Title
The endogenous progenitor response following traumatic brain injury: a target for cell therapy paradigms.

Permalink
https://escholarship.org/uc/item/4hg825xf

Journal
Neural regeneration research, 17(11)

ISSN
1673-5374

Authors
Badner, Anna
Cummings, Brian J

Publication Date
2022-11-01

DOI
10.4103/1673-5374.335833

Copyright Information
This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

Peer reviewed
The endogenous progenitor response following traumatic brain injury: a target for cell therapy paradigms

Anna Badner1,*, Brian J. Cummings2,4,5

Abstract
Although there is ample evidence that central nervous system progenitor pools respond to traumatic brain injury, the reported effects are variable and likely contribute to both recovery as well as pathophysiology. Through a better understanding of the diverse progenitor populations in the adult brain and their niche-specific reactions to traumatic insult, treatments can be tailored to enhance the benefits and dampen the deleterious effects of this response. This review provides an overview of endogenous precursors, the associated effects on cognitive recovery, and the potential of exogenous cell therapeutics to modulate these endogenous repair mechanisms. Beyond the hippocampal dentate gyrus and subventricular zone of the lateral ventricles, more recently identified sites of adult neurogenesis, the meninges, as well as circumventricular organs, are also discussed as targets for endogenous repair. Importantly, this review highlights that progenitor proliferation alone is no longer a meaningful outcome and studies must strive to better characterize precursor spatial localization, transcriptional profile, morphology, and functional synaptic integration. With improved insight and a more targeted approach, the stimulation of endogenous neurogenesis remains a promising strategy for recovery following traumatic brain injury.

Key Words: cell therapy; endogenous repair; neurogenic niche; progenitors; traumatic brain injury

Traumatic Brain Injury
Traumatic brain injury (TBI) remains one of the primary causes of death and disability around the world, with estimates of more than 50 million people experiencing a TBI each year (Maas et al., 2017). Defined as brain dysfunction and pathology caused by an external force (Menon et al., 2010), TBI can result in long-term cognitive deficits (van Gils et al., 2020) as well as an increased risk of dementia (Mendez, 2017). For this reason, TBI presents a considerable health as well as economic burden, warranting a significant need for novel therapeutics.

In terms of pathophysiology, TBI is typically separated into two phases; referred to as primary and secondary injury. The primary injury corresponds to the damage inflicted at the time of trauma and is considered largely irreversible. Yet, this impact is followed by hours, days, weeks and even months of secondary injury that exacerbates the initial insult, triggering a majority of tissue loss. The secondary injury, which remains the target of most treatment strategies, is mediated by several factors, including excitotoxicity, neuroinflammation, mitochondrial dysfunction, oxidative stress, axonal degeneration, and apoptosis. While the mechanisms of secondary injury are predominantly detrimental to the injury milieu, there is also evidence for the associated activation of various central nervous system progenitor pools with potential regenerative capabilities. A better understanding of this progenitor response may be instrumental in the development of improved treatment paradigms.

Further, an exogenous stem cell therapy need not result in new transplanted cells integrating with the host tissue, but rather the exogenous cells may modulate endogenous progenitor responses. This article aims to provide an overview of the niche-specific progenitor response to TBI, the associated effects of aberrant regeneration on cognitive function, and the potential application of cell therapeutics to target these events.

Search Strategy and Selection Criteria
The studies cited in the current review, published between 1993 to 2021, were searched on PubMed and Web of Science databases using the following keywords/terms: traumatic brain injury; endogenous progenitors; neural stem cells; oligodendrocyte progenitor cells; neurogenic niches; neurogenesis. Diverse variations of the search terms were applied to reach the greatest amount of literature.

