Review

Impact of pediatric traumatic brain injury on hippocampal neurogenesis

https://doi.org/10.4103/1673-5374.297057

Date of submission: May 12, 2020

Date of decision: June 21, 2020

Date of acceptance: August 4, 2020

Date of web publication: November 16, 2020

Mariam Rizk, Justin Vu, Zhi Zhang*

Abstract

Traumatic brain injury (TBI) is a major cause of mortality and morbidity in the pediatric population. With advances in medical care, the mortality rate of pediatric TBI has declined. However, more children and adolescents are living with TBI-related cognitive and emotional impairments, which negatively affects the quality of their life. Adult hippocampal neurogenesis plays an important role in cognition and mood regulation. Alterations in adult hippocampal neurogenesis are associated with a variety of neurological and neurodegenerative diseases, including TBI. Promoting endogenous hippocampal neurogenesis after TBI merits significant attention. However, TBI affects the function of neural stem/progenitor cells in the dentate gyrus of hippocampus, which results in aberrant migration and impaired dendrite development of adult-born neurons. Therefore, a better understanding of adult hippocampal neurogenesis after TBI can facilitate a more successful neuro-restoration of damage in immature brains. Secondary injuries, such as neuroinflammation and oxidative stress, exert a significant impact on hippocampal neurogenesis. Currently, a variety of therapeutic approaches have been proposed for ameliorating secondary TBI injuries. In this review, we discuss the uniqueness of pediatric TBI, adult hippocampal neurogenesis after pediatric TBI, and current efforts that promote neuroprotection to the developing brains, which can be leveraged to facilitate neuroregeneration.

Key Words: adult hippocampal neurogenesis; astrocytes; development; microglia; neuroinflammation; neuroregeneration; oxidative stress; pediatric traumatic brain injury; plasticity; stem cell

Introduction

Traumatic brain injury (TBI) is a major cause of mortality and morbidity in the pediatric population. Children aged 0–4 years old have the highest rate of emergency department (ED) visits. As TBI mortality rates have declined, more children and adolescents are living with TBI-related cognitive and emotional impairments (Cheng et al., 2020). Especially, children who have sustained a brain injury at a younger age are at a high risk of experiencing deficits in cognitive, social, and behavioral sequelae over time, which negatively affects the quality of their life (Neumane et al., 2020). To date there is no therapy that shows a significant benefit in pediatric clinical trials for TBI, and there are unmet needs to develop new age-appropriate treatments for pediatric patients. In this review, we will discuss the uniqueness of pediatric TBI, adult hippocampal neurogenesis after pediatric TBI, factors and potential therapeutics that augment endogenous hippocampal neurogenesis.

Search Strategy and Selection Criteria

This review was compiled by using "PubMed" and "Web of Science Core Collection" with sources within the last 5 years, with an emphasis on the most recent, novel, and comprehensive papers. If the topic did not have relevant information within the last 5 years, we used the most recent paper. Due to the strict limit of 50–100 references, we could not cite all of the relevant publications.

Unique Considerations in the Pathophysiology of Pediatric Traumatic Brain Injury

The pathophysiology of TBI consists of primary and secondary injuries. The primary brain injury is inevitable; however, the secondary brain injury provides a window of treatment. The secondary injury triggers a series of complex pathophysiological events including oxidative stress, neuroinflammation, and apoptosis, leading to disruption of the neural networks and compromise of behavioral and cognitive functions (Ryan et al., 2019). Pediatric TBI populations are heterogenic due to the unique characteristics of the immature brain, including axonal outgrowth, synaptogenesis, and myelination, which exhibit a specific pathological response to brain injury (Sta Maria et al., 2019). Moreover, the heterogeneous outcomes in pediatric TBI patients are determined by mediating variables, such as age at the time of injury. The age at the time of injury is a crucial factor that impacts neuropsychological outcomes. There are neuroanatomical and functional changes at different maturational stages (infant, toddler, and adolescent). Studies in humans show 0–2 years of age is characterized by rapid and dynamic brain development to establish cognitive abilities and behaviors, while brain development after 2 years of age mainly focuses on "fine-tuning" of the existing major circuits and networks (Gilmore et al., 2018). For example, white matter tracks are largely formed at birth, and myelination and

Department of Natural Sciences, University of Michigan-Dearborn, Dearborn, MI, USA

*Correspondence to: Zhi Zhang, MD, PhD, zhizhan@umich.edu.

https://orcid.org/0000-0001-6256-9516 (Zhi Zhang)

Funding: This work was supported by the Startup Grant for ZZ from the Department of Natural Sciences, University of Michigan-Dearborn and "CASL Faculty Summer Research Grant" for ZZ from Office of Research & Sponsored Programs, University of Michigan-Dearborn.

How to cite this article: Rizk M, Vu J, Zhang Z (2021) Impact of pediatric traumatic brain injury on hippocampal neurogenesis. Neural Regen Res 16(5):926-933.

maturation of existing white matter network develop rapidly after birth (Gilmore et al., 2018). Brain development during adolescence shows region-specific structural and functional changes that correlate with the development of higher cognitive and executive functions. For example, myelination progresses further in the prefrontal cortex, and the thickness and density of the gray matter increase in the primary language cortex (Vijayakumar et al., 2016). Therefore, injuries occurred at different stages of brain development in children can have different impacts on their academic performance and executive functions, some of which only become apparent months or even years after the initial injury.

It has been found that injuries sustained at a younger age can cause more persistent deficits when compared to older children with injuries of similar severity, suggesting that immature brains exhibit increased vulnerability to environmental disruption and heightened susceptibility to insult (Sta Maria et al., 2019). It is well-known that a critical period in brain development correlates with enhanced plasticity and sensitivity which is heavily influenced by environmental demands. Therefore, injury-induced plasticity in an immature brain can alter or even cease brain developmental processes entirely (Hagberg et al., 2015).

In the context of brain injury associated disruption to programmed developmental processes, the immature brain may be more 'vulnerable' due to derailed developmental processes and depleted neural resources (Zamani et al., 2020). Infancy and childhood are critical developmental stages associated with rapid dendritic growth and synaptogenesis. Brain insults at infancy and childhood disrupt normal development in the damaged brain regions, alter neural circuitry and cellular environment, and result in delayed recovery in pediatric patients, compared with adult patients with TBI (Zamani et al., 2020). For example, pediatric TBI patients have demonstrated prominent gray and white matter volume loss, compared to age matched controls (Cox et al., 2019). Therefore, the interruption of brain development during critical period places a child at additional risk for neuropsychological deficits beyond those that are the direct result of brain injury. Currently, there is no effective therapy in the treatment of pediatric TBI, and there are urgent needs to develop age-appropriate therapeutics for pediatric patients.

Dysregulation of Adult Hippocampal Neurogenesis after Pediatric Traumatic Brain Injury

Evidence shows that recovery from TBI can be limited by the irreversible loss of neurons, leading to significant impairment of cognitive, motor, and emotional functions (Neumane et al., 2020). There is an ever-expanding interest in incorporating adult-born granule cells to the hippocampal circuitry to rescue neuronal loss and cognitive deficits. Stem cell-based therapies and/or cellular therapies have been used to promote tissue replacement, and modify neuroinflammation and immune responses. For example, administration of secretome from umbilical cord mesenchymal stem cells can promote adult hippocampal neurogenesis and improve cognitive function after TBI (Liu et al., 2020). However, the potential therapeutic efficacy is significantly affected by the timing and route of cell delivery, and the cellular microenvironment at the site of the injury (Cox et al., 2019). It has been indicated that neural stem cell (NSC) transplantation in a hostile environment can lead to severe gliosis (Cox et al., 2019). Therefore, stimulation of innate neuro-regenerative mechanisms to support or replace damaged neurons may provide a promising alternative.

