Received: 22 January 2020 | Accepted: 24 August 2020

DOI: 10.1002/sctm.20-0026

PERSPECTIVES

STEM CELLS TRANSLATIONAL MEDICINE

Progenitor cell therapy for acquired pediatric nervous system injury: Traumatic brain injury and acquired sensorineural hearing loss

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Abstract

While cell therapies hold remarkable promise for replacing injured cells and repairing damaged tissues, cell replacement is not the only means by which these therapies can achieve therapeutic effect. For example, recent publications show that treatment with varieties of adult, multipotent stem cells can improve outcomes in patients with neurological conditions such as traumatic brain injury and hearing loss without directly replacing damaged or lost cells. As the immune system plays a central role in injury response and tissue repair, we here suggest that multipotent stem cell therapies achieve therapeutic effect by altering the immune response to injury, thereby limiting damage due to inflammation and possibly promoting repair. These findings argue for a broader understanding of the mechanisms by which cell therapies can benefit patients.

KEYWORDS

autologous stem cell transplantation, bone marrow, clinical translation, progenitor cells, umbilical cord blood

1 | INTRODUCTION

This review will first consider two neurological conditions with unappreciated similarities: traumatic brain injury (TBI) and sensorineural hearing loss (SNHL), paying particular attention to the role of the immune system in each. Next, it will review laboratory and clinical findings showing improved outcomes for TBI and SNHL upon treatment with allogenic or autologous stem cells, including mesenchymal progenitor cells (MPCs)—a range of nonhematopoietic, mesodermal lineage, multipotent stem cells.[1] Finally, it will evaluate the possible mechanisms of action, concentrating on the immune modulatory properties of MPCs.

1.1 | Pediatric TBI

TBI is the most significant cause of death and disability in children. In the United States, approximately 473 000 children aged 0-14 years sustain TBI annually. Of these 37 000 require hospitalization and nearly 3000 die as a result of their injuries. Boys are hospitalized more frequently than girls following TBI. The mortality for TBI is higher for children less than 4 years of age than for children 5-14 years of age, which may reflect the contribution of nonaccidental (abuse) related TBI.[2-5]

TBI is a cataclysmic insult which initiates a cascade of local and systemic effects. Traditionally, TBI is divided between the primary

injury (head hitting the pavement) and secondary injury, which occurs in reaction to the primary injury. Whereas primary injury refers tearing cerebral tissues and blood vessels and other immediate mechanical damage, secondary injury is a progressive process, lasting months, during which brain cells are progressively lost and brain volume decreases.

Exacerbating the challenge of managing TBI in children is the fact that the mechanism, type of injury and presentation are all age dependent. The age specific properties of the developing skull, brain, cervical spine and face make children susceptible to injuries distinct from those seen in adult TBI patients. These differences manifest both in the primary and secondary injuries.[5]

Many anatomical and developmental factors influence the primary injuries seen in children. One such factor is the structure of the developing skull. The pediatric skull is less rigid and more deformable than the adult skull. In addition, the cranial sutures are "open" in younger children allowing additional skull motion in response to mechanical stress.[6,7] The higher deformability of the pediatric skull can allow shearing forces between the cortical vessels of the brain and overlying skull. This is particularly likely when nonaccidental TBI includes shaking.

Furthermore, because children's heads are relatively larger than adults when compared to the overall size of their respective bodies, a child's head is more likely to experience injury during a traumatic event.[8] Skull and facial bone development also serve a protective function. In older children, the frontal sinuses and facial bones are more prominent and can serve to absorb energy from frontal impacts, protecting underlying brain tissue.[5-8]

The changing character of the developing brain also plays a role. In neonates, the brain is poorly myelinated and has a relatively high-water content. As the brain develops, it becomes more myelinated and relatively more dense. Myelination follows a programmed pattern progressing in both caudo-cranial and posterior-anterior directions. Less myelinated brain is more susceptible to injury from traumatic forces than myelinated brain.[8]

Another factor influencing TBI in children is the relative weakness of the neck and spine. In infants, the cervical spine is cartilaginous and undergoes progressive ossification with development. The head is relatively larger and heavier than in adult patients. The neck muscles are weaker and cranio-cervical stability depends more upon ligaments and soft tissues than on vertebrae. In younger children, the level of cervical spinal fractures tends to be higher (occiput to C2) than in older patients (C3-C7).[7,9] In cases of severe trauma, the ligaments can fail resulting in occipitocervical dissociation (separation of the skull from the cervical spine) causing direct injury to the cervico-medullary junction and the carotid and vertebral arteries. This so called "occipitocervical dissociation" is more frequent in children than in adolescents and adults.[10]

Pediatric TBI is further complicated by the smaller blood volume in children. The scalp and soft tissues of the neck and face are highly vascular. Because the blood volume of children is smaller than that of adolescent or adult patients, blood loss is less well tolerated in children. In neonates, toddlers and infants, bleeding under the scalp or intracranially (even without obvious external bleeding) can cause significant hemodynamic instability. External bleeding from scalp or other soft tissue injuries can rapidly become life threatening in children.

Significance statement

Progenitor cell therapy is an underappreciated and underutilized treatment for central nervous system insults. In the present study, the authors compare the use of this treatment in the acute aftermath of severe pediatric traumatic brain injury and in acquired sensorineural hearing loss. The authors' aim is to demonstrate that in both acute and subacute settings, the immunomodulatory effects of progenitor cell treatment can reduce the secondary effects of these injuries. In addition, the data presented here suggest that a repair machinery may be unmasked by progenitor cell treatment. This repair may allow the recovery of lost function in tissues long thought to be postmitotic and irreparable.

The interplay of these and other factors during development results in the following age dependent patterns of TBI: Newborns can experience delivery related injury including skull vault fractures, intracranial, subperiosteal, and subgaleal hemorrhages. Infants are frequently victims of nonaccidental TBI, falls, and motor vehicle accidents. Toddlers and school children usually experience accidental TBI most frequently from falls or motor vehicle accidents. Adolescents also experience TBI from motor vehicle accidents, falls, sports related injuries, and bicycle and motorcycle related injuries.[4]

Once the above-mentioned primary injuries have occurred, secondary injuries develop. As the occurrence of primary injury is unpredictable and no reparative therapies yet exist, TBI treatment concentrates on minimizing the effects of secondary injury. In the acute phase, treatment focuses on maintaining adequate brain perfusion and maintaining normal intracranial pressure (ICP). Significant intracranial hemorrhages are evacuated, and medical management of intracranial pressure is pursued. Other non-CNS traumatic injuries must also be addressed. Cerebral edema caused in part by transient disruption of the blood brain barrier (BBB) is a major secondary injury management challenge. If ICP can be controlled and adequate cerebral perfusion maintained, the patient can survive. Unfortunately, the secondary sequala of the primary TBI continue months following injury.

