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

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

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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 damage that exacerbates the initial insult, triggering a majority of tissue loss. The secondary injury, which remains the target of most treatments, 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., 2016a; 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. Furthermore, 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 (Encinas and Sierra, 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., 2017).
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 supporting a proliferative response among SVZ progenitor cells post-injury (Chang et al., 2016). However, as SVZ precursors are largely responsible for the replacement of olfactory bulb interneurons through the rostral migratory stream in rodents, they have potent migration capabilities that complicate analysis of their role following TBI (Chen et al., 2013). 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 tissue. 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 differentiate into interneurons in the olfactory bulb (Bennett et al., 2009). Progenitors of 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 essential for astrocyte 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 cortical 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 understood. In particular, the circumventricular organs (CVOs) (Bennett et al., 2009, 2010), along with the third and fourth ventricles, as well as the meninges (Nakagomi et al., 2015; Bifari et al., 2017; Nakagomi and Matsuyama, 2017; Badner et al., 2021) have been characterized as novel stem cell niches in the adult brain. In vitro, cells from the CVOs form neurospheres and express neural progenitor markers (Bennett et al., 2009). Akin to the other progenitor pools discussed above, the CVOs, consisting of the area postrema, medulla oblongata, and subfornical organ, all display an increased proliferative response to TBI (Falnikar et al., 2018). These CVO-derived Sox2+ proliferating progenitors, especially in the area postrema, displayed doublecortin expression at 4 days post-injury, suggesting neuronal potential, although their functional role following TBI remains uncertain. Despite potential roles in TBI, progenitors of the CVOs may contribute to recovery is necessary for the development of effective treatment strategies aimed at endogenous repair.

Exogenous Cell Transplantation As a Strategy to 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, 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 neural progenitor proliferation. Specifically, adult neurogenesis has 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 (Liu et al., 2020), further validating the significance of trophic support in endogenously applied 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. In the controls, high GFAP expression post-injury was inversely associated 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 were found to exhibit changes in functional morphology (Bergles et al., 2000), a more severe injury also results in OPC morphological changes, proliferation and migration to the site of injury (von Streitberg et al., 2012). Furthermore, although OPC numbers remain 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.

Non-Cellular Strategies for An Enhanced Endogenous Progenitor Response Following 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 (DBona et al., 2018). Most importantly, metformin is found to increase expression of CREP protein kinase C-pathway and enhance endogenous neurogenesis (Wang et al., 2012). Future work should explore the spatial distribution and cellular population and their relevance in models of trauma.
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 stem/stromal cells or neural stem cells), metformin administration or the use of neurotrophic factors. Accurately tracking endogenous progenitors is essential to injury repair, as this will go a significant distance 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 (Henry et al., 2007; Choi et al., 2009). Specifically, heterozygous BDNF knockout has been shown to limit basal levels of hippocampal neurogenesis (Lee et al., 2002) and osmotic pump-mediated exogenous BDNF infusion reportedly increased hippocampal neurogenesis (Scharffman et al., 2005). In contrast, within the SVZ, neurogenesis was unaffected by knockdown of the BDNF receptor tropomyosin receptor kinase B, in mice (Galvão et al., 2008). To further elaborate interpretation, in the context of TBI, mRNA expression of BDNF and its receptors (tropomyosin receptor kinase B as well as p75) 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 tumor 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 et al., 1993; Barker, 1997). For this reason, use of BDNF as a strategy for endogenous repair is likely dependent 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 (Caciagli, 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 (Johansen et al., 2021; Houlton et al., 2019; Caciagli, 2021).

Limitations in Tracking the Endogenous Progenitor Response

Accurately tracking endogenous progenitors, especially following neurotrauma, continues to be a major challenge in the field. Therefore, some of the reported discrepancy, described throughout this review, may stem from use of unique species, strains, and tools to assess progenitor populations. Viral as well as genetic lineage tracking and, more recently, single cell sequencing, spatial transcriptomics and two-photon in vivo imaging all present distinct strengths and weaknesses in analysis. Further, as each presents a different perspective in the progenitor response, interpretation may vary widely based on the tools applied. For example, while genetic lineage tracing provides a large-scale overview of the cell population of interest as well as allowing for temporal assessment, the identified population is likely heterogeneous, limiting understanding of interactions among subpopulations. In opposition, single cell sequencing highlights detailed transcriptional differences among specific subpopulations with limited spatiotemporal information. Future work will need to apply multiple approaches for a more complete picture.

Concluding Perspective

Overall, as highlighted throughout this review, there is significant evidence that BDNF 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 of each neurosphere of adult brain progenitors, stimulation of endogenous neurogenesis remains a promising strategy for repair following neurotrauma.

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