential applications (Matsumoto et al., 2016).

As iPSCs can elicit disease-related, non-transformed human cell phenotypes that possess the genomic information of the subjects from which iPSC lines were originally derived, iPSCs have been used to establish various disease models *in vitro*. The results of the *in vitro* iPSC studies offer insight into the mechanisms underlying various disorders and may be useful in the screening of novel therapeutic targets (Sproul, 2015). However, there are also obstacles that impede the application of iPSCs as cell-based therapies, such as tumor formation and limited and immature reprogramming (Kazmerova et al., 2013).

4.3. Somatic stem cells (SSCs)

SSCs also have high proliferative and self-renewal capacities (Belenguer et al., 2016). They provide the basis for tissue maintenance and response to injury in areas with high cell turnover, such as the blood and skin (Tumbar et al., 2004). In addition, SSCs are derived from some tissues with low rates of cell turnover, such as brain and muscle (Montarras et al., 2005). SSCs generally consist of hematopoietic stem cells (HSCs), MSCs, NSCs, and endothelial stem cells.

4.3.1. HSCs—HSCs are mainly collected from the bone marrow and can develop into mature blood cells (Kim et al., 2016). HSCs can also transform into skin, liver, lung epithelium, and the gastrointestinal tract (Krause et al., 2001). The differentiation of HSCs into neurons and microglia has been reported in *both in vitro* and *in vivo* studies, and can be triggered by the specific microenvironment in damaged tissues, even though it occurs infrequently in the intact adult brain (Kan et al., 2007). HSC transplantation has been demonstrated to eliminate the dysfunctional immune system, and reconstruct a new immune system that is more compatible with the nervous system, together with significant and sustained inhibition of inflammation (Blanco et al., 2005). HSCs can migrate to the damaged lesion site and rebuild viable endothelia, enhance neurogenesis/angiogenesis, modulate immune responses, as well as suppress oxidative stress and inflammatory activity (Baker et al., 2007; Shin et al., 2011; Sobrino et al., 2011). The short-term side effects of HSC transplantation include infections and engraftment syndrome, whereas the long-term complications include secondary malignancies, endocrine disorders, and autoimmune diseases (Blanco et al., 2005; Epstein et al., 2009; Orio et al., 2014).

4.3.2. MSCs—MSCs found in various tissues can differentiate into bone, cartilage, fat, and epithelial cells of the liver, lung, skin, kidney, and gastrointestinal tract (Sanchez-Ramos, 2002). Several studies have demonstrated that MSCs possess a neural predisposition and can differentiate into neural and glial cells (Glat and Offen, 2013). MSCs can produce and secrete neurotrophic factors, such as brain-derived neurotrophic factor and glial-derived neurotrophic factor (GDNF), and facilitate cell survival and promote their migration toward

lesion sites (Sadan et al., 2009b). MSCs can also express stromal-derived factor 1 and angiopoietin-1, thereby recruiting and supporting neural progenitors (Ohab et al., 2006). In addition, MSCs release angiogenic cytokines and extracellular matrix components, which are known to stimulate angiogenesis (Kinnaird et al., 2004; Hung et al., 2007). MSCs can activate microglia and cause their proliferation, enhance microglial phagocytosis, and modulate immune responses (Lee et al., 2010b; Lee et al., 2012). Finally, MSCs can mitigate oxidative stress, which facilitates the production of anti-inflammatory cytokines, inhibits glial activation, and suppresses cell apoptosis (Lee et al., 2010a).

4.3.2.1. Umbilical cord-derived MSCs (UC-MSCs): UC-MSCs are isolated from umbilical cord tissue, which is generally discarded after childbirth or stored for further use, thereby avoiding ethical concerns (Shetty et al., 2013). As an intermediate link between embryonic and adult tissue, UC-MSCs are a promising source of material for allogeneic stem cell therapies, as they can be harvested painlessly and noninvasively in abundance. UC-MSCs present both an immunoprivileged and immunomodulatory phenotype with low levels of human leukocyte antigen (Chao et al., 2012). UC-MSCs possess strong proliferation and stem cell properties, giving rise to multiple lineages and transforming into adipocytes, osteocytes, chondrocytes, cardiomyocytes, neurons, and oligodendrocytes (Koh et al., 2008). UC-MSCs exert neuroprotective and neuroregenerative effects through various mechanisms (Dalous et al., 2012). In the presence of the appropriate chemical factors, UC-MSCs can move to specific injury sites, and differentiate into and replace damaged or dead cells (Liao et al., 2009a; Yan-Wu et al., 2011). By releasing a plethora of growth and neurotrophic factors, UC-MSCs activate endogenous repair mechanisms to recruit and enhance proliferation and differentiation of host cells, leading to neurogenesis and angiogenesis (Koh et al., 2008; Zhou et al., 2015). By balancing anti- and pro-inflammatory cytokines, UC-MSCs exert immunomodulatory functions, thereby inhibiting inflammation (Liao et al., 2009b; Cheng et al., 2015). No studies to date have reported tumorigenesis after UC-MSC transplantation *in vivo* (Xiong et al., 2011).

4.3.2.2. Bone marrow-derived MSCs (BM-MSCs): BM-MSCs, the non-blood forming fraction of bone marrow, can differentiate into multiple cell types, including osteoblasts, chondrocytes, adipocytes, and vascular smooth muscle cells (Kan et al., 2007). Besides the properties of self-renewal, proliferation, and adherence to plastic surfaces, BM-MSCs stain positively for CD44, CD73, CD90, and CD105, and do not stain for CD14, CD19, CD34, CD45, and HLA-DR (Hilfiker et al., 2011). Several studies have demonstrated that BM-MSCs can differentiate into neurospheres and neuron-like cells in the host brain, increasing their neurogenic transplant potential (Chung et al., 2013). Furthermore, BM-MSCs can be induced into astrocyte-like cells, which can release neurotrophic factors such as brain-derived neurotrophic factor, GDNF, vascular endothelial growth factor, and nerve growth factor (Razavi et al., 2013). Through cell fusion-like processes, BM-MSCs can stimulate the expression of neurotransmitter receptors that are involved in synaptic transmission and neuronal network formation (Bae et al., 2007). In addition, BM-MSCs can improve the integrity of the BBB via upregulation of the tight junction-associated protein occludin and collagen IV (Wang et al., 2015a). BM-MSCs have strong potential as therapies for neurological diseases, given their capacity for reducing cell death and promoting cellular

proliferation, neurogenesis, oligodendrogenesis, angiogenesis, and synaptogenesis, (Gutierrez-Fernandez et al., 2013). BM-MSC transplantation *in vivo* has been regarded as safe over the past few decades, although BM-MSCs exhibit some neoplastic transformation *ex vitro* after a long period in culture (Sadan et al., 2009a). However, acquisition of BM-MSCs is an invasive procedure, as they are confined to a small niche of adult tissues. With advancing age, the quantity, maximum life-span, and differentiation potential of BM-MSCs decline, somewhat limiting the application of BM-MSCs in the clinical setting (Ikegame et al., 2011; Yan et al., 2013).

4.3.2.3. Adipose tissue-derived MSCs (AD-MSCs): AD-MSCs, also called adipose tissue-derived stem cells (ADSCs), are unique because they can be obtained easily in a minimally invasive manner from adipose tissue (Merceron et al., 2011; Bourin et al., 2013). AD-MSCs possess two crucial features: efficient and convenient production at a large scale and *in vitro* proliferation (Yeh et al., 2015). Besides providing a cellular source for adipogenesis, AD-MSCs can differentiate into osteoblasts, neural cells, endothelial cells, myocytes, hepatocytes, and other cell types (Chan et al., 2014b), all of which are useful for tissue or cell replacement therapies. As they secrete high levels of self-renewal supporting factors, AD-MSCs may be able to reprogram into iPSCs with higher efficiencies than other cell types (Sugii et al., 2011). Through the release of chemokine receptors and ligands, AD-MSCs can also home to the site of injury (Ong and Sugii, 2013). Due to deficiencies in surface expression of type II major histocompatibilty complex and co-stimulatory factors, AD-MSCs are immunoprivileged and enable allotransplantation into immunocompetent hosts with minimal immunoreactions in the recipients (Lindroos et al., 2011). Additionally, AD-MSCs exert suppressive effects on graft-versus-host disease, inflammation, and autoimmunity via cell-cell interactions or the secretion of immunomodulatory molecules AD-MSCs (Kokai et al., 2014). AD-MSCs can also release angiogenic, anti-apoptotic, trophic, and hematopoietic factors, which increase their potential to enhance tissue regeneration (Ong and Sugii, 2013; Pak et al., 2016; Wankhade et al., 2016). Thus, AD-MSCs are characterized by versatile differentiation, manifold immunobiological functions, paracrine secretion of cytokines, and migration to the injury sites, all of which increase the therapeutic utility of AD-MSCs in regenerative medicine (Kokai et al., 2014).

4.3.3. NSCs—NSCs are precursors to both neurons and neuroglia. They are self-renewing cells that generate the main cellular phenotypes of the nervous system. NSCs have been isolated from various regions of both the embryonic and the fetal human brain (Belenguer et al., 2016; Harris et al., 2016). Adult human NSCs can also be obtained from brain tissue of patients undergoing surgical therapies. These cells are able to give rise to three major neural lineages—neurons, astrocytes, and oligodendrocytes (Brignier and Gewirtz, 2010). In models of brain injury, endogenous NSCs in the neurogenic niches propagate and migrate toward the areas of damage and then repair the damaged tissues (Arvidsson et al., 2002; Iwai et al., 2007). Furthermore, newborn neural cells can establish synaptic connections with surrounding neurons, integrate into existing circuitry, and repair the impaired network (Ming and Song, 2011). NSCs also engage in gliogenesis. Through the release of bioactive molecules, the newly generated astrocytes may regulate neuronal excitability, synaptic activity, and plasticity, and modulate neural circuitry and information coding (Araque et al.,

2014). NSCs can also produce and release synergistic and antagonistic molecules, initiating signaling cascades that trigger intracellular NSC regulatory mechanisms, such as transcription factors, epigenetic responses, and metabolism (Bond et al., 2015).

Due to their capacity to differentiate into functional neural cells, their genetic stability, limited propagation, lack of tumorigenicity, and the circumvention of ethical concerns, NSCs are a promising therapeutic strategy for neurological disorders (Nam et al., 2015). However, limited sources, difficulties in isolation, proliferation and expansion, as well as immunological rejection remain major obstacles in the therapeutic application of NSCs. Although the NSC research field is still in its infancy, it nevertheless offers significant promise for the future treatment of CNS diseases.

