INVITED REVIEW

Brain injury and neural stem cells

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Abstract
Many therapies with potential for treatment of brain injury have been investigated. Few types of cells have spurred as much interest and excitement as stem cells over the past few decades. The multipotentiality and self-renewing characteristics of stem cells confer upon them the capability to regenerate lost tissue in ischemic or degenerative conditions as well as trauma. While stem cells have not yet proven to be clinically effective in many such conditions as was once hoped, they have demonstrated some effects that could be manipulated for clinical benefit. The various types of stem cells have similar characteristics, and largely differ in terms of origin; those that have differentiated to some extent may exhibit limited capability in differentiation potential. Stem cells can aid in decreasing lesion size and improving function following brain injury.

Key Words: *brain injury; brain trauma; infarction; ischemia; neural stem cells; neuronal regeneration; stroke*

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Introduction
Brain injury is a major cause of injury and death in both the United States and around the world. Many therapies have been investigated for the treatment of brain injury and stroke, and many investigations continue. The properties and characteristics of neural stem cells have been researched, and are being applied in therapeutic measures that could improve patient condition following brain injury.

Neural stem cells (NSCs) are plastic and are involved in creating new connections in adaptation, and in response to injury (Kennea and Mehmet, 2002; Teng et al., 2002; Galli et al., 2003; Imitola et al., 2004). NSCs play a fundamental role in development, and in the ability to respond to stimuli in the environment and injury.

Brain Injury
There are many ways in which the brain can be compromised or injured. Congenital defects such as neural tube defects, and neurodegenerative conditions like Parkinson's disease have dramatic impacts on survival, function, and overall health. Other conditions such as multiple sclerosis and varied infections similarly can have debilitating effects. This section, however, will focus on more acute and vascular processes. Traumatic brain injuries (TBI) are suffered in large numbers annually. It is estimated that approximately 500,000–700,000 children and 2.5 million adults experience TBI each year (Wilde et al., 2012; Li and Liu, 2013; Centers for Disease Control and Prevention, 2015; Dewan et al., 2016; Doan et al., 2016). More than 795,000 people have strokes each year in the United States alone (Centers for Disease Control and Prevention (CDC), 2012). Stroke is one of the leading causes of death and impairment in industrialized countries (Taylor et al., 1996).

Ischemia/Infarction
The brain requires a continuous supply of glucose and oxygen which is provided through the cerebral vasculature. Even though the brain only accounts for about 2% of the total body weight, it consumes approximately 20% of the oxygen pumped through the body. There are many regulatory systems relating to baroreceptors and their pathways controlling vascular dilation, constriction, and overall resistance that maintain relatively constant blood flow to the brain despite changes in blood pressure and intracranial pressure through autoregulation. Being a highly vascular organ, reduction in blood flow to the brain causes interruption of oxidative metabolism and a consequent deprivation of adenosine triphosphate (ATP). The inability of the brain to effectively metabolize substrates other than glucose, and perform glycolysis heighten its dependence on constant blood flow. This loss of ATP and appropriate membrane potential in an ischemic event causes impairment of neuronal function, and eventual cell death. Calcium ions also play a cytotoxic role in ischemic injury. Cells experience an influx of calcium due to the activation of glutamate receptors such as N-methyl-d-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate (KA), or through the opening of other channels, activation of transporters, or release of intracellular calcium stores. This final mechanism is mediated by physical damage to organelles such as the mitochondria or endoplasmic reticulum, or by malfunction of their associated receptors or channels (Szydlowska and Tymianski, 2010). This excessive cytoplasmic calcium leads to the activation of several enzymes and processes that lead to cell death and impair neuronal function (Dirnagl et al., 1999). While calcium ions are required by neurons for proper function and maintenance (Penn and

Loewenstein, 1966), they can be induced to toxic levels by release of the excitatory neurotransmitter, glutamate, due to deficiency of high-energy carrier molecules and substrates needed for energy production (Lucas and Newhouse, 1957; Olney, 1969; Simon et al., 1984; Dirnagl et al., 1999; Orrenius et al., 2003).

It should also be noted that cells are presumed to die by apoptosis as an illustration of secondary injury. This is suggested by the concept of the penumbra, the area of at-risk tissue that can be saved in animal models through the administration of anti-apoptotic agents (Yepes et al., 2000; Nakase et al., 2003; Xu et al., 2003; Lei et al., 2004; Price et al., 2010; Kumar et al., 2015). Damage sustained in the penumbra in ischemic injury results from excitotoxicity as well as indirect mechanisms such as peri-infarct depolarization, inflammation, and/or apoptosis which spread from the point of injury in an expansive manner. Peri-infarct depolarization is the repetitive depolarization of cells in the penumbral region that consumes energy in the face of its deficiency. This type of depolarization has been shown to increase the size of infarcts in animals, and similar electrocorticographic depression in humans indicates that these depolarization events may cause tissue damage in ischemic injury (Mies et al., 1993; Dirnagl et al., 1999; Hartings et al., 2003; Fabricius et al., 2006; Strong et al., 2007).

Inflammation can cause substantial tissue damage throughout the body and the brain. Many pro-inflammatory factors are induced by second messenger systems activated by calcium ions, and oxygen radicals. Some of these include nuclear factor kappa beta (NF-κB), hypoxia-inducible factor 1 (HIF-1), interferon regulatory factor 1 (IRF1), and signal transducer and activator of transcription 3 (Stat3), which upregulate tumor necrosis factor alpha (TNFα), platelet-activating factor (PAF), and interleukin 1 beta (IL-1β) (Astrup et al., 1981; Iijima et al., 1992; Obrenovitch, 1995; Furlan et al., 1996; Read et al., 1998; Dirnagl et al., 1999). Adhesion molecules such as selectins and integrins recruit neutrophils in the inflammatory process, which are followed by macrophages and monocytes (Etzioni, 1996; Iadecola, 1997). In addition to blood-borne inflammatory agents, native neural cells such as astrocytes and microglia also contribute to inflammatory processes following ischemia (Planas et al., 1996; Dirnagl et al., 1999). It has been shown that neutrophils can worsen ischemia by blocking microvasculature, and that inducible toxins like nitric oxide, superoxide, and toxic prostanoids, produced by native cells, cause additional damage (Nogawa et al., 1997; Gong et al., 1998; Zhang et al., 1998).

