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Age-Dependent Responses Following Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a growing health concern worldwide that affects a broad range of the population. As TBI is the leading cause of disability and mortality in children, several preclinical models have been developed using rodents at a variety of different ages; however, key brain maturation events are overlooked that leave some age groups more or less vulnerable to injury. Thus, there has been a large emphasis on producing relevant animal models to elucidate molecular pathways that could be of therapeutic potential to help limit neuronal injury and improve behavioral outcome. TBI involves a host of different biochemical events, including disruption of the cerebral vasculature and breakdown of the blood-brain barrier (BBB) that exacerbates secondary injuries. A better understanding of age-related mechanism(s) underlying brain injury will aid in establishing more effective treatment strategies aimed at improving restoration and preventing further neuronal loss. This review looks at studies that focus on modeling the adolescent population and highlights the importance of individualized aged therapeutics to TBI.

Keywords: childhood, juvenile, traumatic brain injury, brain development, functional outcome, age dependence

1. Introduction

Traumatic brain injury (TBI) is a leading cause of long-term disability among all age groups with the adolescent population having a higher incidence of TBI [1]. Males sustain TBI at a much higher rate compared to females [1], and functional outcomes vary across patient's age and severity of injury [2, 3]. Studies have shown that younger patients are more likely to demonstrate continued improvements, while older patients are more likely to decline [2, 4].

On the other hand, childhood TBI (<6 years of age) presents poorer recovery of function compared to early adolescent or adolescent-aged patients [5, 6], with severe TBI in early childhood resulting in long-term impairment. Although better neuroplasticity or adaptation to brain injury in children has once been attributed to better recovery, the effect of age on outcome depends upon the function under study and the stage of development at the time of injury. In fact, the effects of childhood TBI may take years to “grow into deficit” as the developing brain hits milestones of maturation [7, 8]. Multiple regression analyses has also identified that age-at-injury onset is a major contributor to post-injury IQ [6]. While there are distinct periods of vulnerability in the developing brain, evidence from animal models also show that metabolic and physiological alterations specific to the juvenile or early adolescent brain may induce acute protection compared to adults [9–11]. These potentially distinct age-related responses are currently understudied and require a more accurate correlation of disease outcome with the maturation stage of the brain. Moreover, both small and large animal models need to be interpreted with caution since developmental milestones are distinct between swine, mice, and rat species as well as across different strains during the postnatal stages of growth. These differences make age comparisons to human infancy, childhood, early adolescence, adolescence, and adulthood challenging. To that end, correlating age-specific TBI outcomes from rodent to human thus requires consideration of key neurobiological maturation events, rather than chronological age, to predict differential responses to TBI which may eventually help guide effective diagnostic and treatment strategies. Here, we will review key events that accompany brain development in both humans and rodents to identify temporal “benchmarks” that may positively or negatively influence age-at-injury outcome. We will also provide an overview of research findings from clinical and preclinical age-related TBI studies.

1.1. Human brain structure and development

The human brain is a remarkably complex organ which we still do not fully understand. Representing 2% of the entire body weight in adulthood, the brain requires 20% of the body's oxygen supply to accommodate its extreme metabolic demands. Human brain development is a highly dynamic process which can be broken down into orchestrated cellular and molecular epochs. The neocortex is the newest and arguably most sophisticated structure in the human brain and accounts for most of the brain size. By adulthood, the neocortex will have amassed approximately 20 billion neurons each capable of forming an average of 7000 connections with other neurons [12, 13]. The brain is considered to be immune privileged as it is isolated from the bloodstream by the blood-brain barrier (BBB). Cerebral spinal fluid (CSF) flows through the ventricles located in the center of the brain also provides a cushion. The cerebrum is described as having four lobes: frontal, parietal, temporal, and occipital. The frontal lobe is involved in higher-order executive functions such as planning, reasoning, abstract thinking, decision-making, attention, and personality. Gray and white matters represent the two broad components of the brain. Gray matter is heavily populated with neuronal cell bodies which are essential for transmitting/communicating information throughout the brain. White matter accounts for 50% of the human brain volume and is white in appearance

because it is highly composed of myelin [14], a specialized membrane, densely enriched with lipids, which can accelerate neuronal communication throughout the brain.

