REVIEW

Neuroprotection offered by mesenchymal stem cells in perinatal brain injury: Role of mitochondria, inflammation, and reactive oxygen species

Syam Nair[1,2,3] (ID) | Eridan Rocha-Ferreira[1,2,3] | Bobbi Fleiss[4,5] | Cora H Nijboer[6] | Pierre Gressens[5] | Carina Mallard[1,2] | Henrik Hagberg[1,3]

[1]Centre of Perinatal Medicine and Health, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2]Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[4]School of Health and Biomedical Sciences, RMIT University, Bundoora, Victoria, Australia

[5]Université de Paris, NeuroDiderot, Paris, France

[6]Department for Developmental Origins of Disease, University Medical Center Utrecht Brain Center and Wilhelmina Children's Hospital, Utrecht University, Utrecht, Netherlands

Correspondence
Syam Nair, Institute of Neuroscience and Physiology, Department of Physiology, Sahlgrenska Academy, University of Gothenburg, Box 432, SE-405 30, Gothenburg, Sweden.
Email: syam.nair@neuro.gu.se

Abstract

Preclinical studies have shown that mesenchymal stem cells have a positive effect in perinatal brain injury models. The mechanisms that cause these neurotherapeutic effects are not entirely intelligible. Mitochondrial damage, inflammation, and reactive oxygen species are considered to be critically involved in the development of injury. Mesenchymal stem cells have immunomodulatory action and exert mitoprotective effects which attenuate production of reactive oxygen species and promote restoration of tissue function and metabolism after perinatal insults. This review summarizes the present state, the underlying causes, challenges and possibilities for effective clinical translation of mesenchymal stem cell therapy.

KEYWORDS

inflammation, intraventricular hemorrhage, mesenchymal stem cells, mitochondria, mitophagy, neonatal brain injury, neonatal hypoxia-ischemia, reactive oxygen species

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1 | INTRODUCTION

Intraventricular hemorrhage (IVH) in preterm neonates, stroke in preterm and term neonates, and neonatal encephalopathy (NE) in term neonates constitute three major destructive brain lesions observed during the perinatal period (Ferriero et al., 2019; Hill & Volpe, 1981). Treatment options for neonatal HI brain injury are limited to supportive care and therapeutic hypothermia (Hagberg et al., 2016; Jacobs et al., 2013). Hypothermia is only advised in term and late preterm infants with moderate-to-severe NE if identified before 6 hr of age (Jacobs et al., 2013). For cases of IVH unfortunately only supportive care can be provided. Pharmacological neuroprotective therapies have been thoroughly explored in multiple animal models of hypoxic-ischemic encephalopathy (HIE) and IVH (Bel & Groenendaal, 2016). However, none have been successfully translated into a therapy to prevent or regenerate brain injury in newborn infants.

Inflammation is strongly recognized as a major cause leading to long-term injury (Hagberg et al., 2015). Inflammation causes systemic up-regulation of pro-inflammatory cytokines and diffuse activation of microglia in the neonatal brain (Berger et al., 2012). Cytokine-activated cells secrete toxic substances, such as ROS and toxic granules, including proteolytic enzymes and myeloperoxidase (Okazaki et al., 2006). This results in cell death causing white matter damage and long-term neurological injury among pre-term and term neonates (Leviton et al., 2005).

Cell death associated with HI and IVH can be classified as apoptotic, necrotic, or autophagic (Bobinger et al., 2018; Northington et al., 2011). Pro-apoptotic proteins act directly (BAX and BAK) or indirectly (BAD, PUMA, BIM) as triggers of mitochondrial membrane permeabilization leading to activation of caspase activation and apoptosis-inducing factor (AIF) translocation to nuclei which is believed to be crucial for injury to advance beyond the point of no return (Blomgren et al., 2001; Hagberg et al., 2009, 2014). Recruitment of mixed lineage kinase-like protein (MLKL) to the necrosome results in mitochondria-associated endoplasmic reticulum membranes triggering increased reactive oxygen species, fission, and necroptosis (Galluzzi et al., 2016). Death receptors trigger apoptotic death via caspase-8 and necroptotic cell death through the formation of the necrosome, with both apoptotic and necrotic pathways converging at the mitochondria (Chavez-Valdez et al., 2012, 2016; Galluzzi et al., 2011). Autophagy is increased in neuronal cells after neonatal HI and may represent a potential protective mechanism in the early stage of the brain injury (Carloni et al., 2008) but most data

show that autophagy aggravates injury (Descloux et al., 2015; Xie et al., 2016).

Experimental results showing regeneration of the injured neonatal brain with stem cell-based therapies are promising. Studies have shown that exogenous administration of stem cells significantly decreases brain injury in models of IVH (Ahn et al., 2013, 2015), HIE (Park et al., 2015), and neonatal stroke (Kim et al., 2012). These findings together with studies from adult neurological conditions (Caicedo et al., 2015) suggest that exogenous MSC transplantation might be a promising new therapy in the not too distant future for treating neonatal brain damage resulting from IVH, NE, or neonatal stroke.

2 | MSCS—THE CELL OF CHOICE?

Major types of stem cells include embryonic stem cells, chemically induced pluripotent stem cells, neural stem cells, UCB cells, and MSCs. Embryonic stem (ES) cells have multiple characteristics such as self-renewal, highly expandable, and possibility to derive neural stem cells and other neurogenic lineages (Svendsen & Smith, 1999) (Hynes & Rosenthal, 2000). Although ES seems an obvious choice for repairing brain injury, they can induce the formation of teratomas after transplantation (Bjorklund et al., 2002). Similarly, multipotent neural stem cells have the capacity to derive all neural lineages, but they also carry a significant risk of tumor formation (Comi et al., 2008; Fleiss et al., 2014). UCB contains MSCs, endothelial progenitor cells, and UCB-mononuclear cells (Ingram et al., 2004). The advantages of UCB cells include easy access, limited ethical issues, and low immunogenicity. Administration of MSCs several days after neonatal HI markedly improves functional outcome, reduces infarct volume, and stimulates neurogenesis (Hawkins et al., 2018; van Velthoven et al., 2010a).

MSCs are characterized by their multi-lineage differentiation capacity (Keating, 2012; Phinney et al., 2015; Pittenger et al., 1999), they express specific cell surface markers which include CD105 (Barry et al., 1999), CD73 (Barry et al., 2001), CD90 (Dominici et al., 2006), CD79 (Chu & Arber, 2001) and CD44 (L Ramos et al., 2016), but not CD79, CD19, CD14 (Wright et al., 1990), CD11b (Coxon et al., 1996), HLA-DR (Dominici et al., 2006), and the hematopoietic marker CD45 (Irie-Sasaki et al., 2001). They also lack co-stimulatory proteins like CD80, CD40, and CD86 which makes them less immunogenic (Tse et al., 2003). Additionally, other non-specific MSCs surface markers, like Stro-1, SSEA-4, CD271, and CD146, have also been proposed for positive characterization of MSCs (Lv et al., 2014). The International Society

for Cellular Therapy has provided a consensus perspective on immune functional assays, functionally relevant surface markers etc., for MSCs as potency release criterion for clinical trials (Galipeau et al., 2016).

MSCs can be isolated from human placenta, umbilical cord (blood and Wharton's jelly), spleen, and adipose tissue-derived mesenchymal stem cells (AT-MSCs) (Gothard et al., 2014; Strioga et al., 2012) other than bone marrow. Other sites of MSC isolation include skin (Shih et al., 2005), dental pulp (Gronthos et al., 2000) and amniotic fluid (Nadri & Soleimani, 2007). Although these MSCs share common properties, they also exhibit differences in the expressed cell markers, in their differentiation potential and phenotypes (Gothard et al., 2014; Strioga et al., 2012).

Isolated MSCs from human submandibular skin tissues exhibit MSC characteristics and express a neural precursor marker, suggesting that human skin is a source of stem cells. However, the in vitro chemical neuronal induction of hMSC does not produce long-lasting nerve cells and more studies are required before their use (Byun et al., 2012).

Recent studies have shown that tissue-resident MSCs also express CD34, originally thought to be a hematopoietic marker as it is normally not found in culture-expanded MSCs (Lin et al., 2012; Togarrati et al., 2017). CD146, a pericyte marker has been proposed to give rise to MSCs following blood vessel damage or inflammation (Bouacida et al., 2012; da Silva Meirelles et al., 2016). The secretome of MSCs has also been examined (although it varies by culture condition), and includes several growth factors such as vascular endothelial growth factor, brain-derived neurotrophic factor, nerve growth factor, basic fibroblast growth factor as well as anti-inflammatory cytokines (Qu et al., 2007). Growth factors secreted by MSCs mediates the proliferation and differentiation of progenitor cells (Ge et al., 2018; Martins et al., 2017).

MSCs have many favorable properties, they are non-tumorigenic, have a positive safety profile, exhibit low immunogenicity and are easy to isolate/propagate reviewed in (Fleiss et al., 2014; Wagenaar et al., 2017). Also, MSCs have multiple therapeutic actions. They reduce inflammation and oxidative stress, restore energy failure, and

decrease cell apoptosis (Li et al., 2012). MSCs boost the growth-promoting environment for neural stem cells (Yoo et al., 2008). It has been shown that MSC mediated cell-cell contacts provide additional signaling to improve adipogenic and osteogenic differentiation (Peng et al., 2012) through the increased gap junction or cadherin signaling (Lee et al., 2012; Tang et al., 2010). These effects of MSCs address many of the complex multifactorial factors driving tissue injury after severe IVH (Ballabh, 2010, 2014), or HIE (Aslam et al., 2019; Thornton et al., 2017; Wagenaar et al., 2018). A multifaceted therapeutic agent like MSCs may be suitable to improve outcomes of patients with these neonatal disorders (Park et al., 2018) (Figure 1).

3 | EVIDENCE FOR MSC-MEDIATED PROTECTION AND REPAIR OF PERINATAL BRAIN INJURY

The protective effects of MSCs, have been observed in various animal models of severe IVH (Ahn et al., 2013, 2015, 2017) and HIE (Gonzales-Portillo et al., 2014; Pimentel-Coelho & Mendez-Otero, 2010). In an animal model of HIE, intranasal MSC transplantation at 10 days after the initial HI insult was still able to reduce brain damage (Donega et al., 2013), suggesting that MSCs also stimulate endogenous brain repair in addition to being solely neuroprotective early following injury (Donega et al., 2014; van Velthoven et al., 2013).

Ischemia-reperfusion and/or infection-inflammation are important factors in etiology of white matter injury (Hagberg et al., 2002). (Oppliger et al., 2016) showed that intranasal delivery of human Wharton's jelly-MSC in rats prevented hypomyelination and microgliosis in a model of white matter injury in the premature rat pups. Following this another study showed the effect of human Wharton's jelly-derived MSCs on white matter injury caused by intraperitoneal lipopolysaccharide (LPS) injection (0.1 mg/kg) in P3 rat pups followed by ligation of the left carotid artery and 40 min of hypoxia (8% O_2) at P4.
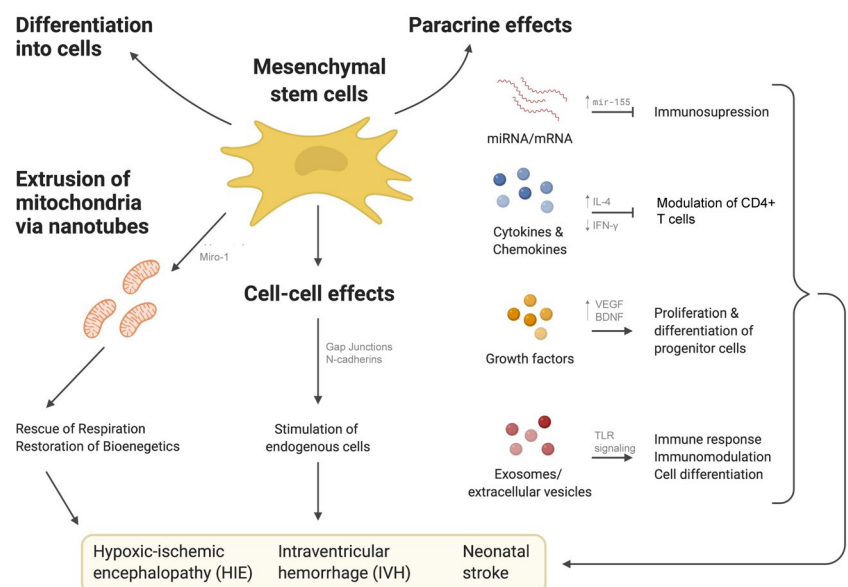