Cells that are damaged during brain injury by excessive cytoplasmic calcium, reactive oxygen species (ROS), or other mechanisms can continue toward cell death by necrosis or apoptosis. A primary factor contributing to apoptosis is the degree of damage and associated signaling (Loddick and Rothwell, 1996). Necrosis tends to follow the more severe ischemic injuries, but in milder cases, apoptosis can contribute significantly to the overall damage induced in the penumbra (Dirnagl et al., 1999). Ischemia induces increased expression of caspase-encoding genes, which causes cleavage of proteins involved in homeostasis, and the consequent death of cells. Caspases 1 and 3 seem to be particularly involved in programmed cell death in ischemic events; it has been specifically noted that mice without Caspase 1 are resistant to apoptotic ischemic insult (Bruce et al., 1996; Chopp et al., 1996; Baird et al., 1997; Nogawa et al., 1997; Dirnagl et al., 1999). Attenuation of the effects of apoptosis following ischemic injury could potentially reduce damage, and should continue to be explored.

Hemorrhage

While the majority of strokes (87% in the United States) are ischemic, hemorrhagic strokes account for approximately 13% of the total insults, being divided into 10% intracerebral hemorrhage (ICH) and 3% subarachnoid hemorrhage (SAH) (Benjamin et al., 2017). Despite the greater occurrence of ischemic strokes, of the 6.5 million people who died of strokes in 2013, 3.3 million died of ischemic stroke, and 3.2 million died of hemorrhagic stroke (Benjamin et al., 2017). Cerebral hemorrhage includes intraparenchymal, subdural, and epidural bleeds, and has a mortality rate around 50% (Frizzell, 2005). These hemorrhages are typically the result of trauma, but can also occur due to vascular malformations (**Table 1**). It is common to see more rapid progression of symptoms in epidural hematomas, and less rapid progression in subdural hematomas. Also, cerebral hemorrhage events often result from ruptured cerebral arteries. The devastating results of these strokes are often due to their effect on the surrounding tissue. It is not uncommon for pressure to be exerted on sensitive structures, or for tissue adjacent to the initial clot to become necrotic even following its resolution and reduction in size (Messing, 2003). Surrounding vessels can be irritated upon contact with hemorrhagic blood, causing vasospasm. Vascular malformations are also a reported cause of intracranial hemorrhage (Malik et al., 1988; Brouillard and Vikkula, 2007; Sayama et al., 2009).

Upon cerebral artery rupture, blood can spread in the brain and subdural space, depending on its location (**Table 1**). If blood moves into the ventricles, there is an increased risk of mortality (Smith et al., 2005). However, hemorrhages of hypertensive origin typically present with a rapid onset of symptoms, whereas those caused or triggered by anticoagulant therapy often have a much slower onset (Frizzell, 2005). The blood from acute hemorrhage can exert pressure on the surrounding tissue which leads to ischemic injury and ensuing edema and necrosis if not managed. Around 48 hours following the initial injury, macrophages are onsite phagocytizing both blood and necrotic tissue. This action and the corresponding inflammation cause cavitation of the brain tissue. Astrocytes are recruited to reside in the cavity, and initiate angiogenesis (Frizzell, 2005; Kumar et al., 2015).

Brain trauma synopsis

Beyond ischemic injury, there are varying gross and microscopic observations that can be made in different types of TBI (**Table 2**). Open injuries are those involving penetration

Table 1 Patterns of vascular injury based on location, etiology and pathological features

Location	Common Etiology	Features
Epidural space	Trauma	Often associated with skull fracture; rapidly developing neurological symptoms
Subdural space	Trauma	Can occur with mild insult; slowly developing symptoms
Subarachnoid space	Arteriovenous malformation and aneurysm	Severe headache with sudden onset, often accompanied by rapidly developing neurological deficit; potential for secondary injury and vasospasm
	Trauma	Usually involves capillary rupture
Intraparenchymal	Trauma	Contusions largely cause involvement of the crests of gyri that contact the inner surface of the skull
	Hemorrhagic event following ischemic infarction	Petechial hemorrhages in an area of brain that was previously ischemic; may present with cortical ribboning on magnetic resonance imaging (MRI)
	Cerebral amyloid angiopathy	Hemorrhage of the cerebral cortex, often with extension into the subarachnoid space
	Hypertension	Primarily affects the brainstem, thalamus, basal ganglia, or deep white matter, and may involve the ventricular system
	Tumors	Often associated with gliomas or metastases such as melanoma, choriocarcinoma, or renal cell carcinoma