Human brain development commences during the third week of gestation and continues through adolescence [15]. Within the first year of life, the brain doubles in volume and will grow another 15% over the following year [16]. By the age of 6, the brain will have increased in size by fourfold which is roughly 90% of the size achieved in adulthood [15]. At the beginning of the fetal period of development, the brain is smooth, and later becomes convoluted with folds and ridges. This drastic increase in cortical volume is primarily through an increase in surface area, as opposed to an increase in thickness, which is how the cortex constitutes up to 80% of the total brain mass [17]. Higher-order cognitive function requires precise connections and communication throughout the brain. For example, cortical neurons can form connections with neighboring and distant cells to enable communication and integration of sensory, cognitive, and motor modalities. The corpus callosum is the largest white matter tract in the brain and serves as a major highway of axons connecting the left and right cerebral hemispheres. These axons are wrapped in myelin to foster rapid interhemispheric communication of information. Myelination is a process that begins around the middle of the second trimester, is most appreciably robust up to the second year of life, and continues throughout adolescence, though to a much lesser degree during adulthood [18, 19]. White matter development in the human brain is an asynchronous process, commencing earlier and more rapidly in sensory than motor pathways, and is later highly prominent in the frontal and temporal lobes at 6–8 months of age [19]. The left and right cerebral hemispheres serve different functions and do not develop in a completely symmetric manner [19]. One explanation for such spatial and temporal asymmetries is a hierarchy of connections formed in an experience-dependent order, such that brain regions involved with lower-level processes need to be established earlier in life before higher-order integrative regions are required. For example, the somatosensory cortex—important for tactile information—matures earlier in development than the prefrontal cortex which is involved in higher-level executive functions such as planning [20].

Our knowledge of human brain development has primarily been gathered from noninvasive neuroimaging measurements and their functional correlates to neurological outcomes, in addition to cellular associations with histopathology. It has become increasingly clear that the brain is extremely vulnerable during key developmental epochs. During these sensitive maturation-dependent time windows, childhood TBI may increase the risk of brain dysmaturation and atypical development depending on the severity and location of the injury [21–23]. For example, generalized (frontal/extrafrontal) or extrafrontal lesion severity but not frontal lesion alone was predictive of poor performance in children who sustained a moderate to severe TBI at ages 1–9 years of age [23]. Mechanistic insights into the etiologies of the neurological deficits and age-specific regions of vulnerability are vital to the understanding and treatment of pediatric TBI. However, rodent models of childhood and adolescent TBI in the postnatal growth stage may be difficult to translate into chronological age in humans. A better understanding of the major developmental processes in the brain across species and strains at the time of injury may be more instrumental for interpreting key findings. A few of these major milestones in neurodevelopment are noted below in **Table 1**.

Embryonic day (E), postnatal day (P), months (M), years (Y)	Mouse	Rat	Human	Reference
Sexual maturation [#]	F: P23 M: P42	F: P32-34 M: P45-48	F: 10-17Y M: 11-17Y	[1, 24]
Peak brain volume (MRI)	P20	P60	F: 10.5Y M: 14.5Y	[8, 25, 26]
Developmental processes/milestones				
Neurogenesis completed by ^{*,†}	P16.5	P15	7.5 M	[8]
Astrocytogenesis peak	At birth	At birth	At birth	[8, 27]
Prefrontal cortex peak synaptic density [*]	P27.5	P25	12.4 M	[28]
Corpus callosum body myelination onset [*]	P15.5	P14	2.6 M	[28]
Corpus callosum body myelination end [*]	P35.5	P32	20.4 M	[28]
Internal capsule myelination onset [*]	P13.5	P12	1.4 M	[28]
Functional blood-brain barrier	E15.5	E14	10w gestation	[29]

^{*}Estimates determined across species with www.translatingtime.net, based on Workman et al. [28].