The effects of secondary injury progress over time and manifests most strikingly in a reduction of overall brain volume. Follow-up neuroimaging reveals post-TBI volume loss. MRI based volumetric studies of pediatric TBI patients before and 1 year after injury demonstrate loss of whole brain matter, gray matter, white matter with corresponding increases in CSF volume when compared to age matched controls at 1-year postinjury.[10,11] A study by Sideros showed a 9% loss of gray and white matter at 8 weeks post-injury with an additional 4% loss in whole brain volume over the ensuing 10 months.[12] A similar study by Ding showed an 8%-13% whole brain volume loss at

6 months post-TBI.[13] The corpus callosum loses volume and structural integrity following TBI in pediatric patients compared with age matched controls.[14,15] Global and callosal volume loss are associated with poor neurocognitive outcomes.[16] This volume loss is thought to be the result of progressive histopathologic damage mediated by the post-TBI immune response.[17]

Because of the rapidly changing developmental state of the central nervous system and variable age dependent mechanism(s) of trauma, pediatric TBI includes an extremely heterogeneous spectrum of injury. The existing classification schemes Glasgow Coma Scale (GCS) and Glasgow Outcome Score (GOS) are not designed to capture this complexity of injury. In addition, studies evaluating TBI outcome do not typically include preinjury baseline assessments. Given the consistency and physiological relevance of brain volume loss, we will argue that changes in brain volume are a useful surrogate marker for evaluating TBI outcomes.

1.2 | Pediatric SNHL

In contrast to TBI, SNHL represents a more restricted injury, primarily affecting cochlear function. SNHL can, however, lead to broad neurodevelopmental changes. Typical language development requires normal or near normal hearing. With SNHL, damaged hair cells of the organ of Corti interfere with typical hearing and as a result may impair language development. Untreated SNHL causes significant neurocognitive issues in affected children.[18]

SNHL is a permanent sensory disorder affecting more than 270 million people worldwide. The incidence of SNHL increases from 2-4/1000 in newborns to 5-8/1000 in children aged 3-17 years and 33% of adults aged 65-74 years.[19,20]

The causative pathology of SNHL is loss of hair cells in the organ of Corti. Inner, outer and structural hair cells are necessary for hearing. Sound waves from the middle ear are transformed into electrical impulses transmitted to the brain via the spiral ganglion and eighth cranial nerve. Hair cells loss reduces auditory input to the brain. With sufficient hair cell loss, hearing impairment develops. Hair cell damage can be caused by both genetic mutations and environmental insults. Among infants and children, 23%-50% of SNHL is the result of a genetic mutation (Connexin 26 mutation, Usher syndrome, Waardenburg syndrome, mitochondrial disorders, etc).[21-25] The remaining infants and children have acquired SNHL, which is thought to result from infection (in utero or postnatally), prematurity, and exposure to noise or ototoxic drugs.[26] Compounding this challenge is the fact that the organ of Corti is postmitotic at birth in mammals and spontaneous hair cell replacement does not occurs thereafter. Currently no regenerative treatment exists for SNHL and existing treatments (hearing aids and cochlear implants) are designed to augment the damaged organ of Corti.[18]

1.3 | Hearing loss and auditory development

Spoken language is learned and its development depends on environmental stimulation and the innate ability of the human auditory cortex. Because of neuroplasticity, the period during which the cortex is capable of learning a first spoken language is finite.[18,27] Neuroplasticity refers to changes in neural connections, pathways and networks caused by maturation and development, sensory deprivation, injury, disease, dysfunction, and learning.[28] Though some degree of neuroplasticity is present throughout life, it is especially robust during early development when neuronal groups can most readily adjust function based upon input. This period of heightened learning, called the critical period, ends at approximately 42 months of age. The brain can effortlessly rewire in response to environmental input during the critical period. After the critical period ends, there is a significant reduction in neuroplasticity.[18,27]

Auditory development is especially sensitive to the critical period. The earliest stages of auditory learning occur in utero[29] when synapses are formed, and networks strengthen rapidly.[30] At roughly 4 years of age, the auditory cortex undergoes a rapid pruning phase, during which unused neurons and synapses are eliminated.[31,32] In the normal hearing children, this pruning fundamentally alters the auditory cortex and results in improved language efficiency. In the unamplified child with SNHL, abnormal pruning results in an inability to process auditory input and develop spoken language. If adequate auditory stimulation is not delivered during the early optimal period of cortical plasticity, deficiencies in spoken language are observed even after the child is amplified.[33,34] The latency rate of the P1 component of the cortical auditory evoked potentials (CAEP) is an established biomarker for auditory cortical maturation. The P1 component of the CAEP shows age-related decreases in latency, meaning faster transmission of electrical impulses from cochlea to brain, in children without hearing loss. In their series of 245 children with congenital deafness, Sharma and Dorman found that the latency of the P1 CAEP improves to within normal limits in children who undergo cochlear implantation by 3.5 years of age. Children who underwent cochlear implantation after 7 years of age continued to have abnormal P1 CAEP responses even after years of cochlear implant use. Children implanted between 3.5 and 7 years had variable auditory cortical development, with some children achieving normal P1 CAEP responses and others never reaching normal central auditory maturational status.[35] When speech and language skill developmental outcomes are measured in children implanted at various ages, significantly improved outcomes are reported following younger implantation age.[36,37] The improved outcomes are especially true for oral spoken language development.[18,38]

If auditory access through hearing aids or a cochlear implant is provided to a child with SNHL in a timely manner during the critical period, auditory development and language acquisition may occur near normally or normally. Conversely, when children experience long periods of auditory deprivation, large-scale reorganization of the auditory cortex areas responsible for the perception of speech and language can occur.[39] The reorganization results from auditory deprivation can cause areas of auditory cortex to be recruited for visual and tactile input.[38,39] Task specific reorganization of the auditory cortex has been demonstrated in deafened cats. In their study comparing cats with SNHL to those with normal hearing, Meredith and Lomber demonstrated that distinct regions of auditory cortex

which support auditory localization in normal cats supported peripheral visual localization and visual motion in cats with SNHL.[18,40]

Children with acquired SNHL are a much more homogeneous treatment population than children with TBI. Existing audiologic and speech language testing provides quantitative assessments that measure cochlear and language function in a validated age appropriate fashion. Studies evaluating acquired SNHL treatment(s) also benefit from the possibility of obtaining comprehensive pretreatment assessments.[41]

1.4 | CNS immune response

The immune system differs substantially from that of the peripheral tissues, so much so that the CNS is often referred to as "immune privileged."[42,43] The BBB allows relatively small numbers of circulating leukocytes to enter the CNS. In a resting state, immune functions within the CNS are primarily carried out by microglia and astrocytes. Following TBI, the immune system undergoes a rapid and well characterized response. As the role of the immune system in TBI has been reviewed recently by McKee and Lukens,[44] this review will focus on the aspects most relevant to progenitor cell therapy.

The immune system plays a central role in both TBI and SNHL. In general, the neuroinflammatory reaction following TBI initiates an intricate interaction between the innate and adaptive immune systems. Immediately after TBI, the BBB-which is composed of and coordinated by complex interactions between glial cells, neurons and endothelial cells-is broken down by mechanical insult and brain edema.[45-48] The compromised BBB facilitates the entry of immune cells into the injured brain and their migration to the site of injury.[49] Shortly after injury, the resident microglia become activated and neutrophils and other cells of the innate immune system infiltrate the lesion. Next, macrophages derived from circulating monocytes, lymphocytes and other cells of the adaptive immune system reach the site of injury.[45] Cell death leads to the release of intracellular molecules referred to as damage and pathogen associated molecular patterns (DAMPs and PAMPs), though the effect is more pronounced in nonprogrammed forms of cell death, such as necrosis.[45,50] The release of these molecules activates the innate immune system initiating inflammation and subsequently the adaptive immune system.[51-53] Following the acute immune response, microglia can return to their normal nonactivated state or, with sufficient inflammatory damage, become chronically activated.[45]