Table 2 The types, etiology and features of strokes and ischemia

	Type	Etiology	Features
Strokes/ ischemia, hypertension	Global cerebral ischemia	Cardiac arrest, shock, severe hypotension	Range of severity may result in anything from temporary confused state to brain death; neurons most sensitive to ischemia, but glial cells also vulnerable
	Focal cerebral ischemia	Embolus from other location, in-situ thrombus, vasculitides	Commonly associated with atherosclerosis and plaque rupture; collateral flow exists through the Circle of Willis, and some may reach distal branches of the anterior, middle, and posterior cerebral arteries along the surface of the brain, but deep penetrating branches are largely devoid of anastomoses
	Lacunar infarcts	Hypertension	Cavitary infarcts less than 15 mm wide which may occur in the thalamus, lenticular nucleus, deep white matter, internal capsule, caudate nucleus, and pons
	Slit hemorrhages	Hypertension	Hemorrhage of small penetrating vessels, later resorbed to leave behind focal tissue destruction, pigment-laden macrophages, and gliosis
	Hypertensive encephalopathy	Malignant hypertension	Increased intracranial pressure causes cerebral damage, and may cause transtentorial or tonsillar herniation; dysfunction may include headaches, vomiting, confusion, convulsions, and coma
	Intraparenchymal hemorrhage	Hypertension, cerebral amyloid angiography, vascular malformations, aneurysms, vasculitis, neoplasms, coagulation disorders	Hypertension is most commonly associated with deep parenchymal hemorrhages; cerebral amyloid angiography is most commonly associated with lobar hemorrhages; in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a mutation in neurogenic locus notch homolog protein 3 (NOTCH3) causes vascular smooth muscle dysfunction
	Subarachnoid hemorrhage	Ruptured berry aneurysms, trauma, or other extensions of hemorrhaging sites	Can be accompanied by vasospasm causing additional ischemic injury; meningeal fibrosis and scarring can also cause obstruction of cerebrospinal fluid flow
	Vascular malformations	Defect in vasculogenesis, angiogenesis, or lymphangiogenesis due to somatic mutation or in conjunction with an inherited phenotype	Arteriovenous malformations and cavernous malformations pose risk of hemorrhage and neurological symptoms; capillary telangiectasias are clinically benign; venous angiomas are largely incidental, but may be associated with ischemic and hemorrhagic injury

of the scalp and skull by bullets or sharp objects, or skull fracture with associated skin laceration (Parikh et al., 2007). Closed injuries do not involve penetration, but rapid acceleration or deceleration of the brain, typically due to striking or shaking of the head. This can cause damage in coup/contrecoup patterns or diffusely, with the anterior tips of the frontal and temporal lobes being particularly susceptible. This often leads to shearing or tearing of axons or vasculature.

Concussion is a temporary and reversible alteration in mental status. Concussion results in temporary disability and deficit in aspects such as memory, and may cause nausea, dizziness, headache, and other symptoms (Parikh et al., 2007). While concussion alone has not been shown to cause permanent neurological damage, concussive injuries can be accompanied by axonal injury or progressive tauopathy which may have more lasting effects, particularly if multiple injuries are sustained (McCrea et al., 2003; Parikh et al., 2007; McKee et al., 2009).

Diffuse axonal injury (DAI) results from rapid deceleration of the head which causes generalized, damage to axons and their myelin sheaths. Petechial hemorrhages in the white matter are often observable on magnetic resonance imaging (MRI) following DAI, and may rarely be visualized using computed tomography (CT) imaging. DAI can be associated with transient alteration in mental status, and can have dangerous repercussions in cases in which increased

intracranial pressure ensues (Gentry et al., 1988a, b; Blumbergs et al., 1989; Parikh et al., 2007).

Contusions of the brain are associated with both open and closed injuries, and can have varying effects depending on their size and location. The contusions that involve more tissue are more likely to cause significant edema and increased intracranial pressure, with increased likelihood of neurological deficit (Adams et al., 1985; Parikh et al., 2007).

Skull fractures are often classified as linear, depressed, or comminuted. They range in severity from posing great risk of mortality, to being relatively benign. Depressed fractures are often the most dangerous as they are associated with the greatest risk of dural tear and brain damage. In most cases, linear skull fractures do not pose a large risk unless there is underlying neurological damage or the affected individual is particularly susceptible, usually due to young age (Parikh et al., 2007).

The damage in TBI can occur from the direct tissue injury, or from secondary events following the initial insult (DeWitt and Prough, 2003; Nortje and Menon, 2004). As previously discussed, these secondary events largely result from mass effect due to edema or hemorrhage, increased intracranial pressure, or ischemia. Secondary injury following brain trauma has a particular impact on the hippocampus; hippocampal injuries are typically associated with memory and learning disabilities (Sun, 2014).

Regenerative Changes Associated with Brain Injury

Glial cells are involved in the formation of scars in neural tissue following damage. While astrogliosis, other forms of glial scarring, and various obstructive processes can complicate the healing process, or reduce neural function, much of the disability following brain injury results from a loss of tissue or cells. This is well illustrated by cavitation and other signs of neuronal and glial loss after injury. The progression from intraparenchymal hemorrhage, to necrosis, to cavitation has been observed in animal models, and has also been demonstrated in pathological studies of humans (Edward Dixon et al., 1991; Rosenfeld et al., 2013). Reactive astrogliosis is the response of astrocytes to CNS insult or injury; this could include anything from trauma or ischemia, to infection or degenerative conditions. In this process, alterations in the gene expression and morphology of astroctyes, and the formation of glial scar tissue is prevalent (Eddleston and Mucke, 1993; Pekny and Nilsson, 2005; Sofroniew, 2005, 2009; Maragakis and Rothstein, 2006; Correa-Cerro and Mandell, 2007). In reactive astrogliosis, it has been noted that astrocytes can suffer loss of function due to injury, but may also exhibit abnormal gain of function (Sofroniew, 2009). Both effects could contribute to deleterious disease processes or neural deficit following the initial injury.

The loss of neurons and glia in the process of brain injury can have devastating effects. It has been shown that NSCs or multipotent neural progenitor cells continue to be produced in the subventricular zone (SVZ), and the dentate gyrus of the hippocampus throughout the life of an animal (Lois and Alvarez-Buylla, 1993; Gage et al., 1998; Sun, 2014). Recently, there has been much interest in the therapeutic potential of NSCs or neuroepithelial cells. It has been noted that the brain can replenish or regenerate lost neurons through the division and differentiation of NSCs in response to neuronal damage or death; this cell proliferation and neurogenesis increases in response to trauma (Sun, 2014).