[†]Estimate based off of neurogenesis completion in rat by postnatal day 15 [8]. F, female; M, male; P, postnatal days; Y, years; M, months; E, embryonic days; na, not applicable.

[#]Sexual maturation is strain dependent.

Table 1. Developmental processes and milestones across mammals.

1.2. Age-at-injury response to clinical TBI

The widespread conception that the young brain is more resilient in its response to TBI has been challenged as there is considerable evidence that childhood TBI results in poorer outcomes. The developing brain may actually fair much worse compared to adults in cognitive and motor functions [30–32]. *Levin and colleagues* utilized the Glasgow Coma Scale (GCS), the primary measure of functional impairment, in children at 0–4 years of age and 5–10 years of age following TBI. The 0–4-year-olds were found to suffer the worst clinical outcome, comparatively. These and other findings analyzed the long-term behavioral outcomes in children who sustained a moderate to severe head injury [33]. Moreover, given the longevity of white matter development and maturation, TBI negatively impacts white matter integrity in the chronic (13–19 post-injury) but not acute (1–5 months) phase of injury which was linked to cognitive impairments in patients at 8–19 years of age [34, 35]. Patients with a history of neurological illness, brain tumor, seizures, psychosis, ADHD, Tourette’s disorder, and other developmental disabilities were excluded from the study. This study also showed that the GCS was not significantly associated with white matter tract changes, as measured by diffuse tensor imaging (DTI), suggesting that advanced imaging modalities are vital to clinical tracking of disease progression and may be a more sensitive measure of outcome compared to GCS alone. Indeed, DTI coupled with functional MRI and perhaps other imaging strategies would greatly advance our understanding of the age-related mechanisms of repair and plasticity following TBI [36–39]. White matter dysregulation after childhood TBI may also affect motor recovery and social cognitive skills which are realized once the skills reach maturity [40–43].

Therefore, given the lengthy developmental course of myelination and synaptogenesis, TBI may disrupt the maturation of functions that support higher-order cognitive outcomes later in life [39, 44, 45]. The expression of glutamate receptors NMDA and AMPA greatly changes during development [46, 47]. Typically, there is an imbalance between excitatory and inhibitory neurotransmission in the developing brain, which could heighten the sensitivity of the young brain to glutamatergic excitotoxicity after trauma that may not be amplified in a mature brain [48]. Interestingly, the younger brain has less antioxidant capacity compared to the more matured brain, which during TBI increases the amount of reactive oxygen species (ROS) that could exacerbate the injury in the younger brain [49]. Inflammation also plays a critical role in brain tissue recovery after TBI [50]. In early childhood TBI, microglial cells that have infiltrated the brain may become overactive exacerbating secondary tissue damage [51]. Taken together, improving our understanding of developmentally related differences will be vital for predicting differential, age-specific outcomes and treatment responses to TBI.

