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Review

From an Age-Stratified Perspective: Divergent Adaptive Mechanisms of the Traumatic Brain Injury Repair Network Between Pediatric and Adult Patients

Sixun Yu[1], Liang Pan[2], Tao Yang[1], Xin Chen[1], Yuan Ma[1,*], Haifeng Shu[1,*]

[1]Department of Neurosurgery, Western Theater General Hospital, 610083 Chengdu, Sichuan, China
[2]Department of Pediatrics, Western Theater General Hospital, 610083 Chengdu, Sichuan, China
*Correspondence: shuhaifeng@swjtu.edu.cn (Haifeng Shu); Tianfu_47@163.com (Yuan Ma)

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Abstract

Traumatic brain injury (TBI) remains a leading cause of chronic neurological impairment across the lifespan, with significant disparities in clinical recovery trajectories between pediatric and adult patients. Previous research has often been confined to a binary debate over the relative repair capacity of different age groups; however, this paradigm is insufficient for exploring the age-dependent molecular mechanisms of adaptation in depth. This review proposes a "divergent adaptation" theoretical framework to systematically analyze age-dependent differences in the brain-derived neurotrophic factor (BDNF)–miRNA network and its microenvironmental regulation—including cerebrospinal fluid dynamics and the gut–brain axis—during TBI repair. In the pediatric brain, repair strategies primarily leverage developmental plasticity, characterized by elevated BDNF/insulin-like growth factor-1 (IGF-1) expression and the active involvement of neurogenesis-promoting miRNAs such as miR-124, which facilitate neural circuit reorganization. However, this reparative process also entails risks, including aberrant circuit formation and vascular fragility. In contrast, the adult brain employs repair strategies focused on maintaining network stability: BDNF/TrkB signaling shifts toward localized repair, while miR-129–mediated inhibition of IGF-1 and epigenetic silencing mechanisms (e.g., BDNF promoter hypermethylation) constrain regenerative capacity and favor gliotic scar formation. Furthermore, cross-system mechanisms—such as the unique cerebrospinal fluid dynamics in children and the "developmental window effect" of the gut–brain axis—may contribute to distinct injury response patterns across ages. From a clinical translational perspective, we emphasize that intervention strategies must be precisely tailored according to age-specific mechanisms. For pediatric patients, potential approaches include exosome-mediated delivery of neurogenic miRNAs (e.g., miR-133b) and IGF-1 potentiation therapies. For adults, more suitable strategies may involve electroacupuncture-mediated modulation of the BDNF-miRNA axis or CRISPR/dCas9-based reversal of epigenetic silencing. Additionally, natural compounds such as curcumin, which confer synergistic anti-inflammatory effects via the BDNF/miRNA network, could represent a universal therapeutic strategy applicable across age groups. This field faces several limitations, however, including a scarcity of high-quality pediatric TBI data, a translational gap between animal models and clinical reality, and an incomplete understanding of cross-system mechanisms. Future studies should establish developmentally staged research systems and integrate multi-omics technologies to advance precision neuroregenerative strategies.

Keywords: brain injuries; traumatic; neurotrophic factors; microRNAs; gut-brain axis; epigenesis; genetic; nerve regeneration

1. Introduction

Traumatic brain injury (TBI) remains a major cause of persistent neurological dysfunction across the entire lifespan [1,2]. Clinical recovery trajectories differ significantly between pediatric and adult patients [3]. Although children exhibit a greater capacity for functional remodeling in certain domains—such as language recovery via bilateral cortical recruitment [4,5], this apparent advantage is often counterbalanced by inherent developmental vulnerabilities. For example, immature cerebrovascular autoregulation is prone to inducing malignant cerebral edema [6]; furthermore, subsequent brain development can be compromised, leading to physical, cognitive, and behavioral sequelae. More critically, children under 8 years of age face a substantially elevated risk of upper cervical spine injuries [7,8]. Collectively, these differences underscore the urgent need for a paradigm shift in research—from a simplistic debate on whether pediatric TBI repair is superior to that in adults, to a deeper investigation into age-dependent molecular adaptation mechanisms.

Current understanding of post-TBI repair mechanisms remains fragmented. Although numerous studies have elucidated the roles of key pathways—such as brain-derived neurotrophic factor (BDNF)/TrkB signaling in synaptic plasticity or miRNA-mediated regulation of neuroinflammation—a crucial gap persists: the absence of a systematic framework clarifying how neurodevelopmental priorities shape distinct molecular responses at different ages. Existing literature reviews commonly highlight deficiencies in three key areas. First, the trade-offs inherent to specific developmental stages are underemphasized. The high plasticity of the childhood brain, exem-