NSCs

Neuroepithelial cells are originally derived from the neural plate that forms along the midline of the embryo, and continues to fold into the neural tube (Clarke, 2003). Neuroepithelial cells then begin to differentiate, either into neurons or glial cells. Differentiation patterning is largely dependent on inductive organizing centers, such as those at the basal and alar plates, which stimulate different types of growth depending on the signaling gradients. Sonic hedgehog (SHH) induces ventral signaling patterns, and bone morphogenetic proteins (BMP) and growth differentiation factor (GDF) induce dorsal patterning (Altmann and Brivanlou, 2001). Fibroblast growth factor (FGF), Wingless-type MMTV integration site family member (Wnt), and retinoic acid signaling pathways have been shown to be involved in the caudalization of neural tissue. It is suggested that Hox gene patterning affects the antero-posterior axis of development. Activin has been implicated in left-right axis development (Altmann and Brivanlou, 2001). These signaling pathways interact with neural tissue in a concentration-dependent manner to effect the differentiation and development of neural tissue (Lumsden and Krumlauf, 1996; Kobayashi et al., 2002; Clarke, 2003). Migration of neuroepithelial cells occurs along the lattices or pathways formed by radial glia from the ventricular zone to the SVZ. The radial glia connects the ventricular surface of the neural tube with the pial surface. This connection enables neuronal cells to migrate to the SVZ where a secondary germinal center is established. It is thought that glial cells primarily originate from neuroepithelial cells that remain in the ventricular zone until differentiation into glioblasts, following which they migrate to the SVZ to proliferate and become astrocytes and oligodendrocytes (Price and Thurlow, 1988; Levison and Goldman, 1997; Rao and Mayer-Proschel, 1997; Barres and Barde, 2000; Clarke, 2003). Some SVZ cells can give rise to multiple lineages such as astrocytes and oligodendrocytes, and in some cases, both neurons and glial cells can differentiate from the same cell, though this is not universally accepted (Levison and Goldman, 1993; Price, 1994; Clarke, 2003).

During development, the ventricular zone disappears, and remaining neuroepithelial cells largely develop into ependymal cells which line the ventricular system. The SVZ persists throughout adulthood, and is directly adjacent to the ependymal layer around most of the ventricular regions. As continued development and compartmentalization of the CNS occurs, NSCs are primarily concentrated in the regions of the olfactory bulb, the SVZ of the forebrain, the hippocampus, the cerebellum, the cerebral cortex, and the spinal cord, though these distributions vary with species (Clarke,

2003). Interestingly, the stem cells found in these locations appear to be distinct from one another, those cells in a particular region will give rise to progeny typical of the cells in that region (Gaiano and Fishell, 1998; Kalyani et al., 1998; Temple, 2001).

While in typical scenarios *in vivo*, NSCs differentiate into either neuronal or glial cells, it is thought that this preferential differentiation results from the environment and signaling factors to which the stem cells are exposed. It has been shown that NSCs can differentiate into hematopoietic cells and muscle cell types *in vitro* (Bader et al., 1982; Bjornson et al., 1999; Clarke et al., 2000). This plasticity appears to be multifaceted as bone marrow stem cells have likewise been demonstrated to develop into astroglia and microglia (Eglitis and Mezey, 1997; Price and Williams, 2001). Clark et al. (2000) found that a mouse blastocyst injected with lactose operon Z (lacZ)-expressing NSCs develops into a chimera, with the NSCs developing into all cell types. Nerve growth factor (NGF) has been shown to increase the differentiation of mouse embryonic stem cells into neurons (Antonov et al., 2017).

Cell markers

Rushing and Ihrie categorized the currently-known markers for neural cells and their progenitors (Rushing and Ihrie, 2016). Beginning with patterns of differentiation characteristic of embryonic development, notable markers for neuroepithelial cells include Nestin (neuroectodermal stem cell marker), sex determining region Y-box 2 (SOX2), Vimentin, and RC2 (type of radial glia antibody). Radial glia also express these markers, along with paired box gene 6 (Pax6), L-glutamate/L-aspartate transporter (GLAST), and brain lipid binding protein (BLBP). Neuronal-restricted precursors, arising from the neuroepithelium are marked by embryonic neural cell adhesion molecule (E-NCAM), and the mature neurons developing from them express neuronal-specific nuclear protein (NeuN), microtubule-associated protein 2 (MAP2), neuron-specific enolase (NSE), and beta III tubulin (TuJ1). It appears to be from the radial glia that all glial cells develop, though they are still capable of developing into neurons through the pathway of intermediate progenitor cells which are marked by T-brain factor 2 (Tbr2). The mature neurons that arise from radial glia express T-brain factor 1 (Tbr1), NeuN, MAP2, NSE, and TuJ1. Radial glia develops into oligodendrocyte precursor cells expressing neural/glial antigen 2 (NG2), ganglioside precursor disialohematoside (GD3), and platelet-derived growth factor receptor alpha (PDGFRα), with fully-differentiated oligodendrocytes being marked by myelin-associated glycoprotein (MAG), BMP, and O4 (common oligodendrocyte marker). Mature astrocytes express S100β (multifunctional protein abundant in astrocytes), GLAST, and glial fibrillary acidic protein (GFAP). It has been suggested that cluster of differentiation 44 (CD44) serves as a marker for astrocyte-restricted precursors, but the existence of such precursors remains largely unsubstantiated (Liu et al., 2004).