In the short term, immune cells play important roles in containing and mitigating damage resulting from the lesion. Live imaging studies have shown that microglia processes are highly dynamic and motile, serving to continually scan and monitor nearby cells and the local microenvironment. In response to acute lesions, microglial processes rapidly localize to the site of injury, apparently functioning to quarantine the lesion.[54] Microglia and other immune cells, such as neutrophils, are potent phagocytes that rapidly engulf and degrade cellular debris and damaged cells. Numerous animal model studies demonstrate that microglial phagocytosis helps to limit the spread of DAMPs and other proinflammatory or otherwise problematic signals. For instance, in an in vivo zebrafish model, microglial phagocytosis of debris and dead cells shortly following TBI was shown to be neuroprotective, as blocking microglial phagocytosis yielded increased excitotoxicity and neuronal cell death.[55] There is in vivo evidence that the metabolism of microglia and macrophages functions in the pathophysiology of CNS injury. Proinflammatory macrophages and microglia re-direct gylcolytic intermediates toward the oxidative phase of the pentose phosphate pathway (PPP) generating reactive oxygen species (ROS) through production of NADPH and NADPH oxidases.[56,57] Anti-inflammatory macrophages use the nonoxidative phase of the PPP to provide redox support glutathione and other cellular antioxidants.[57,58] After TBI, macrophage specific nitrous oxide (NOX) activity (NOX2) is increased in microglia and macrophages responding to injury.[57,59-65] Increased NOX activity is accompanied by increased production of ROS in microglia and macrophages and NOX inhibition improves outcome following TBI and spinal cord injury.[57,60-65] In TBI, NOX2 inhibition reduces proinflammatory macrophage/microglial activation in vivo.[60,63,66,67] The observed changes in polarization associated with NOX2 inhibition implicate altered metabolism and the oxidative phase of the PPP in proinflammatory macrophage/microglial activation following neurotrauma.[57]

Chronic inflammation likely plays a critical role in the loss of brain volume during the secondary injury phase of TBI. CNS inflammation has been observed to persist for years after TBI.[68-70] Furthermore, immune cells appear to play a role in neuronal cell death in TBI and TBI-like conditions. Depletion of neutrophils has also been shown to alleviate neuronal apoptosis and neuronal tissue loss in a mouse model of TBI.[71] Laboratory studies in mice, rats, and cell culture systems have shown that microglia are responsible for substantial amounts of neuron loss in response to inflammation, ischemia, and excitotoxicity.[72-74] When stressed, neurons exhibit early apoptotic markers, such as displaying phosphatidyl serine on the outer leaflet of the cell membrane. Many recent studies have shown that these early apoptotic markers are, in fact, reversible, and neurons can recover from sublethal insults. Interestingly, these stress markers also function as prophagocytic signals, causing stressed or apoptotic cells to be engulfed and degraded by microglia. Thus, microglia have been shown to engulf and kill stressed but otherwise nonapoptotic neurons.[75] This form of phagocytosis-dependent cell death has been termed "phagoptosis." Blocking phagocytosis and phagoptosis has been shown to preserve neurons following a range of insults.[72-74] Experimental evidence indicates that preserving neurons in this manner can also improve neurological function after injury. For instance, blocking phagocytosis in a mouse model of focal ischemia resulted in improved motor function following injury.[75] This, therefore, indicates that microglia engulf and kill many still functional neurons. Unresolved inflammation, therefore, likely contributes to the continued loss of brain volume following TBI.

Further complicating our understanding of this process is the discovery of sex differences in microglial colonization, maturation and function in the developing brain. This microglial sexual dimorphism may contribute to differences in outcome between male and female

TBI patients.[76-80] Recently nonparenchymal brain macrophages (NPBMs) along with resident microglia have been identified as the resident myeloid lineage cells of the brain. Both cell types share a distinct ontogenetic origin developing from the yolk sac during early embryonic development. NPBMs populate the perivascular spaces, the choroid plexus and the meninges and are the first brain immune cells to interact with invading cells or pathogens.[78] Microglia represent a population of functionally diverse and complex cells with brain region specific phenotypes that require local cues to be maintained. Microglial anatomical, membrane properties, lysosomal content and transcriptome profile differ significantly across brain areas.[79-82] So the CNS immune response to TBI varies by mechanism-of-injury, developmental age, anatomic site of injury and sex making the treatment population for any study terrifically diverse.

1.5 | Cochlear immune response

The cochlea is protected by the blood-labyrinth-barrier (BLB), a structure similar to, but less restrictive than the BBB. The BLB is a highly specialized capillary network within the stria vascularis that controls the exchanges between the intrastitial space of the cochlea and the blood. It is critical in maintaining the proper environment for cochlear function and hearing. The BLB is made up of endothelial cells, elaborated tight and adherens junctions, pericytes, basement membrane and perivascular resident macrophage-like melanocytes (PVMLMs).[83,84] In response to acute acoustic trauma, there is a decrease in the integrity of the BLB endothelial tight junctions and an increased infiltration of monocytes into the cochlea across the BLB.[83,84]

The immune response at the epithelial surface of the ear caused by exposure to ototoxic drugs or excessive noise is not a response to a pathogen and is therefore termed "sterile inflammation."[83-85] The response is proportional to the degree of acoustic trauma experienced by the cochlea, with milder injury generating a less aggressive immune response and a less severe decrease in hearing. The hallmark of hearing loss following acoustic trauma is a temporary or permanent threshold shift (TTS or PTS) in which higher sound intensity is required to achieve cochlear activation and hearing. Mild acoustic trauma can induce a TTS in which the cochlea transiently experiences a threshold shift that recovers to normal over hours to weeks following injury.[85] In TTS, the ribbon synapses between the hair cells and neurons of the spiral ganglion can be damaged.[86,87] This synaptopathy can contribute to neurodegeneration in the spiral ganglion and hearing loss. Cochlear macrophages appear to serve a protective function for spiral ganglion neurons in TTS and may facilitate ribbon synapse repair following injury.[88,89] More significant acoustic trauma causes a more aggressive immune response and a severe nonreversible PTS and irreversible hearing loss.[85] Recent studies have demonstrated differences in the immune response in general and in macrophage activation in particular in these two forms of sterile inflammation.[90-98]

Macrophages make up roughly 80% of the hematopoietic cells in cochlear tissue and are the primary immune cell population in the cochlear.[90-96] Many studies have shown that cochlear macrophage populations expand following acoustic injury in respond to signals from the organ of Corti and spiral ganglion.[83,84,90,92,94-100] Cochlea macrophages are divided into two populations: (a) "Resident macrophages" found within the connective tissue, neurons and supporting cells often localizing to the perivascular space and (b) macrophages recruited from monocytes circulating in the blood in response to damaged and dying hair cells.[100] Much like microglia within the brain, there appear to be subpopulations of cochlear "resident macrophages" with differing site-specific characteristics within the cochlea. These include osseous spiral lamina macrophages (closely associated with the spiral ganglion), basilar membrane macrophages (immediately below the cochlear sensory cells), luminal surface, scala tympani macrophages and lateral wall macrophages.[92] Damaged cells release DAMPs that activate pattern recognition receptors (PRRs).[101] PRR activation rapidly causes activation of resident macrophages, proinflammatory cytokine release, and production of reactive oxygen species (ROS) resulting in infiltration of immune cells and apoptosis of damaged cells.[102-105] Following acoustic trauma there is a release of cytokines (TNF-α, IL-1β, and Il-6) followed by chemokine release (CXCL12, CCL2, and CCL4) then activation of resident macrophages and infiltration of monocytes from the blood.[87,104-108] In this process, along with controlling vascular permeability and contraction, the PVMLM also function as antigen-presenting cells.[106] Cochlear pericytes are also active in controlling blood flow in the BLB as well as contributing to maintenance of tight junctions and participating in the cochlear immune response.[109]