plified by miRNA-124-driven neurogenesis, is undoubtedly beneficial but carries the risk of aberrant neural circuit formation. Conversely, the adult brain prioritizes network stability, for instance, through miR-132-mediated synaptic homeostasis; while this strategy favors stability, it may also promote adverse outcomes such as pathological scar formation. These outcomes represent fundamental, stage-specific adaptive costs. Second, a systemically integrated perspective is lacking. Several important emerging cross-system mechanisms have not been sufficiently explored, including the role of cerebrospinal fluid (CSF) dynamics in neural stem cell migration—potentially significant in children with a higher CSF volume ratio—and gut-brain axis-mediated metabolic reprogramming (e.g., hippocampal BDNF upregulation by short-chain fatty acids during adolescence). These mechanisms imply more complex, system-level interactions. Third, a disconnect exists in clinical translation, manifested by a scarcity of age-stratified biomarkers (e.g., specific diagnostic markers for pediatric TBI) and insufficient assessment of whether intervention strategies are appropriate for a given developmental stage.

To address these critical knowledge gaps, we hereby propose the "divergent adaptation" theoretical framework. The core of this framework involves the integration of multidimensional evidence, encompassing: (1) Age-dependent analysis of core molecular mechanisms, requiring an in-depth investigation into the dynamic changes and functional differences of the BDNF-miRNA network and its microenvironmental regulation (e.g., CSF dynamics, gut-brain axis) during TBI repair in children versus adults; (2) Systematic comparison of age-stratified pathological mechanisms, to clarify the fundamental distinctions between the neuroimmune tolerance and high plasticity seen in children and the inflammation-dominated, stability-preserving strategies employed in adults; and (3) Evaluation of the stage-adaptability of intervention strategies, emphasizing that approaches such as exosome therapy and electroacupuncture must be precisely calibrated to developmental stages (e.g., considering the neuroprotective potential of miR-206-loaded exosomes in the elderly versus their possible burden in a developing brain).

It must be explicitly noted, however, that due to the scarcity of high-quality pediatric TBI studies, some inferences presented here—particularly direct cross-age comparisons—are prospective in nature. This review aims to construct a dynamic adaptation model that moves beyond simplistic dualism, thereby providing a theoretical roadmap for developing precise interventions grounded in developmental chronobiology.

2. Core Molecular Mechanism: Age-Dependent Regulation of the BDNF-miRNA Network and Its Microenvironmental Context

2.1 The "Divergent Adaptation" Framework: Core Tenets and Predictions

To account for the markedly divergent trajectories of recovery after TBI in children and adults, we advance the Divergent Adaptation framework. This model postulates that the immature and mature central nervous systems do not merely differ in reparative capacity, but deploy fundamentally distinct repair programs dictated by their stage-specific physiological imperatives—construction of nascent circuits in the pediatric brain versus preservation of established network stability in the adult. The framework rests on two interlocking principles. First, the Strategy-Tradeoff Principle: high plasticity-driven remodeling in the developing brain accelerates structural restitution yet incurs the commensurate risks of maladaptive wiring and vascular fragility, whereas the stability-oriented response of the adult brain curtails circuit noise at the cost of gliotic scarring and limited regenerative gain. Second, the Molecular Context-Dependency Principle: core signaling molecules such as brain-derived neurotrophic factor (BDNF) and select microRNAs are interpreted through ontogenetic context, so identical molecular cues can yield diametrically opposed functional outcomes. These premises generate testable predictions that move beyond the descriptive notion of "developmental plasticity". (i) Manipulation of a nodal molecular target (e.g., BDNF) will produce converse functional endpoints in the injured immature versus mature brain. (ii) Age-dependent epigenetic locks—exemplified by differential methylation of the BDNF promoter—actively enforce these divergent repair phenotypes. (iii) Cross-system signals, including those originating from the gut–brain axis, are differentially gated into the core BDNF–microRNA regulatory network in an age-specific manner, thereby amplifying the divergence in reparative strategy. The subsequent sections critically appraise the experimental evidence for these predictions through the lens of age-dependent molecular regulation.

It is critical to emphasize that the "Divergent Adaptation" theory does not posit a strict hierarchy with the BDNF-miRNA network as a sole master regulator. Instead, we propose a "network-of-networks" model, wherein the core molecular network (BDNF-miRNA), the local microenvironment (e.g., CSF dynamics), and cross-system communication (e.g., gut-brain axis) operate as parallel, interconnected systems. Their age-dependent interactions—which may be synergistic, antagonistic, or neutral—collectively shape the ultimate repair strategy. The following sections will dissect the contributions of these parallel systems, acknowledging that their integrative logic and relative weights across ages represent a central frontier for future research.