Adult neural cell populations express some of the same markers as those of embryonic populations, but also some that are different. Adult NSCs or B1 cells (subpopulation of adult neural stem cells with astroglial properties) are noted to express GFAP, integrin alpha 6 (ITGA6/CD49f), 3-fucosyl-N-acetyl-lactosamine (LeX/CD15/SSEA-1), SOX2, Vimentin, and GLAST; additionally, BLBP, epidermal growth factor receptor (EGFR), and mammalian achaete scute homolog-1 (Mash1) are expressed on activated B1 cells, vascular cell adhesion molecule 1 (VCAM-1) is expressed on quiescent B1 cells, prominin-1 (CD133) is present on the primary cilia, and Nestin is often found on adult NSCs, but depends on regulatory processes. Transit amplifying (TA) precursors differentiate from B1 cells, and express distal-less homeobox 2 (DLX2), ITGA6/CD49f, GLAST, and in some cases, EGFR and Mash1. TA precursors may then differentiate into immature neuroblasts which express Tuj1, DLX2, polysialylated-neural cell adhesion molecule (PSA-NCAM), doublecortin (DCX), and low levels of cluster of differentiation 24 (CD24). Mature neurons that differentiate postnatally still express Tuj1, NeuN, MAP2, and NSE. It was also noted that ependymal cells express Nestin, CD133, CD24, and Vimentin. The understanding of neural cell lineages and their markers and effective characterization continues to progress (Rushing and Ihrie, 2016).

Activation, migration, and differentiation of neural stem cells

In adults, NSCs have been identified in areas near blood vessels in the dentate gyrus, SVZ, and in the high vocal center of songbirds (Louissaint et al., 2002; Shen et al., 2004). Shen et al. (2014) demonstrated that endothelial cells release factors that are important for the self-renewal of NSCs, and also inhibit their differentiation and increase the production of neurons. It has been observed that co-culturing NSCs with endothelial cells promotes that growth of epithelial sheets with increased junctional contact, and this could play a role in increasing the self-renewing qualities of stem cells by influencing β-catenin pathways, modifying the mode of cell division, and affecting Notch expression through Hes1 upregulation (Nakamura et al., 2000; Lu et al., 2001; Ohtsuka et al., 2001; Chenn and Walsh, 2002; Hitoshi et al., 2002; Chojnacki et al., 2003; Shen et al., 2004). It was shown that despite the ability of fibroblast growth factor-2 (FGF2) to promote NSC proliferation, endothelial factors were required to perpetuate self-renewal (Shen et al., 2004). FGF2 has been shown to be a potent activator of latent NSCs from varying regions of the adult brain to promote proliferation and neurogenesis (Palmer et al., 1999).

'Niches' for stem cell property modulation have been identified; these niches consist of various growth or signaling factors and the environments conducive to promoting certain characteristics or developmental steps in stem cells (**Figure 1**). The niches for NSCs in adults are those previously mentioned: namely the SVZ, and the dentate gyrus. Aguirre et al noted the delicate balance that must be maintained between NSCs and neural progenitor cells in order to continue providing the brain with the needed populations

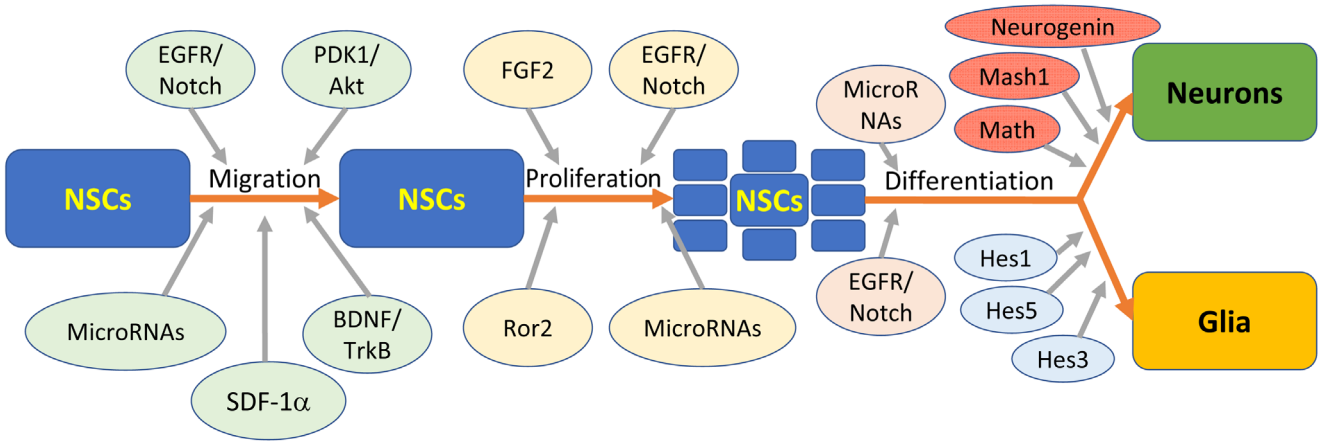

Figure 1 The general process of neural stem cell (NSC) migration, proliferation, and differentiation involves many factors.
Many nuances that have been determined are not illustrated in this figure; for example, certain microRNAs induce proliferation of, and differentiation to specific cell types. It is also notable that the distinction between the specific functions or mechanisms of many factors is not yet well-defined in many cases; it has been observed that a certain factor results in an increase of neurons or astrocytes, but the mechanism, whether it acts on proliferation or differentiation, for example, is yet to be determined. EGFR: Epidermal growth factor receptor; PDK1: phosphoinositide dependent kinase 1; FGF2: fibroblast growth factor-2; Mash1: mammalian achaete scute homolog-1; Math: mammalian atonal homolog protein; SDF-1α: stromal cell-derived factor 1α; BDNF: brain derived neurotrophic factor; Ror2: receptor tyrosine kinase like orphan receptor 2.