In addition to directly damaging sensory hair cells, acoustic trauma also disrupts blood flow and the BLB in the stria vascularis creating an ischemic and hypoxic environment. Monocytes/macrophages from the blood are attracted to and play a critical role in the repair of the noise damaged microvasculature of the stria vascularis and recovery from noise induced hearing loss.[110]

In summary, both TBI and SHNL affect significant numbers of pediatric patients. The distribution and severity of the injuries to the central nervous system associated with TBI are variable and age dependent. TBI can affect movement, sensation, memory, vision and higher cognitive function. In SHNL, injury is localized to the hair cells of the organ of Corti. By diminishing auditory access, SNHL can adversely impact language development and communication. Both conditions adversely affect school performance. Both injuries induce an immune response which adversely impacts patient recovery. Currently, no reparative treatments exist, and current management is primarily supportive. As we will discuss below, it is possible that cellular therapies may blunt the injurious effects of the post-TBI/SNHL immune response and allow repair of damaged tissue.

1.6 | Preclinical data supporting progenitor cell treatment for TBI and SNHL

As the damage inflicted by TBI and SNHL are permanent, researchers developed an interest in reparative therapies, and one promising

avenue was cell therapy. The biologic rationale for using progenitor or stem cells to treat TBI and other CNS insults falls into two approaches: neural or support cell replacement or a modification of the immune/anti-inflammatory/paracrine response.[111] In the late 1980s and early 1990s, the concept of "transdifferentiation" was proposed as a mechanism to achieve neural and support cell replacement using hematopoietic progenitor cells by many investigators.[111-113] Although positive results were obtained using progenitor cell treatment in preclinical TBI and SNHL studies, transdifferentiation fell out of favor as an explanation for the observed improvement.[114] Anti-inflammatory/paracrine/immune response modification currently has received more attention by researchers in this field.[111]

Studies using rodent TBI models treated with a variety of bone marrow derived cell populations delivered via a variety routes showed promising results.[111,115] Cells were delivered either directly into injured brain, or systemically through intraperitoneal, intravenous or intra-arterial injections in the acute or subacute phase after TBI. Following these treatments, significant reductions in neurologic deficits including motor, sensory and cognitive performance were found in treated animals vs controls.[115-119] An improvement in sensorimotor function was seen even when cell therapy was delivered 2 months after experimental TBI.[116] When cells are delivered via an intravascular route, most cells do not cross the BBB. The exact roles of cell populations which do and do not cross the BBB are under investigation.[119,120] Human umbilical cord blood-derived cells can survive and facilitate host neuronal survival within sites of injury in ischemic brain and spinal cord injury animal models.[121] Jackson performed a meta-analysis evaluating the effects of cellular therapy on preclinical outcome measures following controlled cortical contusion in rodents. This study demonstrated a strong effect of cell therapy on reducing lesion volume, improving neurosensory (Rota-Rod) and memory (Morris water maze) outcomes.[122] Preclinical data supports progenitor cell therapy for TBI.[123-125]

Somewhat surprisingly, progenitor cell therapy yielded similar beneficial outcomes in SNHL as in TBI. In experimentally deafened animals, mesenchymal progenitor cell treatment has provided intriguing results. After experimentally deafening nod-scid mice with kanamycin and noise, Revoltella et al demonstrated recovery of auditory function following intravenous treatment of the mice with CD133+ cells derived from human umbilical cord blood (hUCB). Some of the CD133+ cells reached the cochlea.[126] In a subsequent study by Bettini et al, nod-scid mice deafened with kanamycin were treated with human mesenchymal stem cells obtained from either adipose tissue or bone marrow. Both cell types engrafted into the cochlea of deafened mice, inducing regeneration of the damaged sensory structures (Figure 1). Hybrid human-mouse fusion cells were found within the support cell layer of the cochlea, but all hair cells found in the repaired cochlea were of murine origin.[127] The data suggest that human progenitor cells do not directly replace lost hair cells but could facilitate hair cell regeneration through systemic and local paracrine effects.[126,127]

In a guinea pig SNHL model, Choi et al showed both anatomic and physiological improvement in the cochlea of animals following treatment with hUCB derived mesenchymal stem cells. In treated animals, auditory brainstem response (ABR) thresholds were improved by 40-50 dB and distortion product otoacoustic emissions (DPOAEs) were decreased. In addition, compared to control animals, treated animals demonstrated an increase in both hair cells and spiral ganglion cells.[18,128]

Strikingly for both TBI and SNHL, progenitor cell therapy yielded improved neurological outcomes without directly replacing damaged neurological structures. These data indicate that progenitor cell treatment can have a common benefit to these two distinct neurological conditions via systemic effects or by inducing local changes.

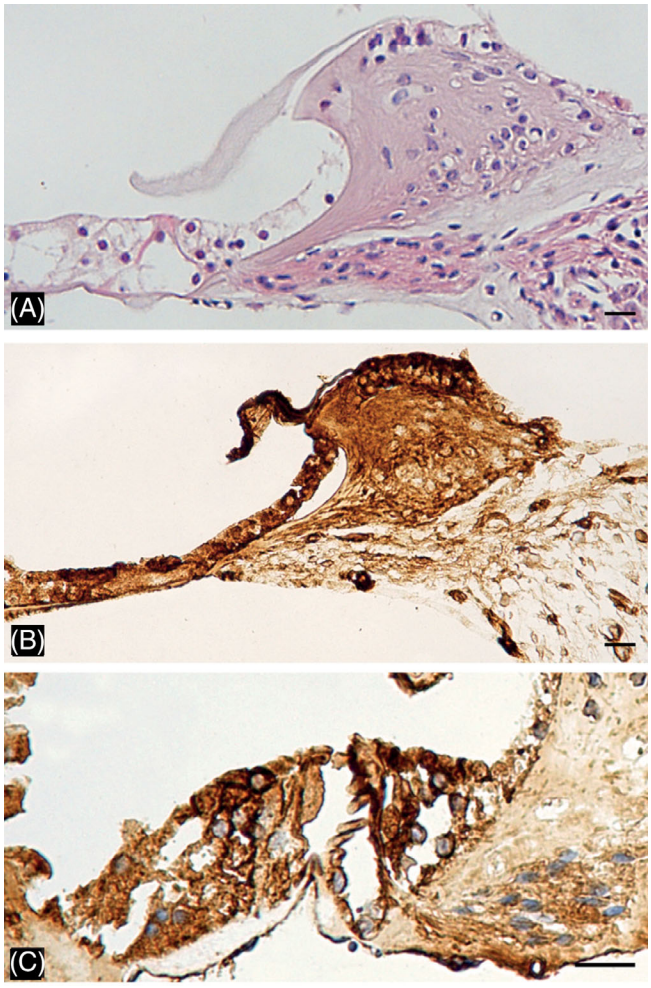

FIGURE 1 Mesenchymal stem cell treatment promotes cochlear regeneration in a mouse model of hearing loss. A, Section of organ of Corti (OC) from a control mouse stained with hematoxylin–eosin showing a healthy, intact OC. B, Section of OC from a kanamycin-treated mouse stained with *Lycopersicon esculentum* agglutinin (LEA) showing severe degeneration of the OC. C, Section of OC from a kanamycin-treated mouse 30 days following mesenchymal stem cell injection. The basilar membrane, support cells, hair cells, and overall OC morphology were similar to that of control mice, indicating that mesenchymal stem cell treatment promoted tissue regeneration[52]