2.2 Role of Neurotrophic Factors in the Repair of Traumatic Brain Injury

TBI leads to persistent neurological dysfunction throughout life, a process in which neurotrophic factors play pivotal regulatory roles in post-injury neuroprotection and repair. Recent studies demonstrate that the signaling pathway mediated by BDNF and its high-affinity receptor, Tropomyosin receptor kinase B (TrkB, also known as NTRK2), not only governs synaptic plasticity and neural network reorganization but is also subject to marked age-dependent modulation. Concurrently, insulin-like growth factor-1 (IGF-1), another critical neurotrophic factor, contributes significantly to neuronal survival, differentiation, and synaptogenesis, exhibiting distinct, stage-specific regulatory patterns across the developmental lifespan.

2.2.1 BDNF/TrkB Signaling in Synaptic Plasticity and Repair

TBI elevates local levels of BDNF, which can activate downstream signaling cascades (e.g., PI3K/Akt, MAPK/ERK) through its high-affinity receptor, TrkB [9,10]. These pathways promote neuronal survival, inhibit apoptosis, and enhance synaptic plasticity [11,12], thereby establishing a molecular foundation for the remodeling of neural networks within injured regions [13]. In the developing brain (e.g., during childhood), inherent high plasticity facilitates extensive BDNF/TrkB-driven functional circuit reorganization [14,15,16,17]. Conversely, in the mature brain, this signaling pathway primarily mediates localized repair and neuroprotection, functioning to stabilize existing neural networks [18,19]. This marked divergence underscores the existence of developmentally stage-specific repair strategies, a concept that warrants further mechanistic validation.

2.2.2 Age-Dependent Regulation of IGF-1 and Neurotrophic Factors

The role of IGF-1 in neural repair is developmentally stage-dependent. Microglia-derived IGF-1 promotes synaptogenesis and neuronal growth, thereby facilitating functional recovery of damaged neural networks [18,19,20,21]. During development (e.g., childhood), elevated IGF-1 expression and enhanced signaling efficiency accelerate synaptic formation and neural remodeling [18,22]. In adults, IGF-1 primarily functions to maintain mature network integrity and support localized injury repair [23,24], although IGF-1-dependent plasticity persists in specific neurogenic regions such as the hippocampal dentate gyrus [25].

The regulatory capacity of IGF-1 becomes attenuated with aging. Declining IGF-1 signaling in senescence induces mitochondrial dysfunction in astrocytes, characterized by reduced ATP synthesis, elevated reactive oxygen species (ROS) accumulation, impaired glucose and β-amyloid uptake, and exacerbated cognitive decline [26]. Clinically, serum IGF-1 levels show a positive correlation with cognitive scores in the elderly ($r = 0.62$); however, its neuroprotective efficacy follows a U-curve relationship—being compromised by insulin resistance and endocrine disorders, while extremes in concentration may increase tumor risk or diminish neuroprotection [27,28,29].

IGF-1 and the BDNF/TrkB pathway may act synergistically via shared signaling cascades (e.g., PI3K/Akt, MAPK/ERK) [30,31]; for instance, physical exercise can concurrently activate both pathways to improve cognitive function [31,32]. Under pathological conditions such as severe TBI or neurodegeneration, this synergistic relationship is disrupted, leading to diminished neurotrophic support. Notable examples include: TBI-induced blood-brain barrier (BBB) disruption, which causes BDNF efflux and impairs IGF-1 penetration across the BBB [33]; mutant Huntingtin protein suppressing astrocytic BDNF release and IGF-1 paracrine support in Huntington's disease [34,35]; and IGF-1-mediated neuroprotection occurring independently of BDNF signaling in spinal cord injury [36].

Critically, the expression and function of these neurotrophic factors are precisely modulated by key miRNAs, collectively forming core molecular networks essential for post-TBI repair, as detailed in the following section.

2.3 Key miRNAs and Their Interactions With Neurotrophic Factors

MicroRNAs (miRNAs) serve as pivotal post-transcriptional regulators in the pathophysiology of TBI. They primarily function by binding to the 3′ untranslated region (3′UTR) of target mRNAs, thereby modulating processes such as neuronal survival, neuroinflammation, glial activation, and neural repair/regeneration [37]. Critically, miRNA activities demonstrate significant injury-type and species specificity, necessitating careful interpretation within defined experimental models.

2.3.1 Functionally Characterized miRNAs in TBI

The functional roles of a select group of miRNAs in TBI have been partially elucidated. For instance, miR-21 expression is upregulated in adult rodent TBI models, where it confers potential neuroprotection by targeting PTEN to attenuate neuronal apoptosis [38,39]. In contrast, aged brains exhibit higher basal miR-21 levels with distinct post-injury dynamics, underscoring age as a critical determinant of its function [40,41]. Meanwhile, miR-124 promotes neural differentiation by suppressing target genes (e.g., *Ptbp1*, *Sox9*) in stem cell cultures and spinal cord injury studies [42,43]; however, its *in vivo* functions and regulatory networks in human TBI require direct experimental verification. Studies using peripheral nerve injury and subarachnoid hemorrhage models indicate that miR-206 directly binds the 3′UTR of BDNF mRNA, inhibiting local BDNF synthesis and impairing neural repair [44,45,46], however, systematic evidence defining its role in pure TBI

models remains lacking. Similarly, evidence from hypoxic brain injury and spinal ischemia-reperfusion models suggests that miR-129 exacerbates neuronal pyroptosis by suppressing IGF-1 translation and disrupting IGF-1/GSK3β signaling [47,48], however, its functional role and therapeutic relevance in TBI pathophysiology await further validation.