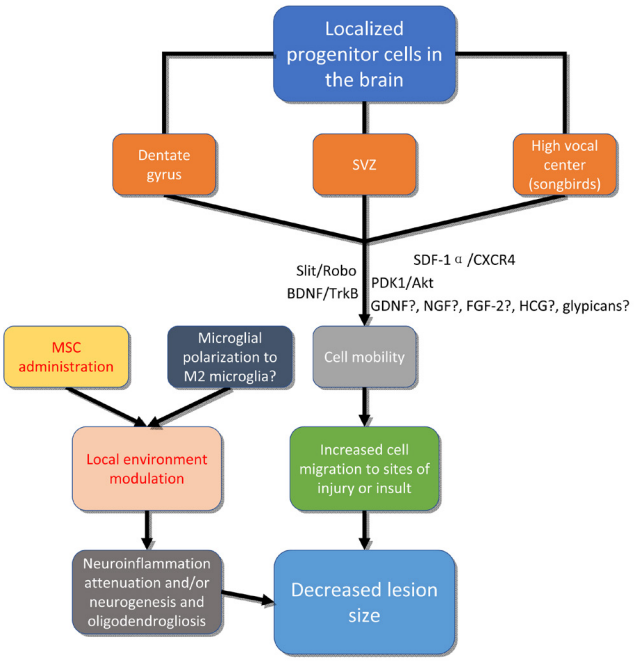

Figure 2 Therapeutic approaches to the treatment of brain injury may be adopted based on an understanding of factors involved in encouraging mobility of neural stem/progenitor cells, or local environment modulation.
Several factors such as GDNF, FGF-2, NGF and glypicans have roles in neural cell proliferation and development, and could be implicated in migratory processes by future studies. As noted, the concept of microglial polarization is somewhat ambiguous. SVZ: Subventricular zone; Robo: roundabout; BDNF: brain-derived neurotrophic factor; TrkB: tyrosine receptor kinase B; SDF-1α: stromal cell-derived factor 1α; PDK-1:phosphoinositide depend kinase1; HCG: human choionic gonadotophin; GDNF: glial cell line-derived neurotrophic factor; NGF: nerve growth factor; FGF2: fibroblast growth factor-2; CXCR4: C-X-C chemokine receptor type 4.

of neural cells (Aguirre et al., 2010). Moreover, the interplay between epidermal growth factor receptor (EGFR) and Notch signaling pathways is essential to maintenance of appropriate niches for self-renewal, differentiation, and proliferation of NSCs. In examination of the SVZ niche, it was observed that Notch influences NSC identity and self-renewal, while EGFR is primarily responsible for neural progenitor cell proliferation and migration (Lillien and Raphael, 2000; Hitoshi et al., 2002; Alexson et al., 2006; Breunig et al., 2007; Aguirre et al., 2010).

The maintenance of NSC populations with multipotent abilities requires stromal cell-derived factor 1 (SDF-1) and its main receptor, C-X-C chemokine receptor type 4 (CXCR4) as their removal causes neurogenic differentiation (Ho et al., 2017). Ho et al. (2017) observed that in response to the elimination of SDF-1 in mice, expression of the proneural gene, achaete-scute homolog 1 (Ascl1), and the antiproliferative gene, p27, was increased significantly, which could account for the maintenance of the 'stemness' of the population.

NSC differentiation is largely dependent on the expression of basic helix-loop-helix (bHLH) genes. As was noted by Kageyama et al. (2005), NSC populations initially proliferate exclusively, and then differentiate first into neurons and later into glial cells. Repressor-type bHLH genes include Hes1, Hes3, and Hes5 (genes encoding hairy enhancer of split proteins), and appear to be crucial for the proliferation of glial cells such as astrocytes and ependymal cells. It was also observed that in the absence of repressor-type bHLH genes, proliferation was inadequate to give rise to significant glial populations. The activator-type bHLH genes include Mash1, Math, and Neurogenin, and promote the differentiation of NSCs to neurons. These genes are also involved in the induction of Notch ligands that regulate Hes1 and Hes5 expression. In this manner, the activator-type and the repressor-type bHLH genes inter-regulate each other in maintenance of appropriate signals for proliferation of both neurons and glia (Kageyama et al., 2005) (**Figure 1**).

MicroRNAs also play a role in bHLH regulation and neurogenesis with miR-1297 being an inhibitor of Hes1 expression (Zheng et al., 2017). Also, miR-199 and miR-214 have been shown to disrupt neurogenesis and neuron migration in mice (Mellios et al., 2017). It has been observed that miR-338-3p is highly expressed in the dentate gyrus, and is involved in neuronal maturation regulation; the influence of microRNAs on neurogenesis in the dentate gyrus is largely attributable to effects on gene expression (Howe et al., 2017). Many microRNAs are expressed in the dentate gyrus; miR-19 has also been shown to play a role in the migration of neurons in adults (Han and Gage, 2016). miR-410 appears to play a role in the differentiation of multipotent NSCs, as it has been noted to promote astrocyte differentiation while inhibiting neuron and oligodendrocyte differentiation (Tsan et al., 2016). It has been demonstrated that the miR-200 family is involved in regulation of neuronal maturation in normal, postnatal neurogenesis (Beclin et al., 2016). miR-193a has been observed to enable neurogenesis in F11 cells (Oh et al., 2017). miR-9 is involved in gene expression regulation, and is needed for neurogenesis, and sustaining and differentiation of neuronal progenitors (Radhakrishnan and Alwin Prem Anand, 2016). MicroRNA let-7a is reported to be involved in the regulation of NSC differentiation through its modulation of regulator expression (Song et al., 2016). Also, miR-17-92 has an effect on the regulation of neurogenesis in the adult hippocampus (Jin et al., 2016). This is not a comprehensive accounting of the functions of microRNAs in NSC activation, migration, and differentiation, but rather aims to convey that vast amounts of research continue to be done on the neuromodulatory effects of these molecules (**Figure 1**).