Activation of Adult Neural Stem Cells in the Hippocampal Dentate Gyrus Following Traumatic Brain Injury
The hippocampal dentate gyrus subgranular zone (SGZ) is a well characterized reservoir of adult neural stem/progenitor cells, where neurogenesis is a tightly controlled process in healthy tissue (Nguyen and Danzer, 2018) and occurs throughout an individual’s lifespan, albeit at a diminished rate over time (Kase et al., 2020). In the context of trauma, there is substantial evidence in support of injury-induced activation of SGZ progenitors and an accompanying increase neurogenesis (Dash et al., 2001; Urrea et al., 2007; Yu et al., 2008) that correlates with injury severity (Wang et al., 2016a) and may be mediated by the mammalian target of rapamycin pathway (Lee et al., 2016; Wang et al., 2016b) as well as insulin-like growth factor-1 (Carlson et al., 2014; Littlejohn et al., 2021). This has also been shown in humans following a TBI (Zheng et al., 2013).

Despite consensus on the injury-induced proliferative response, the role of endogenous progenitors in repair and injury pathogenesis remains controversial. Specifically, ablation of injury-mediated neurogenesis has been reported to limit cognitive recovery (Blais et al., 2011), highlighting an innate mechanism that may be responsible for some spontaneous recovery. However, treatments aimed at increasing SGZ neurogenesis have also been implicated in improved neurological outcome following TBI (Lu et al., 2003a). In contrast, others have reported that TBI-mediated progenitor proliferation depletes the regenerative pool (Ennas and Sierras, 2012; Neuberger et al., 2017) and the proliferative cells exhibit various morphological as well as physiological abnormalities that impair cognition (Ibrahim et al., 2016; Robinson et al., 2021).

How to cite this article: Badner A, Cummings BJ (2022) The endogenous progenitor response following traumatic brain injury: a target for cell therapy paradigms. Neural Regen Res 17(11):2351-2354.
Activation of Subventricular Zone Progenitors Following Traumatic Brain Injury

The subventricular zone (SVZ) of the lateral ventricles is another well-established neurogenic niche implicated in TBI. While the literature varies based on the injury model, severity, and species of study, there is consistent data to suggest a supportive response among SVZ progenitor cells post-injury (Chang et al., 2016). However, as SVZ progenitors are largely responsible for the replacement of olfactory bulb interneurons through the rostral migratory stream in rodents, they have potential mitogenic capabilities that complicate any simple translation of the following observations to humans. Briefly, studies have documented SVZ progenitor cell migration along the corpus callosum (Costine et al., 2015), the rostral migratory stream (Goings et al., 2004; Urrea et al., 2007), and even into the injured cerebral cortex (Sundholm-Peters et al., 2005; Radomska et al., 2013; Saha et al., 2013; Dixon et al., 2015) in response to various TBI models. Further, in contrast to the SGZ, the SVZ niche is incredibly heterogeneous (Xie et al., 2020), where progenitors also display transcriptomic variation. For this reason, cell fate analysis post-injury has been susceptible to differences stemming from study design. In the context of a cortical lesion, retroviral labelling of SVZ-derived progenitors in adult mice has demonstrated that they can migrate into the corpus callosum and different regions of the olfactory bulb, while an increased proliferating response has been reported in the lesioned cortex become astrocytes (Goings et al., 2004). This SVZ-derived astroglial response is reportedly mediated by Thbs4 via direct Notch1 receptor binding and endocytosis to activate downstream transcription factors for gliogenesis and astroglial cell production (Bennett et al., 2013). In terms of function, depletion of SVZ progenitors following TBI has been found to hinder spontaneous motor recovery and increase giall hypertrophy at the injury site (Dixon et al., 2015). Although this suggests a supportive role in cortex repair, there is evidence that progenitors in the juvenile brain, widely used in the presented studies, have a more substantial response than those in the adult (Goodus et al., 2015). Much work is needed to explore the SVZ post-TBI as a potential therapeutic target, as it is significantly less understood than the hippocampal SGZ.