4.4. In situ stem cell reprogramming

After brain injury, glial cells are activated and become hyperplastic and hypertrophic in order to fill up the area of tissue loss (Guo et al., 2014), a process called gliosis. Reactive gliosis exerts both beneficial and detrimental effects on brain function. In the acute phase, reactive glial scars can isolate/seal the injury site and act as protective barriers to minimize the area of inflammation and cellular degeneration. However, scar formation impedes axonal outgrowth/regeneration in the chronic phase, either by acting as a physical barrier or by secreting inhibitory extracellular matrix molecules, such as chondroitin sulfate proteoglycan (Pekny and Nilsson, 2005; Robel et al., 2011). Thus, endogenous reactive astrocytes might be a promising target for neuronal conversion and repair following brain lesions (Niu et al., 2013).

Astrocytes are the most abundant and widely distributed non-neuronal cells in the adult CNS. Through the expression of specific transcription factors, astrocytes can be directly differentiated into neurons (Heinrich et al., 2011). *In vitro* experiments have shown that neurons derived from reprogrammed postnatal astrocytes in culture can acquire the functional identities of mature neurons and receive synaptic inputs from co-cultured cortical neurons (Berninger et al., 2007; Blum et al., 2011). Reactive astrocytes *in vivo* can be reprogrammed into proliferative neuroblasts in both adult and aged brains, which can be maintained for months and develop into functional and mature neurons, and ultimately integrate into existing neural circuitry. (Niu et al., 2013). By forced overexpression of three transcription factors, astrocytes can be successfully reprogrammed into oligodendrocytes, which not only repair injured white matter in experimental stroke and traumatic brain injury, but also attenuate the formation of the glial scar (unpublished data from Dr. Cao lab). These findings confirm the remarkable plasticity of astrocytes *in vivo* and show that astrocytes can be reprogrammed into fully differentiated neurons across cell lineages. Apart from astrocytes, NG2 cells in the cortex also can be reprogrammed into functional neurons *in vivo* (Guo et al., 2014). Thus, glial cells from the same individual may be an ideal source of cells for neuronal restoration, not only preventing an immune response, but also establishing a more natural or physiological neural network.

4.5. Routes of stem cell delivery

Stem cells can be delivered by intracerebral or intracerebroventricular injection, intravascular infusion, and intranasal delivery (Misra et al., 2012). Transplanted stem cells not only appear in the lesion core area, but also in the region surrounding the lesion (Savitz et al., 2004). Different administration routes influence the migration, distribution, and the quantity of transplanted cells in the target area (Li et al., 2010). In addition, the type of disease, dosage of stem cells, and timing of cell delivery must be carefully considered (Misra et al., 2012). To date, there are few studies directly comparing the efficacy of diverse transplantation routes, and the optimum delivery route for specific cell types has therefore not been determined (Liu et al., 2014).

4.5.1. Intracerebral or intracerebroventricular (ICV) transplantation— Intracerebral injection of stem cells requires fewer stem cells and is a precise delivery route, which may be most appropriate for NSC implantation (Liu et al., 2014). However, due to invasive procedures and severe adverse effects, such as seizures, motor exacerbations, syncope, chronic subdural hematoma, and tumorigenicity, direct stereotaxic injection has been used less often in clinical trials (Savitz et al., 2005). ICV injection is relatively less invasive than intracerebral injection, and has not shown cell-related tumorigenicity. However, only a small fraction of transplanted cells migrate to the target site, and ICV injection may cause higher risk of fever, infection, and meningitis (Rabinovich et al., 2005).

4.5.2. Intravascular infusion—Intravascular infusion is a safe and convenient administration approach for stem cell therapy in the clinic, and is far less invasive than ICV and intracerebral administration (Du et al., 2014). Intravenously-delivered cells can penetrate through BBB and migrate to the damaged tissue via a chemoattractant gradient (Bacigaluppi et al., 2008). However, cell homing to the lesion site is greatly compromised by peripheral filtering, such as in the lungs, liver, and spleen, (Yang et al., 2011) and there is a delay in functional recovery due to lengthy migration periods (Du et al., 2014). Nevertheless, intravenously delivered stem cells exert neuroprotection by stabilization of the BBB, and modulation of immune responses and anti-apoptotic pathways; these effects are actually independent of intracerebral migration and homing. Due to less invasive and convenient delivery, intravenous delivery is so far the most commonly used approach for stem cell delivery in clinical trials (Yang et al., 2013). However, intravenous administration also raises safety concerns, such as microembolus formation due to cell-to-cell adhesion, which can lead to lethal pulmonary emboli (Liu et al., 2014). Intra-arterial delivery of stem cells appears to be an attractive approach that results in faster initial accumulation, more widespread distribution, and relatively higher concentrations of transplanted cells in the target area than intracisternal or intravenous administration (Li et al., 2010). However, intra-arterial delivery raises serious safety concerns in term of microvascular occlusion, injury exacerbation, and higher mortality (Li et al., 2010). The use of mononuclear cells via microneedles rather than catheters may circumvent these adverse events (Brenneman et al., 2010; Chua et al., 2011).

4.5.3. Intranasal delivery—Intranasal administration can directly deliver cells to the CNS with minimal peripheral exposure (Chapman et al., 2013). The olfactory area is a

specific interface between the CNS and the external environment that bypasses the BBB (Chartoff et al., 2011). After intranasal injection, transplanted cells can migrate into the olfactory bulb, enter into the cerebrospinal fluid (CSF), and then migrate to the injured region. Adhesive interactions and chemokine gradients generated from injured cells may facilitate the homing of stem cells to target areas (Wei et al., 2013). Several studies have demonstrated that high quantities of intranasally delivered stem cells can enter the CNS, concentrate specifically at disease foci, and exert effects for several months post-infusion (Li et al., 2015). The safeness and efficiency of the intranasal delivery has been investigated in animal models of various neurological diseases (Tang et al., 2015). However, intranasal delivery has some disadvantages, such as active mucociliary clearance, enzymatic degradation, and low pH of the nasal epithelium, low permeability without absorption enhancers, as well as individual variability, which may cause low CNS delivery efficiencies and necessitate the delivery of high doses (Lochhead and Thorne, 2012). Despite these obstacles and a dearth of studies in the relatively novel field of intranasal delivery, it offers great potential for the implantation of stem cells into the brain, especially in neurological disorders.

5. Stem cell therapies in age-related central nervous system diseases

5.1. Alzheimer's disease (AD)

AD, the most common neurodegenerative disease and the sixth leading cause of death in the United States (Xu et al., 2016), is characterized by progressive loss in memory, disorientation, language, problem-solving, mood swings, as well as loss of motivation and other cognitive functions that affect daily activities and quality of life (Wilson et al., 2012). Advancing age is the greatest risk factor for AD, which accounts for 60% to 70% of cases of dementia. Approximately 5.3 million Americans suffer from AD, including 5.1 million individuals over the age of 65 (Hebert et al., 2013). The cause of Alzheimer's disease is poorly understood. The deposition of beta-amyloid plaques outside neurons and anomalous forms of tau tangles inside neurons lead to the failure of information transmission at synapses and neuronal death, contributing to the evolution of AD. Due to the decline and death of neurons, AD causes a profound shrinkage in brain volume and weight, especially in the telencephalon (Huang and Mucke, 2012). As a result, areas of the brain related to cognition and memory are severely affected, and eventually the patient is rendered unable to perform basic bodily functions (2012).

5.1.1. Age-related changes in the brain of AD victims—The main pathological changes in the AD brain are the extracellular accumulation of neuritic plaques containing beta-amyloid peptides, and the intraneuronal deposition of aberrant forms of tau proteins in neurofibrillary tangles, both of which contribute to synaptic injury and neuronal death (Montine et al., 2012). In addition, a second but non-amyloid process may be conducive to the formation of tangles in the medial temporal lobe (Mungas et al., 2014). Imbalances in mitochondrial dynamics and synaptic pathology are both early events in AD progression, and age-related mitochondrial dysfunction is associated with accumulating oxidative stress, elevation of intracellular calcium concentrations, and decreased mitochondrial adenosine triphosphate levels (Reddy et al., 2012).

5.1.2. Current status of therapies for AD—The current treatments for AD include pharmacologic as well as non-pharmacologic therapies, such as music and reminiscence therapy. There are six drugs approved by the U.S. Food and Drug Administration (FDA) that can temporarily ameliorate symptoms of AD. However, the efficacy of these drugs differs across individuals. There are no curative treatments, including among the non-pharmacological approaches, that have truly changed the progression of AD (2015; Hunsberger et al., 2015).

5.1.3. Stem cell therapies for AD—MSCs initiate neural reconstruction, remyelination, and immune adjustment (Urdzikova et al., 2014). MSCs can also influence amyloidogenesis and/or microglial activation, resulting in a reduction in amyloid-β peptide (Aβ) accumulation and recovery from cognitive deficits (Lee et al., 2009). MSCs also can produce neurotrophic factors, which can stimulate endogenous neurogenesis, angiogenesis, and neuronal defense systems (Martinez-Morales et al., 2013). As a result, transplantation of MSCs into an AD model can induce the proliferation, differentiation, and maturation of endogenous NSCs toward a neuronal phenotype (Kan et al., 2011). Several studies have shown that MSCs can remove Aβ plaques and diminish vascular injury (Garcia et al., 2014; Salem et al., 2014). AD-MSCs can alleviate memory impairments and decrease the amount of amyloid plaques and Aβ in AD mouse models by upregulating the levels of interleukin-10 and vascular endothelial growth factor and modulating microglial activation in the brain AD-MSCs(Kim et al., 2012; Ma et al., 2013). NSC transplantation can increase synaptic plasticity, reduce pathology and ameliorate spatial learning and memory dysfunction by increasing the expression of multiple cognition-related proteins in AD models (Blurton-Jones et al., 2014; Chen et al., 2014c; Zhang et al., 2014). iPSC-derived macrophage-like cells have also been found to reduce the levels of Aβ (Takamatsu et al., 2014). However, aberrant metabolism of the Aβ precursor protein may interfere with stem cell biologic functions, leading to gliogenesis activation, and finally disable NSC migration or differentiation into neurons (Sugaya, 2005).

In 2015, the FDA approved the first phase 2A clinical trial of MCSs for AD treatment, and similar trials are currently underway or being designed in Europe and Asia (Hunsberger et al., 2015). The “Allogeneic Human MSCs for Alzheimer’s Disease” study (NCT02833792) is a phase IIa multicenter, single-blind, randomized, placebo-controlled and crossover study in the US, and is designed to assess the safety, tolerability and preliminary efficacy of ischemia-tolerant allogeneic human MSCs in patients with mild to moderate dementia due to AD. The “Safety and Exploratory Efficacy Study of NEUROSTEM® Versus Placebo in Patients With Alzheimer’s Disease” study (NCT02054208) is a combined phase 1/2a double-blind, single-center clinical trial in Korea and is still in the recruiting stage.

