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REVIEW PAPER

Stem cells for brain repair in neonatal hypoxia–ischemia

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Abstract Neonatal hypoxic–ischemic insults are a significant cause of pediatric encephalopathy, developmental delays, and spastic cerebral palsy. Although the developing brain's plasticity allows for remarkable self-repair, severe disruption of normal myelination and cortical development upon neonatal brain injury are likely to generate life-persisting sensory-motor and cognitive deficits in the growing child. Currently, no treatments are available that can address the long-term consequences. Thus, regenerative medicine appears as a promising avenue to help restore normal developmental processes in affected infants. Stem cell therapy has proven effective in promoting functional recovery in animal models of neonatal hypoxic–ischemic injury and therefore represents a hopeful therapy for this unmet medical condition. Neural stem cells derived from pluripotent stem cells or fetal tissues as well as umbilical cord blood and mesenchymal stem cells have all shown initial success in improving functional outcomes. However, much still remains to be understood about how those stem cells can safely be administered to infants and what their repair mechanisms in the brain are. In this review, we discuss updated research into pathophysiological mechanisms of neonatal brain injury, the types of stem cell therapies currently being tested in this context, and the potential mechanisms through which exogenous stem cells might interact with and influence the developing brain.

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Introduction

Despite major advances in monitoring technology and knowledge of fetal and neonatal pathologies, hypoxic–ischemic (HI) strokes remain the most common form of damage to the neonate brain [51], causing significant mortality and persistent neurobiological morbidity. In most cases, exact timing and underlying causes of the injury are unknown. Etiologies are complex and most often multifactorial. Reported precipitating insults include placental abnormalities [21], intrauterine growth restriction [115], preeclampsia [115], maternal infections [15, 33, 72], circulation disorders [34, 61, 114], and perinatal asphyxia [87]. Genetic makeup, sex, and degree of brain development also affect vulnerability and the mechanisms of brain injury [44, 105]. Neonatal HI occurs in 1–3 per 1,000 live full-term births and dramatically increases to 40 per 1,000 in preterm children with very low birth weight [33, 47]. Of affected newborns, 25 % develop severe and persistent neuropsychological impairments, including mental retardation, motor deficits, cerebral palsy, and epilepsy [104].

Upon neonatal HI insult, oxygen and glucose supplies are transiently depleted from the brain, causing an energy failure and initiating a cascade of biochemical events leading to cell dysfunction and oxidative stress [97]. Depending on the strength and duration of this initial insult, secondary injuries are likely to follow which include mitochondrial dysfunction, apoptosis, and excitotoxicity [97]. Tertiary effects may persist in the brain such as sensitization to inflammation, impaired oligodendrocyte maturation/myelination, persistent gliosis, and epigenetic changes [14, 26, 97]. Although those enduring damages might predispose patients to developmental disruption and sensitization to further injury, this also creates an extended window of opportunity for further treatment.

White matter damages in the developing brain

Brain white matter consists of glia and myelinated axons and plays a crucial role in fast signal transmission throughout the CNS. The process of active myelination reflects the progression of functional brain maturation and connectivity in the first years of life and renders the infant brain particularly vulnerable to injuries such as pediatric stroke and epilepsy [73]. Consequently, white matter injury and disruption of normal myelination is a hallmark of neonatal HI. Clinical diffusion tensor imaging (DTI) studies have shown that the majority of children with spastic types of cerebral palsy present white matter injuries and the importance of myelin loss correlates with the severity of motor impairments and learning disabilities [65, 80]. Together with perinatal inflammation, hypoxia–ischemia is considered the principal initiating mechanism for pathogenesis of periventricular leukomalacia (PVL), a condition characterized by coagulation and necrosis of white matter near the lateral ventricles, accompanied by gliosis/necrosis evolving from diffuse to focal cyst formation [45]. Non-cystic diffuse PVL accounts for most of the cerebral white matter injury in the newborn and is associated with loss of pre-myelinating oligodendrocytes, astrogliosis, and microglial infiltration [72]. Studies indicate that pre-myelinating late oligodendrocyte progenitors (pOPC) are crucial in renewing the pool of oligodendrocyte progenitor (OPC) and driving their differentiation towards myelinating oligodendrocytes. These pOPC are particularly vulnerable to the hypoxic stress generated during ischemic insults, and hence, rapidly undergo apoptosis in the injured environment [4, 85]. Systemic upregulation of pro-inflammatory cytokines associated with astrogliosis and microglial infiltration as well as resulting oxidative stress are also likely to restrict white matter development and affect existing and forming myelin fibers [47, 109].

While experimental models have been proposed to prevent or ameliorate white matter injury-associated mechanisms separately [45], therapies targeting the overall neurogenic niche are likely to be the most effective in restoring progression of white matter formation and alleviate long-term disabilities following neonatal HI injuries.

Preclinical approach

Animal models

Because of the large heterogeneity in factors potentially contributing to cerebral palsy, it has been difficult to achieve a reliable animal model. The Levine and Rice-Vannucci model of neonatal HI[54, 78, 103], involving unilateral temporary or permanent ligation of the common carotid artery and subsequent exposure to hypoxic condition (8–10% O_2) on postnatal day 7 (P7) animals, is the most commonly used paradigm to model neonatal HI and neurobehavioral outcomes reminiscent of cerebral palsy. Multiple variations of this model have been explored including global hypoxia without carotid artery ligation, bilateral carotid occlusion, and temporary carotid occlusions using aneurysm clips. The neonatal hypoxia model has been applied in rats, mainly Sprague Dawley and Wistar rats. It has been shown that a more consistent injury was achieved in Wistar rats as compared to Sprague Dawley rats probably because of differences in collateral circulation [69]. Other adjunct interventions have been explored such as the combination with low doses of lipopolysaccharide—a potent trigger of the innate immune system—which dramatically increased injury response to HI challenge [53, 110] and suggested that inflammation may further sensitize the immature central nervous system.

Stem cell therapy

First studies on cell therapy for neonatal HI were designed to evaluate the ability of transplanted cells in replacing damaged tissue and utilized fetal cortical grafts or polymer scaffolds seeded with neural stem cells [22, 43, 71]. However, several reports subsequently demonstrated that transplanted stem cells promote CNS tissue repair not merely through cell replacement but by providing trophic and immunomodulatory support for endogenous repair mechanisms [60]. Different types of stem cells have been considered to mediate brain repair including stem cells derived from umbilical cord blood, bone marrow, fetal central nervous system, embryonic tissues as well as reprogrammed somatic [99] cells. Because each stem cell type have unique characteristics, it is likely that they use distinct machineries to interact with the ischemic environment and trigger regenerative mechanisms. On the other hand, some mechanisms are common to all stem cell types, and those might be particularly relevant for the induction of repair mechanisms in the brain. In the following paragraphs, we will review cell type-specific characteristics that might be relevant to regeneration in the injured neonatal brain. We will also discuss current concepts of the potential mechanisms of action that induce repair/regeneration of the injured CNS.