Progenitor Response Among Novel Neurogenic Niches Following Traumatic Brain Injury

Beyond the aforementioned “classical” progenitor niches, there have been several more recently described sites of possible adult neurogenesis that are less well-characterized and less thoroughly investigated. The area postrema is an established neurogenic niche implicated in TBI. While the literature varies based on the injury model, severity, and species of study, there is consistent data to suggest a supportive response among SVZ progenitor cells post-injury (Chang et al., 2016). However, as SVZ progenitors are largely responsible for the replacement of olfactory bulb interneurons through the rostral migratory stream in rodents, they have potential mitogenic capabilities that complicate any simple translation of the following observations to humans. Briefly, studies have documented SVZ progenitor cell migration along the corpus callosum (Costine et al., 2015), the rostral migratory stream (Goings et al., 2004; Urrea et al., 2007), and even into the injured cerebral cortex (Sundholm-Peters et al., 2005; Radomska et al., 2013; Saha et al., 2013; Dixon et al., 2015) in response to various TBI models. Further, in contrast to the SGZ, the SVZ niche is incredibly heterogeneous (Xie et al., 2020), where progenitors also display transcriptomic variation. For this reason, cell fate analysis post-injury has been susceptible to differences stemming from study design. In the context of a cortical lesion, retroviral labelling of SVZ-derived progenitors in adult mice has demonstrated that they can migrate into the corpus callosum and different regions of the olfactory bulb, while an increased proliferating response has been reported in the lesioned cortex become astrocytes (Goings et al., 2004). This SVZ-derived astroglial response is reportedly mediated by Thbs4 via direct Notch1 receptor binding and endocytosis to activate downstream transcription factors for gliogenesis and astroglial cell production (Bennett et al., 2013). In terms of function, depletion of SVZ progenitors following TBI has been found to hinder spontaneous motor recovery and increase giall hypertrophy at the injury site (Dixon et al., 2015). Although this suggests a supportive role in cortex repair, there is evidence that progenitors in the juvenile brain, widely used in the presented studies, have a more substantial response than those in the adult (Goodus et al., 2015). Much work is needed to explore the SVZ post-TBI as a potential therapeutic target, as it is significantly less understood than the hippocampal SGZ.

Non-Cellular Strategies for An Enhanced Traumatic Brain Injury

Metformin

The re-purposing of metformin (Potts and Lim, 2012), a drug previously applied to manage type II diabetes, has been repeatedly shown to mobilize endogenous progenitors in the hippocampus following neonatal ischemia (Dadwal et al., 2015), irradiation (Derkach et al., 2021), chemotherapy-related neurocognitive impairment (Sritawan et al., 2020) as well as TBI (DiBona et al., 2021). Most importantly, metformin has been found to mobilize NSCs with an altered endogenous progenitor morphology following TBI, where NSC treatment was linked to reorganization of endogenous neural progenitor processes through the granule cell layer of the hippocampal SGZ (Badner et al., 2021). While this suggests that NSC transplantation may help promote an environment for healthy versus aberrant neurogenesis (Figure 1), there is a significant need to better understand the endogenous cell transcriptional profile, spatial distribution and morphology following TBI.

Enhance the Endogenous Progenitor Response

Mesenchymal stem/stromal cells

Mesenchymal stem/stromal cells (MSCs) are trilineage progenitors, identified by their ability to adhere to plastic and differentiate into adipocytes, osteoblasts, and chondroblasts as well as osteoblasts (Dominici et al., 2006). Widely recognized to have potent anti-inflammatory effects (Badner et al., 2017), chiefly through trophic support; MSCs have also been implicated in driving endogenous neurogenesis. Specifically, astrocytic responses to injured or transplanted NSCs have been reported in both, the SVZ as well as the SGZ, following MSC transplant in rat (Yoo et al., 2008; Bao et al., 2011) and mouse (Kan et al., 2011) models of cerebral ischemia. Several neurotrophic factors, either directly derived from transplanted MSCs or via their interactions with the inflammatory microenvironment, are inferred in this response. In the context of TBI, the MSC secretome alone has been found to enhance endogenous neurogenesis (Li et al., 2020), further validating the significance of trophic support in endogenous application of these cells.