5.2. Parkinson’s disease (PD)

PD is the second most common age-related neurodegenerative disease and is characterized by the progressive degeneration of dopamine (DA) neurons of the nigrostriatal system in the midbrain and loss of other neurotransmitter phenotype neurons in non-DA brain areas (Buddhala et al., 2015; Schneider and Obeso, 2015). As a result of the depletion of dopamine release from the nigrostriatal pathway, afflicted individuals suffer from motor

dysfunctions such as tremor, rigidity, bradykinesia and postural instability, usually in their fifth to seventh decade of life (Ye et al., 2007). The motor pathologies are typically clinically manifested when ~60–80% of DAergic neurons in the substantia nigra are irreversibly lost (Cheng et al., 2010). The prevalence of PD ranges between 40 ~328 per 100,000 and rises in incidence from 50 years of age onwards, with a sharp increase after 60 years of age (Behari and Singhal, 2011). Thus, age is the largest risk factor for the occurrence and development of PD. Compared with younger onset patients, older onset PD patients become demented earlier and have more inclusion bodies throughout the brain and additional age-related plaque pathology (Halliday and McCann, 2010). Furthermore, aging may influence the clinical manifestation of PD with alterations in responsiveness to medications and drug adverse effects, and increased risk of dementia.

5.2.1. Age-related changes in the brain of PD victims—Apart from the degeneration of DA-containing neurons, PD is classified as a synucleinopathy and is characterized by the aggregation of misfolded alpha-synuclein and other proteins in intracytoplasmic inclusions called Lewy bodies and Lewy neurites (Goedert, 2001; Braak et al., 2003; Singh et al., 2007). Lewy pathology is not limited to the ventral mesencephalon but is found in multiple vulnerable brain regions, including the medulla oblongata and the olfactory bulb (Goedert, 2001; Braak et al., 2003; Singh et al., 2007). Mitochondrial impairments, oxidative damage and abnormal metabolism play crucial roles in the regulation of biochemical reactions triggered by the known risk factors and causes of PD (Schapira et al., 2009). In addition, PD may reflect a loss of endogenous compensatory mechanisms in vulnerable brain areas, a susceptibility that is enhanced by aging (Hindle, 2010).

5.2.2. Current status of therapies for PD—Current treatments focus on promoting the level of DA or simulating the effects of DA in brain, including pharmacological therapies such as dopamine agonists and surgical interventions (Trzaska and Rameshwar, 2007). Although all these measures appear to be effective in alleviating the symptoms, they are unable to arrest or reverse the disease progression. Furthermore, these therapeutic effects wane over time, and the incidence and severity of side effects increase as the disease progresses. Aged patients are particularly sensitive to the pharmacological therapies, potentially leading to confusion, hallucinations, orthostatic hypotension, and fatigue. Due to the possible adverse side effects such as brain hemorrhage, infarction, seizures, and even death, invasive surgical methods are not recommended for elderly patients (Singh et al., 2007).

5.2.3. Stem cell therapies for PD—As there is massive DA neuron loss in PD, stem cell therapies have been proposed as a novel method for treating this condition (Chiu and Hall, 2006). MSCs have been shown reduce dopamine depletion and rebuild the damaged striatal dopaminergic nerve terminal network in experimental PD *in vivo* (Sadan et al., 2009b). Adult human MSCs can develop into neural progenitor cells (NPCs), with the ability to express both DAergic and GABAergic characteristics *in vitro*. However, transplanted human NPCs differentiate into GABA but not DA neurons in the Parkinsonian rat, and the survival duration of neurons is short (Suon et al., 2006).

AD-MSCs have been shown to inhibit 6-OHDA-induced neurotoxicity and ROS production in neurons, thereby protecting rostral mesencephalic neurons against 6-OHDA neurotoxicity. ADSC therapy also exhibits neuroprotective effects in methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-lesioned hemi-parkinsonian rhesus monkeys, with symptom amelioration and autograft survival (Zhou et al., 2013).

SVZ NSCs naturally exhibit a DAergic interneuron phenotype and may be a potential autologous source of substitution cells for PD therapy (Cave and Baker, 2009). Several studies have shown that DAergic neurons derived from ESCs or iPSCs grafted into PD model systems can both survive and integrate into the host network with remarkable functional improvements (Cave et al., 2014). Thus, the use of iPSCs and induced dopamine neurons (iDA) neurons offers a suitable approach for autologous cell-based therapy in PD (Han et al., 2015).

Transplantation of autologous BM-MSCs causes marginal amelioration of symptoms but nevertheless improves quality of life in PD patients, in the absence of significant adverse effects (Venkataramana et al., 2010). Human retinal pigment epithelial (hRPE) cells, an alternative to human fetal tissue transplants, possess the features of NPCs that permit differentiation into DA neurons. In a pilot clinical trial on 12 patients with idiopathic PD, Yin et al found that intrastriatal transplantation of hRPE cells with stereotactic operation was safe and tolerable, and elicited behavioral and motor improvements (Yin et al., 2012). However, in a randomized, double-blind study enrolling 71 eligible patients with advanced PD, implantation of hRPE cells provided no advantage over placebo (Gross et al., 2011). Benefits in open-label studies that have not reproduced in controlled studies are associated with patient bias, observer bias, or both, and a placebo controlled, double-blind design is therefore quite important. Overall, the outcomes of stem cell transplantation in PD have been quite diverse and adverse events such as dyskinesia have diminished the therapeutic effects (Karussis et al., 2013).

5.3. Stroke

Stroke is caused by reduction or interruption of the blood flow to the brain by blocked or disrupted vessels, leading to cerebral infarction, intracerebral hemorrhage (ICH), and/or subarachnoid hemorrhage (SAH). Worldwide, stroke is the second most common cause of mortality and the leading cause of adult disability (Gutierrez-Fernandez et al., 2015), with 795,000 new or recurring cases reported per year in the USA alone (Roger et al., 2012). Aging is a major risk factor for stroke, increasing the risk of stroke by 9% for each year lived (Asplund et al., 2009). Due to progressive atherosclerosis, higher incidence of cardiac arrhythmia, hypertension and hypercholesterolemia, and vascular alterations in the aged population (Shuaib and Boyle, 1994), the incidence of stroke increases significantly with aging.

5.3.1. Age-related changes in the brain of stroke victims—Previous research suggested that aged animals exhibit earlier destruction of the BBB, enhanced neuronal damage, larger infarct sizes, higher death rates, and poorer prognosis than younger animals after ischemic stroke (Dong et al., 2014). Increased oxidative stress, protein and DNA

modifications and damage, mitochondrial dysfunction, as well as impaired energy metabolism contribute to the enhanced susceptibility of the aged brain to ischemia. Although aged brains still reserve the capacity for cytoproliferation after injury, newly generated neural cells are more likely to differentiate into astrocytes rather than neurons in the aged brain (Popa-Wagner et al., 2006), leading to rapid formation of the glial scar surrounding the infarcted area, which impedes the genesis of new axons, neurons, and blood vessels (Badan et al., 2003). Finally, the premature appearance of proliferating astrocytes and enhanced cellular degeneration contributes to a rapid emergence and development of the infarction as well as poor prognosis (Popa-Wagner et al., 2007).

5.3.2. Current status of stroke therapies—Despite positive results in animal models, all neuroprotectants have failed in clinical trials (Hoyte et al., 2004). Currently, recombinant tissue plasminogen activator (rt-PA) is the only validated approach for ischemic stroke. However, less than 5% of stroke patients received tPA therapies due to the narrow therapeutic time window and potential for hemorrhage side effects.

5.3.3. Stem cell therapies for stroke—Ischemic stroke results in brain tissue infarction and massive loss of neural cells. Although ischemia can trigger endogenous neurogenesis and angiogenesis, the majority of newly generated cells die rapidly and few of them migrate to ischemic regions and differentiate into mature neurons. Cell-based therapies can increase neuroplasticity, improve the architecture and physiology of cerebral tissue, and promote neurological recovery after ischemic stroke (Chen et al., 2014b). Thus, ischemic stroke might be more suitable for cell-based therapies than other CNS diseases. The underlying mechanisms for these therapeutic effects include cell replacement, nutritional support, immunomodulation, and activation of endogenous pro-survival processes such as neurogenesis, vasculogenesis, and oligodendrogenesis (Liu et al., 2014). A variety of cell-based therapies have been investigated in ischemic stroke, including BM-MSCs, AD-MSCs, NSCs, and iPSCs.

MSCs can secrete multiple angiogenic factors, develop into other cell phenotypes, and promote proliferation of endogenous NSCs. Transplantation of human MSCs into ipsilateral brain parenchyma in animal models of middle cerebral artery occlusion (MCAO) may promote endogenous neurogenesis, migration, survival and mature of neuroblasts, which may lead to reductions in infarct volume and improvements in neurological function (Bao et al., 2011). MSCs also can facilitate axonal regeneration by inhibiting neurocan generation in astrocytes around the infarction zone (Shen et al., 2008). In addition, MSCs are known to promote angiogenesis (Liao et al., 2009a). ADSC transplantation can reduce infarct sizes and improve clinical outcomes, which offers promise for both ischemic and hemorrhagic stroke (Gutierrez-Fernandez et al., 2015). NSCs can mitigate white matter injury and regulate microglial/macrophage function and have emerged as a robust neuroprotective therapy against cerebral ischemia (Wang et al., 2015b). Transplantation of human ESC-derived endothelial cells increases neovascularization and consequently reduces infarct volume with neurological recovery after stroke in a transient MCAO model (Oyamada et al., 2008). Human ESC-derived neuronal precursor cells survive the transplantation procedure, migrate into the infarct zone, and differentiate into mature neural cells, resulting in reduced

infarct volume and enhanced behavioral recovery (Kim et al., 2007). Several studies have also shown neuroprotective effects of iPSCs in reducing infarct size and restoring neurological functions after ischemic stroke (Jiang et al., 2011; Yuan et al., 2013). In a parallel comparison of the curative effects of iPSCs and ESCs in a rat MCAO model, transplanted cells of both types survived and migrated close to the ischemic area, followed by development into mature astrocytes or neurons, with similar protective effects in functional, histological, and metabolic assays (Wang et al., 2013).