FIGURE 1 Mechanisms of neuroprotection offered by mesenchymal stem cells
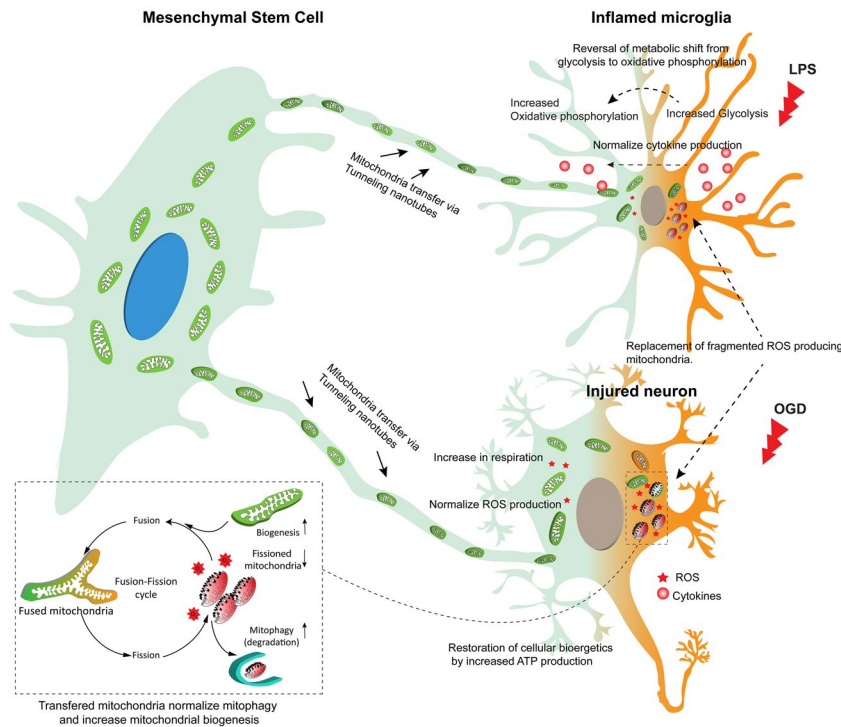
FIGURE 2 Mitochondrial transfer from mesenchymal stem cells via tunneling nanotubes for attenuation of brain inflammation and injury

These animals then received intracranial MSC treatment at P11 which led to an improvement in locomotor activity, reduced myelin loss and astrocyte activation (Mueller et al., 2017). Several other studies have demonstrated that MSCs migrate to the ischemic boundary zone, induce changes in the brain environment, and support neurogenesis (van Velthoven et al., 2010a, 2011). It is also known that administration of MSCs after HI markedly induced cell proliferation in the hippocampus and cortex, stimulate neuronal cell differentiation, and formation of new neuroblasts within the subventricular zone (Chen et al., 2003; Donega et al., 2013; van Velthoven et al., 2010a; Yoo et al., 2008).

White matter involvement is recently realized as a common finding in mitochondrial disorders. Studies have shown that mitochondrial disorders play a principal role in the pathogenesis of white and grey matter injury (Galluzzi et al., 2009; Hagberg, 2004; Hagberg et al., 2014; Koning et al., 2019). Following HI, a primary phase of energy failure occurs because of ATP depletion, failure of mitochondrial respiration, increased excitotoxicity and associated influx of Ca^{2+} and Na^+. Thereafter, a phase of recovery ensues usually referred to as the latent phase. This is followed by a secondary phase of energy depletion and tertiary phases of injury where inflammation, protein misfolding, increased ROS production, and disruption of mitochondrial integrity/function leading to cell death (Fleiss & Gressens, 2012; Hagberg et al., 2015).

4 | MSC MECHANISMS OF ACTION

4.1 | MSCs—neuroprotection via mitochondrial transfer

MSCs inhibit apoptosis and rejuvenate damaged cells by transferring mitochondria during reoxygenation after oxygen glucose deprivation

(OGD) in vitro (Liu et al., 2014). This transfer of mitochondria was achieved through tunneling nanotubes (TNTs). Another in vitro study shows that besides mitochondria, TNTs also mediate cell-to-cell transfer of plasma membrane components, cytosolic molecules, and other cell organelles (Pasquier et al., 2013) (Figure 2). TNTs are membranous channels with a diameter of 50–200 nm and mediate continuity between the plasma membranes of connected cells (Gerdes et al., 2007; Rustom et al., 2004). Delivery of functional mitochondria via TNTs aid in the recovery of PC12 cells during early stages of apoptosis (Wang & Gerdes, 2015). A logical next step would be the development of a selective interference for TNT formation in vivo to unravel their functional role. TNTs are stated to be a potential defense response to stress since it is only stressed cells that develop TNTs (Zhang, 2011). In addition to OGD, described above, Wang et al. have shown that TNTs can be induced in rat hippocampal astrocytes and neurons by H_2O_2 or serum depletion (Wang et al., 2011).

Although the mechanisms associated with TNT formation have not been well studied, motor proteins, like calcium-sensitive dynamin-related Rho-GTPases Miro1 and Miro2 (Ahmad et al., 2014; Fransson et al., 2006), KLF 5 kinesin motor protein (Falnikar et al., 2011), and accessory proteins like TRAK 1 and TRAK 2 (Glater et al., 2006; Stowers et al., 2002), and Myo 19 and Myo 10 (Bohil et al., 2006) facilitate efficient shipping of cargo between cells via an actin–myosin-dependent mechanism (Nawaz & Fatima, 2017). Over-expression of Miro1 in MSCs led to enhanced mitochondrial transfer and rescue of epithelial injury, while Miro1 knockdown led to reduced mitochondrial transfer (Ahmad et al., 2014). An important result of mitochondria transfer from MSCs is the restoration of cell functions such as mitochondrial respiration in the recipient cells (Caicedo et al., 2015). Mitochondria also have an innate ability to find their ways into a host cell. Isolated mitochondria can be incorporated

in vitro into cells by a simple co-incubation, without the need for transfection reagents or medium supplements. The incorporated mitochondria can increase ATP production and oxygen consumption inside the recipient cells (Kesner et al., 2016).

Mitochondria were isolated and transferred to target cells in a rabbit model of regional cardiac ischemia (Masuzawa et al., 2013). An injection of autologous mitochondria (~10^7) at the site of ischemia lead to their internalization within 8 hr of their administration and resulted in reduced apoptosis and infarct size, as detected 4 weeks later (Masuzawa et al., 2013). Chang et al have shown that alloge-neic/xenogeneic injection of peptide-labeled mitochondria into the medial forebrain bundle of adult rats restored mitochondrial functions and attenuated 6-hydroxydopamine-induced neurotoxicity in a model of Parkinson's disease (Chang et al., 2016). In a clinical study, it has been shown that healthy autologous mitochondria from non-ischemic skeletal muscle in pediatric patients can be safely injected into damaged myocardium after ischemic injury for improvement of ventricular function (Emani et al., 2017). Similar studies have not been reported in neonatal models of brain injury or performed in patients with neonatal brain injury.

Besides improving the metabolic situation, transfer of healthy mitochondria to injured cells via TNTs can increase the turnover of damaged mitochondria by mitophagy (Li et al., 2017). Mitophagy is the selective autophagy of damaged mitochondria through the au-tophagosomal-lysosomal pathway (Rodolfo et al., 2018; Thornton et al., 2018). Mitophagy plays a vital role in maintaining cellular homeostasis and defending against oxidative stress because this process controls mitochondrial quality and quantity by eliminating dysfunctional or damaged mitochondria (Hagberg et al., 2014). HI-induced brain damage increases mitophagy and the inhibition of mi-tophagy aggravates brain damage in neonatal rats (Li et al., 2017). In stroke, most studies support the hypothesis that mitophagy favors neurons adapted to the stress by removing impaired mito-chondria and suppressing cell death signaling cascades. In perma-nent MCAO, mitophagy was triggered at 1 hr and in the reperfusion phase (Zhang et al., 2013) (Zuo et al., 2014). Rapamycin treatment improves mitochondrial function after experimental ischemic stroke (Li et al., 2014). Infusion of MSCs restored PTEN-induced kinase (Pink1)/ PTEN-induced kinase 1 (Parkin)-mediated mitophagy, improved mitochondrial dysfunction and attenuated apoptosis in en-dothelial cells in diabetic rats (Zhu et al., 2018).

4.2 | MSCs—neuroprotection by modulation of immune-inflammatory response

Inflammation is another important risk factor for injury in the developing brain (Bokobza et al., 2019; Hagberg et al., 2012, 2015). Intranasal administration of UC-MSCs in postnatal day 10 Sprague-Dawley rat pups after HI significantly reduced markers of neuroinflammation and significantly decreased the number of ac-tivated microglia, the brains innate immune cells (McDonald et al. 2019).

In clinical cases of IVH, microglial density, particularly IBA1/CD68 microglia, was higher within the affected brain regions when compared to healthy infants. Severe cases also had increased TNFa expression (Supramaniam et al., 2013). Following IVH, bleeding may extend into the intraventricular CSF, with cell-free hemoglobin pro-posed as an inducer of inflammation, and hemoglobin metabolites inducing pro-inflammatory cytokine expression (Gram et al., 2013) causing inflammation of the choroid plexus and ventricular ependy-mal lining (Simard et al., 2011). Inflammation and scarring may also prevent the flow of CSF reducing drainage (Strahle et al., 2012). Clinical studies have shown that the CSF inflammatory response to IVH is directly proportional to the extension of bleeding (Fam et al., 2017). Injury to the germinal matrix and HI, both possibly mediated by cytotoxins from blood products, are linked to the mechanisms of injury after IVH (du Plessis, 1998). Interestingly, brain-derived neurotrophic factor (BDNF) secreted by MSCs, after contact with thrombin is an important factor in MSC therapy for IVH. MSCs with siRNA-induced BDNF knockdown lose their ther-apeutic capacity in severe IVH-induced brain injury in newborn rats (Ahn et al., 2017).

MSCs are capable of homing from the circulation to sites of in-jury and inflammation (Rustad & Gurtner, 2012). This can result in the resolution of the glial scar surrounding the lesion, decrease in reactive astrocytes and microglia and polarization of microglia to-ward the anti-inflammatory phenotype (Donega et al., 2014). Lin et al. have shown that infusion of MSCs in a global cerebral ischemia mouse model increased release of TNF-α-induced protein (TSG-6) thereby inhibiting local inflammation and improving function of the nervous system (Lin et al., 2013). Van Velthoven et al have demon-strated in the damaged area of the brain after MSC treatment, the up-regulation of gene expression profiles associated with cell pro-liferation (Spp1 and IL17), neurogenesis (NRCAm and NGF), mi-gration (CXCR4), and neuronal survival (glial-derived neurotrophic factor) whereas genes involved in inflammation (e.g. IL1-β) were down-regulated.

Since the immunomodulatory properties of MSCs were first reported by Bartholomew and colleagues (Bartholomew et al., 2002), subsequent studies have shown that MSCs mediate immunosuppression via up-regulation of miR-155 (Xu et al., 2013). MSCs have the capacity to interact with immune cells like B cells, T cells, dendritic cells (DCs), natural killer (NK) cells, neutrophil, and macrophages (Wang et al., 2014) and the MSCs secretome alters both adaptive and innate immune responses (Aslam et al., 2009; Bruno et al., 2015).

MSCs induce persistent peripheral T-cell tolerance in a preterm sheep model and reduced invasion of T cells into the brain following global HI (Jellema et al., 2013). Besides T-cell modulation, MSCs in-hibit B cell proliferation, neutrophil and monocyte function, and NK toxicity (Duffy et al., 2011; Gerdoni et al., 2007; Jellema et al., 2013). Although these modulatory effects are only partially understood, direct cell-to-cell contact and soluble factors appear both to be rele-vant (Rahmat et al., 2013). MSCs recognize activated NK cells and in-hibit their proliferation by downregulating their activation via IL-2 or

IL-15 (Spaggiari & Moretta, 2012). MSCs inhibit CD14 + monocyte differentiation toward dendritic cells (DC) (Jiang et al., 2005). MSCs also suppress TNFα and IFN-γ secretion by CD4 + T cells while promoting IL-4 secretion (Aggarwal & Pittenger, 2005). Artificial transfer of isolated MSC-derived mitochondria also affects inflammation via actions on adaptive immune cells. Specifically, transfer of mitochondria from MSCs to T cells increases the expression of mRNA transcripts involved in T-cell activation and T regulatory cell differentiation including FOXP3, IL2RA, CTLA4, and TGFβ1, leading to an increase in a highly suppressive CD25 + FoxP3+ population (Court et al., 2020).