Dentate gyrus (DG), a hippocampal subfield, plays an important role in learning and memory. DG is particularly vulnerable to TBI even when it is not directly injured (Zhang et al., 2015a, 2020). Injury-induced neuronal loss in the hippocampal DG has been associated with cognitive deficits after pediatric TBI (Zhang et al., 2020). The DG of hippocampus has the ability for self-renewal through the process of adult neurogenesis in the mammalian brain, including human (Moreno-Jimenez et al., 2019). The adult-born DG granule cells play an important role in learning and memory (Goncalves et al., 2016; Anacker and Hen, 2017; Miller and Sahay, 2019), and emotional regulation (Yun et al., 2016). Although adult neurogenesis occurs throughout life, it decreases with age in adult humans (Sorrells et al., 2018). The impaired adult hippocampal neurogenesis has been correlated with cognitive decline during aging and in neurodegenerative disorders (Moreno-Jimenez et al., 2019).

The outcomes of pediatric TBI are impacted by the severity of injury, which is typically categorized as mild, moderate, or severe. More severe injuries, such as larger, more diffused, and bilateral injuries, are associated with worse physical and cognitive performance in pediatric patients with TBI (Neumane et al., 2020). Studies have shown an enhanced NSC proliferation in correspondence to increased TBI severity, leading to compensation of mature neuron loss (Wang et al., 2016). Longitudinal studies indicate that mild to moderate TBI recovery typically shows an asymptotic pattern in human patients, with rapid improvement within the first weeks and months of injury, followed by a slower rate of improvement, and a plateau or even deterioration afterwards (Ledoux et al., 2019). Interestingly, TBI can induce an acute upregulation of newborn neurons, followed by a chronic reduction of baseline neurogenesis, which may be due to the depletion of neural progenitors and/or the death of immature hippocampal neurons (Ngwenya and Danzer, 2018). Therefore, the neuronal loss and impaired endogenous neurogenesis in the hippocampus may contribute to TBI-induced neuropathological outcomes.

In theory, augmentation of adult hippocampal neurogenesis after TBI could facilitate cognitive recovery (Villasana et al., 2015). However, neurons born after various neuronal injuries can have morphological and functional abnormalities, which can result in negative outcomes (Ibrahim et al., 2016). For example, TBI results in aberrant migration and impaired dendrite development of adult-born neurons, which may cause dysregulated neural network connectivity (Ibrahim et al., 2016; Zhang et al., 2020). Therefore, a better understanding of post-injury hippocampal neurogenesis can facilitate a more successful repair of the damaged immature brain.

Factors that Affect Adult Hippocampal Neurogenesis

Adult hippocampal neurogenesis is a complex process, which includes NSC proliferation, differentiation, migration, maturation, and functional integration into the existing neuronal network (Alvarez et al., 2016). Adult hippocampal neurogenesis is dynamically regulated by a number of intrinsic as well as extrinsic factors (Vicidomini et al., 2020). A variety of therapeutic approaches have been proposed for promoting post-injury neurogenesis and ameliorating secondary injuries after TBI. Manipulations, such as exercise, and an enriched environment increase adult hippocampal neurogenesis (Alvarez et al., 2016). However, a successful regenerative response to injury requires not only NSC proliferation but also proper migration and integration of new neurons into the existing hippocampal circuitry (Villasana et al., 2015; Ibrahim et al., 2016). Aberrant migration of adult-born neurons can lead to the malfunction of neural network and increase seizure susceptibility (Villasana et al., 2015). Developing effective therapeutics for neuroprotection or neurorestoration is particularly difficult due to the complexity and heterogeneity of TBI. Dynamic interactions between inflammatory and

metabolic pathways is a hallmark of secondary injury after TBI, therefore, a successful therapy requires targeting multiple injury pathways. In the following section, we will discuss the impact of neuroinflammation, mitochondrial oxidative stress, lipid metabolism, tryptophan metabolism, and epigenetic regulation on the adult hippocampal neurogenesis after pediatric TBI (**Figure 1**).

The role of neuroinflammation

Neuroinflammation, a secondary injury response following TBI, plays an important role in determining TBI outcomes. Neuroinflammation is a complex interaction between neurons and glial cells (e.g., astrocytes and microglia), and soluble components (e.g., cytokines and chemokines), which can be beneficial for debris clearance, and regeneration of injured tissues. However, dysregulated neuroinflammation can cause more neuronal death and progressive neurodegeneration. The neurogenic niche, an intrinsic microenvironment, regulates adult-born neurons by different components (Sofroniew, 2015; Vicidomini et al., 2020). Neuroinflammation at the neurogenic niche is regulated, in part, by activated microglia, the resident macrophages of the brain, which plays an important role in maintaining central nervous system homeostasis under physiological conditions (Vicidomini et al., 2020). Microglia are highly proliferative, and regulate synaptic pruning and survival of newborn neurons (Weinhard et al., 2018). Moreover, the neuron-microglia interaction determines the distinct profiles of microglia-secreted chemokines and cytokines. For example, neuron-derived fractalkine (CX3CL1; FKN) acting on the CX3CR1 receptors expressed in microglia can promote adult hippocampal neurogenesis (Vicidomini et al., 2020). TBI-induced microglial activation can be both detrimental and beneficial. For example, microglial activation can increase nitric oxide synthesis and pro-inflammatory cytokine release, which leads to blood-brain barrier (BBB) dysfunction and neuronal apoptosis (Corrigan et al., 2016; Kumar et al., 2017). However, microglia can also serve a neuroprotective role by clearing damaged cell debris, releasing anti-inflammatory cytokines, and promoting tissue repair (Russo and McGavern, 2016; Willis et al., 2020).

Neuroinflammation and long-lasting microglial activation play a key role in the cognitive deficits and impairment of adult hippocampal neurogenesis following pediatric TBI (Zhang et al., 2015a, 2020). Microglia are involved in all of the steps of adult hippocampal neurogenesis, including NSC proliferation, differentiation, and incorporation into the existing neural network. Microglial activation can be correlated with increased or decreased neurogenesis, which may be due to the heterogeneity of microglia (Masuda et al., 2019). Pro-inflammatory microglia release pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, which increase the death of neurogenic NSC lineage, and decrease the complexity of neurites of immature newborn neurons (Hueston et al., 2018). However, the role of microglia after TBI is still contradictory. A recent study shows that the removal of microglia has little effect on the outcome of TBI, but induction of a neuroprotective microglial phenotype can profoundly improve the survival of newborn neurons and alleviate cognitive function via IL-6/IL-6 receptor (IL-6R) signaling pathway (Willis et al., 2020).

Astrocytes maintain BBB integrity, modify neuronal excitability and metabolism, and regulate synapse formation and neurotransmission (Farhy-Tselnicker et al., 2017; Blanco-Suarez et al., 2018). Astrocytes provide structural and functional support for NSC proliferation, differentiation and maturation in the neurogenic niche (Vicidomini et al., 2020). Astrocytes express a variety of membrane-bound and secreted factors that regulate the development and maturation of newborn neurons (Sultan et al., 2015; Clarke et al., 2018). Astrocytes undergo morphological changes after TBI, and

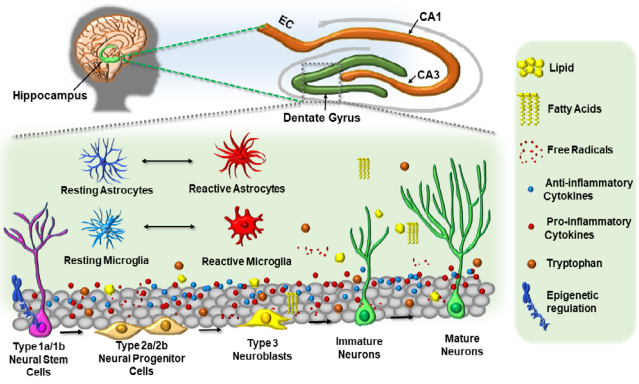

Figure 1 | **The impact of neuroinflammation, mitochondrial oxidative stress, lipid metabolism, tryptophan metabolism, and epigenetic regulation on the adult hippocampal neurogenesis after pediatric traumatic brain injury.**

secrete both pro-inflammatory cytokines such as IL-1β, and neurotrophic factors such as transforming growth factor beta (TGF-β) (Clement et al., 2020). Therefore, reactive astrocytes act as a double-edged sword, and plays an important role in pathophysiological processes after pediatric TBI (Clement et al., 2020). Excessive activation of astrocytes potentiate inflammatory response and lead to formation of glial scars, which limits neural regeneration and neuroplasticity.