Neural stem cells

Neural stem cells (NSCs) are self-renewing precursor cells with trilineage potential, able to differentiate into neurons, oligodendrocytes, and astrocytes. Like MSCs, NSCs have been reported to secrete various neurotrophic factors (Lu et al., 2003b) that can drive endogenous neurogenesis post-ischemia (Lin et al., 2011; Mine et al., 2013) as well as Alzheimer disease (Blurt-Jones et al., 2009). However, consistent with previous studies, the work has been limited to endogenous progenitor cell counts among NSC-treated animals versus control. The advantages, however, are more apparent when NSCs are transplanted with exogenous NSC transplantation. Nevertheless, as emphasized above, proliferation alone provides an incomplete view of the complex endogenous repair mechanism, linked to recovery as well as pathogenesis. Addressing this limitation, exogenous NSCs can facilitate neuronal activity through proper differentiation and integration and directionality of endogenous newly born neurons (Badner et al., 2021). There is also recent evidence that ablation of these proliferative neural progenitors can limit deficits in learning and memory following repeat mild traumatic brain injury (Cameron et al., 2011). Taken together, while hippocampal neurogenesis remains to be assessed in response to ischemia (Nakagomi et al., 2011, 2012), spinal cord injury (Sanin et al., 2013; Lin et al., 2015), impact on cognitive recovery remains to be assessed (Falnikar et al., 2018). While inferring from these studies to TBI has limitations, the data shows that OPCs in healthy and diseased states, especially as there is growing evidence of their synaptic integration (Bergles et al., 2000; Hughes and Appel, 2019), this cell population may also be a suitable target for enhanced recovery post-TBI.

Exogenous Cell Transplantation As A Strategy to Enhance the Endogenous Progenitor Response

Ectopic migration/implantation in a model of epilepsy (Kan et al., 2011) and even into the injured cerebral cortex (Sundholm-Peters et al., 2005), display tripotential differentiation, which may be more robust in models of stroke (Sanin et al., 2013; Lin et al., 2015). Specifically, evidence suggests that progenitors in the juvenile brain, widely used in the presented studies, have a more substantial response than those in the adult (Goodus et al., 2015). Much work is needed to explore the SVZ post-TBI as a potential therapeutic target, as it is significantly less understood than the hippocampal SGZ.

Oligodendrocyte Progenitor Cell Response Following Traumatic Brain Injury

Also known as NG2-glia, oligodendrocyte progenitor cells (OPCs) are progenitors, unrestricted to a specific niche, that differentiate into oligodendrocytes in both, the developing as well as adult brain (Dimou et al., 2008). Although their primary role is believed to be oligodendrogenesis during developmental myelination and myelin plasticity (Otahal et al., 2010). Although the OPC population remains unchanged following small laser-induced injury, with tightly controlled cell-renewal (Hughes et al., 2013), a more severe injury also results in OPC morphological changes, proliferation and migration to the site of injury (von Streitberg et al., 2013). Further, ablation of proliferating OPCs has been reported to impair and delay wound closure (von Streitberg et al., 2013), highlighting a potential role of OPCs in the endogenous repair response. While there is still much to understand about OPCs in healthy and diseased states, especially as there is growing evidence of their synaptic integration (Bergles et al., 2000; Hughes and Appel, 2019), this cell population may also be a suitable target for enhanced recovery post-TBI.
Figure 1  Comparison between healthy and pathological hippocampal neurogenesis following traumatic brain injury.