Besides the actions mentioned above, mitochondria also act as central hubs in the innate immune system by regulating RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), and Toll-like receptors (TLR). The incorporation of mitochondria into this arm of immunity can result in increased cellular energy output and significant metabolic reprogramming (West et al., 2011). Microglia are the immune cells of the brain and our previous study demonstrated that their inflammatory activation is linked to changes in mitochondrial function (Nair et al., 2019). Specifically, a short exposure to a low dose of lipopolysaccharide (LPS) causes a transient increase in oxidative phosphorylation (OXPHOS) whereas prolonged exposure to high dose LPS causes suppression of OXPHOS and mitochondrial respiration. This suppression of OXPHOS forces a metabolic shift toward glycolysis (Nair et al., 2019), a phenomenon similar to the Warburg effect (Kelly & O'Neill, 2015). Although glycolysis results in less ATP production overall, the preferential use of glycolysis over OXPHOS enables immune cells to produce ATP at a faster rate (Marelli-Berg et al., 2012) and to produce intermediates for cytokine production (Chang et al., 2013) (Figure 2).

MSCs alleviate inflammation and the anti-inflammatory effects include a shift from pro-inflammatory cytokines such as IL-1β, IL-6, TNFα, IFNγ, IL-1Rα, and prostaglandin E2 to anti-inflammatory cytokines like IL-10 (Bartosh et al., 2010; Chaubey et al., 2018; Chou et al., 2016; Ding et al., 2017; Nemeth et al., 2009; Ortiz et al., 2007; Park et al., 2013) (Figure 2). IL-10 inhibits LPS-induced glucose uptake and glycolysis and promotes OXPHOS in macrophages. IL-10 also eliminates dysfunctional mitochondria by promoting mitophagy (Ip et al., 2017) which may drive them toward an anti-inflammatory phenotype.

MSCs impact the metabolic phenotype of primary macrophages in co-cultures (Vasandan et al., 2016). However, we do not know if MSC-mediated factors directly lead to a metabolic shift in brain cells such as microglia. Islam et al. demonstrated in a comprehensive study that transfer of mitochondria via gap junctional channels from MSCs to pulmonary alveolar epithelial cells in a murine model of LPS-induced acute lung injury is protective (Islam et al., 2012). They demonstrated that the neuroprotective effect was because of transferred mitochondria by including studies using gap-junction channel-deficient MSCs. Gap-junction channels mediate shorter range cell-to-cell interactions, whereas TNTs allow long-range communication and mediate the exchange of larger organelles and vesicles (Gerdes et al., 2013; Okafo et al., 2017).

4.3 | MSCs—neuroprotection by regulation of ros production

During HI, oxidative stress induced by ROS 'bursts' plays a vital role in mitochondrial dysfunction and subsequent cell death (Forman et al., 2004; Piantadosi & Zhang, 1996; Singh-Mallah et al., 2019). Elevated levels of intracellular ROS caused by dysfunctional mitochondria attenuate global protein synthesis (Topf et al., 2018) and will indiscriminately attack phospholipids, proteins and DNA (Singh-Mallah et al., 2019). Oxidative stress is an early feature after cerebral ischemia and experimental studies targeting the formation of free radicals demonstrate various degrees of protection after perinatal insults (Singh-Mallah et al., 2019). The premature brain, in particular, is vulnerable to ROS-induced damage because of the deficient antioxidant stores due of their insufficient ability to synthesize antioxidant enzymes at birth and impaired up-regulation in response to oxidative stress (Lee & Davis, 2011; Singh-Mallah et al., 2019).

The main species of ROS which include $O^{2\bullet-}$ and H_2O_2 is produced from the dismutation of $O^{2\bullet-}$ by MnSOD within the mitochondria (Singh-Mallah et al., 2019). Ischemia also results in succinate accumulation in the immature brain (Koning et al., 2019) which is rapidly oxidized in the first minutes of reperfusion, generating large amounts of $O^{2\bullet}$(Sahni et al., 2018)$^-$. The underdeveloped antioxidant system in the immature brain limits the inactivation of H_2O_2, which can cross lipid membranes and cause tissue damage. Mitochondrial ROS production and inflammation are increased after neonatal brain injury associated with altered Krebs cycle and succinate accumulation in the mitochondria (Koning et al., 2019). Excessive inflammation causes mitochondrial fragmentation and a metabolic switch in microglia cells, which is accompanied by increased ROS production (Nair et al., 2019).

MSCs reduce increased oxidative stress levels in pathophysiological conditions. Paliwal et al. (2017) investigated abilities of tissue-specific MSCs (bone marrow, adipose tissue, dental pulp and umbilical cord), from young or old donors (<30 versus > 30 years of age) to reduce ROS and thereby mitigate cellular damage. They found that both donor's age and source of tissue affected the ability of MSCs to reduce increased ROS levels in injured cells, with young donor supplied dental pulp MSCs having the greatest efficacy (Paliwal et al., 2017). The importance of donor age in stem cell treatment has also been investigated in the use of UCB derived from term or preterm sheep, administered in a sheep model of HIE. Although both cell sources were protective, UCB from term (but not preterm) reduced markers of circulating oxidative stress (Li et al., 2018).

ROS levels can be efficiently reduced by stimulating mitophagy by rapamycin (Bin-Umer et al., 2014; Kurihara et al., 2012). As damaged mitochondria are a primary source of ROS, failure to remove dysfunctional mitochondria results in increase ROS production. MSCs can ameliorate ROS overproduction by restoration of autophagic flux (Zhu et al., 2018). These findings indicate that MSCs are important regulators of oxidative stress production, enhance cell migration, and support their role to improve neuroprotection and brain recovery following injury.

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5 | HOW TO BUILD A BETTER MSC

Targeting metabolism is an important way to improve MSC function. Studies have shown that in a nutrient-rich culture medium MSCs rapidly proliferate, and reconfigure their central energy metabolism to become significantly more dependent on oxidative phosphorylation (OXPHOS) (Pattappa et al., 2011). Whereas in their native (lower nutrient) environment MSCs exist in a quiescent state characterized by low proliferation and high multi-potentiality (Yuan et al., 2019). In this state they are primarily glycolytic, with mitochondria maintained by active biogenesis-mitophagy cycling (Katajisto et al., 2015; Sbrana et al., 2016). Dependence on OXPHOS-fueled metabolic profile (in a nutrient-rich environment) results in accumulation of reactive oxygen species (ROS) (Shyh-Chang et al., 2013), that reduce basal autophagy and mitophagy rates while simultaneously increasing the fraction of senescent cells that have reduced clinical potency (Ho et al., 2017). Another important feature of MSCs for cell therapy is their immunomodulatory secretome—cytokines and cellular components such as microRNA and extracellular vesicles that affect their repair and regenerative capacities.

In vivo studies show that MSCs can home toward the ischemic lesion site via interaction between stromal cell-derived factor-1α and its receptor CXCR4 present on MSCs (Wang et al., 2008). The Stromal cell-derived factor-1α expression is upregulated near the lesion site and expressed for at least 14 d after induction of HI brain injury (Rosenkranz et al., 2010). The interaction of locally produced SDF-1alpha and CXCR4 expressed on the MSC plays an important role in the migration of transplanted MSCs, suggests that it might be a potential approach to modulate the expression of the two molecules in order to promote the therapeutic effects of MSCs (Wang et al., 2008).

The characteristics of the secretome is significantly influenced by metabolism (Yuan et al., 2019), which itself is linked to MSC phenotype. MSC phenotype, is the state of the cell as a result of the interaction between the paracrine factors with receptors such as Toll-like receptors (TLR) (Delarosa et al., 2012; Sangiorgi & Panepucci, 2016). (Waterman et al., 2010) has described two different MSC phenotypes distinguished as proinflammatory MSC phenotype (MSC1; induced by TLR4 activation) and anti-inflammatory MSC phenotype (MSC2; induced by TLR3 activation).

Donald et al. have shown that MSCs manage intracellular oxidative stress by targeting depolarized mitochondria to the plasma membrane via arrestin domain-containing protein 1-mediated microvesicles (Phinney et al., 2015). Subsequently, these microvesicles are engulfed and re-utilized via a process involving mitochondrial fusion by macrophages which results in enhanced bioenergetics (Phinney et al., 2015). In this process MSCs simultaneously shed micro RNA-containing exosomes that inhibit macrophage activation by suppressing TLR signaling, thereby de-sensitizing macrophages to the ingested mitochondria (Phinney et al., 2015).

Methods to manipulate MSCs to reduce ROS during their culture expansion phase and in the injured tissue microenvironment may also promote MSC engraftment and enhance tissue repair (Denu &

Hematti, 2016). One potential method to reduce oxidative stress in MSCs is by modulating sirtuin expression and/or activity. Multiple studies have shown a protective role for SIRT1 in various models of neuronal injury and neurodegeneration (Della-Morte et al., 2009). It is shown that SIRT1 over-expression quenches age-related MSCs senescence by enhancing TPP1 expression, telomerase activity, and reducing DNA damage. ROS levels in stem cells increase with age (Ito et al., 2006). Majority of ROS is produced in the mitochondria and SIRT3 is the major protein deacetylase in the mitochondria, where its actions decrease ROS production. In addition, SIRT3 initiates metabolic reprogramming toward more efficient electron transport and fuel usage away from carbohydrate catabolism, reducing excessive ROS (Denu, 2017). Data suggest that overexpressing SIRT3 (major mitochondrial deacetylase involved in reducing oxidative stress while preserving oxidative metabolism) might represent a strategy to increase the quality and quantity of MSCs that could be utilized for clinical applications (Denu, 2017).

6 | CHALLENGES IN MSC-BASED THERAPY

Researchers have made significant progress in enhancing the therapeutic properties of MSCs. Transplantation time and injected cell dose are key factors that determine the therapeutic effect of stem cell therapy (Wang et al., 2017). Studies with incomparable or conflicting results prevent the advancement of MSCs for clinical use. These discrepancies are mostly because of variabilities in dosage, administration route, timing, and the limited ability of animal models to mimic the extremely complex process of human physiology and etiology of encephalopathy. Possible routes for MSCs infusion in animals are, (i) systemic delivery [intra-venous (IV) and intra-arterial (IA) , intra-peritoneal (IP), and intracardiac (IC) (ii) local/topical/regional delivery (cell-spray, gel or subcutaneous injection with a carrier hydrogel intramuscular, intranasal, and intrathecal injection) or (iii) scaffold/bioengineered construct (cells embedded in a scaffold, such as vascular grafts and intra-osseous injection), with each route having its advantages and disadvantages for specific disorders. Although intracerebral administration ensures direct and targeted delivery and a minimum loss of stem cells, it is an invasive procedure, especially as the sites for delivery are often deep in the brain. However, these approaches should not be considered inappropriate to develop, as invasive neurosurgical techniques have been developed for the treatment of severe IVH and these have had astounding positive effects on long-term outcomes; a 23-point increase in childhood IQ (Luyt et al., 2019). To avoid intracerebral injections, multiple studies have looked at systemic MSC administration routes: either intravenous (IV) or intra-arterial or intranasal applications (Li et al., 2018, McDonald et al. 2019, Danielyan et al., 2009, van Velthoven et al., 2010b). IV injections by retro-orbital injections, although may seem aesthetically distasteful, can be performed rapidly without requiring mechanical restriction or heat-induced vasodilation. This route is ultimately more humane than alternative

intravascular injection techniques in small animals (Leon-Rico et al., 2015; Ukai et al., 2007; Yardeni et al., 2011).

Therapeutic modalities must not only be efficacious but also safe for the patient. While the majority of preclinical and clinical studies have found MSCs to be safe and well-tolerated (Lalu et al., 2012), uncontrolled stem cell interventions have resulted in adverse incidents (Bauer et al., 2018; Moll et al., 2019). Systemic injections may be practical but they can activate the host innate immune cascade systems, such as complement and coagulation, termed the instant blood mediated inflammatory reaction (IBMIR) (Leibacher & Henschler, 2016; Moll et al., 2012, 2019). A meta-analysis of preclinical studies of MSCs in ischemic stroke models found that although direct injection of MSCs provided the greatest benefit, although other methods of delivery such as IA and IV injections also demonstrated significant improvement in outcomes (Vu et al., 2014). Therefore, the present data, based on some preclinical studies and limited clinical trials, is not adequate to make any sound conclusions as to whether one delivery method is superior to another.

In addition to routes of administration, the delivery of sufficient MSCs is required to discern a significant therapeutic effect. Neuroprotective therapy for HIE such as hypothermia, needs to be started within 6 hr to be effective (Davidson et al., 2015). However, the therapeutic window of MSC treatment is probably wider in neonatal HI mice as it has been shown that MSCs improved functional outcome and lesion volume when administered at least until 10 days after induction of the insult (Donega et al., 2013). A single dose of 0.5×10^6 MSCs administered intranasally was identified as the minimally effective dose with a therapeutic window of at least 10 days but less than 17 days post-HI was sufficient for a marked beneficial effect in neonatal mice (Donega et al., 2013). Velthoven et al have shown that intracranial administration of 100,000 MSCs at 3 and 10 days after neonatal HI markedly improves functional outcome, reduces infarct volume, and stimulates neurogenesis, with each injection having distinct effects on regenerative processes. Briefly, they find that a single injection of MSCs increased cell proliferation and differentiation of newly divided cells into NeuN- and olig2-positive cells and reduced the percentage of BrdU+-microglia, whereas a second additional injection with MSCs induced axonal outgrowth and remodeling, myelination and synaptogenesis which led to improved functional outcome (van Velthoven et al., 2010a).