Oligodendrocyte progenitor cells (OPCs), a subtype of glial cells in the central nervous system, provide the basis for myelination in their mature form as oligodendrocytes (OLGs). TBI can cause traumatic axonal injuries (TAI), leading to demyelination in intact axons and oligodendrocyte death. Axon recovery after TBI becomes extremely dependent on the capabilities of OPCs and their contribution to myelin regeneration. Evidence indicates that neuroinflammation dynamically regulates the proliferation and recruitment of OPCs following TBI. For example, pro-inflammatory cytokines can initiate the death of proliferative OPCs and mature oligodendrocytes (Braun et al., 2017), which might be responsible for progressive white matter injury and long-term functional deficits in pediatric TBI patients (Dennis et al., 2015; Genc et al., 2017).

Neuroinflammation is a complex process that can enhance or suppress neurogenesis, depending on the phenotypes of glia cells, and the duration of inflammation. Therefore, a better understanding of the entire neuroinflammatory cascade can facilitate targeted anti-inflammatory treatments to improve outcomes following TBI.

The role of lipid metabolism

The highly variable outcomes after pediatric TBI can be attributed to the intrinsic nature of the developing brain, including lipid metabolism. Lipids are essential for a variety of functions, including myelination, membrane integrity, and neurotransmission (Bowman et al., 2019). Polyunsaturated fatty acids, such as arachidonic acid and docosahexaenoic acid (DHA), are particularly abundant in brain phospholipids and essential for axonal outgrowth. Polyunsaturated fatty acids are a target for lipid peroxidation following TBI due to their highly oxidizable structure, generating numerous oxidized free fatty acid (FFA) that correlate with both injury severity and mortality in human patients with TBI (Bowman et al., 2019). Oxidized FFA are important signaling molecules involved in numerous cellular responses, including neuroinflammation (Dennis and Norris, 2015). Studies demonstrate that FFA metabolism significantly changed after pediatric TBI (Chitturi et al., 2018). Increased FFA following TBI is associated with poor outcomes by promoting apoptosis and stimulating pro-inflammatory responses (Chen et al., 2017). Oxidized FFA can be produced

via calcium-dependent or mitochondrial-based/calcium-independent pathways (Tyurina et al., 2014). In the calcium-dependent pathway, the polyunsaturated fatty acids derived from cellular and organellar membranes are hydrolyzed from phospholipid precursors via calcium-dependent phospholipase A2 (PLA2), and subsequently peroxidazed by cyclooxygenases, lipoxygenases, and cytochrome P450 (Tyurina et al., 2014). Cytochrome P450 enzymes are monooxygenase and oxidize arachidonic acid to epoxyeicosatrienoic acids and hydroxy-eicosatetraenoic acids. The cytochrome P450 4A (CYP4A) catalyzes the ω-hydroxylation of arachidonic acid to 20-hydroxyeicosatetraenoic acid (20-HETE) (Tyurina et al., 2014). Studies have shown that 20-HETE can increase reactive oxygen species and promote inflammation. Administration of a 20-HEHE synthesis inhibitor improves outcome after pediatric TBI (Shu et al., 2019).

Lipid metabolism can also influence proliferation and differentiation of adult neural progenitors (Knobloch et al., 2017). Oxidized fatty acids play an important role in energy production, and inhibition of fatty acid oxidation in hippocampal neurogenesis niche leads to increased quiescent NSC death and reduced NSC proliferation (Knobloch et al., 2017). Evidence shows defects in oxidized fatty acids lead to enhanced progenitor generation, but subsequently reduce embryonic NSC pool during brain development (Xie et al., 2016). Aberrant lipid metabolism in the neurogenic niche reduces NPC differentiation towards the neuronal lineage (Engel et al., 2019).

Lipid metabolism is regulated by different factors, such as apolipoprotein E (ApoE) and adiponectin. ApoE is mainly secreted by astrocytes and regulates lipid transport and homeostasis, and supports neuronal development, beta-amyloid metabolism, and BBB integrity (Koizumi et al., 2018). There are three major isoforms of ApoE, including ApoE2, ApoE3, and ApoE4. ApoE4 is associated with late-onset Alzheimer's disease, cognitive impairment, and tau hyper-phosphorylation after TBI (Koizumi et al., 2018). Injury can induce rapid ApoE synthesis in neurons, which participate in lipid transport and redistribution for membrane repair and remodeling. Studies have shown that ApoE mimetic peptide reduces BBB disruption, tau accumulation, inflammatory microglia activation, and ameliorates brain edema and neuronal degeneration (Qin et al., 2017). However, neurons can generate abnormal and neurotoxic ApoE fragments, especially ApoE4, which can be targeted for proteolytic cleavage, and translocate into the cytosol, leading to mitochondrial dysfunction and neurodegeneration (Mahley and Huang, 2012). ApoE4-associated phospholipid dysregulation impairs BBB integrity and results in tau hyper-phosphorylation after TBI (Cao et al., 2017; Teng et al., 2017). Studies indicate that ApoE regulates the development of adult newborn hippocampal neurons, and modulates injury-induced dendritogenesis and synaptogenesis of hippocampal NSCs (Tensaouti et al., 2020). Moreover, ApoE acts as a negative regulator of NSC proliferation at later ages of injury when the progenitor pool is depleted (Tensaouti et al., 2020), while ApoE ablation shifts NSPC differentiation towards astrogenesis instead of neurogenesis (Hong et al., 2016).

Adiponectin is involved in several physiological processes, such as glucose and lipid homeostasis, neuroinflammation, and neurogenesis (Bloemer et al., 2018). Two major types of adiponectin receptors, Adipor1 and Adipor2, are expressed in different brain regions, including the neurogenic niche at hippocampal DG (Bloemer et al., 2018). Adiponectin increases proliferation of hippocampal NSCs, mediates physical exercise-induced hippocampal neurogenesis, and reduces depression-like behaviors (Yau et al., 2015). Adiponectin deficiency reduces NSC proliferation and differentiation, decreases dendritic length and complexity of DG granule cells, and increases susceptibility to cognitive deficits and depression (Zhang et al., 2016a, 2017).

Abnormal lipid metabolism contributes to the secondary injury following pediatric TBI. The transient metabolic disturbance after pediatric TBI can interrupt highly orchestrated metabolic processes that are essential for healthy brain development, leading to long-term impairment of NSC function. Evidence indicates that the increase in neurogenic response at the acute phase after TBI is transient, while the long-term survival rate of newly formed neurons is reduced compared to control levels (Bramlett and Dietrich, 2015). Therefore, therapeutic strategies that can reduce delayed and progressive neurodegeneration is an area that needs to be emphasized in future research.

The role of mitochondria and oxidative stress

Mitochondria play an important role in ATP synthesis, intracellular calcium buffering, oxidative stress, and apoptosis (Fischer et al., 2016). Under physiological conditions, mitochondria undergo fission and fusion to maintain metabolic homeostasis; however, TBI can induce an imbalance in this process, which contributes to neuronal death (Balog et al., 2016). For example, abnormally increased fission can cause mitochondria fragmentation, while inhibition of fission can reduce the loss of hippocampal neurons and improve learning and memory after TBI (Wu et al., 2016). Mitochondria also play a key role in the proliferative and differentiation of NSCs. Mitochondrial inhibition promotes selective death of immature adult-born neurons, while mitochondrial protection improves survival of immature adult-born neurons under inflammatory conditions (Volobouеva et al., 2017).