The methyl-CpG-binding domain protein, methyl-CpG-binding domain protein 1 (MBD1) has been shown to be necessary for effective neurogenesis (Lax and Sapozhnikov, 2017). The ability of MBD1 to enable neurogenesis may be facilitated primarily by methylated DNA promoter stabilization and gene expression silencing (Jørgensen et al., 2004; Lax and Sapozhnikov, 2017). It has also been suggested that MBD1 may perpetuate its effect through an indirect mechanism by inhibiting specific transcriptional repressors which causes an upregulation of transcription (Jobe et al., 2017; Lax and Sapozhnikov, 2017). Additional research will help to clarify the underlying mechanism of the effect of MBD1.

Cardiovascular exercise improves learning, memory, and executive function in humans, and has been shown to reduce the risk of developing neurodegenerative disorders; it is thought that this effect may be related to the increase in brain volume in regions prone to degeneration in old age (Cotman et al., 2007; Hillman et al., 2008; Blackmore et al., 2009). Neurogenesis declines significantly with age in mice, and it has been demonstrated that voluntary exercise and exposure to an enriched environment increases neurogenesis in the hippocampal and periventricular zones of mice (Kempermann et al., 1998, 2002; van Praag et al., 1999, 2005; Lindsey and Tropepe, 2006; Wu et al., 2008; Blackmore et al., 2009). Insulin-like growth factor-1 (IGF-1), brain derived neurotrophic factor (BDNF), and vascular endothelial-derived growth factor (VEGF) are important mediators of hippocampal neurogenesis augmentation due to exercise (Cotman et al., 2007). Blackmore et al. (2009) also observed that growth hormone and growth hormone receptor signaling (GH/GHR) was vital to the exercise-induced activation of neural progenitor cells in regions outside of the hippocampus. Interestingly, it has been noted that successful learning in the context of 'mental training' can improve neuronal survival in the wake of neurogenesis (Curlik 2nd and Shors, 2013).

The physical space and structural components in the environment of the NSCs appear to play a role in their differentiation. Christopherson et al. (2009) demonstrated that the diameter of fibers comprising laminin-coated electrospun polyethersulfone meshes had a significant impact on the NSC proliferation and differentiation. Cells were cultured for five days on tissue culture polystyrene (TCPS) plates, and 283 nm-, 749 nm-, and 1,452 nm-diameter fiber meshes. In the presence of FGF2 and serum-free medium, increasing fiber diameter correlated with decreased NSC migration and proliferation. In the presence of 1 μM retinoic acid and 1% fetal bovine serum (FBS), stem cells on the two-dimensional (2D) culture plate and the 283 nm fiber mesh were more prone to spread and differentiate into glia such as oligodendrocytes, whereas the stem cells cultured on the 749 nm and 1,452 nm fiber meshes were seen to elongate and differentiate in higher proportions to neuronal lineages. Ostensibly, this appears to indicate that the structural aspects in the stem cell environment influence migration, proliferation, and differentiation.

Historically, an efficient way of measuring the absence, occurrence, or level of neurogenesis has been lacking. Such measurements could aid researchers in examining the growth of neurons following injury in response to various treatments. The proteoglycan Glypican-2 (Gpc2) which can be measured in the cerebrospinal fluid, has been identified as being expressed in levels strongly correlative with adult hippocampal neurogenesis (Lugert et al., 2017). Gpc2 may prove to be an important factor in neurogenesis, or may serve as a useful measure of adult neurogenesis; however, more research is needed to illuminate the involvement of the glycoprotein in neural cell proliferation and differentiation.

There has been some recent interest in the potential difference in response between NSCs and differentiated cells to DNA damage, and the ways in which that may affect differentiation and proliferation (Barazzuol et al., 2017; Beckta et al., 2017; Shimura et al., 2017). However, the information reviewed does not readily prompt conclusion as to the existence, applicability, or influence of substantial difference in response. This underscores the need for further research in this area. There have also been some studies into the effects of melatonin on NSCs (Niles et al., 2004; Moriya et al., 2007; Kong et al., 2008; Sotthibundhu et al., 2010; Fu et al., 2011). Melatonin may enhance NSC differentiation into oligodendrocytes and neurons and engraftment following transplantation (Mendivil-Perez et al., 2017). It is thought that this

may result from an increase in mitochondrial activity due to melatonin administration, and from protection of NSCs from the effects of inflammation (Song et al., 2015; Mendivil-Perez et al., 2017).

The role of sonic hedgehog (Shh) in neural progenitor cell migration and differentiation in development was mentioned previously. The effect of Shh pathway on NSCs following stroke was examined by Jin et al. (2017). They report that following administration of a sonic hedgehog agonist one month after ischemic stroke, there was improved survival of new NSCs in the subgranular and subventricular zones, as well as neuroblast cells and neurons. Continued investigation into the effects of the sonic hedgehog pathway on NSCs could be of benefit.

Endo and Minami (2018) reviewed the influence of Ror-family receptor tyrosine kinases (RTKs) on neural and glial cell development. They noted that receptor tyrosine kinase like orphan receptor 1 (Ror1) and receptor tyrosine kinase like orphan receptor 2 (Ror2) likely play an important role in nervous system development as they are found in relative abundance in neural progenitor cells during development, and in neurons in some regions. It has also been observed that the levels of Ror1 and Ror2 expressed decreases over the course of development. These particular RTKs have been found in extending neurites, and may be implicated in the extension process (Paganoni and Ferreira, 2003, 2005). Ror1, Ror2, and Wnt5a also play an important role in synaptogenesis, as their suppression significantly reduces the number and density of presynaptic clusters per neuron (Paganoni et al., 2010). Ror2 has been shown to be crucial to N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic transmission as well as astrocyte function and proliferation during neural repair following injury (Cerpa et al., 2015; Endo and Minami, 2018). It is of interest that Ror2 expression is also increased in demyelinating disorders (Shimizu et al., 2016; Endo and Minami, 2018).