7 | CONCLUSION and FUTURE DIRECTIONS

MSCs secrete many paracrine factors which can impart pleiotropic effects in response to microenvironmental cues in the injured brain. MSCs attenuate pro-inflammatory responses and the adverse effects of excessive ROS production. MSC mediated mitochondria transplantation could be a game-changer for treating perinatal and neonatal brain injury. Future meticulous studies should be performed to delineate the mitochondria-mediated protective mechanisms specifically for neonatal brain injury. For instance, the development of

a selective inhibitor for TNT formation can help unravel its functional role. Another example is accelerated mitochondrial transfer by Miro1 over-expression, as this may be a way to rejuvenate injured cells. Scientists are investigating the role of artificial transfer of isolated mitochondria as it can emerge as a regenerative or immunomodulatory therapy.

CONFLICT OF INTEREST
We report no conflict of interest.

ORCID
Syam Nair https://orcid.org/0000-0001-8470-2162

REFERENCES

Aggarwal, S., & Pittenger, M. F. (2005). Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood*, *105*, 1815–1822. https://doi.org/10.1182/blood-2004-04-1559

Ahmad, T., Mukherjee, S., Pattnaik, B., Kumar, M., Singh, S., Kumar, M., Rehman, R., Tiwari, B. K., Jha, K. A., Barhanpurkar, A. P., Wani, M. R., Roy, S. S, Mabalirajan, U., Ghosh, B., & Agrawal, A. (2014). Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. *The EMBO Journal*, *33*, 994–1010.

Ahn, S. Y., Chang, Y. S., Sung, D. K., Sung, S. I., Ahn, J. Y., & Park, W. S. (2017). Pivotal role of brain-derived neurotrophic factor secreted by mesenchymal stem cells in severe intraventricular hemorrhage in newborn rats. *Cell Transplantation*, *26*, 145–156. https://doi.org/10.3727/096368916X692861

Ahn, S. Y., Chang, Y. S., Sung, D. K., Sung, S. I., Yoo, H. S., Im, G. H., Choi, S. J., & Park, W. S. (2015). Optimal route for mesenchymal stem cells transplantation after severe intraventricular hemorrhage in newborn rats. *PLoS One*, *10*, e0132919. https://doi.org/10.1371/journal.pone.0132919

Ahn, S. Y., Chang, Y. S., Sung, D. K., Sung, S. I., Yoo, H. S., Lee, J. H., Oh, W. I., & Park, W. S. (2013). Mesenchymal stem cells prevent hydrocephalus after severe intraventricular hemorrhage. *Stroke*, *44*, 497–504. https://doi.org/10.1161/STROKEAHA.112.679092

Aslam, M., Baveja, R., Liang, O. D., Fernandez-Gonzalez, A., Lee, C., Mitsialis, S. A., & Kourembanas, S. (2009). Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. *American Journal of Respiratory and Critical Care Medicine*, *180*, 1122–1130. https://doi.org/10.1164/rccm.200902-0242OC

Aslam, S., Strickland, T., & Molloy, E. J. (2019). Neonatal encephalopathy: Need for recognition of multiple etiologies for optimal management. *Frontiers in Pediatrics*, 7, 142. https://doi.org/10.3389/fped.2019.00142

Ballabh, P. (2010). Intraventricular hemorrhage in premature infants: Mechanism of disease. *Pediatric Research*, 67, 1–8.

Ballabh, P. (2014). Pathogenesis and prevention of intraventricular hemorrhage. *Clinics in Perinatology*, 41, 47–67. https://doi.org/10.1016/j.clp.2013.09.007

Barry, F. P., Boynton, R. E., Haynesworth, S., Murphy, J. M., & Zaia, J. (1999). The monoclonal antibody SH-2, raised against human mesenchymal stem cells, recognizes an epitope on endoglin (CD105). *Biochemical and Biophysical Research Communications*, 265, 134–139. https://doi.org/10.1006/bbrc.1999.1620

Barry, F., Boynton, R., Murphy, M., Haynesworth, S., & Zaia, J. (2001). The SH-3 and SH-4 antibodies recognize distinct epitopes on CD73 from human mesenchymal stem cells. *Biochemical and Biophysical Research Communications*, 289, 519–524. https://doi.org/10.1006/bbrc.2001.6013

Bartholomew, A., Sturgeon, C., Siatskas, M., Ferrer, K., McIntosh, K., Patil, S., Hardy, W., Devine, S., Ucker, D., Deans, R., Moseley, A., & Hoffman, R. (2002). Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. *Experimental Hematology*, 30, 42–48. https://doi.org/10.1016/S0301-472X(01)00769-X

Bartosh, T. J., Ylostalo, J. H., Mohammadipoor, A., Bazhanov, N., Coble, K., Claypool, K., Lee, R. H., Choi, H., & Prockop, D. J. (2010). Aggregation of human mesenchymal stromal cells (MSCs) into 3D spheroids enhances their antiinflammatory properties. *Proceedings of the National Academy of Sciences*, 107, 13724–13729. https://doi.org/10.1073/pnas.1008117107

Bauer, G., Elsallab, M., & Abou-El-Enein, M. (2018). Concise review: A comprehensive analysis of reported adverse events in patients receiving unproven stem cell-based interventions. *Stem Cells Translational Medicine*, 7, 676–685. https://doi.org/10.1002/sctm.17-0282

Bel, F., & Groenendaal, F. (2016). Drugs for neuroprotection after birth asphyxia: Pharmacologic adjuncts to hypothermia. *Seminars in Perinatology*, 40, 152–159. https://doi.org/10.1053/j.semperi.2015.12.003

Berger, I., Peleg, O., & Ofek-Shlomai, N. (2012). Inflammation and early brain injury in term and preterm infants. *Israel Medical Association Journal*, 14, 318–323.

Bin-Umer, M. A., McLaughlin, J. E., Butterly, M. S., McCormick, S., & Tumer, N. E. (2014). Elimination of damaged mitochondria through mitophagy reduces mitochondrial oxidative stress and increases tolerance to trichothecenes. *Proceedings of the National Academy of Sciences*, 111, 11798–11803. https://doi.org/10.1073/pnas.1403145111

Bjorklund, L. M., Sanchez-Pernaute, R., Chung, S., Andersson, T., Chen, I. Y. C., McNaught, K. S. P., Brownell, A.-L., Jenkins, B. G., Wahlestedt, C., Kim, K.-S., & Isacson, O. (2002). Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. *Proceedings of the National Academy of Sciences of the United States of America*, 99, 2344–2349. https://doi.org/10.1073/pnas.022438099

Blomgren, K., Zhu, C., Wang, X., Karlsson, J. O., Leverin, A. L., Bahr, B. A., Mallard, C., & Hagberg, H. (2001). Synergistic activation of caspase-3 by m-calpain after neonatal hypoxia-ischemia: A mechanism of "pathological apoptosis"? *Journal of Biological Chemistry*, 276, 10191–10198. https://doi.org/10.1074/jbc.M007807200

Bobinger, T., Burkardt, P., Huttner, B. H., & Manaenko, A.(2018). Programmed cell death after intracerebral hemorrhage. *Current Neuropharmacology*, 16, 1267–1281. https://doi.org/10.2174/1570159X15666170602112851

Bohil, A. B., Robertson, B. W., & Cheney, R. E. (2006). Myosin-X is a molecular motor that functions in filopodia formation. *Proceedings of the National Academy of Sciences*, 103, 12411–12416. https://doi.org/10.1073/pnas.0602443103

Bokobza, C., Van Steenwinckel, J., Mani, S., Mezger, V., Fleiss, B., & Gressens, P. (2019). Neuroinflammation in preterm babies and autism spectrum disorders. *Pediatric Research*, 85, 155–165. https://doi.org/10.1038/s41390-018-0208-4

Bouacida, A., Rosset, P., Trichet, V., Guilloton, F., Espagnolle, N., Cordonier, T., Heymann, D., Layrolle, P., Sensébé, L., & Deschaseaux, F. (2012). Pericyte-like progenitors show high immaturity and engraftment potential as compared with mesenchymal stem cells. *PLoS One*, 7, e48648. https://doi.org/10.1371/journal.pone.0048648

Bruno, S., Deregibus, M. C., & Camussi, G. (2015). The secretome of mesenchymal stromal cells: Role of extracellular vesicles in immunomodulation. *Immunology Letters*, 168, 154–158. https://doi.org/10.1016/j.imlet.2015.06.007

Byun, J.-H., Kang, E.-J., Park, S.-C., Kang, D.-H., Choi, M.-J., Rho, G.-J., & Park, B.-W. (2012). Isolation of human mesenchymal stem cells from the skin and their neurogenic differentiation in vitro. *Jkaoms*, 38, 343–353.

Caicedo, A., Fritz, V., Brondello, J.-M., Ayala, M., Dennemont, I., Abdellaoui, N., de Fraipont, F., Moisan, A., Prouteau, C. A., Boukhaddaoui, H., Jorgensen, C., & Vignais, M.-L. (2015). MitoCeption as a new tool to assess the effects of mesenchymal stem/stromal cell mitochondria on cancer cell metabolism and function. *Scientific Reports*, 5, 9073. https://doi.org/10.1038/srep09073

Carloni, S., Buonocore, G., & Balduini, W. (2008). Protective role of autophagy in neonatal hypoxia-ischemia induced brain injury. *Neurobiology of Diseases*, 32, 329–339. https://doi.org/10.1016/j.nbd.2008.07.022

Chang, C.-H., Curtis, J. D., Maggi, L. B., Faubert, B., Villarino, A. V., O'Sullivan, D., Huang, S.-C., van der Windt, G. J. W., Blagih, J., Qiu, J., Weber, J. D., Pearce, E. J., Jones, R. G., & Pearce, E. L. (2013). Posttranscriptional control of T cell effector function by aerobic glycolysis. *Cell*, 153, 1239–1251. https://doi.org/10.1016/j.cell.2013.05.016

Chang, J.-C., Wu, S.-L., Liu, K.-H., Chen, Y.-H., Chuang, C.-S., Cheng, F.-C., Su, H.-L., Wei, Y.-H., Kuo, S.-J., & Liu, C.-S. (2016). Allogeneic/xenogeneic transplantation of peptide-labeled mitochondria in Parkinson's disease: Restoration of mitochondria functions and attenuation of 6-hydroxydopamine–induced neurotoxicity. *Translational Research*, 170, 40–56.e43. https://doi.org/10.1016/j.trsl.2015.12.003

Chaubey, S., Thueson, S., Ponnalagu, D., Alam, M. A., Gheorghe, C. P., Aghai, Z., Singh, H., & Bhandari, V. (2018). Early gestational mesenchymal stem cell secretome attenuates experimental bronchopulmonary dysplasia in part via exosome-associated factor TSG-6. *Stem Cell Research & Therapy*, 9, 173. https://doi.org/10.1186/s13287-018-0903-4

Chavez-Valdez, R., Flock, D. L., Martin, L. J., & Northington, F. J. (2016). Endoplasmic reticulum pathology and stress response in neurons precede programmed necrosis after neonatal hypoxia-ischemia. *International Journal of Developmental Neuroscience*, 48, 58–70. https://doi.org/10.1016/j.ijdevneu.2015.11.007

Chavez-Valdez, R., Martin, L. J., & Northington, F. J. (2012). Programmed necrosis: A prominent mechanism of cell death following neonatal brain injury. *Neurology Research International*, 2012, 257563. https://doi.org/10.1155/2012/257563

Chen, J., Li, Y., Katakowski, M., Chen, X., Wang, L., Lu, D., Lu, M., Gautam, S. C., & Chopp, M. (2003). Intravenous bone marrow stromal cell therapy reduces apoptosis and promotes endogenous cell proliferation after stroke in female rat. *Journal of Neuroscience Research*, 73, 778–786. https://doi.org/10.1002/jnr.10691

Chou, H. C., Li, Y. T., & Chen, C. M. (2016). Human mesenchymal stem cells attenuate experimental bronchopulmonary dysplasia induced by perinatal inflammation and hyperoxia. *American Journal of Translational Research*, 8, 342–353.