Umbilical cord blood-derived mesenchymal stem cells

The human umbilical cord is a rich source of stem and progenitor cells including mesenchymal stem cells (MSC) and hematopoietic stem/progenitor cells (HPC). Umbilical cord cells are easily available via noninvasive procedures and considered less immunogenic than alternative adult stem cell sources such as bone marrow. MSC derived from cord blood have shown to generate neural stem cells in vitro [19, 28] and to lead to functional improvement in rodent models of perinatal brain injury [55, 116]. Thus, there is a growing

interest in studying the potential of umbilical cord-derived stem cells for the treatment of brain diseases [60, 99, 101]. MSC have demonstrated potent trophic support [8] and immunomodulatory properties in vitro [98, 112], and therefore, appear as particularly interesting candidates to modulate glial activation and pro-inflammatory mechanisms that accompany neonatal ischemic injuries. Furthermore, as those cells are isolated at birth following clamping and elimination of the umbilical cord, they present the considerable advantages of being autologous and freshly available after sorting and expansion. Short-term exposure to mild hypoxia has shown to optimize MSC functions [40], which might further emphasize their therapeutic relevance in the context of HI injury. Besides MSC, other cells can be isolated from the mononuclear fraction of umbilical cord blood, with a relative immature and naive phenotype. Those include HPC and endothelial progenitors, which derive from a common precursor cell called the hemangioblast [52]. Interestingly, while intravenous injection of HPC in the ischemic brain has demonstrated neuroprotective and immunomodulatory effects[84], transplantation of a cord blood fraction enriched in hemangioblastic cells induced neovascularization in a mouse model of stroke [64, 93]. This might further argue that different stem cell types support distinct repair mechanisms depending on their respective lineage, and combinational therapies might be appropriate in major injuries.

Fetal/adult neural stem/progenitor cells

Neural stem/progenitor cells (NPC) can be found in endogenous neurogenic areas such as the subventricular zone or the dentate gyrus of the hippocampus. In the case of human NPC, the primary source can either be donated fetal tissue [25, 92, 95, 107, 108] or adult post-mortem brains [70]. Fetal-derived NPC are typically isolated from the brain tissue by fluorescent-activated cell sorting and then grown as neurospheres under proliferative conditions [95]. Adult human neural stem cells have been isolated from brain tissue obtained from patients undergoing surgical procedures involving removal of brain tissue for the treatment of epilepsy, tumors, or trauma [3, 9, 32]. These studies demonstrate that the adult human brain contains a renewable source of NPC, which can be successfully isolated through various surgical techniques. Regardless of source, these cells can differentiate into oligodendrocytes, astrocytes, and neurons. NPC demonstrated potent ability to migrate in response to endogenous chemokines [41] and can move at a rate of 100–125 μm/day towards the area of injury in the neonatal brain where they can survive for up to 52 weeks following transplantation [67]. As for MSC, mild hypoxia has shown to enhance proliferation and differentiation of a human NPC line towards neuronal and oligodendroglia lineages, emphasizing the potential of fetal NPC to mediate brain repair in HI conditions [83]. Most stem cell therapy studies in neonatal HI utilized rodent NPCs. The only study to date using human NPCs found a change in activation of resident microglia, and most interestingly, a change in gene expression in the brain after cell engraftment, suggesting a potent cross-talk between transplanted and intrinsic cells [13]. In this study, the increase in transcripts for growth factors GDNF, IGF-1, and FGF2; neuronal marker doublecortin; and oligodendrocyte markers Olig2 and myelin basic protein suggest that widespread changes in the brain could be driving the functional improvements seen following NPC engraftment [13].

Embryonic stem cell-derived neural stem cells

Embryonic stem cells (ESC) are derived from the microscopic cluster of cells populating the blastocyst cavity a couple of days following fertilization [96]. ESC have been reported to differentiate into various cell types including NPC and oligodendroglial progenitors [10, 46] and are therefore considered as a potential source for cell replacement therapy in CNS diseases. Among all stem cell types, ESC are the most truly self-renewable and pluripotent populations. These properties confer them the considerable advantages of providing an almost unlimited supply of cells and differentiating toward a whole spectrum of distinct cell types. For instance, human embryonic stem cells have proven to differentiate in vitro towards oligodendrocyte progenitor cells, motoneurons, dopaminergic neurons, astrocytes, and peripheral sensory neurons (reviewed in [24]). However, counterparts to those properties are increased risks of neoplastic transformation ("graft overgrowth") and multigerm layer teratoma formation following transplantation, events which are likely to be supported by factors released by the injured brain, thus raising major safety issues [42, 79, 86]. Furthermore, relative immaturity of ESC-derived lineages might confer protracted development requiring several months of further in vitro or in vivo maturation before demonstrating therapeutic potential [7, 63]. Last but not least, human ESC research is a rather controversial issue, as creation of an ESC line requires the destruction of a human embryo [96].

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSC) are adult somatic cells that have been reprogrammed to an embryonic stem cell-like state by enforced expression of pluripotency transcription factors, mainly Oct3/4, Sox2, Klf4, and c-myc [94]. As iPSC capture the genetic diversity of the donor, provide access to the earliest stages of development, and virtually generate unlimited numbers of patient-specific cells, they are particularly considered as a valuable tool to model human genetic diseases in vitro [59, 74, 91]. In the field of stem cell transplantation, they present the advantages to overcome ethical limitations and to allow for generation of autologous cellular products, while

behaving similar to ESC in morphology, gene expression, and differentiation potential. Although this new field has generated quite some excitement within the scientific community, major safety issues remain associated with the use of iPSC. First, the ectopic expression of the chosen set of pluripotency factors can lead to neoplastic transformation of cells derived from these iPSC [6, 31, 38, 68]. Furthermore, in most existing procedures, these genes are introduced via DNA integrating viruses, which are likely to maintain or reactivate their transcriptional activity in the pluripotent cells or their progeny [68]. Also of major safety concern, there is a growing body of evidence demonstrating genetic and epigenetic instability in human iPSC, likely to originate during in vitro selection of the reprogrammed clones [66] and the reprogramming procedure per se [31]. If iPSC are to be used for clinical regenerative purposes, careful genetic integrity controlling is an absolute requirement. Considerable efforts are currently being made to develop safer and more efficient methods to generate iPSC. For instance, recent promising procedures focus on the use of non-integrating Sendai viruses that can further be removed through temperature shift [5].

Future should confirm the potential use of iPSC in stem cell therapies in the context of stroke. On an optimist note, a recent study in a rat experimental stroke model has reported that iPSC-derived NPC are effective in reducing stroke-induced inflammatory response, gliosis, and apoptosis, contributing to endogenous neurogenesis and inducing behavioral recovery [11].