Overview of hippocampal neurogenesis in the dentate gyrus of healthy (A) versus injured (B) tissue. Pathology is associated with increased proliferation that may deplete the regenerative pool, aberrant circuit integration (linked to epileptogenesis) and abnormal progenitor migration as well as altered morphology. Some pathological features of neurogenesis could be potentially restored (C) through exogenous stem cell transplantation (mesenchymal stromal cells or neural stem cells), metformin administration or the use of neurotrophic factors.

synaptic integration of metformin-mediated endogenous progenitors relative to injury controls, as this would give greater insight to differences in healthy versus aberrant neurogenesis.

Neurotrophins
While various neurotrophic factors have been linked to adult neurogenesis, brain-derived neurotrophic factor (BDNF) has been best studied (Hendry et al., 2007; Choi et al., 2009). In the SGZ, BDNF is secreted and acts on its own receptors (tropomyosin receptor kinase B, in mice (Galvão et al., 2008). To further complicate interpretation, in the context of TBI, mRNA expression of BDNF and its receptors (tropomyosin receptor kinase B as well as p75) was decreased ipsilaterally to the injury and increased on the contralateral side (Rostami et al., 2014). As the p75 BDNF receptor is a member of the tumour necrosis factor receptor superfamily (Baker and Reddy, 1996), it can either either enhance or reduce neurotrophic function as well as independently induce apoptosis (Ip et al., 1993; MacPhee and Barker, 1997). For this reason, use of BDNF as a strategy for endogenous repair is dependant on a balance of its receptors, which would require further spatiotemporal analysis following TBI. Most importantly, BDNF is additionally hindered by limited blood-brain barrier permeability and rapid degradation (Caciabali, 2021), obstacles that would need to overcome for successful therapeutic application. There are additional review articles that provide a comprehensive summary of other neurotrophic factors and their application in TBI (Johanson et al., 2011; Houton et al., 2019, Caciabali, 2021).

Concluding Perspective
Overall, as highlighted throughout this review, there is significant evidence that TBI alone increases the activation and proliferation of various progenitor pools. Yet, as there are conflicting results, what remains unclear is the role of these progenitor responses in injury and repair pathogenesis. For this reason, there needs to be a significant shift in the tools used to study endogenous repair, especially when examining treatment strategies. As progenitor proliferation alone is no longer a meaningful outcome, studies must strive to better understand the precursor spatial localization, transcriptional profile, morphology, and circuit integration. Through greater insights into how progenitors contribute to repair, we can identify better targets for an enhanced response. Therefore, with at least some repair potential to be found each reservoir of adult brain progenitors, stimulation of endogenous neurogenesis remains a promising strategy for recovery following neurotrauma.

Author contributions: Both authors participated in design, writing and review of the manuscript version up to the final version of the manuscript.

Conflicts of interest: The authors declare no conflicts of interest.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNon-Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