The synthesis of reactive oxygen species and reactive nitrogen species, such as nitrous oxide increases after TBI, which is proportional to lipid peroxidation, and causes DNA damage (Kumar Sahel et al., 2019). This is signified by the decrease in antioxidants such as superoxide dismutase, glutathione, and glutathione peroxidase. The alteration in the pro- and antioxidant balance results in oxidative stress, which is linked to axonal injury, impaired synaptic plasticity, and cognitive deficits (Corrigan et al., 2016). Oxidative stress induces acute structural and functional damage to mitochondria, impairs ATP synthesis, and contributes to cell death and poor cognitive outcomes (Fischer et al., 2016). The damages to the mitochondria, such as calcium overload, can result in energy failure, and increase reactive oxygen species production, which further enhances oxidative stress (Kumar Sahel et al., 2019). Drugs that target mitochondrial dysfunction, specifically in the diseased cells, can offer neuroprotection and improve cognition following TBI.

The role of tryptophan metabolism

Pro-inflammatory cytokines, such as IL-1β, can affect neurogenesis via alterations of the tryptophan (TRP)-kynurenine (KYN) pathway (Borsini et al., 2017). TRP, an essential amino acid, is required for protein synthesis to ensure cell survival, and plays an important role in health and disease (Comai et al., 2020). TRP can be metabolized into KYN by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). Under physiological conditions, KYN is mainly metabolized via a "neuroprotective pathway" to kynurenic acid (KYNA), a N-methly-D-aspartate (NMDA) receptor antagonist, by kynurenine-amino-transferase expressed by astrocytes. Under pathological conditions, such as neuroinflammation, KYN is catabolized via a "neurotoxic pathway" into quinolinic acid (QUIN), a NMDA receptor agonist and co-enzyme of nicotinamide adenine dinucleotide (NAD+) by kynurenine monooxygenase (KMO) expressed in microglia (Comai et al., 2020). Therefore, QUIN/KYNA ratio, an indicator of the homoeostasis of glutamatergic neurotransmission, is dynamically regulated by microglia

and astrocytes. Studies show that IDO is upregulated after injury, strengthening the deleterious excitotoxic pathway of the KYN metabolism (Yan et al., 2015; Zhang et al., 2018). Overproduction of QUIN after TBI can increase neurotoxicity, cytosolic calcium level, mitochondrial dysfunction, and oxidative stress in the neurogenic niche, leading to impaired adult hippocampal neurogenesis (Borsini et al., 2017).

TRP can also be hydroxylated to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase (TPH), and decarboxylated into 5-hydroxytryptamine (5-HT; serotonin) by aromatic amino acid decarboxylase (DDC). 5-HT is further metabolized to 5-HIAA via monoamine oxidase (MAO-A) and aldehyde dehydrogenase (AD). Meanwhile, 5-HT can also be converted into N-acetylserotonin via serotonin-N-acetyltransferase, and is then transformed to melatonin (MLT) by hydroxyindole-O-methyltrasferase. 5-HT and MLT are implicated in regulating many processes including mood, sleep, and inflammation (Comai et al., 2020). Studies show that melatonin modulates NSC differentiation in the DG, and enhances cell survival and dendrite maturation of new-born neurons (Figueiro-Silva et al., 2018). Pediatric TBI switches TRP catabolism from serotonin pathway to the KYN pathway, and leads to melatonin depletion (Zhang et al., 2018). The melatonin depletion might contribute to the impaired hippocampal neurogenesis and cognitive deficits in pediatric TBI (Zhang et al., 2020).

The role of epigenetic regulation

The density and function of NSCs in the developing brain are not only regulated by extrinsic factors in the neurogenic niche, but also modulated by intrinsic molecular mechanisms. Epigenetic mechanisms, such as DNA methylation, histone modification, as well as pre- and post-transcriptional modifications, can control proliferation, differentiation and maturation of NSCs in the DG. For example, DNA methylation regulates Notch signaling target gene activity and differentially modulates the proliferation of NSCs after TBI (Zhang et al., 2015b). Histone deacetylase 4 downregulation after TBI induces aberrant activation of the Pax3-Ngn2 signaling pathway, leading to the impairment of hippocampal neurogenesis (Saha et al., 2019). To date, few studies have explored the role of epigenetic regulations of hippocampal NSCs after pediatric TBI, especially between acute injury and long-term impact on NSC's function and pool size. Understanding the molecular mechanisms involved in the epigenetic regulation of NSCs will aid in advancing our knowledge of the role of hippocampal neurogenesis in degeneration and regeneration after TBI. These epigenetic mechanisms can facilitate the development of therapeutics that promote long-lasting self-renewal of NSCs.

Potential Therapeutics Targeting Adult Hippocampal Neurogenesis after Pediatric Traumatic Brain Injury

Neuroprotective strategies targeting secondary injuries after TBI have been explored in both pre-clinical animal models and clinical trials. We will discuss pharmacological agents that have been approved by U.S. Food and Drug Administration (FDA) and currently used in clinical trials.

N-acetylcysteine

N-acetylcysteine (NAC) is a US FDA-approved pharmacological agent that shows neuroprotective agent effects in central and peripheral nervous system injuries (Hoffer et al., 2017). N-acetylcysteine amide (NACA), an amide derivate of NAC, has improved hydrophobicity and lipophilicity and a prolonged plasmatic half-life, leading to increased penetration into the BBB, mitochondria, and other cellular constituents (Bhatti et al., 2017). NAC and NACA have antioxidant and anti-inflammatory properties, which increase brain glutathione, and decrease neuroinflammation and oxidative stress in preclinical animal models of TBI (Hoffer et al., 2017). Clinical studies have shown that NAC decreased neuroinflammation and oxidative stress, reduced imbalance and headache following TBI in military personnel, and improved cognitive functioning and brain perfusion in retired professional football players (Bhatti et al., 2017). Studies using a combination therapy have demonstrated a greater potency using synergistic drug combinations. For example, the combination of minocycline and NAC synergistically prevented cognitive deficits in a mouse model of TBI (Sangobowale et al., 2018). However, the therapeutic efficacy of NAC in pediatric patients remain inconclusive. For example, a recent phase I randomized clinical trial conducted in pediatric patients (2–18 years of age) demonstrates that co-administration of NAC and probenecid (an antimicrobial agent) increases bioavailability of NAC and probenecid without adverse effects. However, this combination therapy did not improve the Glasgow outcome scale upon hospital discharge or at 3 months follow-up (Clark et al., 2017). Although studies conducted in animal models can provide insight and guidance to NAC use in TBI patients, the translation strategies require major efforts and collaboration between clinicians and scientists.

Minocycline

Minocycline is a well characterized, safe, and FDA approved anti-inflammatory drug, and has been used experimentally and clinically. Minocycline has high BBB permeability, decreases neuroinflammation, prevents injury-induced hyperthermia, and improves neurological function in a preclinical model of TBI (Taylor et al., 2018). In addition, minocycline treatment reduces high-mobility group box protein 1 (HMGB1) translocation to cytoplasm, attenuates microglial activation, and improves cognition after pediatric TBI (Simon et al., 2018). Although minocycline reduces neuroinflammation and improves neurological outcome, it does not increase neurogenesis (Ng et al., 2012). Clinical studies of minocycline in TBI have reported varying results. In a recent study, minocycline was administered to patients with moderate to severe TBI at a dose twice that as recommended for treatment of infection, leading to an improved outcome (Meythaler et al., 2019). However, another study indicates that minocycline treatment reduced chronic microglial activation, but increased brain atrophy and neurodegeneration (Scott et al., 2018).

Docosahexaenoic acid

Studies suggest that FFA contributes to the secondary injury after TBI. Enhancing mitochondrial function and FFA oxidation in mitochondria after TBI may improve neuroprotection to lessen post-injury cell death (Bowman et al., 2019). Omega-3 polyunsaturated fatty acid (ω-3 PUFA), such as DHA, provides energy support through lipid synthesis, regulates inflammatory response, and exhibits antioxidative and anti-inflammatory effects by attenuating proinflammatory microglial activation (Chen et al., 2017). Endogenous synthesis of DHA from alpha-linoleic acid (ALA) is very limited in mammals. Therefore, DHA accrual depends mainly upon dietary intake (Zarate et al., 2017). The baseline DHA need is high in infant and children due to the rapidly growing brain, and DHA is widely available as a nutritional supplement for infants and children (Zarate et al., 2017). Under physiological conditions, DHA is a critical "building block" that esterified into membrane phospholipids (Zarate et al., 2017). Under pathological conditions, such as TBI, ATP level decreases after injury, which prevents the reutilization of DHA via re-esterification, and results in the loss of DHA released from disrupted neural membranes. DHA deficiency is associated with poor outcomes after experimental TBI (Desai et al., 2016). Pediatric TBI decreases brain DHA content, and DHA treatment ameliorates oxidative

stress, inflammation, white matter injury, and improves neurologic outcomes in pediatric preclinical TBI models (Schober et al., 2020). However, these effects have been less conclusive in humans due to the heterogeneity of injury, and the differences in endogenous DHA synthesis and recycling in human patients.