Potential therapeutic mechanisms of action

Neuroprotection and neuroplasticity

Although stem cell-induced endogenous repair mechanisms are largely unknown, it is likely that transplanted cells and resident neuronal and glial lineages will mutually interact to support therapeutic effect. In support for the present hypothesis, we have recently demonstrated that NPC-secreted vascular-endothelial growth factor (VEGF) is necessary and sufficient to regulate endogenous microglial proliferation, activation, and phagocytic properties [62]. Although this study was performed with mouse NPC, it strongly suggests that exogenous stem cells assume a role in maintaining tissue integrity and immune function in the CNS apart from their purpose to merely produce and replace neural cells. Neonatal brain injury is accompanied by activation of pathways of oxidative stress, inflammation, and excitotoxicity that can lead to damages progressing over a long period of time and causing persisting disabilities in the growing child. In addition to neuronal damages, injury to non-neuronal types such as oligodendrocytes [4, 85, 89] and astrocytes [89] might also impair neurodevelopment. Neuroprotective and antiapoptotic effects mediated by NPC and stem cells in general have been recognized and largely reviewed in the context of different CNS disorders including neonatal stroke [16, 48, 76, 99]. Based on previous data, it sounds reasonable to postulate that the transplants induce a greater survival of intrinsic brain populations. For instance, it has been shown that intravenously administrated marrow stem cells increase the expression of critical neurotrophic growth factors in the rat brain after traumatic injury [58]. Transplantation of human neural stem cells in a rat model of adult stroke has also shown to modulate dendritic plasticity and axonal transport, mostly through non-cell autonomous secretion of VEGF and thrombospondins [2].

Oligodendrogenesis and white matter regeneration

Brain anatomy is characterized by a dramatic growth from the end of the second trimester through the neonatal stage, with whole brain volume increasing almost 17 times [39]. Brain structures have shown to develop disproportionately during this period, and this might partly explain the extensive inhomogeneity of white matter injuries and their outcomes observed in cerebral palsy patients. Together with the reported increased sensitivity of pOPC to HI insults [4, 85], these observations place oligodendrogenesis and myelination as core processes underlying early brain injuries and life-persisting symptoms. A number of molecules have been critically involved in oligodendrogenesis, including neurotrophic factors such as platelet-derived growth factor-alpha (PDGFα) [27], insulin-like growth factor-1 (IGF-1) [50], brain-derived neurotrophic factor [102], and erythropoietin [117]. Even though different stem cell types have not been compared side by side for their expression of neurotrophic factors, it is likely that secretion of some of those critical factors by NPC will partly explain the bystander effects of stem cell therapies [2, 48, 56]. In a model of multiple sclerosis recapitulating demyelination, it has been demonstrated that NPC induced OPC proliferation and maturation via secretion of PDGFα and FGF2 specifically [20]. In a rat model of neonatal hypoxia–ischemia, a study reported that human NPC graft specifically enhanced axonal transport and sprouting [13] through upregulation of oligodendrogenesis, myelination as well as an increase in neurotrophic factors. Once again, this strongly argues for cross-talk mechanisms between exogenous NPC and intrinsic cells, here the oligodendrocytes, in mediating brain repair and functional recovery through multiple modalities.

Immunomodulation

Several independent observations suggest a pivotal role for the immune system in shaping the central nervous system and contributing to its recovery upon injuries. Firstly, it has been recently demonstrated that immune myeloid cells home to the central nervous system before neurogenesis occurs [30]. Second, brain architecture and myelination are severely compromised in microglia-depleted animals [23]. Third, most of the reported stem cell-secreted factors are potent triggers of

immune-related pathways, including molecules directly involved in chemo-attraction and modulation of inflammation and phagocytosis [1, 13, 62, 77]. It appears that there are direct NPC-mediated immunomodulatory effects on the brain resident immune cells as well as modulation of the systemic immune system. Using NPC transplantation, several groups have demonstrated that induced recovery is partly mediated through modulation of microglial phagocytic activities [13, 62]. Studies in multiple sclerosis and spinal cord injury also emphasize the role of the innate immune system, principally macrophages/microglia, in supporting remyelination processes via phagocytosis of myelin debris [49, 82, 88]. Interestingly, transplantation of HPC, the progenitors of the immune and endothelial lineages, has also proven beneficial in animal models of stroke without reported cell fusion events [84]. In the field of neurodevelopmental disorders, recent studies have also started to unravel the beneficial role of bone marrow transplantation. For instance, in a genetic rodent model of Rett's syndrome, a group strikingly identified microglial phagocytic activity as a major mediator of functional recovery [18]. Interestingly, different types of stem cells have intrinsic phagocytic properties [57, 100], and this might contribute to their beneficial effects in the injured brain.

A second immunomodulatory effect appears to be systemic. Cord blood stem cell infusion in a model of acute stroke has shown to mediate brain protection through specific modulation of the splenic release of inflammatory cells [106]. The same has been shown for stem cell-induced recovery in traumatic brain injury [111]. In this study, stem cell injection led to a preservation of blood brain barrier integrity through modulation of the immune cell response in the spleen. A pharmacologic correlate to this phenomenon relies on the use of sphingosine-1 phosphate receptor agonist fingolimod (FTY720)—a multiple sclerosis market drug. Its main action is to segregate inflammatory cells within the spleen, and it has also demonstrated long-term protection in rodent models of cerebral ischemia [113]. Taken together, these findings support the concept of NPC-mediated local and systemic modulation of the immune response as a potentially important mechanism of action.

Methodologies

Cell delivery and timing

Aside from the type of stem cells used for transplantation in neonatal HI, the route of administration and timing are likely to play crucial roles in the efficacy of the treatment. Stem cells can be delivered systemically or directly into the brain. Our laboratory previously demonstrated that delivery of stem cells to the injured brain via intravascular treatment allows for a widespread distribution of cells in the brain by means of a

Table 1 Clinical trials using stem cells for treatment of neonatal stroke-related disorders. AUCB: autologous umbilical cord blood stem cells, IV: intravenous

Clinical trial ID	Cell type	Specific pathology	Endpoint classification	Patients	Age	Delivery	Completion	Location	Clinical trial title
NCT01147653	AUCB	Cerebral palsy	Efficacy	120	12 m0nths–6 years	IV	January 16	USA	A Randomized Study of Autologous Umbilical Cord Blood Reinfusion in Children With Cerebral Palsy
NCT01072370	AUCB	Cerebral palsy	Safety/efficacy	40	1–12 years	IV	February 14	USA	Safety and Effectiveness of Cord Blood Stem Cell Infusion for the Treatment of Cerebral Palsy in Children
NCT00593242	AUCB	Neonatal encephalopathy	Safety	25	<14 days	IV	December 13	USA	Cord Blood for Neonatal Hypoxic-ischemic Encephalopathy
NCT01700166	AUCB	Arterial ischemic stroke (AIS)	Safety/Efficacy	10	6 weeks–6 years	IV	December 15	USA	Umbilical Cord Blood in the Treatment of Stroke in Children (Pedi Stroke)
NCT01506258	AUCB	Neonatal asphyxia	Safety/Efficacy	20	37 weeks–42 weeks	IV	April 13	Mexico	Autologous Stem Cells in Newborns With Oxygen Deprivation