1.7 | Clinical data supporting autologous cellular therapies for TBI and SNHL

Excitingly, the use of progenitor cell therapies in humans in early clinical studies replicates the improved outcomes in TBI and SNHL seen in laboratory models. In one study, 10 children from 5 to 14 years of age were treated using bone marrow mononuclear cells obtained from autologous bone marrow following severe acute traumatic brain injury. Subjects presented with a postresuscitation Glasgow Coma Score between 5 and 8, were treated within 48 hours of injury and were followed for 12 months. All patients survived and no infusion related toxicities were reported. In this study, researchers sought to assess whether progenitor cell therapies might mitigate loss of brain volume, as loss of brain volume correlates with neuropsychological outcomes. MRI imaging was therefore conducted to assess changes in gray matter, white matter and CSF volumes. In this study, patients showed no global brain volume loss from the time of injury to 6 months postinjury, suggesting that progenitor cell treatment helps preserve brain volume following TBI (Figure 2). GOSs obtained 6 months after injury showed 70% of subjects with good outcomes and 30% with moderate to severe disability.[111] A possible explanation for the preservation of brain parenchymal volume postprogenitor cell treatment is a reduction in the severity of the post-TBI immune response.

In addition to preserving brain parenchymal volume, progenitor cell treatment appears to reduce the intensity of treatment required following severe pediatric TBI as measured using the Pediatric Intensity Level of Therapy (PILOT) scale. Using this scale to reanalyze outcomes of the subjects treated in the above-mentioned pediatric TBI study,[111] PILOT scores were significantly reduced beginning 24 hours after injury through 7 days postinjury in treated subjects. The duration of intracranial pressure monitoring was reduced from 15.6 to 8.2 days in age matched controls compared with treated subjects.[129] ICP monitoring is typically discontinued once ICP returns to a normal pressure range and the subjects GCS and neurological exam improve to allow for meaningful bedside assessment. The most reasonable explanation for the reduced duration of elevated ICP postprogenitor cell treatment is a stabilization of the BBB and a reduction in post-TBI brain swelling.

Cord blood-derived stem cells have also shown promise in treating SNHL which arises because of a genetic syndrome. In a retrospective review of patients with mucopolysaccharidosis (MPS) who underwent allogenic hUCB bone marrow transplantation following myeloablation, DaCosta et al reported audiologic outcomes.[130] The MPSs are a collection of diseases resulting from deficiencies in enzymes responsible for the breakdown of glycosoaminoglycosides (GAGs). The progressive buildup of GAGs in cells causes tissue and organ injury, and most patients with MPS present with a mixed hearing loss. While the exact etiology of the MPS associated SNHL is not clear, the only treatment that demonstrates long-term metabolic correction and neurocognitive improvement in MPS is hematopoietic stem cell transplantation.[131,132] In Da Costa et al's series, patients were treated with allogenic stem cells which were free from any MPS mutations.[130] Twenty of 30 patients experienced an improvement in sensorineural hearing and ABR click threshold improved by an average of 19 dB. Children treated before 25 months of age experienced a more significant improvement in SNHL than those treated later. While this retrospective study does not provide mechanistic insight into how these improvements might arise, it is plausible that the transplanted, nonmutant stem cells functioned as an enzyme replacement therapy and thereby contributed to GAG breakdown.

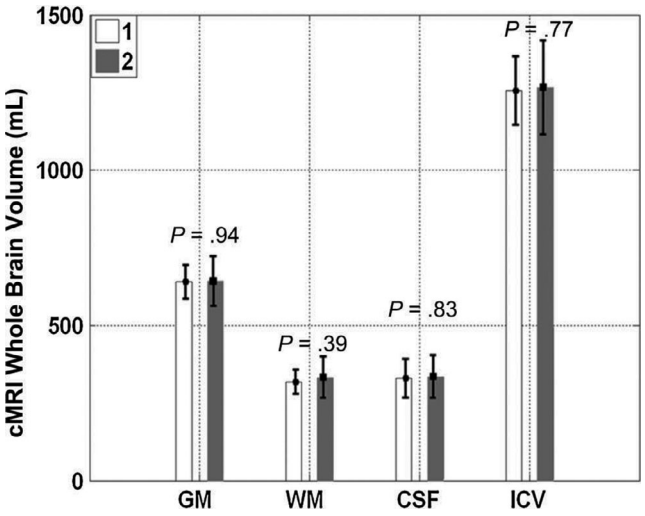

FIGURE 2 Pediatric traumatic brain injury (TBI) patients treated with mesenchymal progenitor cells (MPCs) exhibited no loss in brain volume at 6 months following injury. Typically, after TBI, there is progressive loss of gray and white matter with an associated increase in CSF volumes. This was not observed in pediatric TBI patients following MPC treatment. Magnetic resonance imaging was used to measure the volume of gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and intracranial volume (ICV) immediately following injury and again at 6 months (scan 2) post-TBI and MPC treatment. By 6 months following injury, there was no observed decrease in brain volume or increase in CSF volume[111]

In our study, 11 children with acquired SNHL aged 6 months to 6 years were treated with autologous hUCB cells delivered intravenously. The subjects' SNHL was classified as moderate to severe and the cell dose ranged from 8 to 30 million cells/kg of body weight. After treatment, subjects were followed for 12 months. A statistically significant improvement in ABR thresholds was found across the treatment population. (Figure 3) When present, the ABR improvements were identified at the one-month post-treatment evaluation and were durable throughout the follow-up period. Responding subjects received a cell dose of at least 15 million cells/kg. There was a trend toward improvement in the conduction velocity of the eighth cranial nerve in responding subjects. 3-Tesla MRIs with diffusion tensor imaging (DTI) were obtained before and 12 months post-treatment. These demonstrated a trend toward improvement in fractional anisotropy (FA) a measure of white matter tract integrity along the auditory pathways. The improvement in FA was most evident in the primary auditory cortex also known as Heschl's gyrus (Figure 4).[26] A possible explanation for improved ABR thresholds is replacement of

cochlear hair cells and a possible explanation for improved eighth cranial nerve conduction velocity is repair of the spiral ganglion, though neither has been demonstrated experimentally. The MRI white matter tract changes in FA may be the result of improved auditory input but could also represent a broader repair of the central nervous system substrates for hearing.

These data point to progenitor cells as an exciting therapeutic candidate for two distinct and challenging to treat neurological diseases. In both cases, progenitor cells do not directly repair or form part of the damaged tissue, pointing toward a broader systemic or environmental mechanism.

2 | POSSIBLE MECHANISMS OF PROGENITOR CELL ACTION

Although it remains unknown how progenitor cell treatment might achieve these improved neurological outcomes, MPCs possess many properties by which they could alter the response to injury in the CNS. The definition of MPCs, however, encapsulates a relatively broad range of cells. MPC, as defined by the International Society for Cell Therapy, includes any mesodermal lineage, nonhematopoietic stem cell possessing a specific repertoire of cell surface markers (CD73, CD90, and CD105 positive and CD45, CD34, CD14/11b, CD19/CD20/CD79α, and HLA-DR negative). While MPCs were originally identified in bone marrow tissues, MPCs have been identified and isolated from tissues as diverse as umbilical cord blood, adipose tissue and dental pulp.[1,133] Most therapeutic work has, however, focused on progenitor cells derived from hUCB or bone marrow.