Since the adolescent population sees a disproportionate percentage of hospitalizations and deaths compared to other age groups, this population should have its own outcome category tailoring research findings and treatment outcomes [52]. While adolescents fall between the childhood and adult age groups, how to appropriately treat these patients has been particularly challenging in the hospital setting [53]. Over a 13-year study, Gross and colleagues analyzed the adolescent TBI population (15–17 years of age) treated at pediatric or adult trauma centers. Although this study found no significant differences in outcomes between the centers, it raised an important question regarding how to treat adolescent brain injury, where differences in developmental vulnerability may exist compared to early childhood [53]. While early childhood TBI is associated with deficits in memory [54, 55], attention [56], intellectual functioning [57], and language acquisition [58], few studies have compared the outcomes of adolescent aged or young adults to older adults. A multiple regression model has demonstrated that increased age negatively influences outcome, as measured by the Disability Rating Scale (DRS) [4]. This study found a greater decline in older patients (≥ 40 years) over 5 years post-TBI but also demonstrated that the greatest amount of improvement in disability in young adults (16–26 years) compared to adults (27–39 years) and aged (≥ 40 years) patients. The mechanism(s) underlying this age-specific difference may be due, in part, to a reduction in the capacity to recover or decreased synaptic plasticity and cortical volume as we age or yet undetermined protective factors present during the late adolescence. Although TBI incidence has a bimodal age distribution peaking in adolescence and again in the elderly, few age-related studies have compared acute and chronic effects across the spectrum of age ranges including early childhood, adolescence, adulthood, and elderly. One prospective study of 330 severe TBI patients showed that younger patients (0–19 years of age) had a significantly higher percentage of good outcomes, lower mortality rates, and a reduced incidence of surgical mass lesions compared to adults (20–80 years of age) [11]. Although poorer recovery of function is known to exist in early childhood compared to adolescent-aged TBI patients, it should be noted that the mean age for the abovementioned study was 15–19 years and 39 years, respectively. Taken together, these findings suggest that the greatest vulnerability in age-specific responses lies in early childhood and advanced ages. Interestingly, there may be a narrow time window during which adolescence may confer protection, the mechanism(s) of which may be fully elucidated using animal models of brain injury, discussed below.

1.3. Age-at-injury response to preclinical TBI

Rodents are the most commonly used animal models in TBI research and are therefore well characterized and cross-validated [59–62]. The following sections will comprehensively review the acute and long-term TBI responses in both mice and rats at pre-weanling (P17), post-weanling/juvenile (P21), and adult (P60-90) ages. The commonly used models of TBI are the controlled cortical impact (CCI) injury and lateral fluid percussion injuries (LFPI) which have been adapted and scaled to younger rodent animals to account for differences in animal weight and brain size. However, the initial mechanical forces to the brain depend on an array of factors that are independently determined. These factors include location, severity, focal, or diffuse injury. Similar to clinical findings, there are a spectrum of outcomes following pre-clinical TBI that are not only age dependent but species and strain specific which must be interpreted with caution. Although the importance of gyrification of the human brain, which is fully formed at birth but increases in complexity postnatally, is still under debate [63], this cross species differences should be kept in mind. Nonetheless, animal models of TBI have been instrumental in assessing the vulnerability of the developing brain to mechanical forces applied following CCI or LFP injury models.

Neurogenesis, gliogenesis, synaptogenesis, and myelination are key developmental events that may impact age-at-injury outcomes after TBI [64–66]. While neurogenesis peaks during gestational periods, by adulthood the generation of neurons is restricted to the dentate gyrus (DG) of the hippocampus and the lateral wall of the subventricular zone (SVZ) [64, 67]. Induction of post-injury neurogenesis has been suggested to play a critical role in learning and memory recovery as well as providing neurotrophic factor secretion as neuroprotective cues. While selectively ablating adult neurogenesis can dampen functional recovery [68, 69], the effects on early childhood or adolescence are unclear. Sun and colleagues analyzed the morphological changes within the subgranular zone of the DG and the SVZ following LFPI using P28 juvenile and P90 adult rats [70]. The LFPI model mimics both focal and diffuse mechanical injuries and results in histopathological changes similar to those seen in humans [60]. The study determined that LFPI enhanced proliferation within the DG of both adult and juvenile rats. However, the juvenile response in the SVZ was greater compared to adults. Furthermore, they identified twice as many neurons that were born from the juvenile SVZ compared to adults. Similarly, juvenile mice at P21 subjected to CCI injury show an increased presence of doublecortin-positive neuroblasts in the DG at 2 weeks post-injury [71]. However, a significant decline in these cells was seen at 3 months post-injury suggesting that an acute protective response may be subdued by long-term activation of yet unknown cellular programs. No comparisons to adult CCI injury were made. Unfortunately, data regarding age effects on neurogenesis are still lacking since numerous studies in mice or rats either have not performed adult comparisons [72] or have not used relevant TBI models [67, 73]. Of note, while naïve P9 mice display increased proliferation in the DG compared to P21, hypoxic-ischemic injury adversely affected neurogenesis in P9 but greatly enhanced it in P21 suggesting that early adolescence may display a critical window of regenerative potential that may be lost in adulthood. These findings would need to be confirmed using an appropriately controlled, longitudinal investigation (days, weeks, months) of neurogenesis with

the inclusion of adult mice. Likewise, suitably comparable ages of rats subjected to TBI could support this hypothesis and help demonstrate a cross species phenomenon.