Melatonin

Melatonin is a promising, well-tolerated, neuroprotective agent, and is recommended as part of the management plan of pediatric TBI (Santini et al., 2018). Melatonin reduces oxidative stress, neuroinflammation, and neurodegeneration after TBI (Barlow et al., 2019; Rehman et al., 2019). Amelioration of oxidative stress can create a favorable milieu for NSCs and can be an effective therapeutic approach for neuroprotection and neurofacilitation following TBI. Melatonin activates inhibitory gamma-aminobutyric acid (GABA) receptors, especially $GABA_A$ receptors, which counter-balance glutamate excitotoxicity (Barlow et al., 2019). Melatonin offers therapeutic potential for many of the common post-TBI symptoms such as sleep disruption and mood disturbance (Barlow et al., 2019). A recent study has demonstrated that *N*-acetyl serotonin, a precursor of melatonin, has strong antioxidant and anti-apoptotic effects by activation of tropomyosin-related kinase receptor B-mediated signaling cascades. *N*-acetyl serotonin improves hippocampal neurogenesis and ameliorates cognitive impairments after TBI (Li et al., 2019). Although melatonin significantly improved neurological, cognitive, and motor function in pre-clinical animal models (Barlow et al., 2019), the efficacy of melatonin remains controversial in the treatment of pediatric TBI patients. In a randomized, double-blinded study, melatonin decreased hyperactivity in pediatric patients, but did not improve the overall outcomes (Barlow et al., 2020).

Nanoparticles-guided drug delivery

Most drugs undergoing preclinical and clinical trials for TBI lack the ability to target specific tissues, cells and organelles. Nanoparticles, such as dendrimers, may be helpful by delivering therapeutics specifically to target cells and organelles (Nance et al., 2016; Zhang et al., 2016b). For example, dendrimer-conjugated NAC, dendrimer-conjugated minocycline, and dendrimer-conjugated sinomenine have shown significant promise in target delivery of NAC, minocycline, and sinomenine to activated microglia and astrocytes at the site of brain injury, producing remarkable improvements in neurological outcomes at a lower dose than non-conjugated free drugs (Nance et al., 2017; Sharma et al., 2017, 2018b, 2020). In pre-clinical animal models of pediatric TBI, dendrimer-mediated delivery can target microglial mitochondria at the site of brain injury, which provides a useful tool for reducing mitochondrial dysfunction and oxidative stress (Sharma et al., 2018a). Considering the crucial role that the microglia plays in NSC development and maturation, designing therapies that target microglia cells at the appropriate time points may facilitate long-term recovery after pediatric TBI.

Therapeutic time window and long-term outcomes

The translation of positive pre-clinical findings targeting acute neuroprotection fails to improve long-term functional outcomes in clinical trials of TBI (Bramlett and Dietrich, 2015). Therapeutic time window plays a critical role in the treatment of TBI because most drugs lose efficacy with increasing intervals between the onset of injury and the time to first treatment (Mohamadpour et al., 2019). The therapeutics mentioned above are mostly utilized in the acute phase of injury, and the therapeutic efficacy at different time windows post-injury were not analyzed. In addition, multiple outcome measures, such as cognition, motor, and psychosocial outcomes should be performed during the chronic phase of injury following a therapeutic intervention. It is anticipated that combinational approaches that target different cellular and molecular pathways can extend the therapeutic time window in the treatment of chronic consequences of TBI, and ultimately improve the quality of life in pediatric patients.

Concluding Remarks and Future Directions

In this review, we have taken a holistic view of hippocampal neurogenesis after pediatric TBI, beginning with characteristics of pediatric TBI leading to hippocampal neurogenesis impairment and progressing to potential therapeutics for promoting endogenous neurogenesis and regeneration. We highlight neuroinflammation, lipid metabolism, mitochondrial dysfunction, oxidative stress, tryptophan metabolism, and epigenetic regulation as promising avenues for developing novel therapeutics (**Figures 1** and **2**).

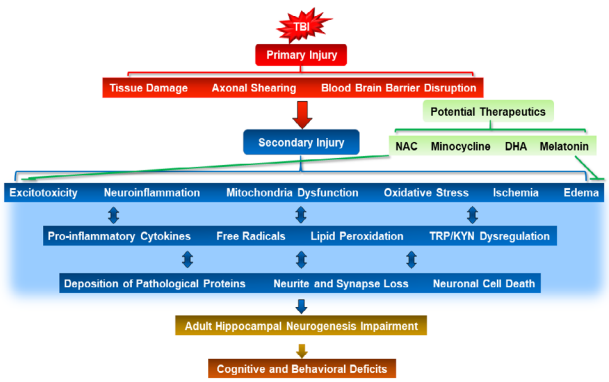

Figure 2 | **Potential therapeutics that targeting the secondary injury after pediatric traumatic brain injury.**

As detailed above, it is well established that secondary injuries post-TBI constitute complex and dynamic responses. Several pharmacological neuroprotective agents have shown promise in pre-clinical models and early phase II clinical trials, but failed to show positive outcomes in larger, phase III trials. This indicates that a multi-pronged approach that targets several pathways may be necessary for enhancing endogenous neurogenesis and improving plasticity and repair. Future pre-clinical studies and clinical trials with multi-mechanistic combinational neuroprotective approaches are urgently needed; however, these studies need to be meticulously designed. Variations in the dosage and duration of the therapeutic agents have to be carefully considered when being tested in pediatric patients since there are differences between the mature and the developing brains.

In conclusion, the discoveries reported in this review may pave the way for future therapeutic interventions that involve enhancing adult hippocampal neurogenesis, promoting the functional incorporation of new neurons into affected neural circuits, and facilitating repair and restoration of brain functions in pediatric TBI patients.

Author contributions: *MR, JV and ZZ participated in writing and editing this review and approved the final version for publication.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Financial support: *This work was supported by the Startup Grant for ZZ from the Department of Natural Sciences, University of Michigan-Dearborn and "CASL Faculty Summer Research Grant" for ZZ from Office of Research & Sponsored Programs, University of Michigan-Dearborn.*

Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

References

Alvarez DD, Giacomini D, Yang SM, Trinchero MF, Temprana SG, Buttner KA, Beltramone N, Schinder AF (2016) A disynaptic feedback network activated by experience promotes the integration of new granule cells. Science 354:459-465.

Anacker C, Hen R (2017) Adult hippocampal neurogenesis and cognitive flexibility- linking memory and mood. Nat Rev Neurosci 18:335-346.

Balog J, Mehta SL, Vemuganti R (2016) Mitochondrial fission and fusion in secondary brain damage after CNS insults. J Cereb Blood Flow Metab 36:2022-2033.

Barlow KM, Esser MJ, Veidt M, Boyd R (2019) Melatonin as a treatment after traumatic brain injury: a systematic review and meta-analysis of the pre-clinical and clinical literature. J Neurotrauma 36:523-537.

Barlow KM, Brooks BL, Esser MJ, Kirton A, Mikrogianakis A, Zemek RL, MacMaster FP, Nettel-Aguirre A, Yeates KO, Kirk V, Hutchison JS, Crawford S, Turley B, Cameron C, Hill MD, Samuel T, Buchhalter J, Richer L, Platt R, Boyd R (2020) Efficacy of melatonin in children with postconcussive symptoms: a randomized clinical trial. Pediatrics 145:e20192812.