Chu, P. G., & Arber, D. A. (2001). CD79: A review. *Applied Immunohistochemistry & Molecular Morphology*, 9, 97–106. https://doi.org/10.1097/00129039-200106000-00001

Comi, A. M., Cho, E., Mulholland, J. D., Hooper, A., Li, Q., Qu, Y., Gary, D. S., McDonald, J. W., & Johnston, M. V. (2008). Neural stem cells reduce brain injury after unilateral carotid ligation. *Pediatric Neurology*, 38, 86–92. https://doi.org/10.1016/j.pediatrneurol.2007.10.007

Court, A. C., Le-Gatt, A., Luz-Crawford, P., Parra, E., Aliaga-Tobar, V., Bátiz, L. F., Contreras, R. A., Ortúzar, M. I., Kurte, M., Elizondo-Vega, R., Maracaja-Coutinho, V., Pino-Lagos, K., Figueroa, F. E., & Khoury, M. (2020). Mitochondrial transfer from MSCs to T cells induces Treg differentiation and restricts inflammatory response. *EMBO Reports*, 21, e48052. https://doi.org/10.15252/embr.20194 8052

Coxon, A., Rieu, P., Barkalow, F. J., Askari, S., Sharpe, A. H., von Andrian, U. H., Arnaout, M. A., & Mayadas, T. N. (1996). A novel role for the β2 integrin CD11b/CD18 in neutrophil apoptosis: A homeostatic mechanism in inflammation. *Immunity*, 5, 653–666. https://doi.org/10.1016/S1074-7613(00)80278-2

da Silva Meirelles, L., Malta, T. M., Panepucci, R. A., & da Silva Jr, W. A. (2016). Transcriptomic comparisons between cultured human adipose tissue-derived pericytes and mesenchymal stromal cells. *Genomics Data*, 7, 20–25. https://doi.org/10.1016/j.gdata.2015.11.009

Danielyan, L., Schäfer, R., von Ameln-Mayerhofer, A., Buadze, M., Geisler, J., Klopfer, T., Burkhardt, U., Proksch, B., Verleysdonk, S., Ayturan, M., Buniatian, G. H., Gleiter, C. H., & Frey, W. H. (2009). Intranasal delivery of cells to the brain. *European Journal of Cell Biology*, 88, 315–324. https://doi.org/10.1016/j.ejcb.2009.02.001

Davidson, J. O., Wassink, G., van den Heuij, L. G., Bennet, L., & Gunn, A. J. (2015). Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy - where to from here? *Frontiers in Neurology*, 6, 198.

Delarosa, O., Dalemans, W., & Lombardo, E. (2012). Toll-like receptors as modulators of mesenchymal stem cells. *Frontiers in Immunology*, 3, 182. https://doi.org/10.3389/fimmu.2012.00182

Della-Morte, D., Dave, K. R., DeFazio, R. A., Bao, Y. C., Raval, A. P., & Perez-Pinzon, M. A. (2009). Resveratrol pretreatment protects rat brain from cerebral ischemic damage via a sirtuin 1-uncoupling protein 2 pathway. *Neuroscience*, 159, 993–1002. https://doi.org/10.1016/j.neuroscience.2009.01.017

Denu, R. A. (2017). SIRT3 enhances mesenchymal stem cell longevity and differentiation. *Oxidative Medicine and Cellular Longevity*, 2017, 5841716. https://doi.org/10.1155/2017/5841716

Denu, R. A., & Hematti, P. (2016). Effects of oxidative stress on mesenchymal stem cell biology. *Oxidative Medicine and Cellular Longevity*, 2016, 2989076. https://doi.org/10.1155/2016/2989076

Descloux, C., Ginet, V., Clarke, P. G., Puyal, J., & Truttmann, A. C. (2015). Neuronal death after perinatal cerebral hypoxia-ischemia: Focus on autophagy-mediated cell death. *International Journal of Developmental Neuroscience*, 45, 75–85. https://doi.org/10.1016/j.ijdevneu.2015.06.008

Ding, H., Zhang, H., Ding, H., Li, D., Yi, X., Ma, X., Li, R., Huang, M., & Ju, X. (2017). Transplantation of placenta-derived mesenchymal stem cells reduces hypoxic-ischemic brain damage in rats by ameliorating the inflammatory response. *Cellular & Molecular Immunology*, 14, 693–701. https://doi.org/10.1038/cmi.2015.99

Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F. C., Krause, D. S., Deans, R. J., Keating, A., Prockop, D. J., & Horwitz, E. M. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*, 8, 315–317. https://doi.org/10.1080/14653 240600855905

Donega, V., Nijboer, C. H., van Tilborg, G., Dijkhuizen, R. M., Kavelaars, A., & Heijnen, C. J. (2014). Intranasally administered mesenchymal stem cells promote a regenerative niche for repair of neonatal ischemic brain injury. *Experimental Neurology*, 261, 53–64. https://doi.org/10.1016/j.expneurol.2014.06.009

Donega, V., van Velthoven, C. T., Nijboer, C. H., van Bel, F., Kas, M. J., Kavelaars, A., & Heijnen, C. J. (2013). Intranasal mesenchymal stem cell treatment for neonatal brain damage: Long-term cognitive and sensorimotor improvement. *PLoS One*, 8, e51253. https://doi.org/10.1371/journal.pone.0051253

du Plessis, A. J. (1998). Posthemorrhagic hydrocephalus and brain injury in the preterm infant: Dilemmas in diagnosis and management. *Seminars in Pediatric Neurology*, 5, 161–179. https://doi.org/10.1016/S1071-9091(98)80032-6

Duffy, M. M., Ritter, T., Ceredig, R., & Griffin, M. D. (2011). Mesenchymal stem cell effects on T-cell effector pathways. *Stem Cell Research & Therapy*, 2, 34. https://doi.org/10.1186/scrt75

Emani, S. M., Piekarski, B. L., Harrild, D., Del Nido, P. J., & McCully, J. D. (2017). Autologous mitochondrial transplantation for dysfunction after ischemia-reperfusion injury. *Journal of Thoracic and Cardiovascular Surgery*, 154, 286–289. https://doi.org/10.1016/j.jtcvs.2017.02.018

Falnikar, A., Tole, S., & Baas, P. W. (2011). Kinesin-5, a mitotic microtubule-associated motor protein, modulates neuronal migration. *Molecular Biology of the Cell*, 22, 1561–1574. https://doi.org/10.1091/mbc.e10-11-0905

Fam, M. D., Zeineddine, H. A., Eliyas, J. K., Stadnik, A., Jesselson, M., McBee, N., Lane, K., Cao, Y., Wu, M., Zhang, L., Thompson, R. E., John, S., Ziai, W., Hanley, D. F., & Awad, I. A. (2017). CSF inflammatory response after intraventricular hemorrhage. *Neurology*, 89, 1553–1560. https://doi.org/10.1212/WNL.0000000000004493

Ferriero, D. M., Fullerton, H. J., Bernard, T. J., Billinghurst, L., Daniels, S. R., DeBaun, M. R., deVeber, G., Ichord, R. N., Jordan, L. C., Massicotte, P., Meldau, J., Roach, E. S., & Smith, E. R. (2019). Management of stroke in neonates and children: A scientific statement from the American heart association/American stroke association. *Stroke*, 50, e51–e96. https://doi.org/10.1161/STR.0000000000000183

Fleiss, B., & Gressens, P. (2012). Tertiary mechanisms of brain damage: A new hope for treatment of cerebral palsy? *The Lancet Neurology*, 11, 556–566. https://doi.org/10.1016/S1474-4422(12)70058-3

Fleiss, B., Guillot, P. V., Titomanlio, L., Baud, O., Hagberg, H., & Gressens, P. (2014). Stem cell therapy for neonatal brain injury. *Clinics in Perinatology*, 41, 133–148. https://doi.org/10.1016/j.clp.2013.09.002

Forman, H. J., Fukuto, J. M., & Torres, M. (2004). Redox signaling: Thiol chemistry defines which reactive oxygen and nitrogen species can act as second messengers. *American Journal of Physiology. Cell Physiology*, 287, C246–256. https://doi.org/10.1152/ajpcell.00516.2003

Fransson, S., Ruusala, A., & Aspenström, P. (2006). The atypical Rho GTPases Miro-1 and Miro-2 have essential roles in mitochondrial trafficking. *Biochemical and Biophysical Research Communications*, 344, 500–510. https://doi.org/10.1016/j.bbrc.2006.03.163

Galipeau, J., Krampera, M., Barrett, J., Dazzi, F., Deans, R. J., DeBruijn, J., Dominici, M., Fibbe, W. E., Gee, A. P., Gimble, J. M., Hematti, P., Koh, M. B. C., LeBlanc, K., Martin, I., McNiece, I. K., Mendicino, M., Oh, S., Ortiz, L., Phinney, D. G., ... Sensebe, L. (2016). International Society for Cellular Therapy perspective on immune functional assays for mesenchymal stromal cells as potency release criterion for advanced phase clinical trials. *Cytotherapy*, 18, 151–159. https://doi.org/10.1016/j.jcyt.2015.11.008

Galluzzi, L., Blomgren, K., & Kroemer, G. (2009). Mitochondrial membrane permeabilization in neuronal injury. *Nature Reviews Neuroscience*, 10, 481–494. https://doi.org/10.1038/nrn2665

Galluzzi, L., Bravo-San Pedro, J. M., Blomgren, K., & Kroemer, G. (2016). Autophagy in acute brain injury. *Nature Reviews Neuroscience*, 17, 467–484. https://doi.org/10.1038/nrn.2016.51

Galluzzi, L., Vanden Berghe, T., Vanlangenakker, N., Buettner, S., Eisenberg, T., Vandenabeele, P., Madeo, F., & Kroemer, G. (2011).

Programmed necrosis from molecules to health and disease. *International Review of Cell and Molecular Biology*, *289*, 1–35.

Ge, Q., Zhang, H., Hou, J., Wan, L., Cheng, W., Wang, X., Dong, D., Chen, C., Xia, J., Guo, J., Chen, X., & Wu, X. (2018). VEGF secreted by mesenchymal stem cells mediates the differentiation of endothelial progenitor cells into endothelial cells via paracrine mechanisms. *Molecular Medicine Reports*, *17*, 1667–1675.

Gerdes, H. H., Bukoreshtliev, N. V., & Barroso, J. F. (2007). Tunneling nanotubes: A new route for the exchange of components between animal cells. *FEBS Letters*, *581*, 2194–2201. https://doi.org/10.1016/j.febslet.2007.03.071

Gerdes, H.-H., Rustom, A., & Wang, X. (2013). Tunneling nanotubes, an emerging intercellular communication route in development. *Mechanisms of Development*, *130*, 381–387. https://doi.org/10.1016/j.mod.2012.11.006

Gerdoni, E., Gallo, B., Casazza, S., Musio, S., Bonanni, I., Pedemonte, E., Mantegazza, R., Frassoni, F., Mancardi, G., Pedotti, R., & Uccelli, A. (2007). Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis. *Annals of Neurology*, *61*, 219–227. https://doi.org/10.1002/ana.21076

Glater, E. E., Megeath, L. J., Stowers, R. S., & Schwarz, T. L. (2006). Axonal transport of mitochondria requires milton to recruit kinesin heavy chain and is light chain independent. *Journal of Cell Biology*, *173*, 545–557. https://doi.org/10.1083/jcb.200601067

Gonzales-Portillo, G. S., Reyes, S., Aguirre, D., Pabon, M. M., & Borlongan, C. V. (2014). Stem cell therapy for neonatal hypoxic-ischemic encephalopathy. *Frontiers in Neurology*, *5*, 147. https://doi.org/10.3389/fneur.2014.00147

Gothard, D., Greenhough, J., Ralph, E., & Oreffo, R. O. (2014). Prospective isolation of human bone marrow stromal cell subsets: A comparative study between Stro-1-, CD146-and CD105-enriched populations. *Journal of Tissue Engineering*, *5*, 2041731414551763. https://doi.org/10.1177/2041731414551763

Gram, M., Sveinsdottir, S., Ruscher, K., Hansson, S. R., Cinthio, M., Akerström, B., & Ley, D. (2013). Hemoglobin induces inflammation after preterm intraventricular hemorrhage by methemoglobin formation. *Journal of Neuroinflammation*, *10*, 100. https://doi.org/10.1186/1742-2094-10-100

Gronthos, S., Mankani, M., Brahim, J., Robey, P. G., & Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proceedings of the National Academy of Sciences*, *97*, 13625–13630. https://doi.org/10.1073/pnas.240309797

Hagberg, H. (2004). Mitochondrial impairment in the developing brain after hypoxia-ischemia. *Journal of Bioenergetics and Biomembranes*, *36*, 369–373. https://doi.org/10.1023/B:JOBB.0000041770.00567.4f

Hagberg, H., David Edwards, A., & Groenendaal, F. (2016). Perinatal brain damage: The term infant. *Neurobiology of Diseases*, *92*, 102–112.