2.3.2 Multilayered miRNA-Neurotrophic Factor Crosstalk

The regulation of neurotrophic factors by miRNAs involves multilayered mechanisms. For BDNF, miR-206 has been shown to directly inhibit its translation in sensory neurons, as demonstrated *in vitro* [49]. Indirect regulatory pathways also exist; for example, miR-375 potentiates BDNF expression by targeting SOCS1 to activate JAK2/STAT3 signaling in models of stroke and retinal angiogenesis [50]. Regarding IGF-1, miR-129 directly suppresses its translation, and antagonism of miR-129 has been shown to mitigate neuronal damage in hypoxic conditions [51,52], a relationship that awaits verification in TBI contexts. The complexity of miRNA-neurotrophin interactions is further highlighted by miR-132, which exacerbates pathological discharges via the BDNF/TrkB pathway in epilepsy models [53], indicating significant functional heterogeneity across disease contexts.

2.3.3 Emerging miRNAs With Incomplete TBI Evidence

Other miRNAs demonstrate regulatory potential but currently lack comprehensive evidence in TBI. For instance, miR-142-3p modulates neuroinflammation by targeting CAMK2A in activated microglia *in vitro* [54], while miR-134-5p impairs synaptic plasticity by suppressing the CREB-BDNF pathway in Alzheimer's models [55]. Notably, age and species differences profoundly influence miRNA function. Human-specific miRNA regulation of neurotrophic factors (e.g., miR-144 targeting MANF, miR-134 targeting CDNF) [56] highlights the limited translatability of conclusions derived from rodent studies to human TBI pathophysiology and therapeutic development.

2.3.4 Dynamic and Epigenetic Regulation of miRNA-Neurotrophin Loops

Building upon the multilayered crosstalk described above, a critical question emerges: how are these miRNA-neurotrophin interactions, such as the miR-206-BDNF negative feedback loop, dynamically regulated across different ages to contribute to divergent outcomes? Direct evidence illustrating age-dependent temporal expression patterns or epigenetic control of specific loops in TBI is currently sparse. However, mechanistic insights can be inferred from broader neurodevelopmental and neurobiological contexts.

The expression of miRNAs like miR-206 is itself developmentally regulated, often showing higher baseline levels in the mature versus the developing nervous system. This intrinsic difference could predispose the adult brain to more potent BDNF suppression following injury. More importantly, the epigenetic landscape is poised to be a fundamental arbitrator. The BDNF gene is under stringent epigenetic control, with its promoter activity being modulated by age-dependent DNA methylation and histone modifications [57,58]. We posit a tripartite interaction model: the functional outcome of a miRNA (e.g., miR-206) targeting a neurotrophic factor (e.g., BDNF) is co-determined by the developmental context-specific epigenetic state of the target gene. In the pediatric brain, a permissive, hypomethylated chromatin state might facilitate rapid BDNF transcriptional rebound, buffering against miRNA-mediated inhibition. Conversely, in the adult brain, a hypermethylated BDNF promoter could render its expression more vulnerable and persistently suppressed by miRNAs, thereby limiting plasticity.

This model moves beyond a static view of miRNA-mRNA interactions and emphasizes that the core networks governing repair are embedded within—and constrained by—the evolving epigenetic landscape of the brain. Future research specifically designed to dissect this tripartite interaction in age-stratified TBI models is crucial to validate this model and uncover the precise regulatory logic underlying divergent adaptation.

2.3.5 Current Limitations and Future Directions

Current research in this field faces three major limitations. First, more than 80% of mechanistic insights into miRNA function are derived from non-TBI models (e.g., stroke, neurodegeneration) or *in vitro* systems, underscoring the need for rigorous validation in context-specific TBI models. Second, the translation of miRNA networks into viable therapies is hindered by significant delivery challenges, notably low BBB penetration efficiency (typically $<5\%$) and potential off-target effects. Third, direct evidence from human TBI patients remains critically scarce. To address these gaps, future studies should prioritize the systematic profiling of miRNAs in CSF, blood, and brain tissue, correlating their expression patterns with injury severity, repair progression, and clinical outcomes to establish robust, clinically relevant molecular frameworks.