Synaptogenesis peaks at 2 years of age in humans and in 3 weeks in both rats and mice [65]. The number of synapses at these time points is greater, and pruning events follow to decrease the number of synapses [74–76]. In addition, myelination is an ongoing process that continues well into adulthood [66]; atypical development of these processes as a result of TBI may significantly impact synaptic reorganization and long-term neurobehavioral development [77–79]. Ajao and colleagues found that TBI in rats at P17 resulted in measurable deficits in motor performance on the rotarod and foot faults at 60 days post-injury well into adulthood [77]. Anxiety-like behaviors were also increased compared to noninjured sham controls. Sensorimotor tasks and anxiety-like behaviors are often linked to histological changes such as cell death in the brain as a consequence of childhood TBI. Neuronal loss due to focal impact can impair major electrical signaling pathways by disconnecting circuits, increasing calcium in dying cells, triggering inflammation, and blunting key trophic support. The immature rat brain is particularly sensitive to excitotoxicity in the neonatal period [80, 81]. This is regulated, in part, by developmental changes in expression of the NR2A and NR2B subunits of the NMDA receptor [82, 83] and/or GABAergic neurotransmission impairments through, for example, cortical loss of GABAergic interneurons [84, 85]. In the second and third postnatal weeks, however, this effect is reduced. In fact, minimal neuronal loss is seen following weight drop and LFPI in juvenile (P15–P19) rats [81, 86, 87] suggesting that long-term behavioral deficits following TBI are due in greater part to neuronal dysfunction rather than neuronal loss. On the other hand, a significant delay in loss of neural tissue is observed in juvenile (P21) mice after CCI injury [71, 88, 89] which correlates with progressive dysfunction. Differences in injury model, rodent species, or time of histopathological assessment after injury may account for these differences. Indeed, a gyrencephalic model of cortical impact delivered at different maturation stages to the piglet brain demonstrated increased vulnerability with age to cortical trauma, with the smallest lesions seen at 7 days post-injury in 5-day-old pigs, modest injury in 1-month-old piglets, and largest lesion volume in 4-month-olds [90, 91]. Progressive histopathological or behavioral changes over time were not evaluated.

While the maturation-dependent response of the resident neuroimmune system (microglial and astrocytes) remains under investigation, a notable difference in peripheral immune activation following TBI has been demonstrated. Bidirectional neural-immune communication exists to clear the brain of dead cellular debris from necrotic spillover of intracellular components. However, when overactivated, the immune system can mediate neurotoxicity and exacerbate secondary injury including free radical formation and oxidative damage as well as activation of microglia [92]. Although TBI increases the presence of leukocytes both in neural tissue, due to BBB disruption, and in the peripheral blood [93], the destructive phenotype of activated immune cell subpopulations is not well understood. Recent findings suggest that progressive injury in P21 mice observed months following CCI injury compared to adult may result from an age-dependent temporal patterns in leukocyte infiltration [88]. While no differences were noted for the CD4⁺ and CD8⁺ populations, CD45⁺ cells and GR-1⁺ granulocytes remained elevated for weeks in P21 mice compared to 3 days in adult. This effect may be regulated, in