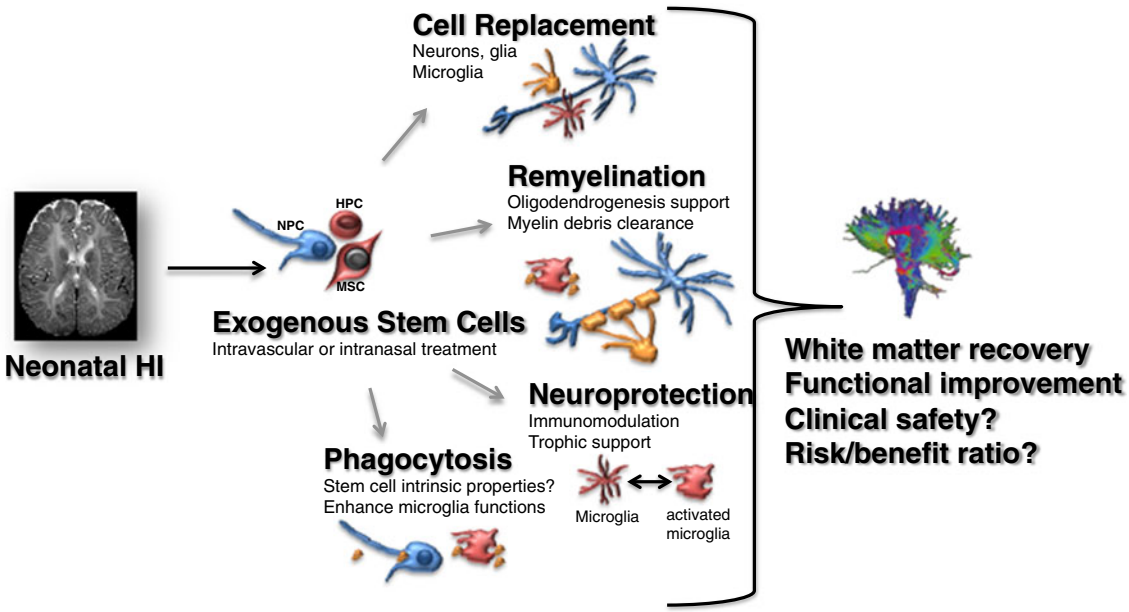

Fig. 1 Potential stem cell-induced brain repair mechanisms. Schematic illustrating main candidate mechanisms of action in stem cell-mediated white matter repair following neonatal hypoxic–ischemic injuries. For detail, cf. text

highly feasible, safe, repeatable, and minimally invasive approach [12, 35, 36, 75]. Our studies suggest an active mechanism of cell recruitment to the brain through cellular expression of adhesion molecules [36] and chemokine receptors [1, 81]. While previous studies involved transplantation of human stem cell grafts 24 h after neonatal hypoxia–ischemia injury [13], we established that intra-arterial transplantation of NPC 3 days after the insult resulted in higher cell engraftment and survival when compared with earlier (6–24 h) or later (7–14 days) time-points [81]. Interestingly, day 3 post-injury correlated with the highest expression of signaling molecules such as VCAM-1, CCL2, and CXCL12, here again supporting a cross-talk hypothesis, where the injured environment is likely to dictate efficiency of exogenous stem cell treatment. Current clinical trials will be using early (48 h and 2 weeks after birth) and chronic time points (up to 12 years of age) for intravenous cell delivery (Table 1).

Imaging

Noninvasive approaches to monitor stem cells upon transplantation are pivotal to therapeutic success and to prediction of graft viability and potential complications. High field magnetic resonance imaging (MRI) remains the modality of choice to evaluate pathogenesis, severity, and evolution of neonatal HI [17]. To evaluate white matter tract integrity and repair, MRI-based DTI has become the main imaging modality [90]. MRI can not only monitor evolving neonatal cerebral injury but also track migration and location of iron oxide nanoparticle (SPIO) labeled exogenous stem cells for prolonged time periods [13, 37, 67, 75]. Other preclinical stem cell imaging approaches have included reporter genes for bioluminescence, proton emission tomography, single photon emission tomography, radioactive tracers, and fluoride labeling for fluoride MR-based imaging (for review, see [29]). To date, however, there is no modality for clinical stem cell imaging.

Conclusions and perspectives

Increased understanding in the pathophysiology of perinatal injuries leading to cerebral palsy has placed white matter injury and myelin loss at the core of the disorder. With their unique regenerative properties, stem cells appear as a promising and versatile tool for therapeutic approaches in pediatric neurology. Moreover, repair mechanisms might be facilitated by the immaturity and plasticity of the neonatal developing brain.

Proof of principle for stem cell-mediated brain repair and functional recovery has been shown with different types of cells in the Rice-Vannucci animal model of neonatal hypoxia–ischemia. Most of those studies argue in favor of a strong communication between transplanted cells and intrinsic brain lineages. More than cell replacement, it becomes more and more obvious that exogenous stem cells are acting as bystander cells, providing a favorable niche for neuroprotection and immunomodulation (Fig. 1). However, knowledge obtained from preclinical models is unable to totally predict clinical outcomes in pediatric patients. Several clinical trials are underway to evaluate the safety and efficacy using autologous cord blood intravenous transplantation (Table 1), and results of

those should partly address safety of cell transplantation in the acute and chronic phase, as well as efficacy of the procedure for the growing child.