References
Ayoub R, Ruddy RM, Cox E, Oyefiade A, Derkach D, Laughlin S, Ades-Aron B, Shirzadi Z, Fieremans E, Macintosh BJ, de Medeiros CB, Skocz J, Bouffet E, Miller FD, Morshead CM, Mabbott DJ (2020) Assessment of cognitive and neural recovery in survivors of pediatric brain tumors in a pilot clinical trial using metformin. Nat Med 26:1225-1228.
Bader N, Reinhardt EK, Nguyen TV, Midtun N, Mabbott AJ, Lepe CA, Echeverria A, Lepe JJ, Torrecampo V, Bertan SH, Tran S, Anderson A, Cummings BJ (2021) Freshly thawed cryopreserved human neural stem cells entrained within endogenous neurogenic niches and restored cognitive function following chronic traumatic brain injury. J Neurotrauma doi: 10.1088/neo.2021.0045.
Bader N, Siddiqui AM, Feilings MG (2017) Spinal cord injuries: how could cell therapy help? Neurosurg Spine Optip Thel doi: 10.1016/j.ptime.2017.05.014.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Bao X, Feng M, Lu S, Liu G, Zhao W, Ma W, Ma S, An Y, Qin C, Zhao RC, Wang R (2011) Transplantation of human bone marrow-derived mesenchymal stem cells promotes behavioral recovery and endogenous neurogenesis after cerebral ischemia in rats. Brain Res 1367:103-113.
Benner EI, Luciano O, Jo R, Abdi K, Paez-Gonzalez P, Sheng H, Warner DS, Liu E, Cerglo C, Kuo CT (2013) Protective astrophenesis from the SVZ niche after injury is controlled by Notch signaling. Nat Neurosci 16:369-374.
Bennett L, Yang M, Enikolopov G, Iacovitti L (2009) Circuiculariin organs: a novel site of neural stem cell activity in the adult brain. Mol Cell Neurosci 41:337-347.
Bennett LB, Ca J, Enikolopov G, Iacovitti L (2010) Heterotopically transplanted CNS neural stem cells generate neurons and migrate with SVZ cells in the adult mouse brain. Neuro Lett 475:1-6.
Beretta S, Cunningham R, Haus DL, Gold EM, Perez H, Lopez-Velazquez L, Cummings BJ (2014) Effects of human ES-derived neural stem cell transplantation and hindig in a rat model of traumatic brain injury. Cell Transplant 26:1247-1261.
Bergles DE, Roberts JD, Somogyi P, Jahr CE (2000) Glutamatergic synapses on dopaminergic midbrain neurons: a role for dopamine? Neuron 27:367-372.
Bifari F, Decimo I, Pino A, Llorens-Bobadilla E, Zhao S, Lange C, Panuccio G, Boeckx B, Tieniopitou B, Vinckier S, Wyns S, Bouche A, Lambrecht G, Diuglichio M, Denerchi M, Martin-Vilallonga A, Carrarese J, Scarsio M, Notch modulator Thbs4. Nature 497:191.
Caciabali P (2021) Neurotrophins time point intervention after traumatic brain injury: from zebraphish to human. Int J Mol Sci doi: 22:1858.
Cameron MC, Zhan RZ, Nadler JV (2011) Morphologic integration of hiler ectopic granule cells into dentate gyrus circuitry in the pilocarpine model of temporal lobe epilepsy. J Comp Neurol 519:2175-2192.
Carlson SW, Madathil SK, Sama DM, Gao X, Chen J, Saatman KE (2014) Conditional overexpression of insulin-like growth factor 1 enhances hippocampal neurogenesis and restoration of immature neurodegeneration following chronic traumatic brain injury. J Neurotrauma doi: 73:734-746.
Chang YH, Adorjan L, Mundin MV, Sun B, Dizon ML, Szele FG (2016) Traumatic brain injury activation of the adult subventricularzone neurogenic niche. Front Neurosci 10:332.
Choi Y, Parada LF, Powell CM, Kernie SG (2011) Pseudopod formation in the adult hippocampus. Cell Transplant 20:360-373.
Chung CA, Yu TS, Zhang G, Chen J, Dimished G, Parada LS, Powell CM, Kerman SG (2011) Temporally specific genetic ablation of neurogenesis impairs cognitive recovery after traumatic brain injury. J Neurosci Off J Soc Neurosci 31:4906-4916.
Blakely MT, Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Baker SJ, Reddy EP (1996) Transducers of life and death: TNF receptor superfamily and associated proteins. Oncogene 12:1-9.
Dillon C, Shah MK, Krause KJ, Zhu W, Voglweide MM, Smith DM, Crookett DP, Zhang H (2021) Metformin reduces neuroinflammation and improves cognitive functions after traumatic brain injury. Neurosci Res 172:99-109.

Dimou E, Comazzi M, Blazquez MA, Moloney G (2008) Pregnenolone of Olig-2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. J Neurosci Off J Soc Neurosci 28:10434-10442.

Donix K, Thues MH, Sumgulishvili I, Traivoso LG, Yu TS, Kernie SG, Liebl DJ (2015) Endogenous neural stem/ progenitor cells stabilize the cortical microenvironment after traumatic brain injury. J Neurotrauma 32:753-764.