Several open clinical studies have shown the safety and feasibility of stem cell therapy in cerebrovascular diseases. Phase I and II trials have indicated that administration of cultured NSCs improves clinical outcomes without cell-related adverse effects in the follow-up period (Kondziolka et al., 2000; Kondziolka et al., 2005). Intra-arterial delivery of autologous CD34+ bone marrow stem cells into the infarct territory has also been shown to be safe in patients with acute ischemic stroke, and can facilitate functional recovery and reduce the lesion volume (Banerjee et al., 2014). A non-randomized phase-I clinical study enrolling eleven patients with subacute ischemic stroke showed that intravenous transplantation of autologous bone marrow mononuclear cells (BMMNCs) seemed safe and feasible, and seven out of 11 total patients exhibited improved functional outcomes (Prasad et al., 2012). Patients with severe embolic stroke who were administered autologous BMMNCs intravenously also displayed a tendency to exhibit improvements in cerebral perfusion and metabolism, followed by favorable neurological recovery without apparent adverse events (Taguchi et al., 2015). Bhasin *et al* demonstrated the tolerance, safety, and feasibility of bone marrow-derived stem cell therapy in patients with chronic stroke, and indicated that stem cells act as “scaffolds” for neural implantation and may support repair mechanisms in stroke (Bhasin et al., 2013). A multicentric, randomized phase II trial on 120 subacute ischemic stroke patients revealed that intravenous BMMNCs therapy was safe but ineffective (Prasad et al., 2014). These negative results may be attributed to patient characteristics, cell therapy timing, dose, and route of cell administration. Furthermore, the location and extension of the lesions, the unstandardized endpoints and outcome assessment also contribute to variance (Kim et al., 2013). Stereotaxic transplantation of autologous peripheral blood stem cells in elderly ischemic stroke patients was safe, feasible and effective, and resulted in amelioration of neurological dysfunction and improvements in corticospinal tract integrity (Chen et al., 2014a). Additionally, intra-artery infusion of umbilical cord MSCs to the proximal end of the injured artery in stroke patients has been found to be safe and effective (Jiang et al., 2013). A study of transplantation of combinations of MSCs and NSCs in ischemic stroke patients with two-year follow-up revealed no evidence of neurological infection, neurological deterioration and tumor formation, and showed improvements in neurological functions (Qiao et al., 2014). Combination therapies of multiple cells based on an intraparenchymal approach appeared to be clinically safe and initially beneficial for chronic stroke patients (Chen et al., 2013). In summary, these clinical data demonstrate the safety and potential of stem cell therapy in stroke, but need to be further verified in full-scale, double-blind, and properly randomized clinical trials (Bliss et al., 2010).

6. Future prospects, limitations, and conclusion

To date, research into cell-based therapies in age-related CNS diseases has not fully matured. Several small clinical trials of cell transplantation have been completed but have not yielded satisfactory evidence favoring substantial clinical improvements. In addition, multiple issues, such as target populations, type and source of cells, cell dosage, optimal timing and administration routes must be given more attention (Leak et al., 2014). Safety considerations such as the potential for malignant transformation and side effects such as epilepsy, injection site injury, and immune allergic reactions remain important concerns (Ding et al., 2013). iPSC-derived specific phenotype stem cells offer promise for future clinical trials as they reduce the potential for side effects and lessen other disadvantages of stem cell therapies. Harvesting sufficient allogeneic or syngeneic iPSCs is relatively easy and the inherent properties of these cells mitigate immune responses and guarantee specific terminal differentiated cell phenotypes. As the pathophysiological environment pushes the differentiation of stem cells toward astrocytes, it would be advantageous to use a pool of different differentiated neural/endothelial cells derived from iPSCs rather than iPSCs themselves. Aged populations exhibit a higher incidence of neurodegenerative diseases and stroke and have an attenuated brain self-repair capacity and poor response to treatment, leading to more severe outcomes. Although much research remains to be completed to ensure safety, tolerability, and efficacy of stem cell delivery in aged populations and to further optimize the delivery protocols, stem cell therapy is a promising approach for the future treatment for age-related neurodegenerative diseases and stroke.

Acknowledgments

This project was supported by National Institutes of Health/NINDS grants NS079345 (to G. C.), VA Merit Review grants BX002346 (to G. C.), and Chinese 12th Five science and technology support program 2013BAI07B01 (to X. J).

References

Alzheimer’s disease facts and figures. Alzheimers Dement. 2012; 8:131–168. [PubMed: 22404854]

Alzheimer’s disease facts and figures. Alzheimers Dement. 2015; 11:332–384. [PubMed: 25984581]

Araque A, Carmignoto G, Haydon PG, Oliet SH, Robitaille R, Volterra A. Gliotransmitters travel in time and space. Neuron. 2014; 81:728–739. [PubMed: 24559669]

Arslan-Ergul A, Ozdemir AT, Adams MM. Aging, neurogenesis, and caloric restriction in different model organisms. Aging Dis. 2013; 4:221–232. [PubMed: 23936746]

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med. 2002; 8:963–970. [PubMed: 12161747]

Asplund K, Karvanen J, Giampaoli S, Jousilahti P, Niemela M, Broda G, Cesana G, Dallongeville J, Ducimetriere P, Evans A, Ferrieres J, Haas B, Jorgensen T, Tamosiunas A, Vanuzzo D, Wiklund PG, Yarnell J, Kuulasmaa K, Kulathinal S. Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. Stroke; a journal of cerebral circulation. 2009; 40:2319–2326.

Bacigaluppi M, Pluchino S, Martino G, Kilic E, Hermann DM. Neural stem/precursor cells for the treatment of ischemic stroke. Journal of the neurological sciences. 2008; 265:73–77. [PubMed: 17610905]

Badan I, Buchhold B, Hamm A, Gratz M, Walker LC, Platt D, Kessler C, Popa-Wagner A. Accelerated glial reactivity to stroke in aged rats correlates with reduced functional recovery. J Cereb Blood Flow Metab. 2003; 23:845–854. [PubMed: 12843788]

Bae JS, Han HS, Youn DH, Carter JE, Modo M, Schuchman EH, Jin HK. Bone marrow-derived mesenchymal stem cells promote neuronal networks with functional synaptic transmission after transplantation into mice with neurodegeneration. Stem cells (Dayton, Ohio). 2007; 25:1307–1316.

Baker AH, Sica V, Work LM, Williams-Ignarro S, de Nigris F, Lerman LO, Casamassimi A, Lanza A, Schiano C, Rienzo M, Ignarro LJ, Napoli C. Brain protection using autologous bone marrow cell, metalloproteinase inhibitors, and metabolic treatment in cerebral ischemia. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:3597–3602. [PubMed: 17360688]

Banerjee S, Bentley P, Hamady M, Marley S, Davis J, Shlebak A, Nicholls J, Williamson DA, Jensen SL, Gordon M, Habib N, Chataway J. Intra-Arterial Immunoselected CD34+ Stem Cells for Acute Ischemic Stroke. Stem Cells Transl Med. 2014; 3:1322–1330. [PubMed: 25107583]

Bao X, Wei J, Feng M, Lu S, Li G, Dou W, Ma W, Ma S, An Y, Qin C, Zhao RC, Wang R. Transplantation of human bone marrow-derived mesenchymal stem cells promotes behavioral recovery and endogenous neurogenesis after cerebral ischemia in rats. Brain Res. 2011; 1367:103–113. [PubMed: 20977892]

Behari M, Singhal KK. Cell based therapies in Parkinson's Disease. Ann Neurosci. 2011; 18:76–83. [PubMed: 25205926]

Belenguer G, Domingo-Muelas A, Ferron SR, Morante-Redolat JM, Farinas I. Isolation, culture and analysis of adult subependymal neural stem cells. Differentiation. 2016

Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol. 2009; 118:103–113. [PubMed: 19319544]

Berninger B, Costa MR, Koch U, Schroeder T, Sutor B, Grothe B, Gotz M. Functional properties of neurons derived from in vitro reprogrammed postnatal astroglia. J Neurosci. 2007; 27:8654–8664. [PubMed: 17687043]

Bhasin A, Srivastava MV, Mohanty S, Bhatia R, Kumaran SS, Bose S. Stem cell therapy: a clinical trial of stroke. Clin Neurol Neurosurg. 2013; 115:1003–1008. [PubMed: 23183251]

Blanco Y, Saiz A, Carreras E, Graus F. Autologous haematopoietic-stem-cell transplantation for multiple sclerosis. The Lancet Neurology. 2005; 4:54–63. [PubMed: 15620857]

Bliss TM, Andres RH, Steinberg GK. Optimizing the success of cell transplantation therapy for stroke. Neurobiol Dis. 2010; 37:275–283. [PubMed: 19822211]

Blum R, Heinrich C, Sanchez R, Lepier A, Gundelfinger ED, Berninger B, Gotz M. Neuronal network formation from reprogrammed early postnatal rat cortical glial cells. Cereb Cortex. 2011; 21:413–424. [PubMed: 20562320]

Blurton-Jones M, Spencer B, Michael S, Castello NA, Agazaryan AA, Davis JL, Muller FJ, Loring JF, Masliah E, LaFerla FM. Neural stem cells genetically-modified to express neprilysin reduce pathology in Alzheimer transgenic models. Stem Cell Res Ther. 2014; 5:46. [PubMed: 25022790]

Bond AM, Ming GL, Song H. Adult Mammalian Neural Stem Cells and Neurogenesis: Five Decades Later. Cell Stem Cell. 2015; 17:385–395. [PubMed: 26431181]

Bourin P, Bunnell BA, Casteilla L, Dominici M, Katz AJ, March KL, Redl H, Rubin JP, Yoshimura K, Gimble JM. Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: a joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). Cytotherapy. 2013; 15:641–648. [PubMed: 23570660]

Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging. 2003; 24:197–211. [PubMed: 12498954]

Bredesen DE, Rao RV, Mehlen P. Cell death in the nervous system. Nature. 2006; 443:796–802. [PubMed: 17051206]

Brenneman M, Sharma S, Harting M, Strong R, Cox CS Jr, Aronowski J, Grotta JC, Savitz SI. Autologous bone marrow mononuclear cells enhance recovery after acute ischemic stroke in young and middle-aged rats. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2010; 30:140–149.