Stem cell-based therapy

The development of stem cell-based therapeutic treatments for brain injury is an emerging area of medical research. Among the promising therapies, mesenchymal stem cell (MSC) administration has been widely followed (**Figure 2**). MSCs alter the environment in brain injury and attenuate the inflammatory response through activation and polarization of macrophages and microglia (Xu et al., 2017). The polarization of microglia to M2 microglia has been shown to promote neurogenesis and oligodendrogenesis from NSCs, though there is a lack of consensus on the distinction between microglial populations in applicable *in vivo* models (Yuan et al., 2017). This regulation of neuroinflammation may facilitate reducing lesion size by prevention of secondary or inflammatory injury. Exosomes derived from MSCs, which are small, membranous vesicles containing various proteins, lipids, and RNAs, have been shown to be effective at altering neuroinflammation and neurogenesis, and have been proposed as a potential therapeutic agent in brain injury (Yang et al., 2017). Extracellular vesicles, such as exosomes, may be among the primary mediators of the positive effects of MSC administration to the site of brain injury.

Some of the most promising novel approaches to brain injury treatment involve the therapeutic manipulation of endogenous precursor cells in the brain. Brain-derived neurotrophic factor (BDNF) has been shown to not only be important in development for the maintenance and growth of neurons, but also plays a vital role in axon remodeling and dendrite branching (Barde, 1994; Conner et al., 1997; Alsina et al., 2001; Ortiz-López et al., 2017b). BDNF has additionally been shown to influence cell migration (Borghesani et al., 2002; Chiaramello et al., 2007; Cao et al., 2012; Matsuda et al., 2012; Grade et al., 2013; Gasanov et al., 2015; Ortiz-López et al., 2017a). This action of BDNF on cell migration appears to be mediated by its action on the tyrosine receptor kinase B (TrkB) receptor, and the role of BDNF seems to be prevalent in normal development as well as response to ischemia or other insult. Ortiz-López et al. (2017b) observed that the migration rate of human NSCs to empty areas i*n vitro* did not differ significantly between those treated with BDNF and controls after 2- and 6-hour-time periods, but that at 24-, 48-, 72-, and 96-hour periods, the stem cells treated with BDNF had migrated to the empty areas significantly more than the untreated cells (**Figure 2**).

Guerrero-Cazares et al. (2017) showed that Slit and roundabout (Robo) proteins and their interaction are important regulators of human fetal neural progenitor cell migration. It has also been noted that the PDK1-Akt pathway has a role in the regulation of the speed of neuronal migration through the mouse neocortical plate; it is likely that this influence is mediated through an interaction with the microtubule structural system (Itoh, 2016). Stromal cell-derived factor 1α (SDF-1α), which is an inflammatory chemoattractant, also plays a vital role in the migration of NSCs to the site of injury (Imitola et al., 2004). This provides the interesting perspective that inflammation may have not only a negative effect on the subject, but is also involved in the migration of regenerative cells to the site of deficit. NSCs are known to secrete neurotrophic factors such as nerve growth factor (NGF), BDNF, and glial cell line-derived neurotrophic factor (GDNF) that may increase resident axonal extension following spinal cord injury (Lu et al., 2003).

In investigating stem cell therapies for Huntington's disease (HD) in an experimental model induced through quinolinic acid administration, Song et al. (2007) found that transplantation of human embryonic stem cell (hESC)-derived NSCs rescued some motor function in the absence of medium-sized spiny projection neurons (MSNs). It is thought that this positive effect could be due to neuroprotective factors expressed by the transplanted NSCs (Connor, 2017). Drago et al. (2013) addressed the concepts of the paracrine hypothesis and the stem cell secretome (SCS) in explaining the therapeutic effect of stem cell transplantation in animal models of CNS disease. The SCS is comprised of cytokines, chemokines, and growth factors, and is involved in the repair or regeneration of injured tissue (Drago et al., 2013).

It should be noted that many of the studies that have been

performed with NSCs have been conducted using embryonic or fetal cells. While it is reasonable to believe that the processes involved in adult subjects in response to injury or in standard repair mechanisms will be similar in many respects, there could be significant benefit derived from replication of studies using adult cells and microenvironments typically encountered.

Future Directions

There is extensive research being performed with stem cells and their potential therapeutic uses. Studies are shedding light on the markers, characteristics, and related factors of NSCs. There is still much to be learned to broaden and deepen our understanding of stem cells and the microenvironments that encourage their proliferation and migration. While our understanding of the niches and signaling, factors involved in NSC population are synergistic and proliferation is still developing, there could be potential for therapeutic benefit in exploring the ability to induce activation or migration of stem cells to sites of injury through administration of growth or signaling factors. However, it should be noted that care should be taken in examining the adverse effects of such therapies as interruption to the critical balance that normally exists can have highly detrimental consequences such as the development of gliomas due to increased EGFR exposure (though absence or mutation of other factors like Ink4a or Arf may contribute) (Holland et al., 1998; Bachoo et al., 2002). The role of microRNAs in modulating the activity and characteristics of NSCs is being aggressively investigated currently. These studies have, and will continue to enlighten our understanding of mechanisms involved in NSC maintenance, proliferation, and migration. Continuation in this area may prove to be of clinical benefit. The development of methods for transportation of stem cells or factors affecting their growth and development to sites of neural tissue damage could be helpful in treating brain injuries. Exosomes exhibit some promise as neuromodulatory agents, and continued research could be of benefit. As mentioned previously, the use of adult NSCs in studies could provide additional information as to the ways in which adult stem cells and embryonic stem cells differ, and the unique or similar characteristics between them.

Brain injury dramatically affects the lives of many people around the world, and the treatments available, while progressing, often produce unsatisfactory results. NSCs are fascinating populations that are being intensely investigated, and that offer potential to provide great therapeutic benefit in the future; this investigation should continue to expand our understanding of stem cell characteristics and their applications.

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