Bhatti J, Nascimento B, Akhtar U, Rhind SG, Tien H, Nathens A, da Luz LT (2017) Systematic review of human and animal studies examining the efficacy and safety of N-acetylcysteine (NAC) and N-acetylcysteine amide (NACA) in traumatic brain injury: impact on neurofunctional outcome and biomarkers of oxidative stress and inflammation. Front Neurol 8:744.

Blanco-Suarez E, Liu TF, Kopelevich A, Allen NJ (2018) Astrocyte-secreted chordin-like 1 drives synapse maturation and limits plasticity by increasing synaptic GluA2 AMPA receptors. Neuron 100:1116-1132.

Bloemer J, Pinky PD, Govindarajulu M, Hong H, Judd R, Amin RH, Moore T, Dhanasekaran M, Reed MN, Suppiramaniam V (2018) Role of adiponectin in central nervous system disorders. Neural Plast 2018:4593530.

Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su KP, Pariante CM, Zunszain PA (2017) Rescue of IL-1 beta-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain Behav Immun 65:230-238.

Bowman CE, Scafidi J, Scafidi S (2019) Metabolic perturbations after pediatric TBI: It's not just about glucose. Exp Neurol 316:74-84.

Bramlett HM, Dietrich WD (2015) Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. J Neurotrauma 32:1834-1848.

Braun M, Vaibhav K, Saad NM, Fatima S, Vender JR, Baban B, Hoda MN, Dhandapani KM (2017) White matter damage after traumatic brain injury: A role for damage associated molecular patterns. Biochim Biophys Acta Mol Basis Dis 1863:2614-2626.

Cao J, Gaamouch FE, Meabon JS, Meeker KD, Zhu L, Zhong MB, Bendik J, Elder G, Jing P, Xia J, Luo W, Cook DG, Cai D (2017) ApoE4-associated phospholipid dysregulation contributes to development of Tau hyper-phosphorylation after traumatic brain injury. Sci Rep 7:11372.

Chen X, Wu S, Chen C, Xie B, Fang Z, Hu W, Chen J, Fu H, He H (2017) Omega-3 polyunsaturated fatty acid supplementation attenuates microglial-induced inflammation by inhibiting the HMGB1/TLR4/NF-kappaB pathway following experimental traumatic brain injury. J Neuroinflammation 14:143.

Cheng P, Li R, Schwebel DC, Zhu M, Hu G (2020) Traumatic brain injury mortality among U.S. children and adolescents ages 0-19 years, 1999-2017. J Safety Res 72:93-100.

Chitturi J, Li Y, Santhakumar V, Kannurpatti SS (2018) Early behavioral and metabolomic change after mild to moderate traumatic brain injury in the developing brain. Neurochem Int 120:75-86.

Clark RSB, Empey PE, Bayir H, Rosario BL, Poloyac SM, Kochanek PM, Nolin TD, Au AK, Horvat CM, Wisniewski SR, Bell MJ (2017) Phase I randomized clinical trial of N-acetylcysteine in combination with an adjuvant probenecid for treatment of severe traumatic brain injury in children. PLoS One 12:e0180280.

Clarke LE, Liddelow SA, Chakraborty C, Munch AE, Heiman M, Barres BA (2018) Normal aging induces A1-like astrocyte reactivity. Proc Natl Acad Sci U S A 115:E1896-1905.

Clement T, Lee JB, Ichkova A, Rodriguez-Grande B, Fournier ML, Aussudre J, Ogier M, Haddad E, Canini F, Koehl M, Abrous DN, Obenaus A, Badaut J (2020) Juvenile mild traumatic brain injury elicits distinct spatiotemporal astrocyte responses. Glia 68:528-542.

Comai S, Bertazzo A, Brughera M, Crotti S (2020) Tryptophan in health and disease. Adv Clin Chem 95:165-218.

Corrigan F, Mander KA, Leonard AV, Vink R (2016) Neurogenic inflammation after traumatic brain injury and its potentiation of classical inflammation. J Neuroinflammation 13:264.

Cox CS, Jr., Juranek J, Bedi S (2019) Clinical trials in traumatic brain injury: cellular therapy and outcome measures. Transfusion 59:858-868.

Dennis EA, Norris PC (2015) Eicosanoid storm in infection and inflammation. Nat Rev Immunol 15:511-523.

Dennis EL, Jin Y, Villalon-Reina JE, Zhan L, Kernan CL, Babikian T, Mink RB, Babbitt CJ, Johnson JL, Giza CC, Thompson PM, Asarnow RF (2015) White matter disruption in moderate/severe pediatric traumatic brain injury: advanced tract-based analyses. Neuroimage Clin 7:493-505.

Desai A, Park T, Barnes J, Kevala K, Chen H, Kim HY (2016) Reduced acute neuroinflammation and improved functional recovery after traumatic brain injury by alpha-linolenic acid supplementation in mice. J Neuroinflammation 13:253.

Engel DF, Grzyb AN, de Oliveira J, Potzsch A, Walker TL, Brocardo PS, Kempermann G, de Bem AF (2019) Impaired adult hippocampal neurogenesis in a mouse model of familial hypercholesterolemia: A role for the LDL receptor and cholesterol metabolism in adult neural precursor cells. Mol Metab 30:1-15.

Farhy-Tselnicker I, van Casteren ACM, Lee A, Chang VT, Aricescu AR, Allen NJ (2017) Astrocyte-secreted glypican 4 regulates release of neuronal pentraxin 1 from axons to induce functional synapse formation. Neuron 96:428-445.

Figueiro-Silva J, Antequera D, Pascual C, Revenga MD, Volt H, Acuna-Castroviejo D, Rodriguez-Franco MI, Carro E (2018) The melatonin analog IQM316 may induce adult hippocampal neurogenesis and preserve recognition memories in mice. Cell Transplant 27:423-437.

Fischer TD, Hylin MJ, Zhao J, Moore AN, Waxham MN, Dash PK (2016) Altered mitochondrial dynamics and TBI pathophysiology. Front Syst Neurosci 10:29.

Genc S, Anderson V, Ryan NP, Malpas CB, Catroppa C, Beauchamp MH, Silk TJ (2017) Recovery of white matter following pediatric traumatic brain injury depends on injury severity. J Neurotrauma 34:798-806.

Gilmore JH, Knickmeyer RC, Gao W (2018) Imaging structural and functional brain development in early childhood. Nat Rev Neurosci 19:123-137.

Goncalves JT, Schafer ST, Gage FH (2016) Adult neurogenesis in the hippocampus: from stem cells to behavior. Cell 167:897-914.

Hagberg H, Mallard C, Ferriero DM, Vannucci SJ, Levison SW, Vexler ZS, Gressens P (2015) The role of inflammation in perinatal brain injury. Nat Rev Neurol 11:192-208.

Hoffer BJ, Pick CG, Hoffer ME, Becker RE, Chiang YH, Greig NH (2017) Repositioning drugs for traumatic brain injury- N-acetyl cysteine and Phenserine. J Biomed Sci 24:71.

Hong S, Washington PM, Kim A, Yang CP, Yu TS, Kernie SG (2016) Apolipoprotein E regulates injury-induced activation of hippocampal neural stem and progenitor cells. J Neurotrauma 33:362-374.

Hueston CM, O'Leary JD, Hoban AE, Kozareva DA, Pawley LC, O'Leary OF, Cryan JF, Nolan YM (2018) Chronic interleukin-1beta in the dorsal hippocampus impairs behavioural pattern separation. Brain Behav Immun 74:252-264.

Ibrahim S, Hu W, Wang X, Gao X, He C, Chen J (2016) Traumatic brain injury causes aberrant migration of adult-born neurons in the hippocampus. Sci Rep 6:21793.

Knobloch M, Pilz GA, Ghesquiere B, Kovacs WJ, Wegleiter T, Moore DL, Hruzova M, Zamboni N, Carmeliet P, Jessberger S (2017) A fatty acid oxidation-dependent metabolic shift regulates adult neural stem cell activity. Cell Rep 20:2144-2155.