References

1. Andres RH, Choi R, Pendharkar AV, Gaeta X, Wang N, Nathan JK, Chua JY, Lee SW, Palmer TD, Steinberg GK, Guzman R (2011) The CCR2/CCL2 interaction mediates the transendothelial recruitment of intravascularly delivered neural stem cells to the ischemic brain. Stroke 42(10):2923–2931. doi:10.1161/STROKEAHA.110.606368
2. Andres RH, Horie N, Slikker W, Keren-Gill H, Zhan K, Sun G, Manley NC, Pereira MP, Sheikh LA, McMillan EL, Schaar BT, Svendsen CN, Bliss TM, Steinberg GK (2011) Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain. Brain 134(Pt 6):1777–1789. doi:10.1093/brain/awr094
3. Ayuso-Sacido A, Roy NS, Schwartz TH, Greenfield JP, Boockvar JA (2008) Long-term expansion of adult human brain subventricular zone precursors. Neurosurgery 62(1):223–229. doi:10.1227/01.NEU.0000311081.50648.4C, discussion 229-231
4. Back SA, Han BH, Luo NL, Chricton CA, Xanthoudakis S, Tam J, Arvin KL, Holtzman DM (2002) Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. J Neurosci 22(2):455–463
5. Ban H, Nishishita N, Fusaki N, Tabata T, Saeki K, Shikamura M, Takada N, Inoue M, Hasegawa M, Kawamata S, Nishikawa S (2011) Efficient generation of transgene-free human induced pluripotent stem cells (iPSCs) by temperature-sensitive Sendai virus vectors. Proc Natl Acad Sci U S A 108(34):14234–14239. doi:10.1073/pnas.1103509108
6. Ben-Porath I, Thomson MW, Carey VJ, Ge R, Bell GW, Regev A, Weinberg RA (2008) An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors. Nat Genet 40(5):499–507. doi:10.1038/ng.127
7. Brederlau A, Correia AS, Anisimov SV, Elmi M, Paul G, Roybon L, Morizane A, Bergquist F, Riebe I, Nannmark U, Carta M, Hanse E, Takahashi J, Sasai Y, Funa K, Brundin P, Eriksson PS, Li JY (2006) Transplantation of human embryonic stem cell-derived cells to a rat model of Parkinson's disease: effect of in vitro differentiation on graft survival and teratoma formation. Stem Cells 24(6):1433–1440. doi:10.1634/stemcells.2005-0393
8. Caplan AI, Dennis JE (2006) Mesenchymal stem cells as trophic mediators. J Cell Biochem 98(5):1076–1084. doi:10.1002/jcb.20886
9. Chaichana K, Zamora-Berridi G, Camara-Quintana J, Quinones-Hinojosa A (2006) Neurosphere assays: growth factors and hormone differences in tumor and nontumor studies. Stem Cells 24(12):2851–2857. doi:10.1634/stemcells.2006-0399
10. Chambers SM, Fasano CA, Papapetrou EP, Tomishima M, Sadelain M, Studer L (2009) Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling. Nat Biotechnol 27(3):275–280. doi:10.1038/nbt.1529
11. Chang DJ, Lee N, Park IH, Choi C, Jeon I, Kwon J, Oh SH, Shin DA, Do JT, Lee DR, Lee H, Moon H, Hong KS, Daley GQ, Song J (2012) Therapeutic potential of human induced pluripotent stem cells in experimental stroke. Cell Transplant. doi:10.3727/096368912X657314
12. Chua JY, Pendharkar AV, Wang N, Choi R, Andres RH, Gaeta X, Zhang J, Moseley ME, Guzman R (2011) Intra-arterial injection of neural stem cells using a microneedle technique does not cause microembolic strokes. J Cereb Blood Flow Metab 31(5):1263–1271. doi:10.1038/jcbfm.2010.213
13. Daadi MM, Davis AS, Arac A, Li Z, Maag AL, Bhatnagar R, Jiang K, Sun G, Wu JC, Steinberg GK (2010) Human neural stem cell grafts modify microglial response and enhance axonal sprouting in neonatal hypoxic-ischemic brain injury. Stroke 41(3):516–523. doi:10.1161/STROKEAHA.109.573691
14. Dammann O (2007) Persistent neuro-inflammation in cerebral palsy: a therapeutic window of opportunity? Acta Paediatr 96(1):6–7. doi:10.1111/j.1651-2227.2007.00097.x
15. Dammann O, Leviton A (1997) Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 42(1):1–8. doi:10.1203/00006450-199707000-00001
16. De Feo D, Merlini A, Laterza C, Martino G (2012) Neural stem cell transplantation in central nervous system disorders: from cell replacement to neuroprotection. Curr Opin Neurol 25(3):322–333. doi:10.1097/WCO.0b013e328352ec45
17. de Vries LS, Jongmans MJ (2010) Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 95(3):F220–F224. doi:10.1136/adc.2008.148205
18. Derecki NC, Cronk JC, Lu Z, Xu E, Abbott SB, Guyenet PG, Kipnis J (2012) Wild-type microglia arrest pathology in a mouse model of Rett syndrome. Nature 484(7392):105–109. doi:10.1038/nature10907
19. Ding DC, Shyu WC, Chiang MF, Lin SZ, Chang YC, Wang HJ, Su CY, Li H (2007) Enhancement of neuroplasticity through upregulation of beta1-integrin in human umbilical cord-derived stromal cell implanted stroke model. Neurobiol Dis 27(3):339–353. doi:10.1016/j.nbd.2007.06.010
20. Einstein O, Friedman-Levi Y, Grigoriadis N, Ben-Hur T (2009) Transplanted neural precursors enhance host brain-derived myelin regeneration. J Neurosci 29(50):15694–15702. doi:10.1523/JNEUROSCI.3364-09.2009
21. Elbers J, Viero S, MacGregor D, DeVeber G, Moore AM (2011) Placental pathology in neonatal stroke. Pediatrics 127(3):e722–e729. doi:10.1542/peds.2010-1490
22. Elsayed MH, Hogan TP, Shaw PL, Castro AJ (1996) Use of fetal cortical grafts in hypoxic-ischemic brain injury in neonatal rats. Exp Neurol 137(1):127–141. doi:10.1006/exnr.1996.0013
23. Erblich B, Zhu L, Etgen AM, Dobrenis K, Pollard JW (2011) Absence of colony stimulation factor-1 receptor results in loss of microglia, disrupted brain development and olfactory deficits. PLoS One 6(10):e26317. doi:10.1371/journal.pone.0026317
24. Erceg S, Ronaghi M, Stojkovic M (2009) Human embryonic stem cell differentiation toward regional specific neural precursors. Stem Cells 27(1):78–87. doi:10.1634/stemcells.2008-0543
25. Flax JD, Aurora S, Yang C, Simonin C, Wills AM, Billinghurst LL, Jendoubi M, Sidman RL, Wolfe JH, Kim SU, Snyder EY (1998) Engraftable human neural stem cells respond to developmental cues, replace neurons, and express foreign genes. Nat Biotechnol 16(11):1033–1039. doi:10.1038/3473
26. Fleiss B, Gressens P (2012) Tertiary mechanisms of brain damage: a new hope for treatment of cerebral palsy? Lancet Neurol 11(6):556–566. doi:10.1016/S1474-4422(12)70058-3
27. Fruttiger M, Karlsson L, Hall AC, Abramsson A, Calver AR, Bostrom H, Willetts K, Bertold CH, Heath JK, Betsholtz C, Richardson WD (1999) Defective oligodendrocyte development and severe hypomyelination in PDGF-A knockout mice. Development 126(3):457–467
28. Fu YS, Shih YT, Cheng YC, Min MY (2004) Transformation of human umbilical mesenchymal cells into neurons in vitro. J Biomed Sci 11(5):652–660. doi:10.1159/000079678
29. Gera A, Steinberg GK, Guzman R (2010) In vivo neural stem cell imaging: current modalities and future directions. Regen Med 5(1):73–86. doi:10.2217/rme.09.79

30. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM, Merad M (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 330(6005):841–845. doi:10.1126/science.1194637
31. Grad I, Hibaoui Y, Jaconi M, Chicha L, Bergstrom-Tengzelius R, Sailani MR, Pelte MF, Dahoun S, Mitsiadis TA, Tohonen V, Bouillaguet S, Antonarakis SE, Kere J, Zucchelli M, Hovatta O, Feki A (2011) NANOG priming before full reprogramming may generate germ cell tumours. Eur Cell Mater 22:258–274, discussio 274
32. Greenfield JP, Ayuso-Sacido A, Schwartz TH, Pannullo S, Souweidane M, Stieg PE, Boockvar JA (2008) Use of human neural tissue for the generation of progenitors. Neurosurgery 62(1):21–37. doi:10.1227/01.NEU.0000311059.87873.46, discussion 27-30
33. Grether JK, Nelson KB (1997) Maternal infection and cerebral palsy in infants of normal birth weight. JAMA 278(3): 207–211
34. Gunther G, Junker R, Strater R, Schobess R, Kurnik K, Heller C, Kosch A, Nowak-Gottl U (2000) Symptomatic ischemic stroke in full-term neonates : role of acquired and genetic prothrombotic risk factors. Stroke 31(10):2437–2441
35. Guzman R, Choi R, Gera A, De Los Angeles A, Andres RH, Steinberg GK (2008) Intravascular cell replacement therapy for stroke. Neurosurg Focus 24(3–4):E15. doi:10.3171/FOC/2008/24/3-4/E14
36. Guzman R, De Los Angeles A, Cheshier S, Choi R, Hoang S, Liauw J, Schaar B, Steinberg G (2008) Intracarotid injection of fluorescence activated cell-sorted CD49d-positive neural stem cells improves targeted cell delivery and behavior after stroke in a mouse stroke model. Stroke 39(4):1300–1306. doi:10.1161/STROKEAHA.107.500470
37. Guzman R, Uchida N, Bliss TM, He D, Christopherson KK, Stellwagen D, Capela A, Greve J, Malenka RC, Moseley ME, Palmer TD, Steinberg GK (2007) Long-term monitoring of transplanted human neural stem cells in developmental and pathological contexts with MRI. Proc Natl Acad Sci U S A 104(24):10211–10216. doi:10.1073/pnas.0608519104
38. Hochedlinger K, Yamada Y, Beard C, Jaenisch R (2005) Ectopic expression of Oct-4 blocks progenitor-cell differentiation and causes dysplasia in epithelial tissues. Cell 121(3):465–477. doi:10.1016/j.cell.2005.02.018
39. Huang H, Zhang J, Wakana S, Zhang W, Ren T, Richards LJ, Yarowsky P, Donohue P, Graham E, van Zijl PC, Mori S (2006) White and gray matter development in human fetal, newborn and pediatric brains. Neuroimaging 33(1):27–38. doi:10.1016/j.neuroimage.2006.06.009
40. Hung SC, Pochampally RR, Hsu SC, Sanchez C, Chen SC, Spees J, Prockop DJ (2007) Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment in vivo. PLoS One 2(5):e416. doi:10.1371/journal.pone.0000416
41. Imitola J, Raddassi K, Park KI, Mueller FJ, Nieto M, Teng YD, Frenkel D, Li J, Sidman RL, Walsh CA, Snyder EY, Khoury SJ (2004) Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1alpha/CXC chemokine receptor 4 pathway. Proc Natl Acad Sci U S A 101(52):18117–18122. doi:10.1073/pnas.0408258102
42. Issa R, AlQteishat A, Mitsios N, Saka M, Krupinski J, Tarkowski E, Gaffney J, Slevin M, Kumar S, Kumar P (2005) Expression of basic fibroblast growth factor mRNA and protein in the human brain following ischaemic stroke. Angiogenesis 8(1):53–62. doi:10.1007/s10456-005-5613-8
43. Jansen EM, Solberg L, Underhill S, Wilson S, Cozzari C, Hartman BK, Faris PL, Low WC (1997) Transplantation of fetal neocortex ameliorates sensorimotor and locomotor deficits following neonatal ischemic-hypoxic brain injury in rats. Exp Neurol 147(2):487–497. doi:10.1006/exnr.1997.6596
44. Johnston MV, Hagberg H (2007) Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol 49(1):74–78. doi:10.1111/j.1469-8749.2007.0199a.x
45. Khwaja O, Volpe JJ (2008) Pathogenesis of cerebral white matter injury of prematurity. Arch Dis Child Fetal Neonatal Ed 93(2): F153–F161. doi:10.1136/adc.2006.108837
46. Kim H, Walczak P, Kerr C, Galpoththawela C, Gilad AA, Muja N, Bulte JW (2012) Immunomodulation by Transplanted Human Embryonic Stem Cell- Derived Oligodendroglial Progenitors in Experimental Autoimmune Encephalomyelitis. Stem Cells. doi:10.1002/stem.1218
47. Kirby RS (2012) Cerebral palsy and birth defects: what is the frame of reference? Dev Med Child Neurol 54(8):677–678. doi:10.1111/j.1469-8749.2012.04331.x
48. Kokaia Z, Martino G, Schwartz M, Lindvall O (2012) Cross-talk between neural stem cells and immune cells: the key to better brain repair? Nat Neurosci 15(8):1078–1087. doi:10.1038/nn.3163
49. Kotter MR, Li WW, Zhao C, Franklin RJ (2006) Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation. J Neurosci 26(1):328–332. doi:10.1523/JNEUROSCI.2615-05.2006
50. Kuhl NM, De Keyser J, De Vries H, Hoekstra D (2002) Insulin-like growth factor binding proteins-1 and -2 differentially inhibit rat oligodendrocyte precursor cell survival and differentiation in vitro. J Neurosci Res 69(2):207–216. doi:10.1002/jnr.10293
51. Kurinczuk JJ, White-Koning M, Badawi N (2010) Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 86(6):329–338. doi:10.1016/j.earlhumdev.2010.05.010
52. Lacaud G, Robertson S, Palis J, Kennedy M, Keller G (2001) Regulation of hemangioblast development. Ann N Y Acad Sci 938:96–107, discussion 108
53. Larouche A, Roy M, Kadhim H, Tsanaclis AM, Fortin D, Sebire G (2005) Neuronal injuries induced by perinatal hypoxic-ischemic insults are potentiated by prenatal exposure to lipopolysaccharide: animal model for perinatally acquired encephalopathy. Dev Neurosci 27(2–4):134–142. doi:10.1159/000085985
54. Levine S (1960) Anoxic-ischemic encephalopathy in rats. Am J Pathol 36:1–17
55. Lim JY, Park SI, Kim SM, Jun JA, Oh JH, Ryu CH, Jeong CH, Park SH, Park SA, Oh W, Chang JW, Jeun SS (2011) Neural differentiation of brain-derived neurotrophic factor-expressing human umbilical cord blood-derived mesenchymal stem cells in culture via TrkB-mediated ERK and beta-catenin phosphorylation and following transplantation into the developing brain. Cell Transplant. doi:10.3727/096368910X557236
56. Lu P, Jones LL, Snyder EY, Tuszynski MH (2003) Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. Exp Neurol 181(2):115–129
57. Lu Z, Elliott MR, Chen Y, Walsh JT, Klibanov AL, Ravichandran KS, Kipnis J (2011) Phagocytic activity of neuronal progenitors regulates adult neurogenesis. Nat Cell Biol 13(9):1076–1083. doi:10.1038/ncb2299
58. Mahmood A, Lu D, Chopp M (2004) Intravenous administration of marrow stromal cells (MSCs) increases the expression of growth factors in rat brain after traumatic brain injury. J Neurotrauma 21(1): 33–39. doi:10.1089/089771504772695922
59. Marchetto MC, Winner B, Gage FH (2010) Pluripotent stem cells in neurodegenerative and neurodevelopmental diseases. Hum Mol Genet 19(R1):R71–R76. doi:10.1093/hmg/ddq159
60. Martino G, Bacigaluppi M, Peruzzotti-Jametti L (2011) Therapeutic stem cell plasticity orchestrates tissue plasticity. Brain 134(Pt 6): 1585–1587. doi:10.1093/brain/awr115