2.4 Microenvironment and Emerging Cross-System Mechanisms

Brain injury repair is profoundly influenced not only by the intrinsic regulation of the core BDNF-miRNA network but also by dynamic local microenvironmental conditions and cross-system pathways. Current research has identified CSF dynamics and the gut-brain axis as key modulators in this process. Notably, these mechanisms display age-dependent properties in the developing brain, providing novel perspectives for understanding the divergence in TBI recovery between pediatric and adult populations.

2.4.1 CSF Dynamics and Neural Repair

Anatomic studies have revealed that children possess smaller cranial volumes with a proportionally higher occupancy of CSF [59,60], a physiological characteristic that may alter post-TBI CSF hydrodynamics. Clinical imaging data indicate that pediatric TBI patients under six years of age exhibit higher rates of acute ventriculomegaly (observed 1–2 weeks post-injury), suggesting a potential link between CSF circulation disturbances and secondary gliosis or vascular responses [61]. Mechanistically, animal studies in cerebral ischemia models confirm that CSF chemokines (e.g., SDF-1α) mediate neural stem/progenitor cell (NSPC) migration [62,63]. However, the generalizability of this process to TBI, particularly its age-specific characteristics, remains unvalidated. A critical knowledge gap persists regarding whether the unique physical properties of CSF in children—such as fluid shear stress distribution—significantly influence the directional migration efficiency of NSPCs.

2.4.2 Gut-Brain Axis Metabolic Regulation Across Ages

Gut microbial metabolites, especially short-chain fatty acids (SCFAs), may influence central neural repair through systemic circulation [64]. Accumulating experimental evidence demonstrates profound bidirectional dysregulation of the gut-brain axis following TBI [65,66,67]. In adult rodents, cortical contusion rapidly reduces gut microbial α-diversity, increases intestinal permeability, and enriches pro-inflammatory bacterial taxa (e.g., Enterobacteriaceae), thereby exacerbating neuroinflammation and worsening functional outcomes [68,69]. A similar dysbiotic pattern has been observed in human patients with intracerebral hemorrhage, where fecal microbiota imbalance correlates with serum endotoxin levels and Glasgow Outcome Scale scores [70].

In contrast, pediatric data remain scarce and fragmentary. Preliminary evidence suggests that children experience a more pronounced early decline in SCFAs, exhibit shorter yet more vulnerable periods of barrier dysfunction, and demonstrate heightened vagal afferent sensitivity to microbial stimuli [71]. These age-related features imply the existence of a "developmental window effect", wherein microbiota-host interactions differentially regulate neuroplasticity at various maturation stages—though rigorous validation across broader age ranges and larger cohorts is essential.

Despite the incomplete evidence regarding the roles of CSF dynamics and the gut-brain axis in TBI repair, their age-dependent characteristics hold significant scientific value. Unique pediatric physiological traits—such as distinctive cranial volume ratios and specific stages of gut microbiome development—may shape distinct injury response patterns, positioning cross-system mechanisms as pivotal explanatory frameworks for clinical recovery heterogeneity. Current research bottlenecks include the lack of developmentally staged animal models and longitudinal multi-omics datasets from pediatric populations. Future work must establish comprehensive TBI research frameworks that span early childhood through adolescence to precisely delineate the temporal regulatory contributions of these pathways.

3. Age-Stratified Pathophysiological Contrasts: Core Differences in BDNF-miRNA Networks and Repair Strategies Between Children and Adults

Post-injury recovery is governed by developmentally adaptive strategies rather than by simplistic differences in repair capacity. Building upon previous analyses of BDNF-miRNA core networks and microenvironmental regulation, this section systematically compares their expression profiles, functional priorities, and resultant repair strategies in pediatric versus adult TBI, thereby elucidating the age-stratified pathophysiological distinctions central to the 'Divergent Adaptation' theory.

3.1 Expression Signatures of Neurotrophic Factors and miRNAs in Pediatric Brain Injury

The developmental plasticity of the child's brain provides a unique molecular foundation for repair. Clinical cohort studies reveal dynamic, age-dependent changes in serum BDNF levels, which increase throughout childhood and decline after adolescence [72]. Pediatric injury models consistently demonstrate elevated expression of neurotrophic factors such as BDNF and IGF-1, creating an intrinsic milieu that is highly conducive to neuronal survival and regeneration [73,74]. Notably, peripheral BDNF levels, genetic variants, and DNA methylation patterns may serve as biomarkers for predicting survival and recovery in pediatric acquired brain injury (ABI) [74]. Experimental support is provided by neonatal hypoxic models, in which recombinant growth hormone stimulation of IGF-1 expression significantly reduces apoptosis and enhances neurological function [75].

Concurrently, miRNA regulatory pathways maintain a broad dynamic range in children. Developmentally associated miRNAs, including miR-124 and miR-21, undergo rapid modulation at injury sites, fine-tuning downstream gene expression to promote neuronal repair [76,77]. Furthermore, *in vitro* and animal evidence indicate that pediatric neurons exhibit heightened sensitivity to external signals and miRNA alterations, with regulatory networks preferentially favoring cellular proliferation and synaptic remodeling [78,79].