Dominquez BL, Leblanc A, Laporte-Canterola H, Marinis F, Krause D, Deans R, Keating A, Prokop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Stem Cells 24:126-136.

Encinas JM, Sierra A (2011) Neurotrophic support for remyelination. J Neurosci Res 89:595-607.

Evans DG, Sahin H, Artigas F (2004) Migration patterns of subventricular zone cells in adult mice after cervical chord transection. Brain 127:1239-1250.

Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL, Wood LS, Inema I, Miller SE, Bieri DL (2016) Brain-derived neurotrophic factor (BDNF) promotes neurogenesis in the subventricular zone and enhances long-term neurogenic potential and promotes seizure susceptibility. Front Cell Neurosci 10:46.

Galvão RP, García-Verdugo JM, Alvarez-Buylla A (2008) Brain-derived neurotrophic factor signaling does not stimulate subventricular zone neurogenesis in adult mice and rats. J Neurosci Off J Soc Neurosci 28:13386-13388.

Galvin EM, Baker D, Mount GW, Goldstein AK, Lan GL, wood LS, Inema I, Miller SE, Bieri DL (2016) Brain-derived neurotrophic factor (BDNF) promotes neurogenesis in the subventricular zone and enhances long-term neurogenic potential and promotes seizure susceptibility. Front Cell Neurosci 10:46.

Georgieva SM, Zhang Y, Zhang S, Chen C, Li XH (2020) Injury-preconditioning secretome of umbilical cord mesenchymal stem cells promotes behavioral recovery after middle cerebral artery occlusion in rats. Neurobiol Dis 135:219-203.

Gineo R, Valsesia G, Tanini D, Rizzuto R, Cifelli A, Proces et al. (2013) Inhibition of IP3- and DAG-induced Ca2+ mobilization by TRPM7 reduces neurodegeneration after ischemic brain injury. Neuroscience 253:35-46.

Houlot J, Aboumaria N, Hinkley SFP, Clarkson AR (2019) Therapeutic potential of neurotoxins for repair after brain injury: a helping hand from biomaterials. Front Neurol 10:329.

Hughes AN, Appel B (2019) Oligodendrocytes express synaptic proteins that modulate axonal transport in vivo. Glia 67:749-759.

Jarvis E, Leslie M, Zambrowicz BP, Zavala MM (2004) Pregnenolone of Olig-2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. J Neurosci Off J Soc Neurosci 28:10434-10442.

Jin K, Li L, Mao X, Greenberg MB, Moore A, Peng B, Greenberg RB, Greenberg DA (2011) Inhibitors of glycogen synthase kinase 3β increase long-term neurogenic potential and enhance spatial memory formation. Cell Stem Cell 11:23-35.

Johnson-Cadwell AM, Johnson-Arrazola ML, Pyle AM, Vose J, Fonder MA (2013) Increased dorsally derived neurogenesis contributes to memory consolidation. Proc Natl Acad Sci U S A 110:8485-8490.

Katherine E., Shumaker O, Schoenfelder J, Zilles K, Kaiser H (2020) A high-resolution mouse subventricular zone stem-cell atlas. Cell 183:120-139.

Krause D, Deans R, Keating A, Prokop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Stem Cells 24:126-136.

Kriz A, Bartha G, Kenway K, Kowalski E, Cerna S, Ocampo CT, Wang YH, Theus MH (2011) Aggregation of astrocytotic injury and vascular-derived EphA4 prevents repeated moderate traumatic brain injury. J Neurotrauma 28:411-422.

Krause D, Deans R, Keating A, Prokop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Stem Cells 24:126-136.

Krause D, Deans R, Keating A, Prokop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Stem Cells 24:126-136.

Liu XY, Wei MG, Liang J, Xu HH, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanjani ED, Jiang J, Zhang Q, Wang KQ, Duan JH, Tu J, Bellocchio L, Zanja...