part, by IL-1 β . Injection of IL-1 β into the P21 rat brain exacerbates rapid neutrophil recruitment, CXC chemokine production, and BBB disruption compared to adult rats [94–96]. While the juvenile immune system may display increased sensitivity to neutrophil chemoattractants (CXCL1, CXCL2, CXC8) [97], extension of neutrophil life span may also translate into increased numbers [98, 99]. Indeed, adult neutrophil depletion studies appear to reduce edema, cell death, and macrophage/microglia activation while having no effect on BBB and functional outcome suggesting that neutrophils may negatively impact TBI outcome and their long-lived nature may cause progressive injury and contribute to other age-related responses [100, 101]. Findings from our laboratory have shown significant neuroprotection in P21 mice subjected to moderate CCI injury compared to adults (unpublished findings). Interestingly, we have identified numerous genes in the whole cell fractions of peripheral blood from P21 mice that are differentially regulated compared to adults (unpublished findings). Next-generation RNA sequencing and ontology analysis identified several pathways that are differentially regulated including (1) metabolic, (2) apoptotic, and (3) inflammatory processes (**Figure 1**). Peripheral blood cells isolated from P21 mice display reduced expression of several Toll-like receptors (Tlr1, Tlr6, Tlr4, Tlr2), TNF receptor (TNFRSF1A), MMP9, and upregulation of the antioxidant superoxide dismutase 2 (SOD2), autophagy-related ATG4A, antiapoptotic Bag1, and a number of other genes that may influence their response once recruited after TBI. Enhanced survival of immune-derived cells in the brain may have long-lasting effects on tissue repair and recovery. There may be beneficial effects of early recruitment and survival in the damaged neural tissue that may be outweighed in the long run if their transient presence is extended. Differences in immune cell-type survival, gene expression, and function need to be further explored.

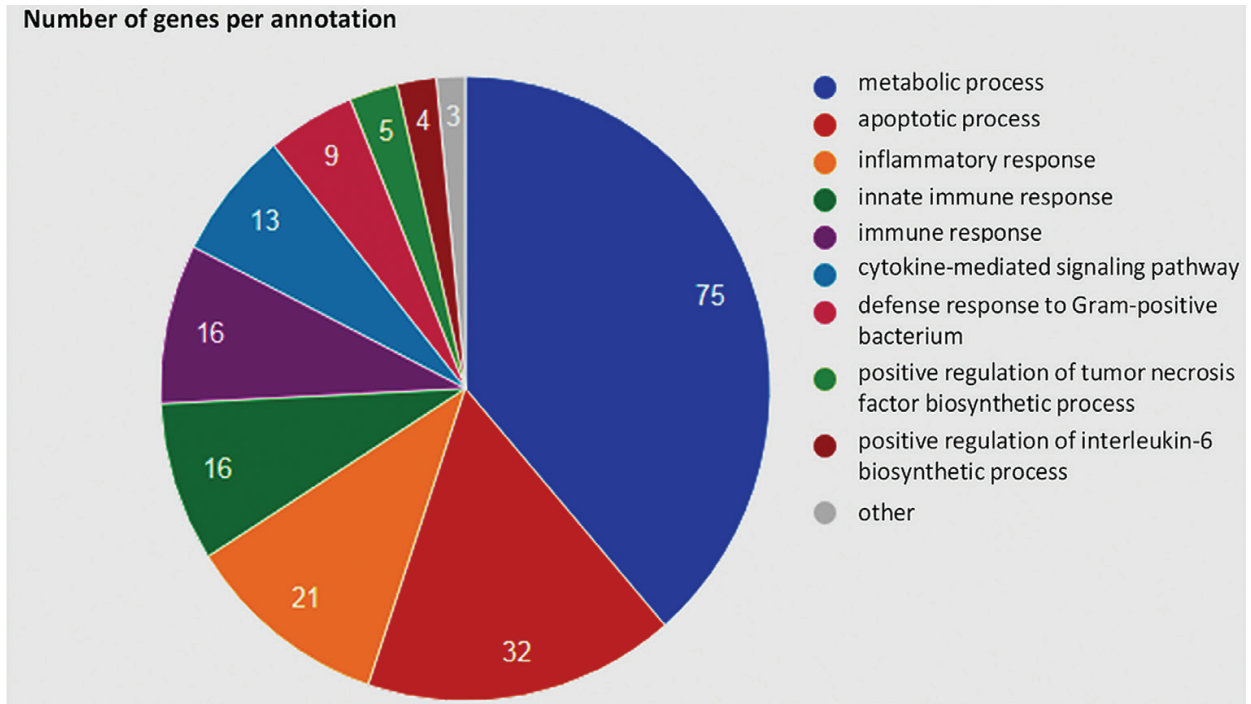


Figure 1. GO analysis of differentially expressed genes between juvenile and adult mouse peripheral blood cells. Six hundred and ten genes showed differential expression ($q < 0.05$) between juvenile and adults. Ontology analysis using GeneCodis (biological process) was performed using this gene list to identify differentially regulated pathways [1–3].