Koizumi K, Hattori Y, Ahn SJ, Buendia I, Ciacciarelli A, Uekawa K, Wang G, Hiller A, Zhao L, Voss HU, Paul SM, Schaffer C, Park L, Iadecola C (2018) Apoepsilon4 disrupts neurovascular regulation and undermines white matter integrity and cognitive function. Nat Commun 9:3816.

Kumar A, Stoica BA, Loane DJ, Yang M, Abulwerdi G, Khan N, Kumar A, Thom SR, Faden AI (2017) Microglial-derived microparticles mediate neuroinflammation after traumatic brain injury. J Neuroinflammation 14:47.

Kumar Sahel D, Kaira M, Raj K, Sharma S, Singh S (2019) Mitochondrial dysfunctioning and neuroinflammation: Recent highlights on the possible mechanisms involved in Traumatic Brain Injury. Neurosci Lett 710:134347.

Ledoux AA, Tang K, Yeates KO, Pusic MV, Boutis K, Craig WR, Gravel J, Freedman SB, Gagnon I, Gioia GA, Osmond MH, Zemek RL, Pediatric Emergency Research Canada Concussion T (2019) Natural progression of symptom change and recovery from concussion in a pediatric population. JAMA Pediatr 173:e183820.

Li Q, Wang P, Huang C, Chen B, Liu J, Zhao M, Zhao J (2019) N-acetyl serotonin protects neural progenitor cells against oxidative stress-induced apoptosis and improves neurogenesis in adult mouse hippocampus following traumatic brain injury. J Mol Neurosci 67:574-588.

Liu XY, Wei MG, Liang J, Xu HH, Wang JJ, Wang J, Yang XP, Lv FF, Wang KQ, Duan JH, Tu Y, Zhang S, Chen C, Li XH (2020) Injury-preconditioning secretome of umbilical cord mesenchymal stem cells amplified the neurogenesis and cognitive recovery after severe traumatic brain injury in rats. J Neurochem 153:230-251.

Mahley RW, Huang Y (2012) Apolipoprotein e sets the stage: response to injury triggers neuropathology. Neuron 76:871-885.

Masuda T, Sankowski R, Staszewski O, Bottcher C, Amann L, Sagar, Scheiwe C, Nessler S, Kunz P, van Loo G, Coenen VA, Reinacher PC, Michel A, Sure U, Gold R, Grun D, Priller J, Stadelmann C, Prinz M (2019) Spatial and temporal heterogeneity of mouse and human microglia at single-cell resolution. Nature 566:388-392.

Meythaler J, Fath J, Fuerst D, Zokary H, Freese K, Martin HB, Reineke J, Peduzzi-Nelson J, Roskos PT (2019) Safety and feasibility of minocycline in treatment of acute traumatic brain injury. Brain Inj 33:679-689.

Miller SM, Sahay A (2019) Functions of adult-born neurons in hippocampal memory interference and indexing. Nat Neurosci 22:1565-1575.

Mohamadpour M, Whitney K, Bergold PJ (2019) The importance of therapeutic time window in the treatment of traumatic brain injury. Front Neurosci 13:07.

Moreno-Jimenez EP, Flor-Garcia M, Terreros-Roncal J, Rabano A, Cafini F, Pallas-Bazarra N, Avila J, Llorens-Martin M (2019) Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med 25:554-560.

Nance E, Zhang F, Mishra MK, Zhang Z, Kambhampati SP, Kannan RM, Kannan S (2016) Nanoscale effects in dendrimer-mediated targeting of neuroinflammation. Biomaterials 101:96-107.

Nance E, Kambhampati SP, Smith ES, Zhang Z, Zhang F, Singh S, Johnston MV, Rangaramanujam K, Blue ME, Kannan S (2017) Dendrimer-mediated delivery of N-acetyl cysteine to microglia in a mouse model of Rett syndrome. J Neuroinflammation 14:252.

Neumane S, Câmara-Costa H, Francillette L, Araujo M, Toure H, Brugel D, Laurent-Vannier A, Ewing-Cobbs L, Meyer P, Dellatolas G, Watier L, Chevignard M (2020) Functional outcome after severe childhood traumatic brain injury: Results of the TGE prospective longitudinal study. Ann Phys Rehabil Med. doi: 10.1016/j.rehab.2020.01.008.

Ng SY, Semple BD, Morganti-Kossmann MC, Bye N (2012) Attenuation of microglial activation with minocycline is not associated with changes in neurogenesis after focal traumatic brain injury in adult mice. J Neurotrauma 29:1410-1425.

Ngwenya LB, Danzer SC (2018) Impact of traumatic brain injury on neurogenesis. Front Neurosci 12:1014.

Qin X, You H, Cao F, Wu Y, Peng J, Pang J, Xu H, Chen Y, Chen L, Vitek MP, Li F, Sun X, Jiang Y (2017) Apolipoprotein E Mimetic Peptide Increases Cerebral Glucose Uptake by Reducing Blood-Brain Barrier Disruption after Controlled Cortical Impact in Mice: An (18)F-Fluorodeoxyglucose PET/CT Study. J Neurotrauma 34:943-951.

Rehman SU, Ikram M, Ullah N, Alam SI, Park HY, Badshah H, Choe K, Kim MO (2019) Neurological enhancement effects of melatonin against brain injury-induced oxidative stress, neuroinflammation, and neurodegeneration via AMPK/CREB signaling. Cells 8:760.

Russo MV, McGavern DB (2016) Inflammatory neuroprotection following traumatic brain injury. Science 353:783-785.

Ryan NP, Reyes J, Crossley L, Beauchamp MH, Catroppa C, Anderson VA (2019) Unraveling the association between pediatric traumatic brain injury and social dysfunction: the mediating role of self-regulation. J Neurotrauma 36:2895-2903.

Saha P, Gupta R, Sen T, Sen N (2019) Histone deacetylase 4 downregulation elicits post-traumatic psychiatric disorders through impairment of neurogenesis. J Neurotrauma 36:3284-3296.

Sangobowale MA, Grin'kina NM, Whitney K, Nikulina E, St Laurent-Ariot K, Ho JS, Bayzan N, Bergold PJ (2018) Minocycline plus N-acetylcysteine reduce behavioral deficits and improve histology with a clinically useful time window. J Neurotrauma 35:907-917.

Santini A, Cammarata SM, Capone G, Ianaro A, Tenore GC, Pani L, Novellino E (2018) Nutraceuticals: opening the debate for a regulatory framework. Br J Clin Pharmacol 84:659-672.

Schober ME, Requena DF, Maschek JA, Cox J, Parra L, Lolofie A (2020) Effects of controlled cortical impact and docosahexaenoic acid on rat pup fatty acid profiles. Behav Brain Res 378:112295.

Scott G, Zetterberg H, Jolly A, Cole JH, De Simoni S, Jenkins PO, Feeney C, Owen DR, Lingford-Hughes A, Howes O, Patel MC, Goldstone AP, Gunn RN, Blennow K, Matthews PM, Sharp DJ (2018) Minocycline reduces chronic microglial activation after brain trauma but increases neurodegeneration. Brain 141:459-471.

Sharma A, Liaw K, Sharma R, Zhang Z, Kannan S, Kannan RM (2018a) Targeting mitochondrial dysfunction and oxidative stress in activated microglia using dendrimer-based therapeutics. Theranostics 8:5529-5547.

Sharma R, Kim SY, Sharma A, Zhang Z, Kambhampati SP, Kannan S, Kannan RM (2017) Activated microglia targeting dendrimer-minocycline conjugate as therapeutics for neuroinflammation. Bioconjug Chem 28:2874-2886.

Sharma R, Sharma A, Kambhampati SP, Reddy RR, Zhang Z, Cleland JL, Kannan S, Kannan RM (2018b) Scalable synthesis and validation of PAMAM dendrimer-N-acetyl cysteine conjugate for potential translation. Bioeng Transl Med 3:87-101.

Sharma R, Kambhampati SP, Zhang Z, Sharma A, Chen S, Duh EI, Kannan S, Tso MOM, Kannan RM (2020) Dendrimer mediated targeted delivery of sinomenine for the treatment of acute neuroinflammation in traumatic brain injury. J Control Release 323:361-375.