Brignier AC, Gewirtz AM. Embryonic and adult stem cell therapy. J Allergy Clin Immunol. 2010; 125:S336–344. [PubMed: 20061008]

Buddhala C, Loftin SK, Kuley BM, Cairns NJ, Campbell MC, Perlmutter JS, Kotzbauer PT. Dopaminergic, serotonergic, and noradrenergic deficits in Parkinson disease. Annals of clinical and translational neurology. 2015; 2:949–959. [PubMed: 26478895]

Burzynska AZ, Preuschhof C, Backman L, Nyberg L, Li SC, Lindenberger U, Heekeren HR. Age-related differences in white matter microstructure: region-specific patterns of diffusivity. Neuroimage. 2010; 49:2104–2112. [PubMed: 19782758]

Carson CT, Aigner S, Gage FH. Stem cells: the good, bad and barely in control. Nat Med. 2006; 12:1237–1238. [PubMed: 17088886]

Cave JW, Baker H. Dopamine systems in the forebrain. Adv Exp Med Biol. 2009; 651:15–35. [PubMed: 19731547]

Cave JW, Wang M, Baker H. Adult subventricular zone neural stem cells as a potential source of dopaminergic replacement neurons. Front Neurosci. 2014; 8:16. [PubMed: 24574954]

Chan TM, Chen JY, Ho LI, Lin HP, Hsueh KW, Liu DD, Chen YH, Hsieh AC, Tsai NM, Hueng DY, Tsai ST, Chou PW, Lin SZ, Harn HJ. ADSC therapy in neurodegenerative disorders. Cell Transplant. 2014a; 23:549–557. [PubMed: 24816450]

Chan TM, Harn HJ, Lin HP, Chiu SC, Lin PC, Wang HI, Ho LI, Chuu CP, Chiou TW, Hsieh AC, Chen YW, Ho WY, Lin SZ. The use of ADSCs as a treatment for chronic stroke. Cell Transplant. 2014b; 23:541–547. [PubMed: 24816449]

Chao YH, Wu HP, Chan CK, Tsai C, Peng CT, Wu KH. Umbilical cord-derived mesenchymal stem cells for hematopoietic stem cell transplantation. Journal of biomedicine & biotechnology. 2012; 2012:759503. [PubMed: 23093863]

Chapman CD, Frey WH 2nd, Craft S, Danielyan L, Hallschmid M, Schioth HB, Benedict C. Intranasal treatment of central nervous system dysfunction in humans. Pharmaceutical research. 2013; 30:2475–2484. [PubMed: 23135822]

Chartoff EH, Damez-Werno D, Sonntag KC, Hassinger L, Kaufmann DE, Peterson J, McPhie D, Cataldo AM, Cohen BM. Detection of intranasally delivered bone marrow-derived mesenchymal stromal cells in the lesioned mouse brain: a cautionary report. Stem cells international. 2011; 2011:586586. [PubMed: 22190964]

Chen DC, Lin SZ, Fan JR, Lin CH, Lee W, Lin CC, Liu YJ, Tsai CH, Chen JC, Cho DY, Lee CC, Shyu WC. Intracerebral implantation of autologous peripheral blood stem cells in stroke patients: a randomized phase II study. Cell Transplant. 2014a; 23:1599–1612. [PubMed: 24480430]

Chen J, Venkat P, Zacharek A, Chopp M. Neurorestorative therapy for stroke. Front Hum Neurosci. 2014b; 8:382. [PubMed: 25018718]

Chen L, Xi H, Huang H, Zhang F, Liu Y, Chen D, Xiao J. Multiple cell transplantation based on an intraparenchymal approach for patients with chronic phase stroke. Cell Transplant. 2013; 22(Suppl 1):S83–91. [PubMed: 23992950]

Chen SQ, Cai Q, Shen YY, Wang PY, Li MH, Teng GY. Neural stem cell transplantation improves spatial learning and memory via neuronal regeneration in amyloid-beta precursor protein/presenilin 1/tau triple transgenic mice. Am J Alzheimers Dis Other Demen. 2014c; 29:142–149. [PubMed: 24265106]

Chen Y, Sun FY. Age-related decrease of striatal neurogenesis is associated with apoptosis of neural precursors and newborn neurons in rat brain after ischemia. Brain Res. 2007; 1166:9–19. [PubMed: 17662700]

Cheng HC, Ulane CM, Burke RE. Clinical progression in Parkinson disease and the neurobiology of axons. Ann Neurol. 2010; 67:715–725. [PubMed: 20517933]

Cheng Q, Zhang Z, Zhang S, Yang H, Zhang X, Pan J, Weng L, Sha D, Zhu M, Hu X, Xu Y. Human umbilical cord mesenchymal stem cells protect against ischemic brain injury in mouse by regulating peripheral immunoinflammation. Brain research. 2015; 1594:293–304. [PubMed: 25449888]

Chiu AY, Hall ZW. Stem cell research: the California experience. J Neurosci. 2006; 26:6661–6663. [PubMed: 16793873]

Chiu AY, Rao MS. Cell-based therapy for neural disorders--anticipating challenges. Neurotherapeutics. 2011; 8:744–752. [PubMed: 21901585]

Chua JY, Pendharkar AV, Wang N, Choi R, Andres RH, Gaeta X, Zhang J, Moseley ME, Guzman R. Intra-arterial injection of neural stem cells using a microneedle technique does not cause microembolic strokes. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2011; 31:1263–1271.

Chung CS, Fujita N, Kawahara N, Yui S, Nam E, Nishimura R. A comparison of neurosphere differentiation potential of canine bone marrow-derived mesenchymal stem cells and adipose-derived mesenchymal stem cells. The Journal of veterinary medical science / the Japanese Society of Veterinary Science. 2013; 75:879–886.

Corbett D, Nguemeni C, Gomez-Smith M. How can you mend a broken brain? Neurorestorative approaches to stroke recovery. Cerebrovasc Dis. 2014; 38:233–239. [PubMed: 25402763]

Dalous J, Larghero J, Baud O. Transplantation of umbilical cord-derived mesenchymal stem cells as a novel strategy to protect the central nervous system: technical aspects, preclinical studies, and clinical perspectives. Pediatric research. 2012; 71:482–490. [PubMed: 22430384]

de Lazaro I, Yilmazer A, Kostarelos K. Induced pluripotent stem (iPS) cells: a new source for cell-based therapeutics? J Control Release. 2014; 185:37–44. [PubMed: 24746625]

Ding DC, Lin CH, Shyu WC, Lin SZ. Neural stem cells and stroke. Cell Transplant. 2013; 22:619–630. [PubMed: 23127719]

Dong P, Zhao J, Zhang Y, Dong J, Zhang L, Li D, Li L, Zhang X, Yang B, Lei W. Aging causes exacerbated ischemic brain injury and failure of sevoflurane post-conditioning: role of B-cell lymphoma-2. Neuroscience. 2014; 275:2–11. [PubMed: 24929064]

Donnellan C, Hevey D, Hickey A, O'Neill D. Adaptation to stroke using a model of successful aging. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2012; 19:530–547. [PubMed: 22225479]

Drouin-Ouellet J, Barker RA. Stem cell therapies for Parkinson's disease: are trials just around the corner? Regen Med. 2014; 9:553–555. [PubMed: 25372072]

Du G, Liu Y, Dang M, Zhu G, Su R, Fan Y, Tan Z, Wang LX, Fang J. Comparison of administration routes for adipose-derived stem cells in the treatment of middle cerebral artery occlusion in rats. Acta histochemica. 2014; 116:1075–1084. [PubMed: 24962764]

Epstein JB, Raber-Durlacher JE, Wilkins A, Chavarria MG, Myint H. Advances in hematologic stem cell transplant: an update for oral health care providers. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 2009; 107:301–312.

Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, Raz N, Dale AM, Walhovd KB. Accelerating cortical thinning: unique to dementia or universal in aging? Cereb Cortex. 2014; 24:919–934. [PubMed: 23236213]

Garcia KO, Ornellas FL, Martin PK, Patti CL, Mello LE, Frussa-Filho R, Han SW, Longo BM. Therapeutic effects of the transplantation of VEGF overexpressing bone marrow mesenchymal stem cells in the hippocampus of murine model of Alzheimer's disease. Front Aging Neurosci. 2014; 6:30. [PubMed: 24639647]

Glat MJ, Offen D. Cell and gene therapy in Alzheimer's disease. Stem Cells Dev. 2013; 22:1490–1496. [PubMed: 23320452]

Goedert M. Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci. 2001; 2:492–501. [PubMed: 11433374]

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage. 2001; 14:21–36. [PubMed: 11525331]

Gross RE, Watts RL, Hauser RA, Bakay RA, Reichmann H, von Kummer R, Ondo WG, Reissig E, Eisner W, Steiner-Schulze H, Siedentop H, Fichte K, Hong W, Cornfeldt M, Beebe K, Sandbrink R. Intrastriatal transplantation of microcarrier-bound human retinal pigment epithelial cells versus sham surgery in patients with advanced Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurol. 2011; 10:509–519. [PubMed: 21565557]

Guo Z, Zhang L, Wu Z, Chen Y, Wang F, Chen G. In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell. 2014; 14:188–202. [PubMed: 24360883]

Gutierrez-Fernandez M, Otero-Ortega L, Ramos-Cejudo J, Rodriguez-Frutos B, Fuentes B, Diez-Tejedor E. Adipose tissue-derived mesenchymal stem cells as a strategy to improve recovery after stroke. Expert Opin Biol Ther. 2015; 15:873–881. [PubMed: 25959243]

Gutierrez-Fernandez M, Rodriguez-Frutos B, Ramos-Cejudo J, Teresa Vallejo-Cremades M, Fuentes B, Cerdan S, Diez-Tejedor E. Effects of intravenous administration of allogenic bone marrow- and adipose tissue-derived mesenchymal stem cells on functional recovery and brain repair markers in experimental ischemic stroke. Stem cell research & therapy. 2013; 4:11. [PubMed: 23356495]

Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Ann N Y Acad Sci. 2010; 1184:188–195. [PubMed: 20146698]

Han F, Baremberg D, Gao J, Duan J, Lu X, Zhang N, Chen Q. Development of stem cell-based therapy for Parkinson's disease. Transl Neurodegener. 2015; 4:16. [PubMed: 26339485]

Hanley J, Rastegarlari G, Nathwani AC. An introduction to induced pluripotent stem cells. British journal of haematology. 2010; 151:16–24. [PubMed: 20666774]

Harris L, Zalucki O, Piper M, Heng JI. Insights into the Biology and Therapeutic Applications of Neural Stem Cells. Stem Cells Int. 2016; 2016:9745315. [PubMed: 27069486]

He LQ, Lu JH, Yue ZY. Autophagy in ageing and ageing-associated diseases. Acta Pharmacol Sin. 2013; 34:605–611. [PubMed: 23416930]

Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013; 80:1778–1783. [PubMed: 23390181]

Heinrich C, Gascon S, Masserdotti G, Lepier A, Sanchez R, Simon-Ebert T, Schroeder T, Gotz M, Berninger B. Generation of subtype-specific neurons from postnatal astroglia of the mouse cerebral cortex. Nat Protoc. 2011; 6:214–228. [PubMed: 21293461]

Henningson CT Jr, Stanislaus MA, Gewirtz AM. Embryonic and adult stem cell therapy. J Allergy Clin Immunol. 2003; 111:S745–753. [PubMed: 12592319]

Hilfiker A, Kasper C, Hass R, Haverich A. Mesenchymal stem cells and progenitor cells in connective tissue engineering and regenerative medicine: is there a future for transplantation? Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie. 2011; 396:489–497.