Hagberg, H., Gressens, P., & Mallard, C. (2012). Inflammation during fetal and neonatal life: Implications for neurologic and neuropsychiatric disease in children and adults. *Annals of Neurology*, *71*, 444–457. https://doi.org/10.1002/ana.22620

Hagberg, H., Mallard, C., Ferriero, D. M., Vannucci, S. J., Levison, S. W., Vexler, Z. S., & Gressens, P. (2015). The role of inflammation in perinatal brain injury. *Nature Reviews. Neurology*, *11*, 192–208. https://doi.org/10.1038/nrneurol.2015.13

Hagberg, H., Mallard, C., Rousset, C. I., & Thornton, C. (2014). Mitochondria: Hub of injury responses in the developing brain. *The Lancet Neurology*, *13*, 217–232. https://doi.org/10.1016/S1474-4422(13)70261-8

Hagberg, H., Mallard, C., Rousset, C. I., & Xiaoyang, W. (2009). Apoptotic mechanisms in the immature brain: Involvement of mitochondria. *Journal of Child Neurology*, *24*, 1141–1146. https://doi.org/10.1177/0883073809338212

Hagberg, H., Peebles, D., & Mallard, C. (2002). Models of white matter injury: Comparison of infectious, hypoxic-ischemic, and excitotoxic insults. *Mental Retardation and Developmental Disabilities Research Reviews*, *8*, 30–38. https://doi.org/10.1002/mrdd.10007

Hawkins, K. E., Corcelli, M., Dowding, K., Ranzoni, A. M., Vlahova, F., Hau, K.-L., Hunjan, A., Peebles, D., Gressens, P., Hagberg, H., de Coppi, P., Hristova, M., & Guillot, P. V. (2018). Embryonic stem cell-derived mesenchymal stem cells (MSCs) have a superior neuroprotective capacity over fetal MSCs in the hypoxic-ischemic mouse brain. *Stem Cells Translational Medicine*, *7*, 439–449. https://doi.org/10.1002/sctm.17-0260

Hill, A., & Volpe, J. J. (1981). Seizures, hypoxic-ischemic brain injury, and intraventricular hemorrhage in the newborn. *Annals of Neurology*, *10*, 109–121. https://doi.org/10.1002/ana.410100202

Ho, T. T., Warr, M. R., Adelman, E. R., Lansinger, O. M., Flach, J., Verovskaya, E. V., Figueroa, M. E., & Passegué, E. (2017). Autophagy maintains the metabolism and function of young and old stem cells. *Nature*, *543*, 205–210. https://doi.org/10.1038/nature21388

Hynes, M., & Rosenthal, A. (2000). Embryonic stem cells go dopaminergic. *Neuron*, *28*, 11–14. https://doi.org/10.1016/S0896-6273(00)00079-9

Ingram, D. A., Mead, L. E., Tanaka, H., Meade, V., Fenoglio, A., Mortell, K., Pollok, K., Ferkowicz, M. J., Gilley, D., & Yoder, M. C. (2004). Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. *Blood*, *104*, 2752–2760. https://doi.org/10.1182/blood-2004-04-1396

Ip, W. K. E., Hoshi, N., Shouval, D. S., Snapper, S., & Medzhitov, R. (2017). Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science (New York, N.Y.)*, *356*, 513–519.

Irie-Sasaki, J., Sasaki, T., Matsumoto, W., Opavsky, A., Cheng, M., Welstead, G., Griffiths, E., Krawczyk, C., Richardson, C. D., Aitken, K., Iscove, N., Koretzky, G., Johnson, P., Liu, P., Rothstein, D. M., & Penninger, J. M. (2001). CD45 is a JAK phosphatase and negatively regulates cytokine receptor signalling. *Nature*, *409*, 349–354. https://doi.org/10.1038/35053086

Islam, M. N., Das, S. R., Emin, M. T., Wei, M., Sun, L. I., Westphalen, K., Rowlands, D. J., Quadri, S. K., Bhattacharya, S., & Bhattacharya, J. (2012). Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nature Medicine*, *18*, 759. https://doi.org/10.1038/nm.2736

Ito, K., Hirao, A., Arai, F., Takubo, K., Matsuoka, S., Miyamoto, K., Ohmura, M., Naka, K., Hosokawa, K., Ikeda, Y., & Suda, T. (2006). Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. *Nature Medicine*, *12*, 446–451. https://doi.org/10.1038/nm1388

Jacobs, S. E., Berg, M., Hunt, R., Tarnow-Mordi, W. O., Inder, T. E., & Davis, P. G. (2013). Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003311.pub3

Jellema, R. K., Wolfs, T. G. A. M., Lima Passos, V., Zwanenburg, A., Ophelders, D. R. M. G., Kuypers, E., Hopman, A. H. N., Dudink, J., Steinbusch, H. W., Andriessen, P., Germeraad, W. T. V., Vanderlocht, J., & Kramer, B. W. (2013). Mesenchymal stem cells induce T-cell tolerance and protect the preterm brain after global hypoxia-ischemia. *PLoS One*, *8*, e73031. https://doi.org/10.1371/journal.pone.0073031

Jiang, X.-X., Zhang, Y., Liu, B., Zhang, S.-X., Wu, Y., Yu, X.-D., & Mao, N. (2005). Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. *Blood*, *105*, 4120–4126. https://doi.org/10.1182/blood-2004-02-0586

Katajisto, P., Dohla, J., Chaffer, C. L., Pentinmikko, N., Marjanovic, N., Iqbal, S., Zoncu, R., Chen, W., Weinberg, R. A., & Sabatini, D. M. (2015). Stem cells. Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness. *Science*, *348*, 340–343. https://doi.org/10.1126/science.1260384

Keating, A. (2012). Mesenchymal stromal cells: New directions. *Cell Stem Cell*, *10*, 709–716. https://doi.org/10.1016/j.stem.2012.05.015

Kelly, B., & O'Neill, L. A. J. (2015). Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Research*, 25, 771–784. https://doi.org/10.1038/cr.2015.68

Kesner, E. E., Saada-Reich, A., & Lorberboum-Galski, H. (2016). Characteristics of mitochondrial transformation into human cells. *Scientific Reports*, 6, 26057. https://doi.org/10.1038/srep26057

Kim, E. S., Ahn, S. Y., Im, G. H., Sung, D. K., Park, Y. R., Choi, S. H., Choi, S. J., Chang, Y. S., Oh, W., Lee, J. H., & Park, W. S. (2012). Human umbilical cord blood-derived mesenchymal stem cell transplantation attenuates severe brain injury by permanent middle cerebral artery occlusion in newborn rats. *Pediatric Research*, 72, 277–284. https://doi.org/10.1038/pr.2012.71

Koning, G., Leverin, A.-L., Nair, S., Schwendimann, L., Ek, J., Carlsson, Y., Gressens, P., Thornton, C., Wang, X., Mallard, C., & Hagberg, H. (2019). Magnesium induces preconditioning of the neonatal brain via profound mitochondrial protection. *Journal of Cerebral Blood Flow & Metabolism*, 39, 1038–1055. https://doi.org/10.1177/0271678X17746132

Kurihara, Y., Kanki, T., Aoki, Y., Hirota, Y., Saigusa, T., Uchiumi, T., & Kang, D. (2012). Mitophagy plays an essential role in reducing mitochondrial production of reactive oxygen species and mutation of mitochondrial DNA by maintaining mitochondrial quantity and quality in yeast. *Journal of Biological Chemistry*, 287, 3265–3272. https://doi.org/10.1074/jbc.M111.280156

Ramos, T., Sánchez-Abarca, L. I., Muntión, S., Preciado, S., Puig, N., López-Ruano, G., Hernández-Hernández, Á., Redondo, A., Ortega, R., Rodríguez, C., Sánchez-Guijo, F., & del Cañizo, C. (2016). MSC surface markers (CD44, CD73, and CD90) can identify human MSC-derived extracellular vesicles by conventional flow cytometry. *Cell Communication and Signaling*, 14, 2. https://doi.org/10.1186/s12964-015-0124-8

Lalu, M. M., McIntyre, L., Pugliese, C., Fergusson, D., Winston, B. W., Marshall, J. C., Granton, J., & Stewart, D. J. (2012). Safety of cell therapy with mesenchymal stromal cells (SafeCell): A systematic review and meta-analysis of clinical trials. *PLoS One*, 7, e47559. https://doi.org/10.1371/journal.pone.0047559

Lee, E. J., Park, S. J., Kang, S. K., Kim, G. H., Kang, H. J., Lee, S. W., Jeon, H. B., & Kim, H. S. (2012). Spherical bullet formation via E-cadherin promotes therapeutic potency of mesenchymal stem cells derived from human umbilical cord blood for myocardial infarction. *Molecular Therapy*, 20, 1424–1433. https://doi.org/10.1038/mt.2012.58

Lee, J. W., & Davis, J. M. (2011). Future applications of antioxidants in premature infants. *Current Opinion in Pediatrics*, 23, 161–166. https://doi.org/10.1097/MOP.0b013e3283423e51

Leibacher, J., & Henschler, R. (2016). Biodistribution, migration and homing of systemically applied mesenchymal stem/stromal cells. *Stem Cell Research & Therapy*, 7, 7. https://doi.org/10.1186/s13287-015-0271-2

Leon-Rico, D., Fernandez-Garcia, M., Aldea, M., Sanchez, R., Peces-Barba, M., Martinez-Palacio, J., Yanez, R. M., & Almarza, E. (2015). Comparison of haematopoietic stem cell engraftment through the retro-orbital venous sinus and the lateral vein: Alternative routes for bone marrow transplantation in mice. *Laboratory Animals*, 49, 132–141. https://doi.org/10.1177/0023677214567915

Leviton, A., Dammann, O., & Durum, S. K. (2005). The adaptive immune response in neonatal cerebral white matter damage. *Annals of Neurology*, 58, 821–828. https://doi.org/10.1002/ana.20662

Li, C.-J., Chen, P.-K., Sun, L.-Y., & Pang, C.-Y. (2017). Enhancement of mitochondrial transfer by antioxidants in human mesenchymal stem cells. *Oxidative Medicine and Cellular Longevity*, 2017, 8510805. https://doi.org/10.1155/2017/8510805

Li, J., Li, D., Liu, X., Tang, S., & Wei, F. (2012). Human umbilical cord mesenchymal stem cells reduce systemic inflammation and attenuate LPS-induced acute lung injury in rats. *Journal of Inflammation (London)*, 9, 33. https://doi.org/10.1186/1476-9255-9-33

Li, J., Yawno, T., Sutherland, A. E., Gurung, S., Paton, M., McDonald, C., Tiwari, A., Pham, Y., Castillo-Melendez, M., Jenkin, G., & Miller, S. L. (2018). Preterm umbilical cord blood derived mesenchymal stem/stromal cells protect preterm white matter brain development against hypoxia-ischemia. *Experimental Neurology*, 308, 120–131. https://doi.org/10.1016/j.expneurol.2018.07.006

Li, M. X., Qu, Y., & Mu, D. Z. (2017). Role of mitophagy in neonatal rats with hypoxic-ischemic brain damage. *Zhongguo Dang Dai Er Ke Za Zhi*, 19, 242–249.