61. Mercuri E, Cowan F, Gupte G, Manning R, Laffan M, Rutherford M, Edwards AD, Dubowitz L, Roberts I (2001) Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 107(6):1400–1404
62. Mosher KI, Andres RH, Fukuhara T, Bieri G, Hasegawa-Moriyama M, He Y, Guzman R, Wyss-Coray T (2012) Neural progenitor cells regulate microglia functions and activity. Nat Neurosci 15(11): 1485–1487. doi:10.1038/nn.3233
63. Muotri AR, Nakashima K, Toni N, Sandler VM, Gage FH (2005) Development of functional human embryonic stem cell-derived neurons in mouse brain. Proc Natl Acad Sci U S A 102(51): 18644–18648. doi:10.1073/pnas.0509315102
64. Murohara T (2001) Therapeutic vasculogenesis using human cord blood-derived endothelial progenitors. Trends Cardiovasc Med 11(8):303–307
65. Nagae LM, Hoon AH Jr, Stashinko E, Lin D, Zhang W, Levey E, Wakana S, Jiang H, Leite CC, Lucato LT, van Zijl PC, Johnston MV, Mori S (2007) Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts. AJNR Am J Neuroradiol 28(7):1213–1222. doi:10.3174/ajnr.A0534
66. Nguyen HT, Geens M, Spits C (2013) Genetic and epigenetic instability in human pluripotent stem cells. Hum Reprod Update 19(2):187–205. doi:10.1093/humupd/dms048
67. Obenaus A, Dilmac N, Tone B, Tian HR, Hartman R, Digicaylioglu M, Snyder EY, Ashwal S (2011) Long-term magnetic resonance imaging of stem cells in neonatal ischemic injury. Ann Neurol 69(2):282–291. doi:10.1002/ana.22168
68. Okita K, Ichisaka T, Yamanaka S (2007) Generation of germline-competent induced pluripotent stem cells. Nature 448(7151):313–317. doi:10.1038/nature05934
69. Oliff HS, Coyle P, Weber E (1997) Rat strain and vendor differences in collateral anastomoses. J Cereb Blood Flow Metab 17(5):571–576. doi:10.1097/00004647-199705000-00012
70. Palmer TD, Schwartz PH, Taupin P, Kaspar B, Stein SA, Gage FH (2001) Cell culture. Progenitor cells from human brain after death. Nature 411(6833):42–43. doi:10.1038/35075141
71. Park KI, Teng YD, Snyder EY (2002) The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue. Nat Biotechnol 20(11):1111–1117. doi:10.1038/nbt751
72. Patrick LA, Smith GN (2002) Proinflammatory cytokines: a link between chorioamnionitis and fetal brain injury. J Obstet Gynaecol Can 24(9):705–709
73. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A (2001) Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull 54(3):255–266
74. Peitz M, Jungverdorben J, Brustle O (2013) Disease-specific iPS cell models in neuroscience. Curr Mol Med 13(5):832–841
75. Pendharkar AV, Chua JY, Andres RH, Wang N, Gaeta X, Wang H, De A, Choi R, Chen S, Rutt BK, Gambhir SS, Guzman R (2010) Biodistribution of neural stem cells after intravascular therapy for hypoxic-ischemia. Stroke 41(9):2064–2070. doi:10.1161/STROKEAHA.109.575993
76. Pimentel-Coelho PM, Rosado-de-Castro PH, da Fonseca LM, Mendez-Otero R (2012) Umbilical cord blood mononuclear cell transplantation for neonatal hypoxic-ischemic encephalopathy. Pediatr Res 71(4 Pt 2):464–473. doi:10.1038/pr.2011.59
77. Pluchino S, Zanotti L, Rossi B, Brambilla E, Ottoboni L, Salani G, Martinello M, Cattalini A, Bergami A, Furlan R, Comi G, Constantin G, Martino G (2005) Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. Nature 436(7048):266–271. doi:10.1038/nature03889
78. Rice JE 3rd, Vannucci RC, Brierley JB (1981) The influence of immaturity on hypoxic-ischemic brain damage in the rat. Ann Neurol 9(2):131–141. doi:10.1002/ana.410090206
79. Rickhag M, Teilum M, Wieloch T (2007) Rapid and long-term induction of effector immediate early genes (BDNF, Neuritin and Arc) in peri-infarct cortex and dentate gyrus after ischemic injury in rat brain. Brain Res 1151:203–210. doi:10.1016/j.brainres.2007.03.005
80. Righini A, Doneda C, Parazzini C, Arrigoni F, Matta U, Triulzi F (2010) Diffusion tensor imaging of early changes in corpus callosum after acute cerebral hemisphere lesions in newborns. Neuroradiology 52(11):1025–1035. doi:10.1007/s00234-010-0745-y
81. Rosenblum S, Wang N, Smith TN, Pendharkar AV, Chua JY, Birk H, Guzman R (2012) Timing of intra-arterial neural stem cell transplantation after hypoxia-ischemia influences cell engraftment, survival, and differentiation. Stroke 43(6):1624–1631. doi:10.1161/STROKEAHA.111.637884
82. Ruckh JM, Zhao JW, Shadrach JL, van Wijngaarden P, Rao TN, Wagers AJ, Franklin RJ (2012) Rejuvenation of regeneration in the aging central nervous system. Cell Stem Cell 10(1):96–103. doi:10.1016/j.stem.2011.11.019
83. Santilli G, Lamorte G, Carlessi L, Ferrari D, Rota Nodari L, Binda E, Delia D, Vescovi AL, De Filippis L (2010) Mild hypoxia enhances proliferation and multipotency of human neural stem cells. PLoS One 5(1):e8575. doi:10.1371/journal.pone.0008575
84. Schwarting S, Litwak S, Hao W, Bahr M, Weise J, Neumann H (2008) Hematopoietic stem cells reduce postischemic inflammation and ameliorate ischemic brain injury. Stroke 39(10):2867–2875. doi:10.1161/STROKEAHA.108.513978
85. Segovia KN, McClure M, Moravec M, Luo NL, Wan Y, Gong X, Riddle A, Craig A, Struve J, Sherman LS, Back SA (2008) Arrested oligodendrocyte lineage maturation in chronic perinatal white matter injury. Ann Neurol 63(4):520–530. doi:10.1002/ana.21359
86. Seminatore C, Polentes J, Ellman D, Kozubenko N, Itier V, Tine S, Tritschler L, Brenot M, Guidou E, Blondeau J, Lhuillier M, Bugi A, Aubry L, Jendelova P, Sykova E, Perrier AL, Finsen B, Onteniente B (2010) The postischemic environment differentially impacts teratoma or tumor formation after transplantation of human embryonic stem cell-derived neural progenitors. Stroke 41(1):153–159. doi:10.1161/STROKEAHA.109.563015
87. Shah PS, Perlman M (2009) Time courses of intrapartum asphyxia: neonatal characteristics and outcomes. Am J Perinatol 26(1):39–44. doi:10.1055/s-0028-1095185
88. Shechter R, London A, Varol C, Raposo C, Cusimano M, Yovel G, Rolls A, Mack M, Pluchino S, Martino G, Jung S, Schwartz M (2009) Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. PLoS Med 6(7):e1000113. doi:10.1371/journal.pmed.1000113
89. Sizonenko SV, Camm EJ, Dayer A, Kiss JZ (2008) Glial responses to neonatal hypoxic-ischemic injury in the rat cerebral cortex. Int J Dev Neurosci 26(1):37–45. doi:10.1016/j.ijdevneu.2007.08.014
90. Sotak CH (2002) The role of diffusion tensor imaging in the evaluation of ischemic brain injury—a review. NMR Biomed 15(7–8):561–569. doi:10.1002/nbm.786
91. Stewart MH (2013) Pluripotency and targeted reprogramming: strategies, disease modeling and drug screening. Curr Drug Deliv
92. Svendsen CN, Caldwell MA, Ostenfeld T (1999) Human neural stem cells: isolation, expansion and transplantation. Brain Pathol 9(3):499–513
93. Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, Yoshikawa H, Tsukamoto Y, Iso H, Fujimori Y, Stern DM, Naritomi H, Matsuyama T (2004) Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. J Clin Invest 114(3):330–338. doi:10.1172/JCI20622
94. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126(4):663–676. doi:10.1016/j.cell.2006.07.024
95. Tamaki S, Eckert K, He D, Sutton R, Doshe M, Jain G, Tushinski R, Reitsma M, Harris B, Tsukamoto A, Gage F, Weissman I, Uchida N