Hindle JV. Ageing, neurodegeneration and Parkinson's disease. Age Ageing. 2010; 39:156–161. [PubMed: 20051606]

Hoyte L, Kaur J, Buchan AM. Lost in translation: taking neuroprotection from animal models to clinical trials. Exp Neurol. 2004; 188:200–204. [PubMed: 15246820]

Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012; 148:1204–1222. [PubMed: 22424230]

Hung CW, Chen YC, Hsieh WL, Chiou SH, Kao CL. Ageing and neurodegenerative diseases. Ageing Res Rev. 2010; 9(Suppl 1):S36–46. [PubMed: 20732460]

Hung SC, Pochampally RR, Chen SC, Hsu SC, Prockop DJ. Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis. Stem Cells. 2007; 25:2363–2370. [PubMed: 17540857]

Hunsberger JG, Rao M, Kurtzberg J, Bulte JW, Atala A, LaFerla FM, Greely HT, Sawa A, Gandy S, Schneider LS, Doraiswamy PM. Accelerating stem cell trials for Alzheimer's disease. Lancet Neurol. 2015

Ikegame Y, Yamashita K, Hayashi S, Mizuno H, Tawada M, You F, Yamada K, Tanaka Y, Egashira Y, Nakashima S, Yoshimura S, Iwama T. Comparison of mesenchymal stem cells from adipose tissue and bone marrow for ischemic stroke therapy. Cytotherapy. 2011; 13:675–685. [PubMed: 21231804]

Isobe K, Cheng Z, Nishio N, Suganya T, Tanaka Y, Ito S. iPSCs, aging and age-related diseases. N Biotechnol. 2014; 31:411–421. [PubMed: 24784583]

Iwai M, Cao G, Yin W, Stetler RA, Liu J, Chen J. Erythropoietin promotes neuronal replacement through revascularization and neurogenesis after neonatal hypoxia/ischemia in rats. Stroke; a journal of cerebral circulation. 2007; 38:2795–2803.

Jiang M, Lv L, Ji H, Yang X, Zhu W, Cai L, Gu X, Chai C, Huang S, Sun J, Dong Q. Induction of pluripotent stem cells transplantation therapy for ischemic stroke. Mol Cell Biochem. 2011; 354:67–75. [PubMed: 21465238]

Jiang Y, Zhu W, Zhu J, Wu L, Xu G, Liu X. Feasibility of delivering mesenchymal stem cells via catheter to the proximal end of the lesion artery in patients with stroke in the territory of the middle cerebral artery. Cell Transplant. 2013; 22:2291–2298. [PubMed: 23127560]

Jinno S. Aging affects new cell production in the adult hippocampus: A quantitative anatomic review. J Chem Neuroanat. 2015

Kan I, Barhum Y, Melamed E, Offen D. Mesenchymal stem cells stimulate endogenous neurogenesis in the subventricular zone of adult mice. Stem Cell Rev. 2011; 7:404–412. [PubMed: 20830611]

Kan I, Melamed E, Offen D. Autotransplantation of bone marrow-derived stem cells as a therapy for neurodegenerative diseases. Handbook of experimental pharmacology. 2007:219–242. [PubMed: 17554511]

Karussis D, Petrou P, Kassis I. Clinical experience with stem cells and other cell therapies in neurological diseases. J Neurol Sci. 2013; 324:1–9. [PubMed: 23107343]

Kazmerova Z, Zilka N, Cente M, Neradil P, Zilkova M, Novak M. Can we teach old dogs new tricks? Neuroprotective cell therapy in Alzheimer's and Parkinson's disease. J Alzheimers Dis. 2013; 37:251–272. [PubMed: 23985419]

Kim DY, Park SH, Lee SU, Choi DH, Park HW, Paek SH, Shin HY, Kim EY, Park SP, Lim JH. Effect of human embryonic stem cell-derived neuronal precursor cell transplantation into the cerebral infarct model of rat with exercise. Neurosci Res. 2007; 58:164–175. [PubMed: 17408791]

Kim J, Kim SJ, Naka K. Transcriptome sequencing of hematopoietic stem cells and chronic myelgenous leukemia stem cells. Genom Data. 2016; 7:57–59. [PubMed: 26981360]

Kim S, Chang KA, Kim J, Park HG, Ra JC, Kim HS, Suh YH. The preventive and therapeutic effects of intravenous human adipose-derived stem cells in Alzheimer's disease mice. PLoS One. 2012; 7:e45757. [PubMed: 23049854]

Kim SJ, Moon GJ, Chang WH, Kim YH, Bang OY. Intravenous transplantation of mesenchymal stem cells preconditioned with early phase stroke serum: current evidence and study protocol for a randomized trial. Trials. 2013; 14:317. [PubMed: 24083670]

Kinnaird T, Stabile E, Burnett MS, Shou M, Lee CW, Barr S, Fuchs S, Epstein SE. Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. Circulation. 2004; 109:1543–1549. [PubMed: 15023891]

Koh SH, Kim KS, Choi MR, Jung KH, Park KS, Chai YG, Roh W, Hwang SJ, Ko HJ, Huh YM, Kim HT, Kim SH. Implantation of human umbilical cord-derived mesenchymal stem cells as a neuroprotective therapy for ischemic stroke in rats. Brain research. 2008; 1229:233–248. [PubMed: 18634757]

Kokai LE, Marra K, Rubin JP. Adipose stem cells: biology and clinical applications for tissue repair and regeneration. Transl Res. 2014; 163:399–408. [PubMed: 24361334]

Kondziolka D, Steinberg GK, Wechsler L, Meltzer CC, Elder E, Gebel J, Decesare S, Jovin T, Zafonte R, Lebowitz J, Flickinger JC, Tong D, Marks MP, Jamieson C, Luu D, Bell-Stephens T, Teraoka J. Neurotransplantation for patients with subcortical motor stroke: a phase 2 randomized trial. J Neurosurg. 2005; 103:38–45. [PubMed: 16121971]

Kondziolka D, Wechsler L, Goldstein S, Meltzer C, Thulborn KR, Gebel J, Jannetta P, DeCesare S, Elder EM, McGrogan M, Reitman MA, Bynum L. Transplantation of cultured human neuronal cells for patients with stroke. Neurology. 2000; 55:565–569. [PubMed: 10953194]

Krause DS, Theise ND, Collector MI, Henegariu O, Hwang S, Gardner R, Neutzel S, Sharkis SJ. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. Cell. 2001; 105:369–377. [PubMed: 11348593]

Lanni C, Stanga S, Racchi M, Govoni S. The expanding universe of neurotrophic factors: therapeutic potential in aging and age-associated disorders. Curr Pharm Des. 2010; 16:698–717. [PubMed: 20388080]

Leak RK, Zheng P, Ji X, Zhang JH, Chen J. From apoplexy to stroke: historical perspectives and new research frontiers. Prog Neurobiol. 2014; 115:1–5. [PubMed: 24373958]

Lee HJ, Lee JK, Lee H, Shin JW, Carter JE, Sakamoto T, Jin HK, Bae JS. The therapeutic potential of human umbilical cord blood-derived mesenchymal stem cells in Alzheimer's disease. Neurosci Lett. 2010a; 481:30–35. [PubMed: 20600610]

Lee JK, Jin HK, Bae JS. Bone marrow-derived mesenchymal stem cells reduce brain amyloid-beta deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model. Neuroscience letters. 2009; 450:136–141. [PubMed: 19084047]

Lee JK, Jin HK, Endo S, Schuchman EH, Carter JE, Bae JS. Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. Stem Cells. 2010b; 28:329–343. [PubMed: 20014009]

Lee JK, Schuchman EH, Jin HK, Bae JS. Soluble CCL5 derived from bone marrow-derived mesenchymal stem cells and activated by amyloid beta ameliorates Alzheimer's disease in mice by recruiting bone marrow-induced microglia immune responses. Stem Cells. 2012; 30:1544–1555. [PubMed: 22570192]

Li L, Jiang Q, Ding G, Zhang L, Zhang ZG, Li Q, Panda S, Lu M, Ewing JR, Chopp M. Effects of administration route on migration and distribution of neural progenitor cells transplanted into rats with focal cerebral ischemia, an MRI study. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2010; 30:653–662.

Li YH, Feng L, Zhang GX, Ma CG. Intranasal delivery of stem cells as therapy for central nervous system disease. Experimental and molecular pathology. 2015; 98:145–151. [PubMed: 25645932]

Liao W, Xie J, Zhong J, Liu Y, Du L, Zhou B, Xu J, Liu P, Yang S, Wang J, Han Z, Han ZC. Therapeutic effect of human umbilical cord multipotent mesenchymal stromal cells in a rat model of stroke. Transplantation. 2009a; 87:350–359. [PubMed: 19202439]

Liao W, Zhong J, Yu J, Xie J, Liu Y, Du L, Yang S, Liu P, Xu J, Wang J, Han Z, Han ZC. Therapeutic benefit of human umbilical cord derived mesenchymal stromal cells in intracerebral hemorrhage rat: implications of anti-inflammation and angiogenesis. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2009b; 24:307–316.