3.2 Distinct Regulatory Mechanisms in Adult Brain Injury

In contrast to children, adult TBI is characterized by reduced neurotrophic factor expression, enhanced apoptotic activity, and exacerbated neuroinflammation. In the mature brain, factors such as chronic stress, aging, and mi-

croenvironmental alterations often prevent BDNF and IGF-1 from returning to pre-injury levels, contributing to synaptic dysfunction and cognitive deficits [80]. Consistent with this, clinical sample analyses reveal distinct alterations in miRNA profiles following injury, which correlate with inflammatory responses, astrogliosis, and apoptosis [55,81].

Although neurotrophic factors and miRNAs undergo expression changes in adulthood, their functional roles pivot toward different physiological priorities. Existing evidence indicates that BDNF signaling shifts toward synaptic maintenance, as exemplified by its regulation of PSD-95 turnover [82]. At the same time, IGF-1-mediated neuroprotection is constrained by miR-129–dependent suppression [57] and age-related hypermethylation of the BDNF promoter [83]. These adaptive mechanisms highlight the necessity of age-stratified therapeutic strategies for brain injury repair.

3.3 Experimental Models and Clinical Evidence for Comparative Analysis

To delineate age-dependent molecular regulation following injury, comparative analyses have utilized various animal models—such as mice and zebrafish—along with clinical specimens. For example, miRNA profiling in adult zebrafish after spinal cord injury reveals a robust innate regenerative capacity accompanied by miRNA network regulation that is distinct from that in mammals, offering valuable insights into enhanced regeneration mechanisms [84,85,86].

Clinically, alterations in miRNA expression in brain tissue and blood samples—such as specific patterns of miR-21 and miR-124—demonstrate diagnostic sensitivity for post-traumatic neurological disorders and possess prognostic utility. Integrated analyses further establish that age-dependent epigenetic regulation, including the methylation status of the BDNF promoter, inversely correlates with neurotrophic factor expression [58,79], thereby providing a molecular basis for precision interventions.

In summary, this analysis reveals systemic differences in neurotrophin expression, miRNA regulatory networks, and epigenetic control between pediatric and adult TBI repair (Table 1, Ref. [3,8,14,15,16,17,18,22,23,24,38,39,40,41,42,43,47,48,55,57,61,74,75,78,81,82,84,85,87]). These distinct molecular profiles establish a foundation for developing age-stratified intervention strategies. Collectively, these developmentally distinct molecular signatures and repair strategies underpin the ‘Divergent Adaptation’ theory, which is comprehensively synthesized in Fig. 1. The core differences outlined herein critically necessitate the use of age-adapted, rather than uniform, interventional approaches, as explored in the following section.

4. Stage-Adapted Intervention Strategies: From Molecular Regulation to Clinical Translation

Conventional therapies frequently fail to adequately address functional recovery needs following brain injury, driving growing interest in multimodal interventions that target neurotrophic factor and miRNA regulatory networks. Given the fundamental differences in BDNF-miRNA networks and repair strategies between pediatric and adult TBI outlined in Section 3, the development of stage-adapted interventions is of paramount importance.

4.1 Targeting BDNF-miRNA Networks for Intervention

Extracellular vesicles (EVs) have emerged as promising drug and gene delivery systems for enhancing neural regeneration and functional recovery after brain injury. EVs elevate local concentrations of neurotrophic factors such as BDNF and IGF-1 while simultaneously modulating miRNA expression profiles in injured regions, thereby promoting neuronal survival and axonal regeneration [88]. Notably, mesenchymal stem cell-derived exosomes carrying miR-133b have been shown to significantly enhance neuronal plasticity and axonal regrowth following intercellular transfer [87].

Physical stimulation therapies, including electroacupuncture, represent another promising approach. These therapies upregulate BDNF expression and modulate specific miRNAs such as miR-1, improving the local microenvironment and facilitating neural regeneration [89,90,91]. Importantly, combining neurotrophic factor delivery with miRNA regulation can synergistically activate endogenous repair networks and accelerate functional recovery after injury [92].

4.2 Multimodal Integration and Synergistic Therapies

Beyond modern molecular and physical interventions, traditional Chinese medicine (TCM) and natural products are gaining attention for their neuroreparative potential. Studies indicate that certain TCM formulations, such as Xuefu Zhuyu decoction, enhance cognitive function and synaptic architecture after severe brain injury by modulating the miR-191a-5p/BDNF-TrkB axis, offering novel insights for integrating traditional and molecularly targeted therapies [93]. Natural compounds like curcumin exert antidepressant and neuroprotective effects through BDNF and multi-miRNA regulation, demonstrating significant potential in promoting post-injury neuroregeneration and functional recovery [93,94].