Lastly, subtype-specific recruitment of monocytes/macrophages (M1 vs. M2) has also been shown to play a critical role in outcome following CNS injury [102, 103]. However, age-dependent effects of these cell types in both acute and chronic TBI outcome have yet to be investigated. Further examination into the temporal-spatial recruitment of immune cell subtypes and the employment of depletion and cell-type-specific knockout studies will help address the important emerging role of the peripheral-derived immune system in responding to brain trauma across the life span.

The BBB is established during embryogenesis in rodents and humans [104, 105]; however, postnatal coverage with astrocytic end feet, which aids in the maturation and maintenance of the BBB, occurs in the first few postnatal weeks [104, 106, 107]. This maturation stage is critical with regard to changes in permeability as a result of insult. For example, systemic inflammation increases BBB permeability in P0 and P8 rats while having no effect at P20 [108, 109]. TBI induces endothelial cell dysfunction that increases the permeability of the BBB including disruption of astrocytic end feet, transporters/channels, and tight junction proteins claudin-5 and occludin-1 causing widespread vasogenic edema [110, 111]. The temporal changes in BBB permeability likely depend on the model of TBI, age-at-injury, and severity of impact. Interestingly, monocarboxylate transporter 2 (MCT2) is substantially increased in the microvessels of juvenile P35 rats following CCI injury compared to P75 adult rats [112]. This increase correlated with improved behavioral outcome and reduced cortical lesion volume in P35 rats receiving a ketogenic diet post-TBI compared to adults [113]. Pop and colleagues observed BBB disruption following CCI injury in P17 rats through high amounts of IgG staining, which is consistent with what is seen after CCI injury [114]. At 1-week after injury, a substantial reduction in BBB permeability correlated with an increase expression of tight junction protein (claudin-5). This was maintained as far out as 2 months post-injury, suggesting that tight junction proteins may modulate early disruption and subsequent repair. Likewise, administration of DHA and EPA, the main sources found in fish oil, after CCI injury in P17 juvenile rats reduces BBB permeability, behavioral deficits, and MMP9 expression [115]. The relevance of these studies to the adult response was not evaluated, and further work needs to be conducted in order to improve our understanding of the age-dependent mechanism(s) regulating the BBB following TBI.

2. Conclusions

There has been intense investigation into the brain's maturation-dependent response to TBI using numerous early childhood and juvenile rodent models. Over recent years, studies have revealed age-specific differences in the regulation of metabolism, oxidative stress, neurogenesis, innate immunity, and BBB function following acute and/or chronic injury. Further exploration into the age-specific elements of vascular function, neuroimmune regulation, and the neurovascular niche would help improve our understanding, not only of typical but also atypical developmental trajectories as a consequence of childhood TBI. The insurgence of these animal models, however, must be met with caution as key maturation stages of the brain vary considerably between murine and rat species. Studies of immature or juvenile

injury must also be accompanied by appropriate comparisons to adult-aged animals, which thus far has been inadequate. The need for larger animal models that more accurately recapitulate human brain structure and maturational age is also warranted. Although predicting the age-specific response to TBI in childhood, adolescence, and young adulthood is limited based on current available animal model data, it is clear that “a window of susceptibility” exists that may deter normal growth and development. On the other hand, it is important not to underestimate the early neuroprotective findings observed in a number of studies, which may yield valuable mechanistic insight into pathways that could be utilized for neuroprotection in the adult brain.

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