Lindroos B, Suuronen R, Miettinen S. The potential of adipose stem cells in regenerative medicine. Stem Cell Rev. 2011; 7:269–291. [PubMed: 20853072]

Liu X, Ye R, Yan T, Yu SP, Wei L, Xu G, Fan X, Jiang Y, Stetler RA, Liu G, Chen J. Cell based therapies for ischemic stroke: from basic science to bedside. Prog Neurobiol. 2014; 115:92–115. [PubMed: 24333397]

Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Advanced drug delivery reviews. 2012; 64:614–628. [PubMed: 22119441]

Ma T, Gong K, Ao Q, Yan Y, Song B, Huang H, Zhang X, Gong Y. Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice. Cell Transplant. 2013; 22(Suppl 1):S113–126. [PubMed: 24070198]

Marner L, Nyengaard JR, Tang Y, Pakkenberg B. Marked loss of myelinated nerve fibers in the human brain with age. J Comp Neurol. 2003; 462:144–152. [PubMed: 12794739]

Martinez-Morales PL, Revilla A, Ocana I, Gonzalez C, Sainz P, McGuire D, Liste I. Progress in stem cell therapy for major human neurological disorders. Stem Cell Rev. 2013; 9:685–699. [PubMed: 23681704]

Matsumoto T, Fujimori K, Andoh-Noda T, Ando T, Kuzumaki N, Toyoshima M, Tada H, Imaizumi K, Ishikawa M, Yamaguchi R, Isoda M, Zhou Z, Sato S, Kobayashi T, Ohtaka M, Nishimura K, Kurosawa H, Yoshikawa T, Takahashi T, Nakanishi M, Ohyama M, Hattori N, Akamatsu W, Okano H. Functional Neurons Generated from T Cell-Derived Induced Pluripotent Stem Cells for Neurological Disease Modeling. Stem cell reports. 2016; 6:422–435. [PubMed: 26905201]

Merceron C, Portron S, Masson M, Lesoeur J, Fellah BH, Gauthier O, Geffroy O, Weiss P, Guicheux J, Vinatier C. The effect of two- and three-dimensional cell culture on the chondrogenic potential of human adipose-derived mesenchymal stem cells after subcutaneous transplantation with an injectable hydrogel. Cell Transplant. 2011; 20:1575–1588. [PubMed: 21294960]

Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron. 2011; 70:687–702. [PubMed: 21609825]

Misra V, Ritchie MM, Stone LL, Low WC, Janardhan V. Stem cell therapy in ischemic stroke: role of IV and intra-arterial therapy. Neurology. 2012; 79:S207–212. [PubMed: 23008400]

Montarras D, Morgan J, Collins C, Relaix F, Zaffran S, Cumano A, Partridge T, Buckingham M. Direct isolation of satellite cells for skeletal muscle regeneration. Science. 2005; 309:2064–2067. [PubMed: 16141372]

Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012; 123:1–11. [PubMed: 22101365]

Mungas D, Tractenberg R, Schneider JA, Crane PK, Bennett DA. A 2-process model for neuropathology of Alzheimer's disease. Neurobiology of aging. 2014; 35:301–308. [PubMed: 24080173]

Nam H, Lee KH, Nam DH, Joo KM. Adult human neural stem cell therapeutics: Current developmental status and prospect. World J Stem Cells. 2015; 7:126–136. [PubMed: 25621112]

Niu W, Zang T, Zou Y, Fang S, Smith DK, Bachoo R, Zhang CL. In vivo reprogramming of astrocytes to neuroblasts in the adult brain. Nat Cell Biol. 2013; 15:1164–1175. [PubMed: 24056302]

Ohab JJ, Fleming S, Blesch A, Carmichael ST. A neurovascular niche for neurogenesis after stroke. J Neurosci. 2006; 26:13007–13016. [PubMed: 17167090]

Ohta K, Iwai M, Sato K, Omori N, Nagano I, Shoji M, Abe K. Dissociative increase of oligodendrocyte progenitor cells between young and aged rats after transient cerebral ischemia. Neurosci Lett. 2003; 335:159–162. [PubMed: 12531457]

Ong WK, Sugii S. Adipose-derived stem cells: fatty potentials for therapy. Int J Biochem Cell Biol. 2013; 45:1083–1086. [PubMed: 23458962]

Orio F, Muscogiuri G, Palomba S, Serio B, Sessa M, Giudice V, Ferrara I, Tauchmanova L, Colao A, Selleri C. Endocrinopathies after allogeneic and autologous transplantation of hematopoietic stem cells. TheScientificWorldJournal. 2014; 2014:282147.

Oyamada N, Itoh H, Sone M, Yamahara K, Miyashita K, Park K, Taura D, Inuzuka M, Sonoyama T, Tsujimoto H, Fukunaga Y, Tamura N, Nakao K. Transplantation of vascular cells derived from human embryonic stem cells contributes to vascular regeneration after stroke in mice. J Transl Med. 2008; 6:54. [PubMed: 18823569]

Pak J, Lee JH, Kartolo WA, Lee SH. Cartilage Regeneration in Human with Adipose Tissue-Derived Stem Cells: Current Status in Clinical Implications. Biomed Res Int. 2016; 2016:4702674. [PubMed: 26881220]

Pakkenberg B, Pelvig D, Marner L, Bundgaard MJ, Gundersen HJ, Nyengaard JR, Regeur L. Aging and the human neocortex. Exp Gerontol. 2003; 38:95–99. [PubMed: 12543266]

Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. Glia. 2005; 50:427–434. [PubMed: 15846805]

Popa-Wagner A, Badan I, Walker L, Groppa S, Patrana N, Kessler C. Accelerated infarct development, cytogenesis and apoptosis following transient cerebral ischemia in aged rats. Acta Neuropathol. 2007; 113:277–293. [PubMed: 17131130]

Popa-Wagner A, Dinca I, Yalikun S, Walker L, Kroemer H, Kessler C. Accelerated delimitation of the infarct zone by capillary-derived nestin-positive cells in aged rats. Curr Neurovasc Res. 2006; 3:3–13. [PubMed: 16472121]

Prasad K, Mohanty S, Bhatia R, Srivastava MV, Garg A, Srivastava A, Goyal V, Tripathi M, Kumar A, Bal C, Vij A, Mishra NK. Autologous intravenous bone marrow mononuclear cell therapy for patients with subacute ischaemic stroke: a pilot study. Indian J Med Res. 2012; 136:221–228. [PubMed: 22960888]

Prasad K, Sharma A, Garg A, Mohanty S, Bhatnagar S, Johri S, Singh KK, Nair V, Sarkar RS, Gorthi SP, Hassan KM, Prabhakar S, Marwaha N, Khandelwal N, Misra UK, Kalita J, Nityanand S. Intravenous autologous bone marrow mononuclear stem cell therapy for ischemic stroke: a multicentric, randomized trial. Stroke; a journal of cerebral circulation. 2014; 45:3618–3624.

Qiao LY, Huang FJ, Zhao M, Xie JH, Shi J, Wang J, Lin XZ, Zuo H, Wang YL, Geng TC. A two-year follow-up study of cotransplantation with neural stem/progenitor cells and mesenchymal stromal

cells in ischemic stroke patients. Cell Transplant. 2014; 23(Suppl 1):S65–72. [PubMed: 25333752]

Rabinovich SS, Seledtsov VI, Banul NV, Poveshchenko OV, Senyukov VV, Astrakov SV, Samarin DM, Taraban VY. Cell therapy of brain stroke. Bulletin of experimental biology and medicine. 2005; 139:126–128. [PubMed: 16142294]

Rafalski VA, Brunet A. Energy metabolism in adult neural stem cell fate. Prog Neurobiol. 2011; 93:182–203. [PubMed: 21056618]

Razavi S, Razavi MR, Zarkesh Esfahani H, Kazemi M, Mostafavi FS. Comparing brain-derived neurotrophic factor and ciliary neurotrophic factor secretion of induced neurotrophic factor secreting cells from human adipose and bone marrow-derived stem cells. Development, growth & differentiation. 2013; 55:648–655.

Reddy PH, Tripathi R, Troung Q, Tirumala K, Reddy TP, Anekonda V, Shirendeb UP, Calkins MJ, Reddy AP, Mao P, Manczak M. Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: implications to mitochondria-targeted antioxidant therapeutics. Biochim Biophys Acta. 2012; 1822:639–649. [PubMed: 22037588]

Robel S, Berninger B, Gotz M. The stem cell potential of glia: lessons from reactive gliosis. Nat Rev Neurosci. 2011; 12:88–104. [PubMed: 21248788]

Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012; 125:e2–e220. [PubMed: 22179539]

Roozbehi A, Joghataei MT, Bakhtiyari M, Mohammadi J, Rad P, Delaviz H. Age-associated changes on axonal regeneration and functional outcome after spinal cord injury in rats. Acta Med Iran. 2015; 53:281–286. [PubMed: 26024702]

Sadan O, Melamed E, Offen D. Bone-marrow-derived mesenchymal stem cell therapy for neurodegenerative diseases. Expert opinion on biological therapy. 2009a; 9:1487–1497. [PubMed: 19821796]

Sadan O, Shemesh N, Cohen Y, Melamed E, Offen D. Adult neurotrophic factor-secreting stem cells: a potential novel therapy for neurodegenerative diseases. Isr Med Assoc J. 2009b; 11:201–204. [PubMed: 19603590]

Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature. 2010; 464:520–528. [PubMed: 20336134]

Salem AM, Ahmed HH, Atta HM, Ghazy MA, Aglan HA. Potential of bone marrow mesenchymal stem cells in management of Alzheimer's disease in female rats. Cell Biol Int. 2014; 38:1367–1383. [PubMed: 25044885]

Sanchez-Ramos JR. Neural cells derived from adult bone marrow and umbilical cord blood. J Neurosci Res. 2002; 69:880–893. [PubMed: 12205681]

Savitz SI, Dinsmore J, Wu J, Henderson GV, Stieg P, Caplan LR. Neurotransplantation of fetal porcine cells in patients with basal ganglia infarcts: a preliminary safety and feasibility study. Cerebrovascular diseases (Basel, Switzerland). 2005; 20:101–107.

Savitz SI, Dinsmore JH, Wechsler LR, Rosenbaum DM, Caplan LR. Cell therapy for stroke. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics. 2004; 1:406–414. [PubMed: 15717044]

Schapira AH, Agid Y, Barone P, Jenner P, Lemke MR, Poewe W, Rascol O, Reichmann H, Tolosa E. Perspectives on recent advances in the understanding and treatment of Parkinson's disease. Eur J Neurol. 2009; 16:1090–1099. [PubMed: 19723294]

Schneider SA, Obeso JA. Clinical and pathological features of Parkinson's disease. Current topics in behavioral neurosciences. 2015; 22:205–220. [PubMed: 24850081]

Shen LH, Li Y, Gao Q, Savant-Bhonsale S, Chopp M. Down-regulation of neurocan expression in reactive astrocytes promotes axonal regeneration and facilitates the neurorestorative effects of

bone marrow stromal cells in the ischemic rat brain. Glia. 2008; 56:1747–1754. [PubMed: 18618668]

Shetty P, Thakur AM, Viswanathan C. Dopaminergic cells, derived from a high efficiency differentiation protocol from umbilical cord derived mesenchymal stem cells, alleviate symptoms in a Parkinson's disease rodent model. Cell biology international. 2013; 37:167–180. [PubMed: 23339105]

Shin JW, Lee JK, Lee JE, Min WK, Schuchman EH, Jin HK, Bae JS. Combined effects of hematopoietic progenitor cell mobilization from bone marrow by granulocyte colony stimulating factor and AMD3100 and chemotaxis into the brain using stromal cell-derived factor-1alpha in an Alzheimer's disease mouse model. Stem cells (Dayton, Ohio). 2011; 29:1075–1089.