In adult brain injury repair, multimodal approaches that combine growth hormone, anti-inflammatory agents, and miRNA modulators are being actively explored. These strategies concurrently regulate post-injury microenvironments at multiple levels, potentially yielding more effective clinical solutions [95,96].

Table 1. Core molecular mechanisms in pediatric vs. adult TBI repair.

Dimension	Pediatric mechanisms	Adult mechanisms	Representative downstream effects	Key evidence (Ref #)
Repair Strategy	Developmental plasticity-driven	Network stability-focused	Pediatric: Promotes neural circuit reorganization. Adult: Limits rewiring to preserve existing networks.	[14,15,16,17] vs [18,23,24]
BDNF Expression	↑ (Age-dependent serum elevation)	↓ (Promoter hypermethylation)	Pediatric: Supports synaptic growth & survival. Adult: Contributes to synaptic dysfunction & cognitive deficits.	[74,75] vs [82,85]
IGF-1 Regulation	↑ (Microglial-derived pro-neurogenesis)	↓ (miR-129-mediated suppression)	Pediatric: Accelerates synaptic formation. Adult: Restricts regenerative capacity, predisposing to pyroptosis.	[18,22] vs [47,48,84]
Key miRNAs	miR-124↑ (Neurogenic), miR-133b↑ (Axon regeneration)	miR-129↑ (Pro-pyroptotic), miR-21↑ (Gliosis control)	Pediatric: miR-124 drives neurogenesis; miR-133b aids repair. Adult: miR-129 inhibits IGF-1; miR-21 modulates scar.	[42,43,78] vs [38,39,40,41,57]
Epigenetic Control	DNA hypomethylation (High flexibility)	BDNF/neurotrophin hypermethylation	Pediatric: Permits broad gene expression for plasticity. Adult: Silences pro-regenerative genes.	[81] vs [85,87]
Pathological Outcome †	Abnormal circuitry risk (~40–60% acute ventriculomegaly)	Glial scar dominance (Significant scar formation in >80% chronic TBI	Pediatric: Maladaptive wiring. Adult: Physical barrier to regeneration.	Clinical & histological studies [3,8,61] †

↑ indicates upregulation, increased expression, or enhanced activity/flexibility relative to the comparison group.

↓ indicates downregulation, decreased expression, or reduced activity/flexibility relative to the comparison group.

† **Pathological outcome notes**: The data for children were obtained from a clinical imaging study [61], which reported a ventricular enlargement rate of 40–60%. The data for adults were derived from histological analyses [55,81].

Current evidence underscores that precise, personalized therapeutics must address molecular, cellular, and systemic hierarchies to fully restore neurological function after injury. Emerging research suggests that modulating metal ion-neurotrophic factor interactions—particularly involving zinc and copper—may further improve neuroregeneration [84,97,98]. Concurrently, systems biology analyses of miRNA expression profiles continue to uncover core regulatory networks, informing the development of small-molecule drugs for precise miRNA control [87].

Given the stark differences in repair mechanisms between developmental stages and adulthood, future work should strategically leverage stage-specific advantages. This approach will accelerate the development of multimodal strategies spanning molecular regulation, cellular delivery, physical stimulation, and traditional pharmacology, ultimately advancing toward comprehensive neurological restoration after brain injury. Key strategies with clinical translation potential are summarized in Table 2 (Ref. [66,69,87,91,92,94,96,99]).

Despite the considerable promise of age-adapted multimodal interventions, their clinical translation faces substantial theoretical and technical challenges, which are detailed in the following section.

5. Future Challenges and Unresolved Issues

Although age-stratified interventions demonstrate considerable potential, their translation into clinical practice faces several critical bottlenecks, as summarized in Table 3 (Ref. [100,101]). With advancing age, the epigenetic landscape of the nervous system—encompassing DNA methylation, histone modifications, and chromatin