2.1 | Immunomodulatory effects of MPCs

Human MPCs have potent immunomodulatory properties (For a detailed review of the immune modulatory properties of MPCs, see References 133, 134). The therapeutic effects of MPCs are at least in part attributable to the secretion of factors with paracrine effects.[134] They can support the maturation and proliferation of multipotent hematopoietic cells, migrating to areas of tissue injury and recruiting tissue-specific progenitor cells.[135] Human MPCs can regulate the immune response through the secretion of immunomodulatory cytokines. MPCs also release microvesicles containing coding and noncoding RNAs, enzymes, growth factors and other bioactive molecules.[136] When exposed to proinflammatory stimuli, MPCs secrete molecules that can alter both the innate and adaptive immune responses.[137] MPCs also release factors that can inhibit the maturation of monocytes and antigen-presenting dendritic cells[138] as well as promote a shift from the M1 to the M2 phenotype for macrophages.[139] These factors can also inhibit the proliferation and activation of B and T lymphocytes[140] and promote the expansion of regulatory T lymphocytes.[133,141] As the immune system serves such a central role in the CNS response to injury, the immune modulatory

Test/Ear	FREQUENCY (Hz)	BASELINE (dB)	1 MONTH AFTER Treatment (dB)	6 MONTHS AFTER Treatment (dB)	1 YEAR AFTER Treatment(dB)	CHANGE FROM BASELINE (dB) 1/6/12 MONTHS
ABR/AC/left	2000	85	75	80	80	-10/-5/-5
ABR/AC/right	2000	95	80	70	70	-15/-25/-25
ABR/TB/left	500	85	85	80	80	0/-5/-5
ABR/TB/right	500	90	70	60	60	-20/-30/-30
ABR/TB/left	1000	85	75	80	70	-10/-5/-15
ABR/TB/right	1000	80	70	60	65	-10/-20/-15
ABR/TB/left	2000	90	80	85	85	-10/-5/-5
ABR/TB/right	2000	80	80	85	80	0/5/0
ABR/TB/left	4000	100	95	100	95	-5/0/-5
ABR/TB/right	4000	90	90	90	90	0/0/0

FIGURE 3 Significant improvements in auditory brainstem response (ABR) thresholds were observed in sensorineural hearing loss (SNHL) patients following human umbilical cord blood (hUCB) treatment. Representative ABR thresholds of a responding subject before (baseline) and at 1, 6, and 12 months after hUCB treatment. ABR was measured in the left and right ears in response to air conduction clicks (AC) or tone burst (BR) at a range of frequencies. A greater than 5 dB reduction in ABR threshold is considered a significant improvement. Significant ABR improvements were typically observed at 1 month following treatment, and these improvements were durable through the 12-month follow-up period
Source: Reprinted with permission, *Journal of Audiology and Otology*[26]

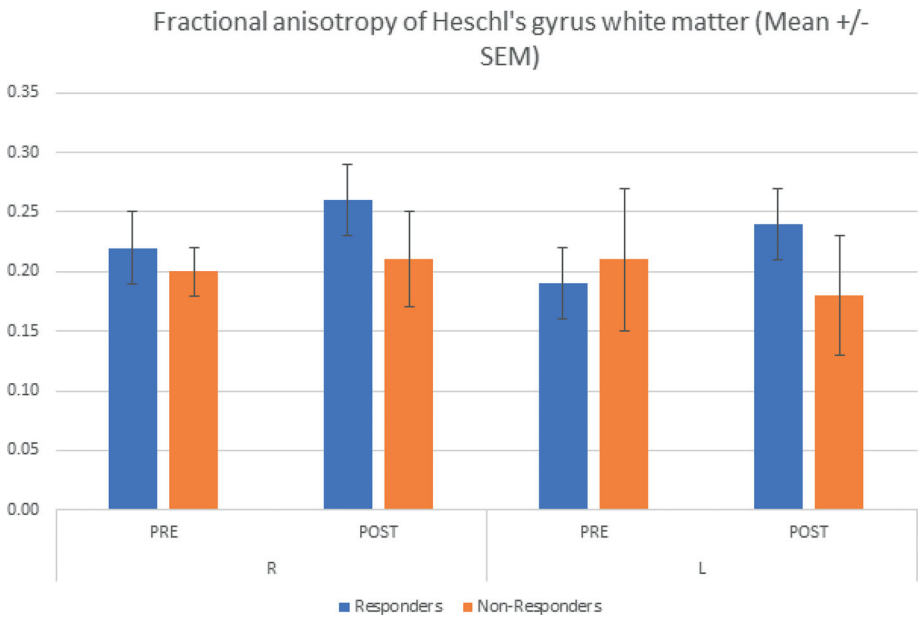

FIGURE 4 Measures of white matter tract integrity correlate with improvements in auditory brainstem response (ABR) threshold in sensorineural hearing loss (SNHL) patients following mesenchymal progenitor cell (MPC) treatment. Mean fractional anisotropy (FA), a measure of white matter integrity, was measured in the left (L) and right Herschel's gyrus before (pre) and after (post) human umbilical cord blood (hUCB) treatment. Patients who showed improved hearing function following treatment (responders), as measured by ABR threshold, exhibited an increase in FA. This increase was not observed in patients who did not exhibit improved ABR thresholds (nonresponders)
Source: Reprinted with permission, *Journal of Audiology and Otology*[26]

and anti-inflammatory properties of MPCs likely have a role in the observed therapeutic outcomes. It is plausible that MPCs could limit neuronal cell death caused by immune cells, such as phagoptosis, and thereby preserve neurons and their functions.

2.2 | MPC-derived exosomes

Exosomes are nanovesicles involved in intercellular communication.

Although most intravenously administered MPCs do not cross the BBB or BLB, they actively secrete exosomes which have been shown to alter macrophage and microglial phenotype attenuating inflammation.[142] Exosomes can penetrate both the BBB and BLB.[143,144] They are taken up by activated primary leukocyte subpopulations and appear to achieve an anti-inflammatory effect. In one study, splenocytes treated with MPC-derived extracellular vesicles exhibited reduced induction of TNF-α and interferon-γ in response to lipopolysaccharide-induced activation. This effect appeared to be downstream of the COX2/PGE_2 pathway.[142] It is possible that over time, the MPC exosome output could change in response to the changing microenvironments that the MPCs reach after delivery, adjusting to the immune response as it develops following injury.

Following experimental TBI there is an increase in the amount of microRNA-124 in extracellular vesicles produced by microglia. This has been associated with decreased inflammation and improved neuronal regrowth after injury. In an experimental rodent TBI system microRNA-124 promoted M2 (alternatively activated, anti-inflammatory) polarization of microglia and exhibited an anti-inflammatory effect by suppressing mTOR signaling. Once taken up by neurons, microRNA-124 also resulted an increase in both neurite branch number and neurite length. There was an associated decrease in the expression of RhoA and the neurodegenerative proteins Aβ-peptide and p-Tau.[145,146]

Less in known about inner ear exosomes. Exosomes have been isolated from rat cochlear cell culture preparations. Following treatment with gentamycin or cisplatin, the animals experienced ototoxic stress and profound hair cell loss. Exosomes isolated from the treatment group were found to have a strikingly different protein profile than those of exosomes isolated from control inner ear cell cultures. Proteins associated with SNHL including Tmem33,[147] Pgm 1,[148] and Cct8 were enriched in exosomes from treated mice but not in control exosomes. The authors suggest that exosomes might serve as biomarkers for cochlear health.[149] Cochlear exosomes could also be used to evaluate the mechanism and efficacy of SNHL treatments including progenitor cells (including MPCs) and exosomes derived from MPCs and other progenitor cell populations.