Shu S, Zhang Z, Spicer D, Kulikowicz E, Hu K, Babapoor-Farrokhran S, Kannan S, Koehler RC, Robertson CL (2019) Administration of a 20-hydroxyeicosatetraenoic acid synthesis inhibitor improves outcome in a rat model of pediatric traumatic brain injury. Dev Neurosci 41:166-176.

Simon DW, Aneja RK, Alexander H, Bell MJ, Bayir H, Kochanek PM, Clark RSB (2018) Minocycline attenuates high mobility group box 1 translocation, microglial activation, and thalamic neurodegeneration after traumatic brain injury in post-natal day 17 rats. J Neurotrauma 35:130-138.

Sofroniew MV (2015) Astrocyte barriers to neurotoxic inflammation. Nat Rev Neurosci 16:249-263.

Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste KI, Chang EF, Gutierrez AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A (2018) Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 555:377-381.

Sta Maria NS, Sargolzaei S, Prins ML, Dennis EL, Asarnow RF, Hovda DA, Harris NG, Giza CC (2019) Bridging the gap: mechanisms of plasticity and repair after pediatric TBI. Exp Neurol 318:78-91.

Sultan S, Li L, Moss J, Petrelli F, Casse F, Gebara E, Lopatar J, Pfrieger FW, Bezzi P, Bischofberger J, Toni N (2015) Synaptic integration of adult-born hippocampal neurons is locally controlled by astrocytes. Neuron 88:957-972.

Taylor AN, Tio DL, Paydar A, Sutton RL (2018) Sex differences in thermal, stress, and inflammatory responses to minocycline administration in rats with traumatic brain injury. J Neurotrauma 35:630-638.

Teng Z, Guo Z, Zhong J, Cheng C, Huang Z, Wu Y, Tang S, Luo C, Peng X, Wu H, Sun X, Jiang L (2017) ApoE influences the blood-brain barrier through the NF-kappaB/MMP-9 pathway after traumatic brain injury. Sci Rep 7:6649.

Tensaouti Y, Yu TS, Kernie SG (2020) Apolipoprotein E regulates the maturation of injury-induced adult-born hippocampal neurons following traumatic brain injury. PLoS One 15:e0229240.

Tyurina YY, Poloyac SM, Tyurin VA, Kapralov AA, Jiang J, Anthonymuthu TS, Kapralova VI, Vikulina AS, Jung MY, Epperly MW, Mohammadyani D, Klein-Seetharaman J, Jackson TC, Kochanek PM, Pitt BR, Greenberger JS, Vladimirov YA, Bayir H, Kagan VE (2014) A mitochondrial pathway for biosynthesis of lipid mediators. Nat Chem 6:542-552.

Vicidomini C, Guo N, Sahay A (2020) Communication, cross talk, and signal integration in the adult hippocampal neurogenic niche. Neuron 105:220-235.

Vijayakumar N, Allen NB, Youssef G, Dennison M, Yucel M, Simmons JG, Whittle S (2016) Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume. Hum Brain Mapp 37:2027-2038.

Villasana LE, Kim KN, Westbrook GL, Schnell E (2015) Functional Integration of adult-born hippocampal neurons after traumatic brain injury(1,2,3). eNeuro 22:ENEURO.0056-15.2015.

Volobouеva LA, Sun X, Xu L, Ouyang YB, Giffard RG (2017) Distinct effects of miR-210 reduction on neurogenesis: increased neuronal survival of inflammation but reduced proliferation associated with mitochondrial enhancement. J Neurosci 37:3072-3084.

Wang X, Gao X, Michalski S, Zhao S, Chen J (2016) Traumatic brain injury severity affects neurogenesis in adult mouse hippocampus. J Neurotrauma 33:721-733.

Weinhard L, di Bartolomei G, Bolasco G, Machado P, Schieber NL, Neniskyte U, Exiga M, Vadisiute A, Raggioli A, Schertel A, Schwab Y, Gross CT (2018) Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. Nat Commun 9:1228.

Willis EF, MacDonald KPA, Nguyen QH, Garrido AL, Gillespie ER, Harley SBR, Bartlett PF, Schroder WA, Yates AG, Anthony DC, Rose-John S, Ruitenberg MJ, Vukovic J (2020) Repopulating microglia promote brain repair in an il-6-dependent manner. Cell 180:833-846.

Wu Q, Xia SX, Li QQ, Gao Y, Shen X, Ma L, Zhang MY, Wang T, Li YS, Wang ZF, Luo CL, Tao LY (2016) Mitochondrial division inhibitor 1 (Mdivi-1) offers neuroprotection through diminishing cell death and improving functional outcome in a mouse model of traumatic brain injury. Brain Res 1630:134-143.

Xie Z, Jones A, Deeney JT, Hur SK, Bankaitis VA (2016) Inborn errors of long-chain fatty acid beta-oxidation link neural stem cell self-renewal to autism. Cell Rep 14:991-999.

Yan EB, Frugier T, Lim CK, Heng B, Sundaram G, Tan M, Rosenfeld JV, Walker DW, Guillemin GJ, Morganti-Kossmann MC (2015) Activation of the kynurenine pathway and increased production of the excitotoxin quinolinic acid following traumatic brain injury in humans. J Neuroinflammation 12:110.

Yau SY, Li A, Xu A, So KF (2015) Fat cell-secreted adiponectin mediates physical exercise-induced hippocampal neurogenesis: an alternative anti-depressive treatment? Neural Regen Res 10:7-9.

Yun S, Reynolds RP, Masiulis I, Eisch AJ (2016) Re-evaluating the link between neuropsychiatric disorders and dysregulated adult neurogenesis. Nat Med 22:1239-1247.

Zamani A, Ryan NP, Wright DK, Caeyenberghs K, Semple BD (2020) The impact of traumatic injury to the immature human brain: a scoping review with insights from advanced structural neuroimaging. J Neurotrauma 37:724-738.

Zarate R, El Jaber-Vazdekis N, Tejera N, Perez JA, Rodriguez C (2017) Significance of long chain polyunsaturated fatty acids in human health. Clin Transl Med 6:25.

Zhang D, Wang X, Lu XY (2016a) Adiponectin exerts neurotrophic effects on dendritic arborization, spinogenesis, and neurogenesis of the dentate gyrus of male mice. Endocrinology 157:2853-2869.

Zhang D, Wang X, Wang B, Garza JC, Fang X, Wang J, Scherer PE, Brenner R, Zhang W, Lu XY (2017) Adiponectin regulates contextual fear extinction and intrinsic excitability of dentate gyrus granule neurons through AdipoR2 receptors. Mol Psychiatry 22:1044-1055.

Zhang F, Nance E, Zhang Z, Jasty V, Kambhampati SP, Mishra MK, Burd I, Romero R, Kannan S, Kannan RM (2016b) Surface functionality affects the biodistribution and microglia-targeting of intra-amniotically delivered dendrimers. J Control Release 237:61-70.

Zhang Z, Saraswati M, Koehler RC, Robertson C, Kannan S (2015a) A new rabbit model of pediatric traumatic brain injury. J Neurotrauma 32:1369-1379.

Zhang Z, Rasmussen L, Saraswati M, Koehler RC, Robertson C, Kannan S (2018) Traumatic injury leads to inflammation and altered tryptophan metabolism in the juvenile rabbit brain. J Neurotrauma.

Zhang Z, Ishrat S, O'Bryan M, Klein B, Saraswati M, Robertson CL, Kannan S (2020) Pediatric traumatic brain injury causes long-term deficits in adult hippocampal neurogenesis and cognition. J Neurotrauma.

Zhang Z, Gao F, Kang X, Li J, Zhang L, Dong W, Jin Z, Li F, Gao N, Cai X, Yang S, Zhang J, Ren X, Yang X (2015b) Exploring the potential relationship between Notch pathway genes expression and their promoter methylation in mice hippocampal neurogenesis. Brain Res Bull 113:8-16.

C-Editors: Zhao M, Song LP; T-Editor: Jia Y