Li, Q., Zhang, T., Wang, J., Zhang, Z., Zhai, Y., Yang, G. Y., & Sun, X. (2014). Rapamycin attenuates mitochondrial dysfunction via activation of mitophagy in experimental ischemic stroke. *Biochemical and Biophysical Research Communications*, 444, 182–188. https://doi.org/10.1016/j.bbrc.2014.01.032

Lin, C.-S., Ning, H., Lin, G., & Lue, T. F. (2012). Is CD34 truly a negative marker for mesenchymal stromal cells? *Cytotherapy*, 14, 1159–1163. https://doi.org/10.3109/14653249.2012.729817

Lin, Q.-M., Zhao, S., Zhou, L.-L., Fang, X.-S., Fu, Y., & Huang, Z.-T. (2013). Mesenchymal stem cells transplantation suppresses inflammatory responses in global cerebral ischemia: Contribution of TNF-α-induced protein 6. *Acta Pharmacologica Sinica*, 34, 784–792. https://doi.org/10.1038/aps.2012.199

Liu, K., Ji, K., Guo, L., Wu, W., Lu, H., Shan, P., & Yan, C. (2014). Mesenchymal stem cells rescue injured endothelial cells in an in vitro ischemia-reperfusion model via tunneling nanotube like structure-mediated mitochondrial transfer. *Microvascular Research*, 92, 10–18. https://doi.org/10.1016/j.mvr.2014.01.008

Luyt, K., Jary, S., Lea, C., Young, G. J., Odd, D., Miller, H., Kmita, G., Williams, C., Blair, P. S., Fernández, A. M., Hollingworth, W., Morgan, M., Smith-Collins, A., Thai, N. J., Walker-Cox, S., Aquilina, K., Pople, I., & Whitelaw, A. (2019). Ten-year follow-up of a randomised trial of drainage, irrigation and fibrinolytic therapy (DRIFT) in infants with post-haemorrhagic ventricular dilatation. *Health Technology Assessment*, 23, 1–116. https://doi.org/10.3310/hta23040

Lv, F.-J., Tuan, R. S., Cheung, K. M., & Leung, V. Y. (2014). Concise review: The surface markers and identity of human mesenchymal stem cells. *Stem Cells*, 32, 1408–1419. https://doi.org/10.1002/stem.1681

Marelli-Berg, F. M., Fu, H., & Mauro, C. (2012). Molecular mechanisms of metabolic reprogramming in proliferating cells: Implications for T-cell-mediated immunity. *Immunology*, 136, 363–369. https://doi.org/10.1111/j.1365-2567.2012.03583.x

Martins, L. F., Costa, R. O., Pedro, J. R., Aguiar, P., Serra, S. C., Teixeira, F. G., Sousa, N., Salgado, A. J., & Almeida, R. D. (2017). Mesenchymal stem cells secretome-induced axonal outgrowth is mediated by BDNF. *Scientific Reports*, 7, 4153. https://doi.org/10.1038/s41598-017-03592-1

Masuzawa, A., Black, K. M., Pacak, C. A., Ericsson, M., Barnett, R. J., Drumm, C., Seth, P., Bloch, D. B., Levitsky, S., Cowan, D. B., & McCully, J. D. (2013). Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. *American Journal of Physiology. Heart and Circulatory Physiology*, 304, H966–982. https://doi.org/10.1152/ajpheart.00883.2012

McDonald, C. A., Djuliannisaa, Z., Petraki, M., Paton, M. C. B., Penny, T. R., Sutherland, A. E., Castillo-Melendez, M., Novak, I., Jenkin, G., Fahey, M. C., & Miller, S. L. (2019). Intranasal delivery of mesenchymal stromal cells protects against neonatal hypoxic–ischemic brain injury. *International Journal of Molecular Sciences*, 20(10), 2449

Moll, G., Ankrum, J. A., Kamhieh-Milz, J., Bieback, K., Ringdén, O., Volk, H. D., Geissler, S., & Reinke, P. (2019). Intravascular mesenchymal stromal/stem cell therapy product diversification: Time for new clinical guidelines. *Trends in Molecular Medicine*, 25, 149–163. https://doi.org/10.1016/j.molmed.2018.12.006

Moll, G., Rasmusson-Duprez, I., von Bahr, L., Connolly-Andersen, A.-M., Elgue, G., Funke, L., Hamad, O. A., Lönnies, H., Magnusson, P. U., Sanchez, J., Teramura, Y., Nilsson-Ekdahl, K., Ringdén, O., Korsgren,

O., Nilsson, B. O., & Le Blanc, K. (2012). Are therapeutic human mesenchymal stromal cells compatible with human blood? *Stem Cells*, *30*, 1565–1574. https://doi.org/10.1002/stem.1111

Mueller, M., Oppliger, B., Joerger-Messerli, M., Reinhart, U., Barnea, E., Paidas, M., Kramer, B. W., Surbek, D. V., & Schoeberlein, A. (2017). Wharton's Jelly mesenchymal stem cells protect the immature brain in rats and modulate cell fate. *Stem Cells and Development*, *26*, 239–248. https://doi.org/10.1089/scd.2016.0108

Nadri, S., & Soleimani, M. (2007). Comparative analysis of mesenchymal stromal cells from murine bone marrow and amniotic fluid. *Cytotherapy*, *9*, 729–737. https://doi.org/10.1080/14653240701656061

Nair, S., Sobotka, K. S., Joshi, P., Gressens, P., Fleiss, B., Thornton, C., Mallard, C., & Hagberg, H. (2019). Lipopolysaccharide-induced alteration of mitochondrial morphology induces a metabolic shift in microglia modulating the inflammatory response in vitro and in vivo. *Glia*, *67*, 1047–1061. https://doi.org/10.1002/glia.23587

Nawaz, M., & Fatima, F. (2017). Extracellular vesicles, tunneling nanotubes, and cellular interplay: Synergies and missing links. *Frontiers in Molecular Biosciences*, *4*, 50. https://doi.org/10.3389/fmolb.2017.00050

Németh, K., Leelahavanichkul, A., Yuen, P. S. T., Mayer, B., Parmelee, A., Doi, K., Robey, P. G., Leelahavanichkul, K., Koller, B. H., Brown, J. M., Hu, X., Jelinek, I., Star, R. A., & Mezey, É. (2009). Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nature Medicine*, *15*, 42–49. https://doi.org/10.1038/nm.1905

Northington, F. J., Chavez-Valdez, R., & Martin, L. J. (2011). Neuronal cell death in neonatal hypoxia-ischemia. *Annals of Neurology*, *69*, 743–758. https://doi.org/10.1002/ana.22419

Okafo, G., Prevedel, L., & Eugenin, E. (2017). Tunneling nanotubes (TNT) mediate long-range gap junctional communication: Implications for HIV cell to cell spread. *Scientific Reports*, *7*, 16660. https://doi.org/10.1038/s41598-017-16600-1

Okazaki, K., Nishida, A., Kato, M., Kozawa, K., Uga, N., & Kimura, H. (2006). Elevation of cytokine concentrations in asphyxiated neonates. *Biology of the Neonate*, *89*, 183–189. https://doi.org/10.1159/000089180

Oppliger, B., Joerger-Messerli, M., Mueller, M., Reinhart, U., Schneider, P., Surbek, D. V., & Schoeberlein, A. (2016). Intranasal delivery of umbilical cord-derived mesenchymal stem cells preserves myelination in perinatal brain damage. *Stem Cells and Development*, *25*, 1234–1242. https://doi.org/10.1089/scd.2016.0027

Ortiz, L. A., Dutreil, M., Fattman, C., Pandey, A. C., Torres, G., Go, K., & Phinney, D. G. (2007). Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. *Proceedings of the National Academy of Sciences*, *104*, 11002–11007. https://doi.org/10.1073/pnas.0704421104

Paliwal, S., Kakkar, A., Sharma, R., Airan, B., & Mohanty, S. (2017). Differential reduction of reactive oxygen species by human tissuespecific mesenchymal stem cells from different donors under oxidative stress. *Journal of Biosciences*, *42*, 373–382. https://doi.org/10.1007/s12038-017-9691-8

Park, D., Lee, S. H., Bae, D. K., Yang, Y.-H., Yang, G., Kyung, J., Kim, D., Choi, E.-K., Hong, J. T., Shin, I. S., Kang, S. K., Ra, J. C., & Kim, Y.-B. (2013). Transplantation of human adipose tissue-derived mesenchymal stem cells restores the neurobehavioral disorders of rats with neonatal hypoxic-ischemic encephalopathy. *Cell Medicine*, *5*, 17–28. https://doi.org/10.3727/215517913X658936

Park, W. S., Ahn, S. Y., Sung, S. I., Ahn, J.-Y., & Chang, Y. S. (2018). Strategies to enhance paracrine potency of transplanted mesenchymal stem cells in intractable neonatal disorders. *Pediatric Research*, *83*, 214–222. https://doi.org/10.1038/pr.2017.249

Park, W. S., Sung, S. I., Ahn, S. Y., Yoo, H. S., Sung, D. K., Im, G. H., Choi, S. J., & Chang, Y. S. (2015). Hypothermia augments neuroprotective activity of mesenchymal stem cells for neonatal hypoxic-ischemic encephalopathy. *PLoS One*, *10*, e0120893. https://doi.org/10.1371/journal.pone.0120893

Pasquier, J., Guerrouahen, B. S., Al Thawadi, H., Ghiabi, P., Maleki, M., Abu-Kaoud, N., Jacob, A., Mirshahi, M., Galas, L., Rafii, S., Le Foll, F., & Rafii, A. (2013). Preferential transfer of mitochondria from endothelial to cancer cells through tunneling nanotubes modulates chemoresistance. *Journal of Translational Medicine*, *11*, 94. https://doi.org/10.1186/1479-5876-11-94

Pattappa, G., Heywood, H. K., de Bruijn, J. D., & Lee, D. A. (2011). The metabolism of human mesenchymal stem cells during proliferation and differentiation. *Journal of Cellular Physiology*, *226*, 2562–2570. https://doi.org/10.1002/jcp.22605

Peng, R., Yao, X., Cao, B., Tang, J., & Ding, J. (2012). The effect of culture conditions on the adipogenic and osteogenic inductions of mesenchymal stem cells on micropatterned surfaces. *Biomaterials*, *33*, 6008–6019. https://doi.org/10.1016/j.biomaterials.2012.05.010

Phinney, D. G., Di Giuseppe, M., Njah, J., Sala, E., Shiva, S., St Croix, C. M., Stolz, D. B., Watkins, S. C., Di, Y. P., Leikauf, G. D., Kolls, J., Riches, D. W. H., Deiuliis, G., Kaminski, N., Boregowda, S. V., McKenna, D. H., & Ortiz, L. A. (2015). Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. *Nature Communications*, *6*, 8472. https://doi.org/10.1038/ncomms9472

Piantadosi, C. A., & Zhang, J. (1996). Mitochondrial generation of reactive oxygen species after brain ischemia in the rat. *Stroke*, *27*, 327–331. discussion 332. https://doi.org/10.1161/01.STR.27.2.327

Pimentel-Coelho, P. M., & Mendez-Otero, R. (2010). Cell therapy for neonatal hypoxic-ischemic encephalopathy. *Stem Cells and Development*, *19*, 299–310. https://doi.org/10.1089/scd.2009.0403

Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., Moorman, M. A., Simonetti, D. W., Craig, S., & Marshak, D. R. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science*, *284*, 143–147. https://doi.org/10.1126/science.284.5411.143

Qu, R., Li, Y., Gao, Q., Shen, L., Zhang, J., Liu, Z., Chen, X., & Chopp, M. (2007). Neurotrophic and growth factor gene expression profiling of mouse bone marrow stromal cells induced by ischemic brain extracts. *Neuropathology*, *27*, 355–363. https://doi.org/10.1111/j.1440-1789.2007.00792.x

Rahmat, Z., Jose, S., Ramasamy, R., & Vidyadaran, S. (2013). Reciprocal interactions of mouse bone marrow-derived mesenchymal stem cells and BV2 microglia after lipopolysaccharide stimulation. *Stem Cell Research & Therapy*, *4*, 12. https://doi.org/10.1186/scrt160

Rodolfo, C., Campello, S., & Cecconi, F. (2018). Mitophagy in neurodegenerative diseases. *Neurochemistry International*, *117*, 156–166. https://doi.org/10.1016/j.neuint.2017.08.004

Rosenkranz, K., Kumbruch, S., Lebermann, K., Marschner, K., Jensen, A., Dermietzel, R., & Meier, C. (2010). The chemokine SDF-1/CXCL12 contributes to the 'homing' of umbilical cord blood cells to a hypoxic-ischemic lesion in the rat brain. *Journal of Neuroscience Research*, *88*, 1223–1233.

Rustad, K. C., & Gurtner, G. C. (2012). Mesenchymal stem cells home to sites of injury and inflammation. *Advances in Wound Care (New Rochelle)*, *1*, 147–152. https://doi.org/10.1089/wound.2011.0314

Rustom, A., Saffrich, R., Markovic, I., Walther, P., & Gerdes, H.-H. (2004). Nanotubular highways for intercellular organelle transport. *Science*, *303*, 1007–1010. https://doi.org/10.1126/science.1093133

Sahni, P. V., Zhang, J., Sosunov, S., Galkin, A., Niatsetskaya, Z., Starkov, A., Brookes, P. S., & Ten, V. S. (2018). Krebs cycle metabolites and preferential succinate oxidation following neonatal hypoxic-ischemic brain injury in mice. *Pediatric Research*, *83*, 491–497. https://doi.org/10.1038/pr.2017.277

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Sangiorgi, B., & Panepucci, R. A. (2016). Modulation of immunoregulatory properties of mesenchymal stromal cells by toll-like receptors: Potential applications on GVHD. *Stem Cells International*, *2016*, 9434250. https://doi.org/10.1155/2016/9434250

Sbrana, F. V., Cortini, M., Avnet, S., Perut, F., Columbaro, M., De Milito, A., & Baldini, N. (2016). The role of autophagy in the maintenance of stemness and differentiation of mesenchymal stem cells. *Stem Cell Reviews and Reports*, *12*, 621–633. https://doi.org/10.1007/s12015-016-9690-4

Shih, D. T., Lee, D. C., Chen, S. C., Tsai, R. Y., Huang, C. T., Tsai, C. C., Shen, E. Y., & Chiu, W. T. (2005). Isolation and characterization of neurogenic mesenchymal stem cells in human scalp tissue. *Stem Cells*, *23*, 1012–1020. https://doi.org/10.1634/stemcells.2004-0125

Shyh-Chang, N., Daley, G. Q., & Cantley, L. C. (2013). Stem cell metabolism in tissue development and aging. *Development*, *140*, 2535–2547. https://doi.org/10.1242/dev.091777

Simard, P. F., Tosun, C., Melnichenko, L., Ivanova, S., Gerzanich, V., & Simard, J. M. (2011). Inflammation of the choroid plexus and ependymal layer of the ventricle following intraventricular hemorrhage. *Translational Stroke Research*, *2*, 227–231. https://doi.org/10.1007/s12975-011-0070-8

Singh-Mallah, G., Nair, S., Sandberg, M., Mallard, C., & Hagberg, H. (2019). The role of mitochondrial and endoplasmic reticulum reactive oxygen species production in models of perinatal brain injury. *Antioxidants & Redox Signaling*, *31*, 643–663. https://doi.org/10.1089/ars.2019.7779

Spaggiari, G. M., & Moretta, L. (2012). Interactions between mesenchymal stem cells and dendritic cells. *Mesenchymal Stem Cells-Basics and Clinical Application II* (pp. 199–208). Springer.