2.3 | BBB and BLB repair/stabilization

In both TBI and SNHL the integrity of the BBB and BLB are compromised following injury. This leakiness facilitates infiltration of monocyte/macrophages, albumen and the development of post-TBI brain edema and retraction of the vasculature of the stria vascularis. In TBI, progenitor cell treatment has been shown to stabilize the BBB and reduce the duration of post-TBI edema.[42,48,111,142] In the reanalysis of the phase 1 data collected by Cox, Baumgartner et al, treating severe acute pediatric TBI, Liao et al demonstrated a significant reduction in the duration of ICP monitoring and treatment required in patients treated with progenitor cells compared with controls.[111,129] Following severe TBI, ICP monitoring is used until the ICP returns to a normal range. Progenitor cell treated patients, therefore, exhibited recovery from TBI-induced high ICP. Though not conclusively demonstrated with thorough neuroradiology, these findings hint that progenitor cell therapy could reduce post-TBI brain edema.

Following acoustic trauma, there is retraction of the vasculature of the stria vascularis and creation of hypoxia in the inner ear.[150] In experimental SNHL progenitor cell treatment has been shown to stabilize the BLB and promote repair and revascularization of the BLB.[110]

2.4 | Antiapoptosis

In the year following TBI in children, there is typically a 11%-15% loss of brain parenchymal volume.[10-15] The secondary injury which follows TBI is a complicated process characterized by abnormal mitochondrial activity, oxidative stress and the release of inflammatory cytokine that promote caspase dependent apoptosis of neurons.[151-153] In addition, the process of autophagy by which proteins and organelles are degraded by lysosomes in response to stress, can occur. Autophagy is increased following TBI.[154,155] In a model of hypoxic ischemic encephalopathy, hUCB derived mesenchymal stem cells inhibited apoptosis.[156] Conditioned media obtained from hUCB cell culture (containing exosomes and high levels of IL-6) exerted a protective effect on neonatal porcine islet cell clusters by inhibiting apoptosis and increasing autophagic activity.[157] Apoptosis and autophagy have a complex and dynamic relationship.[158] In Cox's phase 1 trial, there was a relative preservation of brain volume in the 6 months following treatment.[111] This likely represents a disruption of the post-TBI secondary injury associated neuronal apoptotic process.

Following acoustic trauma hair cell damage, reactive oxygen species accumulate stimulating intracellular stress pathways resulting in programmed or necrotic cell death.[159] The capsase mediated cell death pathway has been implicated in programmed cell death of hair cells.[160-162] While TTS-inducing noise levels upregulate antiapoptotic protein Bcl-xl in hair cells, PTS inducing noise levels upregulate proapoptotic protein Bak.[163,164] The pathophysiologic changes caused by acoustic overstimulation are not limited to the inner ear. After exposure to a single ototoxic insult, analysis of the central auditory pathway reveals apoptosis mediated changes in the dorsal and ventral cochlear nuclei, the central nucleus of the inferior colliculus, the dorsal, ventral and medial subdivision of the medial geniculate body and layers I-VI of the primary auditory cortex. Following TTS-inducing noise exposure, a decrease in cell density was seen in the ventral cochlear nucleus. Following PTS-inducing noise exposure, cell density was significantly reduced in all investigated auditory structures, except in layer II of primary auditory cortex.[165] Repeated exposure to ototoxic noise caused sustained elevation in terminal deoxynucleotidyl transferase dUTP neck end labeling (TUNEL) in the dorsal, medial and ventral medial geniculate body and layers 1 and 3 of primary auditory cortex over a 14-day study period.[166] In Cox's phase 1 trial the acute use of progenitor cell treatment may have induced a long lasting antiapoptotic effect on the brain diffusely.[111] Given the extensive intracranial apoptotic effects of ototoxic trauma, this progenitor cell therapy mediated effect may be effective in the acute management of the central nervous system changes following ototoxic noise exposure.

2.5 | Epigenetic modification

Following TBI, central nervous system epigenetic modification including DNA methylation, chromatin post-translational modification and micro-RNA regulation of gene expression have been identified.[167] These epigenetic changes can be either rapid and transient or long lasting and even heritable.[168] The distribution of post-TBI epigenetic changes is regionally, cell subtype and gene specific. Following experimental blast injury, differences in the expression of enzymes controlling DNA methylation including DNA methyltransferase enzymes (DNMTs), ten-eleven translocation enzymes (TETs), and thymidine-DNA glycosylase (TDG) were identified. The changes in enzyme expression were more pronounced in the hippocampus than prefrontal cortex-correlating with short-term memory deficits following TBI.[169] Following experimental cortical contusion, global hypomethylation was found in regions of necrosis 1 day after injury and in a delayed fashion (day 2 postinjury) in surrounding areas. A more detailed analysis found that hypomethylation occurred primarily in activated microglia/macrophages.[170] DNA methylation alterations have been found in genes and genetic pathways associated with neuropsychiatric changes commonly associated with TBI. Interestingly, genes associated with sleep regulation including Aanat, Nos 1 Il 1r1, Homer 1, Chrna 3, and Per 3 were all found to have increased DNA methylation and decreased gene expression in blast exposed animals.[171] Altered sleep hygiene is common following TBI.[172,173]

Along with the above-mentioned post-TBI epigenetic changes in nuclear DNA, epigenetic modification of mitochondrial DNA has also been identified following TBI. An isoform of DNMT named mitochondrial DNMT1 has been shown to contain mitochondrial targeting sequences and overexpression of DNMT1 causes marked changes in mitochondrial DNA methylation.[174] Another DNMT variant, DNMT3A, has been associated with methylation of neuron mitochondrial DNA.[175,176] It is conceivable that epigenetic modification of mitochondrial gene expression could impact post-TBI bioenergetics and affect outcome.[167]

Preliminary studies aimed at epigenomic modulation following TBI have generated interesting data. Female Yorkshire Swine underwent controlled cortical contusion followed by 2 hours of experimental hemorrhagic shock. Animals were resuscitated with either artificial colloid or artificial colloid plus high dose valproic acid (VPA). VPA is a histone deacetylase inhibitor. VPA treated animals had significant down-regulation of the complement system, natural killer cell communication and dendritic cell maturation. VPA treatment was also shown to down regulate nuclear fator-κB (NF-κB)-mediated cytokine production including TYROBP, TREM2, CCR1, and Il-1β. The authors concluded that the addition of the epigenetic modulator VPA to their resuscitation protocol significantly altered the expression of post-TBI inflammatory pathways.[177]

In mammals, most central nervous system regions and most sensory end-organs, including the organ of Corti, do not generate new neurons or sensory receptor cells after birth. Many nonmammal vertebrates have some regenerative capacity in these same structures,

often with very similar embryology and genetic regulation.[178] In regenerative species, new hair cells are generated in the auditory sensory epithelia through proliferation and differentiation of progenitor cells.[179] The progenitor cells are thought to be nonsensory support cells that typically surround the hair cells of the sensory epithelia. Following hair cell damage, two processes leading to hair cell replacement have been identified: proliferative regeneration and direct transdifferentiation. In proliferative regeneration, the support cells reenter the cell cycle and divide asymmetrically during mitosis giving rise to new hair cells and support cells.[180-190] In direct transdifferentiation, the nonsensory support cells have been shown to spontaneously convert into new hair cells through a process which is a phenotypic conversion of support cells to hair cells without cell cycle reentry.[183-186,191] Proliferative regeneration has the advantage of replenishing the support cell population, while direct transdifferentiation depletes the already diminished support cell population in the injured cochlea. It is, yet, unknown why regenerative species possess this capacity for self-renewal that is absent in mammals. Gene expression differences between regenerative and nonregenerative species may be responsible for this disparity, and a plausible cause for this divergence in gene expression may be epigenetic modifications.[180,181]