(2002) Engraftment of sorted/expanded human central nervous system stem cells from fetal brain. J Neurosci Res 69(6):976–986. doi:10.1002/jnr.10412
96. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic stem cell lines derived from human blastocysts. Science 282(5391):1145–1147
97. Thornton C, Rousset CI, Kichev A, Miyakuni Y, Vontell R, Baburamani AA, Fleiss B, Gressens P, Hagberg H (2012) Molecular mechanisms of neonatal brain injury. Neurol Res Int 2012:506320. doi:10.1155/2012/506320
98. Tipnis S, Viswanathan C, Majumdar AS (2010) Immunosuppressive properties of human umbilical cord-derived mesenchymal stem cells: role of B7-H1 and IDO. Immunol Cell Biol 88(8):795–806. doi:10.1038/icb.2010.47
99. Titomanlio L, Kavelaars A, Dalous J, Mani S, El Ghouzzi V, Heijnen C, Baud O, Gressens P (2011) Stem cell therapy for neonatal brain injury: perspectives and challenges. Ann Neurol 70(5):698–712. doi:10.1002/ana.22518
100. Tso GH, Law HK, Tu W, Chan GC, Lau YL (2010) Phagocytosis of apoptotic cells modulates mesenchymal stem cells osteogenic differentiation to enhance IL-17 and RANKL expression on CD4+ T cells. Stem Cells 28(5):939–954. doi:10.1002/stem.406
101. van Velthoven CT, Kavelaars A, van Bel F, Heijnen CJ (2010) Mesenchymal stem cell treatment after neonatal hypoxic-ischemic brain injury improves behavioral outcome and induces neuronal and oligodendrocyte regeneration. Brain Behav Immun 24(3):387–393. doi:10.1016/j.bbi.2009.10.017
102. Van't Veer A, Du Y, Fischer TZ, Boetig DR, Wood MR, Dreyfus CF (2009) Brain-derived neurotrophic factor effects on oligodendrocyte progenitors of the basal forebrain are mediated through trkB and the MAP kinase pathway. J Neurosci Res 87(1):69–78. doi:10.1002/jnr.21841
103. Vannucci RC (1993) Experimental models of perinatal hypoxic-ischemic brain damage. APMIS Suppl 40:89–95
104. Vannucci RC, Perlman JM (1997) Interventions for perinatal hypoxic-ischemic encephalopathy. Pediatrics 100(6):1004–1014
105. Vannucci SJ, Hagberg H (2004) Hypoxia-ischemia in the immature brain. J Exp Biol 207(Pt 18):3149–3154. doi:10.1242/jeb.01064
106. Vendrame M, Gemma C, Pennypacker KR, Bickford PC, Davis Sanberg C, Sanberg PR, Willing AE (2006) Cord blood rescues stroke-induced changes in splenocyte phenotype and function. Exp Neurol 199(1):191–200. doi:10.1016/j.expneurol.2006.03.017
107. Vescovi AL, Gritti A, Galli R, Parati EA (1999) Isolation and intracerebral grafting of nontransformed multipotential embryonic human CNS stem cells. J Neurotrauma 16(8):689–693
108. Vescovi AL, Parati EA, Gritti A, Poulin P, Ferrario M, Wanke E, Frolichsthal-Schoeller P, Cova L, Arcellana-Panlilio M, Colombo A, Galli R (1999) Isolation and cloning of multipotential stem cells from the embryonic human CNS and establishment of transplantable human neural stem cell lines by epigenetic stimulation. Exp Neurol 156(1):71–83. doi:10.1006/exnr.1998.6998
109. Volpe JJ (2008) Neonatal encephalitis and white matter injury: more than just inflammation? Ann Neurol 64(3):232–236. doi:10.1002/ana.21466
110. Volpe JJ (2008) Postnatal sepsis, necrotizing entercolitis, and the critical role of systemic inflammation in white matter injury in premature infants. J Pediatr 153(2):160–163. doi:10.1016/j.jpeds.2008.04.057
111. Walker PA, Shah SK, Jimenez F, Gerber MH, Xue H, Cutrone R, Hamilton JA, Mays RW, Deans R, Pati S, Dash PK, Cox CS Jr (2010) Intravenous multipotent adult progenitor cell therapy for traumatic brain injury: preserving the blood brain barrier via an interaction with splenocytes. Exp Neurol 225(2):341–352. doi:10.1016/j.expneurol.2010.07.005
112. Wang M, Yang Y, Yang D, Luo F, Liang W, Guo S, Xu J (2009) The immunomodulatory activity of human umbilical cord blood-derived mesenchymal stem cells in vitro. Immunology 126(2):220–232. doi:10.1111/j.1365-2567.2008.02891.x
113. Wei Y, Yemisci M, Kim HH, Yung LM, Shin HK, Hwang SK, Guo S, Qin T, Alsharif N, Brinkmann V, Liao JK, Lo EH, Waeber C (2011) Fingolimod provides long-term protection in rodent models of cerebral ischemia. Ann Neurol 69(1):119–129. doi:10.1002/ana.22186
114. Wu YW, Hamrick SE, Miller SP, Haward MF, Lai MC, Callen PW, Barkovich AJ, Ferriero DM (2003) Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. Ann Neurol 54(1):123–126. doi:10.1002/ana.10619
115. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB (2004) Perinatal stroke in children with motor impairment: a population-based study. Pediatrics 114(3):612–619. doi:10.1542/peds.2004-0385
116. Xia G, Hong X, Chen X, Lan F, Zhang G, Liao L (2010) Intracerebral transplantation of mesenchymal stem cells derived from human umbilical cord blood alleviates hypoxic ischemic brain injury in rat neonates. J Perinat Med 38(2):215–221. doi:10.1515/JPM.2010.021
117. Zhang J, Li Y, Cui Y, Chen J, Lu M, Elias SB, Chopp M (2005) Erythropoietin treatment improves neurological functional recovery in EAE mice. Brain Res 1034(1–2):34–39. doi:10.1016/j.brainres.2004.11.036