Stowers, R. S., Megeath, L. J., Górska-Andrzejak, J., Meinertzhagen, I. A., & Schwarz, T. L. (2002). Axonal transport of mitochondria to synapses depends on milton, a novel Drosophila protein. *Neuron*, *36*, 1063–1077. https://doi.org/10.1016/S0896-6273(02)01094-2

Strahle, J., Garton, H. J., Maher, C. O., Muraszko, K. M., Keep, R. F., & Xi, G. (2012). Mechanisms of hydrocephalus after neonatal and adult intraventricular hemorrhage. *Translational Stroke Research*, *3*, 25–38. https://doi.org/10.1007/s12975-012-0182-9

Strioga, M., Viswanathan, S., Darinskas, A., Slaby, O., & Michalek, J. (2012). Same or not the same? Comparison of adipose tissue-derived versus bone marrow-derived mesenchymal stem and stromal cells. *Stem Cells and Development*, *21*, 2724–2752. https://doi.org/10.1089/scd.2011.0722

Supramaniam, V., Vontell, R., Srinivasan, L., Wyatt-Ashmead, J., Hagberg, H., & Rutherford, M. (2013). Microglia activation in the extremely preterm human brain. *Pediatric Research*, *73*, 301–309. https://doi.org/10.1038/pr.2012.186

Svendsen, C. N., & Smith, A. G. (1999). New prospects for human stem-cell therapy in the nervous system. *Trends in Neurosciences*, *22*, 357–364. https://doi.org/10.1016/S0166-2236(99)01428-9

Tang, J., Peng, R., & Ding, J. (2010). The regulation of stem cell differentiation by cell-cell contact on micropatterned material surfaces. *Biomaterials*, *31*, 2470–2476. https://doi.org/10.1016/j.biomaterials.2009.12.006

Thornton, C., Jones, A., Nair, S., Aabdien, A., Mallard, C., & Hagberg, H. (2018). Mitochondrial dynamics, mitophagy and biogenesis in neonatal hypoxic-ischaemic brain injury. *FEBS Letters*, *592*, 812–830.

Thornton, C., Leaw, B., Mallard, C., Nair, S., Jinnai, M., & Hagberg, H. (2017). Cell death in the developing brain after hypoxia-ischemia. *Frontiers in Cellular Neuroscience*, *11*, 248. https://doi.org/10.3389/fncel.2017.00248

Togarrati, P. P., Sasaki, R. T., Abdel-Mohsen, M., Dinglasan, N., Deng, X., Desai, S., Emmerson, E., Yee, E., Ryan, W. R., da Silva, M. C. P., Knox, S. M., Pillai, S. K., & Muench, M. O. (2017). Identification and characterization of a rich population of CD34+ mesenchymal stem/stromal cells in human parotid, sublingual and submandibular glands.

Scientific Reports, *7*, 3484. https://doi.org/10.1038/s41598-017-03681-1

Topf, U., Suppanz, I., Samluk, L., Wrobel, L., Böser, A., Sakowska, P., Knapp, B., Pietrzyk, M. K., Chacinska, A., & Warscheid, B. (2018). Quantitative proteomics identifies redox switches for global translation modulation by mitochondrially produced reactive oxygen species. *Nature Communications*, *9*, 324. https://doi.org/10.1038/s41467-017-02694-8

Tse, W. T., Pendleton, J. D., Beyer, W. M., Egalka, M. C., & Guinan, E. C. (2003). Suppression of allogeneic T-cell proliferation by human marrow stromal cells: Implications in transplantation. *Transplantation*, *75*, 389–397. https://doi.org/10.1097/01.TP.0000045055.63901.A9

Ukai, R., Honmou, O., Harada, K., Houkin, K., Hamada, H., & Kocsis, J. D. (2007). Mesenchymal stem cells derived from peripheral blood protects against ischemia. *Journal of Neurotrauma*, *24*, 508–520. https://doi.org/10.1089/neu.2006.0161

van Velthoven, C. T., Kavelaars, A., van Bel, F., & Heijnen, C. J. (2010a). Mesenchymal stem cell treatment after neonatal hypoxic-ischemic brain injury improves behavioral outcome and induces neuronal and oligodendrocyte regeneration. *Brain, Behavior, and Immunity*, *24*, 387–393. https://doi.org/10.1016/j.bbi.2009.10.017

van Velthoven, C. T., Kavelaars, A., van Bel, F., & Heijnen, C. J. (2010b). Nasal administration of stem cells: A promising novel route to treat neonatal ischemic brain damage. *Pediatric Research*, *68*, 419–422. https://doi.org/10.1203/PDR.0b013e3181f1c289

van Velthoven, C. T., Kavelaars, A., van Bel, F., & Heijnen, C. J. (2011). Mesenchymal stem cell transplantation changes the gene expression profile of the neonatal ischemic brain. *Brain, Behavior, and Immunity*, *25*, 1342–1348. https://doi.org/10.1016/j.bbi.2011.03.021

van Velthoven, C. T., Sheldon, R. A., Kavelaars, A., Derugin, N., Vexler, Z. S., Willemen, H. L., Maas, M., Heijnen, C. J., & Ferriero, D. M. (2013). Mesenchymal stem cell transplantation attenuates brain injury after neonatal stroke. *Stroke*, *44*, 1426–1432. https://doi.org/10.1161/STROKEAHA.111.000326

Vasandan, A. B., Jahnavi, S., Shashank, C., Prasad, P., Kumar, A., & Prasanna, S. J. (2016). Human Mesenchymal stem cells program macrophage plasticity by altering their metabolic status via a PGE2-dependent mechanism. *Scientific Reports*, *6*, 38308. https://doi.org/10.1038/srep38308

Vu, Q., Xie, K., Eckert, M., Zhao, W., & Cramer, S. C. (2014). Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke. *Neurology*, *82*, 1277–1286. https://doi.org/10.1212/WNL.0000000000000278

Wagenaar, N., de Theije, C. G. M., de Vries, L. S., Groenendaal, F., Benders, M., & Nijboer, C. H. A. (2018). Promoting neuroregeneration after perinatal arterial ischemic stroke: Neurotrophic factors and mesenchymal stem cells. *Pediatric Research*, *83*, 372–384. https://doi.org/10.1038/pr.2017.243

Wagenaar, N., Nijboer, C. H., & van Bel, F. (2017). Repair of neonatal brain injury: Bringing stem cell-based therapy into clinical practice. *Developmental Medicine and Child Neurology*, *59*, 997–1003. https://doi.org/10.1111/dmcn.13528

Wang, X., & Gerdes, H. H. (2015). Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. *Cell Death & Differentiation*, *22*, 1181–1191. https://doi.org/10.1038/cdd.2014.211

Wang, Y., Chen, X., Cao, W., & Shi, Y. (2014). Plasticity of mesenchymal stem cells in immunomodulation: Pathological and therapeutic implications. *Nature Immunology*, *15*, 1009. https://doi.org/10.1038/ni.3002

Wang, Y., Cui, J., Sun, X., & Zhang, Y. (2011). Tunneling-nanotube development in astrocytes depends on p53 activation. *Cell Death and Differentiation*, *18*, 732–742. https://doi.org/10.1038/cdd.2010.147

Wang, Y., Deng, Y., & Zhou, G. Q. (2008). SDF-1alpha/CXCR4-mediated migration of systemically transplanted bone marrow stromal cells towards ischemic brain lesion in a rat model. *Brain Research*, *1195*, 104–112.

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Wang, Z., Wang, L., Su, X., Pu, J., Jiang, M., & He, B. (2017). Rational transplant timing and dose of mesenchymal stromal cells in patients with acute myocardial infarction: A meta-analysis of randomized controlled trials. *Stem Cell Research & Therapy*, *8*, 21. https://doi.org/10.1186/s13287-016-0450-9

Waterman, R. S., Tomchuck, S. L., Henkle, S. L., & Betancourt, A. M. (2010). A new mesenchymal stem cell (MSC) paradigm: Polarization into a pro-inflammatory MSC1 or an Immunosuppressive MSC2 phenotype. *PLoS One*, *5*, e10088. https://doi.org/10.1371/journal.pone.0010088

West, A. P., Shadel, G. S., & Ghosh, S. (2011). Mitochondria in innate immune responses. *Nature Reviews Immunology*, *11*, 389–402. https://doi.org/10.1038/nri2975

Wright, S. D., Ramos, R. A., Tobias, P. S., Ulevitch, R. J., & Mathison, J. C. (1990). CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science*, *249*, 1431–1433. https://doi.org/10.1126/science.1698311

Xie, C., Ginet, V., Sun, Y., Koike, M., Zhou, K., Li, T., Li, H, Wang, X, Uchiyama, Y., Truttmann, A. C., Kroemer, G., Puyal, J., Blomgren, K., & Zhu, C. (2016). Neuroprotection by selective neuronal deletion of Atg7 in neonatal brain injury. *Autophagy*, *12*, 410–423.

Xu, C., Ren, G., Cao, G., Chen, Q., Shou, P., Zheng, C., Du, L., Han, X., Jiang, M., Yang, Q., Lin, L., Wang, G., Yu, P., Zhang, X., Cao, W., Brewer, G., Wang, Y., & Shi, Y. (2013). miR-155 regulates immune modulatory properties of mesenchymal stem cells by targeting TAK1-binding protein 2. *Journal of Biological Chemistry*, *288*, 11074–11079. https://doi.org/10.1074/jbc.M112.414862

Yardeni, T., Eckhaus, M., Morris, H. D., Huizing, M., & Hoogstraten-Miller, S. (2011). Retro-orbital injections in mice. *Lab Animal*, *40*(5), 155–160. https://doi.org/10.1038/laban0511-155

Yoo, S. W., Kim, S. S., Lee, S. Y., Lee, H. S., Kim, H. S., Lee, Y. D., & Suh-Kim, H. (2008). Mesenchymal stem cells promote proliferation of endogenous neural stem cells and survival of newborn cells in a rat stroke model. *Experimental & Molecular Medicine*, *40*, 387–397. https://doi.org/10.3858/emm.2008.40.4.387

Yuan, X., Logan, T. M., & Ma, T. (2019). Metabolism in human mesenchymal stromal cells: A missing link between hMSC biomanufacturing and therapy? *Frontiers in Immunology*, *10*, 977. https://doi.org/10.3389/fimmu.2019.00977

Zhang, X., Yan, H., Yuan, Y., Gao, J., Shen, Z., Cheng, Y., Shen, Y., Wang, R.-R., Wang, X., Hu, W.-W., Wang, G., & Chen, Z. (2013). Cerebral ischemia-reperfusion-induced autophagy protects against neuronal injury by mitochondrial clearance. *Autophagy*, *9*, 1321–1333. https://doi.org/10.4161/auto.25132

Zhang, Y. (2011). Tunneling-nanotube. *Communicative & Integrative Biology*, *4*(3), 324–325. https://doi.org/10.4161/cib.4.3.14855

Zhu, W., Yuan, Y., Liao, G., Li, L., Liu, J., Chen, Y., Zhang, J., Cheng, J., & Lu, Y. (2018). Mesenchymal stem cells ameliorate hyperglycemia-induced endothelial injury through modulation of mitophagy. *Cell Death & Disease*, *9*, 837. https://doi.org/10.1038/s41419-018-0861-x

Zuo, W., Zhang, S., Xia, C. Y., Guo, X. F., He, W. B., & Chen, N. H. (2014). Mitochondria autophagy is induced after hypoxic/ischemic stress in a Drp1 dependent manner: The role of inhibition of Drp1 in ischemic brain damage. *Neuropharmacology*, *86*, 103–115. https://doi.org/10.1016/j.neuropharm.2014.07.002