In support of this hypothesis, drugs which target proteins involved in epigenetic modifications have shown promise in improving cochlear regeneration in animal models and human clinical trials. Histone deacetylases (HDACs) are proteins which catalyze acetyl group removal from histone proteins and are therefore generally involved in promoting heterochromatin formation and reducing gene expression at a given locus. One study investigated the involvement of HDACs in an animal model of the cochlea, the zebrafish lateral line system. Studies using the HDAC inhibitors valproic acid and trichostatin A successfully facilitated hair cell regeneration in zebrafish larvae whose lateral line hair cells were damaged using neomycin.[192,193] This approach has furthermore been tested in a clinical trial evaluating the use of the small molecule HDAC inhibitors delivered to the middle ear in the treatment of SNHL. HDAC inhibiting drugs were suspended in a gel preparation introduced into the middle ear. The drugs diffused through the round window to the base of the cochlea. Treated subjects achieved a 10-dB improvement in ABR threshold at high frequencies as well as an improvement in speech discrimination scores. Taken together, these results suggest that hair cell replacement achieved through epigenetic modification may be possible in the human cochlea. (Will McClean, Frequency Therapeutics, platform presentation, New York Academy of Sciences, Symposium on Hearing Restoration and Hair Cell Regeneration, October 8, 2019.) This approach may allow support cells to return to the cell cycle and asymmetrically divide to generate new hair cells and replacement support cells and points to a role for epigenetics in the discrepancy between species with regenerative cochlea and those without.

Epigenetic changes following ototoxic injury have also been studied in cochlear cell populations. Using genomic analysis, 120 genes and 621 reactions were identified following ototoxic acoustic trauma. Pathways involved in signal transduction, the immune system and cellular response to stress were most prevalent.[194] Further studies analyzed the role of Toll-like receptor pathway genes following acoustic trauma and the role of these gene products in sensory hair cell damage.[195,196] Another study used next-generation RNA sequencing to compare the entire transcriptome of normal and ototoxic injured cochlear sensory epithelium in rats. This analysis suggested that acoustic trauma leads to changes in genes associated with the innate immune response, particularly immune system associated complement proteins.[197] These genes and pathways could also be examined after progenitor cell treatment to evaluate possible epigenetic effects of progenitor cell treatment.

Given the promise of HDAC inhibitors in treating TBI and SNHL, it is worth considering whether progenitor cell treatment might act on the same pathways. Exosomes, produced by progenitor cell populations, are an established mechanism of cell-to cell communication.[198] While direct evidence of progenitor cell mediated epigenetic modification in TBI and SNHL has not been reported to date, exosome/microvesicle-mediated epigenetic reprogramming of cells in the tumor microenvironment has been reported by cancer researchers. Microvesicles derived from endothelial progenitor cells were able to activate an angiogenic program in quiescent endothelial cells adjacent to the tumor, facilitating angiogenesis and tumor invasion.[199] In DaCosta's mucopolysaccharidosis series, the beneficial effect of bone marrow transplantation was more pronounced for children treated by 25 months of age[130] and in our series all responding subjects were below 43 months of age.[26] It is possible that progenitor cell treatment acted through epigenetic modification during the relatively more euchromatic critical period. It is possible that the combination of HDAC inhibitors and progenitor cell treatment might be beneficial in the treatment of TBI and SNHL.

2.6 | Inflammasome modification

A recent study implicate the nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome-mediated inflammatory response as a prominent contributor to the pathophysiologic processes following TBI.[200-202] Additional studies have reported that small molecules and microRNAs can ameliorate the post-TBI inflammasome-mediated response.[203] Although no evaluation of the effect of progenitor cell treatment on this immune regulatory machinery has yet been published, it is an interesting area for further study.

3 | FUTURE DIRECTIONS

The current methodologies and outcome measures are satisfactory to advance SNHL clinical studies to phase 2/3 trials. Improved sensitivity of ABR recordings during the first 2 or 3 milliseconds of analysis may shed light and help segment those factors of sensory vs neural regenerated response components.[26]

For TBI, the extreme variability of the patient population and relative insensitivity of existing classification tools requires a new

approach.[16] In his seminal 1948 monograph "Restoration of Function After Brain Injury," A.R. Luria described his experience treating Russian Soldiers who sustained head injuries during the second World War. Luria found that for a variety of higher cortical functions, the degree and speed of recovery of function was inversely related to the extent of nervous system injury that his patients had sustained.[204] With Luria's work in mind, we suggest that changes in brain volume after injury be used as a surrogate marker for treatment efficacy in pediatric TBI, as others are doing.[205] Advances in neuroimaging software that allow serial volumetric imaging should allow a more quantitative and detailed analysis of the initial TBI injury and volume changes over time with and without progenitor cell treatment.[201] This approach is already being used in the evaluation of post-traumatic epilepsy[206,207] and Alzheimer's disease.[208] Resting state blood oxygen level dependent (BOLD) sequences and functional MRI (fMRI) have been used to analyze connectivity between various brain regions. The emergence of improved artificial intelligence (AI) MRI based connectome analysis could be developed to allow for initial patient classification as well as long-term outcome evaluation.[209]

Finally, newer MRI approaches which allow imaging of inflammation could provide insights into the course and distribution of inflammation throughout the initial and secondary injuries with and without progenitor cell treatment in both TBI and SNHL.[210] This type of imaging could also reveal differences between responders and nonresponders to progenitor cell treatment and possibly inform basic science attempts to define mechanism(s) of action.

4 | CONCLUSION

Progenitor cell therapy has already shown promise treating acquired injuries to the central nervous system and inner ear.[26,111,115] This is a particularly opportune time to leverage our evolving understanding of the neuroimmune response, exosome trafficking, BLB and BBB stabilization, apoptotic pathways and epigenetic modification, to better understand these two related conditions. Advances in neuroimaging may also allow a more quantitative analysis of changes in brain volume and connectivity in the progression and treatment of acquired nervous system injury. With this increased understanding, our ability to apply and understand progenitor cell treatment-based approaches to these devastating nervous system injuries should only improve.

ACKNOWLEDGMENT

The authors wish to acknowledge the assistance of Nancy Aldridge and the library staff at Advent Health Orlando for their support in the preparation of this manuscript.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

J.E.B.: conception and design, manuscript writing, data analysis and interpretation, final approval of manuscript; L.S.B., M.E.B.: conception and design, manuscript writing, final approval of manuscript; E.J.M.: conception and design, data analysis and interpretation, final approval of manuscript; S.A.M.: administrative support, final approval of manuscript; M.D.S.: conception and design, final approval of manuscript; D.R.S.: data analysis and interpretation, final approval of manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Baumgartner JE, Baumgartner LS, Baumgartner ME, et al. Progenitor cell therapy for acquired pediatric nervous system injury: Traumatic brain injury and acquired sensorineural hearing loss. *STEM CELLS Transl Med*. 2021;10:164–180. https://doi.org/10.1002/sctm.20-0026