Shuaib A, Boyle C. Stroke in the elderly. Current opinion in neurology. 1994; 7:41–47. [PubMed: 8173676]

Singh N, Pillay V, Choonara YE. Advances in the treatment of Parkinson's disease. Prog Neurobiol. 2007; 81:29–44. [PubMed: 17258379]

Sobrino T, Arias S, Perez-Mato M, Agulla J, Brea D, Rodriguez-Yanez M, Castillo J. Cd34+ progenitor cells likely are involved in the good functional recovery after intracerebral hemorrhage in humans. Journal of neuroscience research. 2011; 89:979–985. [PubMed: 21488087]

Spits C, Mateizel I, Geens M, Mertzanidou A, Staessen C, Vandeskelde Y, Van der Elst J, Liebaers I, Sermon K. Recurrent chromosomal abnormalities in human embryonic stem cells. Nat Biotechnol. 2008; 26:1361–1363. [PubMed: 19029912]

Sproul AA. Being human: The role of pluripotent stem cells in regenerative medicine and humanizing Alzheimer's disease models. Mol Aspects Med. 2015; 43–44:54–65.

Sugaya K. Possible use of autologous stem cell therapies for Alzheimer's disease. Curr Alzheimer Res. 2005; 2:367–376. [PubMed: 15974902]

Sugii S, Kida Y, Berggren WT, Evans RM. Feeder-dependent and feeder-independent iPS cell derivation from human and mouse adipose stem cells. Nat Protoc. 2011; 6:346–358. [PubMed: 21372815]

Suon S, Yang M, Iacovitti L. Adult human bone marrow stromal spheres express neuronal traits in vitro and in a rat model of Parkinson's disease. Brain Res. 2006; 1106:46–51. [PubMed: 16828720]

Taguchi A, Sakai C, Soma T, Kasahara Y, Stern DM, Kajimoto K, Ihara M, Daimon T, Yamahara K, Doi K, Kohara N, Nishimura H, Matsuyama T, Naritomi H, Sakai N, Nagatsuka K. Intravenous Autologous Bone Marrow Mononuclear Cell Transplantation for Stroke: Phase1/2a Clinical Trial in a Homogeneous Group of Stroke Patients. Stem Cells Dev. 2015; 24:2207–2218. [PubMed: 26176265]

Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126:663–676. [PubMed: 16904174]

Takamatsu K, Ikeda T, Haruta M, Matsumura K, Ogi Y, Nakagata N, Uchino M, Ando Y, Nishimura Y, Senju S. Degradation of amyloid beta by human induced pluripotent stem cell-derived macrophages expressing Neprilysin-2. Stem Cell Res. 2014; 13:442–453. [PubMed: 25460605]

Tang YH, Ma YY, Zhang ZJ, Wang YT, Yang GY. Opportunities and challenges: stem cell-based therapy for the treatment of ischemic stroke. CNS neuroscience & therapeutics. 2015; 21:337–347. [PubMed: 25676164]

Trzaska KA, Rameshwar P. Current advances in the treatment of Parkinson's disease with stem cells. Curr Neurovasc Res. 2007; 4:99–109. [PubMed: 17504208]

Tumbar T, Guasch G, Greco V, Blanpain C, Lowry WE, Rendl M, Fuchs E. Defining the epithelial stem cell niche in skin. Science. 2004; 303:359–363. [PubMed: 14671312]

Urdzikova LM, Ruzicka J, LaBagnara M, Karova K, Kubinova S, Jirakova K, Murali R, Sykova E, Jhanwar-Uniyal M, Jendelova P. Human mesenchymal stem cells modulate inflammatory cytokines after spinal cord injury in rat. Int J Mol Sci. 2014; 15:11275–11293. [PubMed: 24968269]

Venkataramana NK, Kumar SK, Balaraju S, Radhakrishnan RC, Bansal A, Dixit A, Rao DK, Das M, Jan M, Gupta PK, Totey SM. Open-labeled study of unilateral autologous bone-marrow-derived

mesenchymal stem cell transplantation in Parkinson's disease. Transl Res. 2010; 155:62–70. [PubMed: 20129486]

Wang C, Fei Y, Xu C, Zhao Y, Pan Y. Bone marrow mesenchymal stem cells ameliorate neurological deficits and blood-brain barrier dysfunction after intracerebral hemorrhage in spontaneously hypertensive rats. International journal of clinical and experimental pathology. 2015a; 8:4715–4724. [PubMed: 26191161]

Wang J, Chao F, Han F, Zhang G, Xi Q, Li J, Jiang H, Wang J, Yu G, Tian M, Zhang H. PET demonstrates functional recovery after transplantation of induced pluripotent stem cells in a rat model of cerebral ischemic injury. J Nucl Med. 2013; 54:785–792. [PubMed: 23503731]

Wang J, Xia J, Zhang F, Shi Y, Wu Y, Pu H, Liou AK, Leak RK, Yu X, Chen L, Chen J. Galectin-1-secreting neural stem cells elicit long-term neuroprotection against ischemic brain injury. Sci Rep. 2015b; 5:9621. [PubMed: 25858671]

Wang S, Young KM. White matter plasticity in adulthood. Neuroscience. 2014; 276:148–160. [PubMed: 24161723]

Wankhade UD, Shen M, Kolhe R, Fulzele S. Advances in Adipose-Derived Stem Cells Isolation, Characterization, and Application in Regenerative Tissue Engineering. Stem Cells Int. 2016; 2016:3206807. [PubMed: 26981130]

Wei N, Yu SP, Gu X, Taylor TM, Song D, Liu XF, Wei L. Delayed intranasal delivery of hypoxic-preconditioned bone marrow mesenchymal stem cells enhanced cell homing and therapeutic benefits after ischemic stroke in mice. Cell transplantation. 2013; 22:977–991. [PubMed: 23031629]

Wilson RS, Segawa E, Boyle PA, Anagnos SE, Hizel LP, Bennett DA. The natural history of cognitive decline in Alzheimer's disease. Psychol Aging. 2012; 27:1008–1017. [PubMed: 22946521]

Wobus AM, Boheler KR. Embryonic stem cells: prospects for developmental biology and cell therapy. Physiol Rev. 2005; 85:635–678. [PubMed: 15788707]

Xiong N, Zhang Z, Huang J, Chen C, Zhang Z, Jia M, Xiong J, Liu X, Wang F, Cao X, Liang Z, Sun S, Lin Z, Wang T. VEGF-expressing human umbilical cord mesenchymal stem cells, an improved therapy strategy for Parkinson's disease. Gene therapy. 2011; 18:394–402. [PubMed: 21107440]

Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. Natl Vital Stat Rep. 2016; 64:1–119. [PubMed: 26905861]

Yan-Wu G, Yi-Quan K, Ming L, Ying-Qian C, Xiao-Dan J, Shi-Zhong Z, Wang-Ming Z, Chuan-Zhi D. Human umbilical cord-derived Schwann-like cell transplantation combined with neurotrophin-3 administration in dyskinesia of rats with spinal cord injury. Neurochemical research. 2011; 36:783–792. [PubMed: 21243429]

Yan ZJ, Hu YQ, Zhang HT, Zhang P, Xiao ZY, Sun XL, Cai YQ, Hu CC, Xu RX. Comparison of the neural differentiation potential of human mesenchymal stem cells from amniotic fluid and adult bone marrow. Cellular and molecular neurobiology. 2013; 33:465–475. [PubMed: 23478940]

Yang B, Migliati E, Parsha K, Schaar K, Xi X, Aronowski J, Savitz SI. Intra-arterial delivery is not superior to intravenous delivery of autologous bone marrow mononuclear cells in acute ischemic stroke. Stroke; a journal of cerebral circulation. 2013; 44:3463–3472.

Yang B, Strong R, Sharma S, Brenneman M, Mallikarjunarao K, Xi X, Grotta JC, Aronowski J, Savitz SI. Therapeutic time window and dose response of autologous bone marrow mononuclear cells for ischemic stroke. Journal of neuroscience research. 2011; 89:833–839. [PubMed: 21412816]

Yang S, Lu W, Zhou DS, Tang Y. Enriched environment and white matter in aging brain. Anat Rec (Hoboken). 2012; 295:1406–1414. [PubMed: 22777883]

Ye M, Wang XJ, Zhang YH, Lu GQ, Liang L, Xu JY, Chen SD. Transplantation of bone marrow stromal cells containing the neurturin gene in rat model of Parkinson's disease. Brain Res. 2007; 1142:206–216. [PubMed: 17336273]

Yeh DC, Chan TM, Harn HJ, Chiou TW, Chen HS, Lin ZS, Lin SZ. Adipose tissue-derived stem cells in neural regenerative medicine. Cell Transplant. 2015; 24:487–492. [PubMed: 25647067]

Yin F, Tian ZM, Liu S, Zhao QJ, Wang RM, Shen L, Wieman J, Yan Y. Transplantation of human retinal pigment epithelium cells in the treatment for Parkinson disease. CNS Neurosci Ther. 2012; 18:1012–1020. [PubMed: 23190934]

Yuan T, Liao W, Feng NH, Lou YL, Niu X, Zhang AJ, Wang Y, Deng ZF. Human induced pluripotent stem cell-derived neural stem cells survive, migrate, differentiate, and improve neurologic function in a rat model of middle cerebral artery occlusion. Stem Cell Res Ther. 2013; 4:73. [PubMed: 23769173]

Zhang W, Wang PJ, Sha HY, Ni J, Li MH, Gu GJ. Neural stem cell transplants improve cognitive function without altering amyloid pathology in an APP/PS1 double transgenic model of Alzheimer's disease. Mol Neurobiol. 2014; 50:423–437. [PubMed: 24481678]

Zhou X, Gu J, Gu Y, He M, Bi Y, Chen J, Li T. Human Umbilical Cord-Derived Mesenchymal Stem Cells Improve Learning and Memory Function in Hypoxic-Ischemic Brain-Damaged Rats via an IL-8-Mediated Secretion Mechanism Rather than Differentiation Pattern Induction. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2015; 35:2383–2401.

Zhou Y, Sun M, Li H, Yan M, He Z, Wang W, Wang W, Lu S. Recovery of behavioral symptoms in hemi-parkinsonian rhesus monkeys through combined gene and stem cell therapy. Cytotherapy. 2013; 15:467–480. [PubMed: 23403361]

Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011; 12:723–738. [PubMed: 22048062]

Highlights

1. We describe common pathophysiological changes underlying age-related neurodegenerative diseases and stroke.
2. We introduce the properties of different stem cells and discuss stem cell therapies in neurodegenerative diseases and stroke.
3. We describe the benefits and limitations of stem cell therapies in neurodegenerative diseases and stroke.