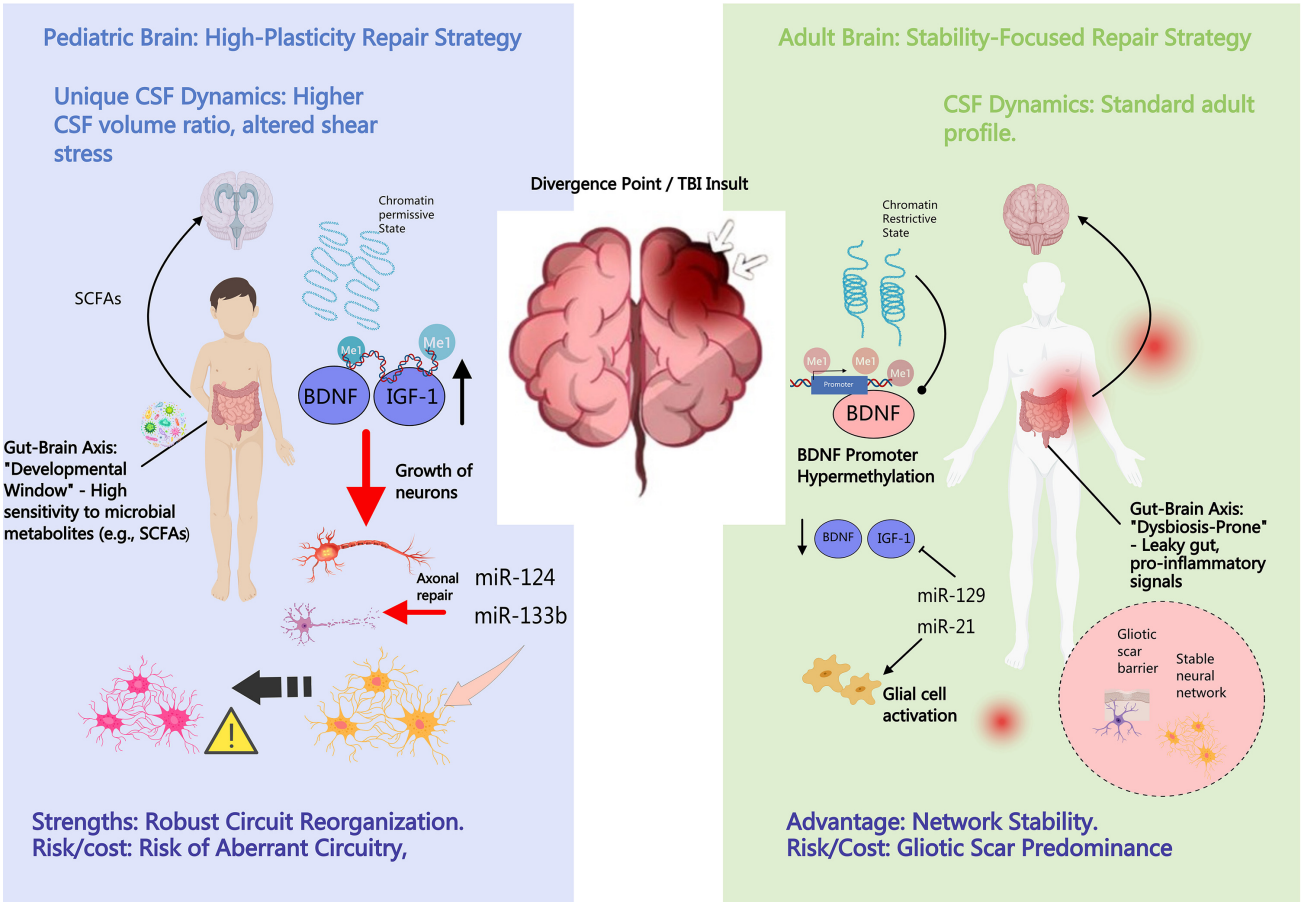

Fig. 1. Schematic illustration of the "Divergent Adaptation" theory: Age-stratified molecular and cellular responses to TBI. The diagram contrasts the distinct repair strategies in the pediatric (left) versus adult (right) brain following TBI, which are driven by divergent molecular networks and microenvironmental contexts. (Left Panel) Pediatric Brain - High-Plasticity Repair Strategy: Microenvironment: Characterized by unique cerebrospinal fluid (CSF) dynamics and a "developmental window" of the gut-brain axis, favouring pro-plasticity signals like short-chain fatty acids (SCFAs). Core Molecular Network: A permissive epigenetic state (e.g., DNA hypomethylation) facilitates high expression of neurotrophic factors (BDNF, IGF-1). Key miRNAs such as miR-124 and miR-133b are upregulated, promoting neurogenesis and axonal regeneration. Cellular Outcome: This milieu supports robust neural circuit reorganization and functional compensation. However, this high degree of plasticity carries the inherent risk of aberrant circuitry formation and vascular fragility. (Right Panel) Adult Brain - Stability-Focused Repair Strategy: Microenvironment: Standard adult CSF dynamics and a gut-brain axis prone to dysbiosis, often propagating inflammatory signals. • Core Molecular Network: A restrictive epigenetic state (e.g., BDNF promoter hypermethylation) and inhibitory miRNAs (e.g., miR-129 targeting IGF-1) constrain neurotrophic support. miR-21 is upregulated, modulating glial responses. Cellular Outcome: The response prioritizes the preservation of existing network stability. This limits maladaptive rewiring but promotes a microenvironment conducive to astrogliosis and the formation of a glial scar, which acts as a physical barrier to regeneration. Created with MedPeer.

remodeling—undergoes highly dynamic and spatiotemporally specific alterations. These changes exhibit substantial variation across different brain regions and even among cellular subpopulations, providing valuable insights into age-dependent neural repair mechanisms. However, current predominant epigenetic detection methodologies—including ChIP-seq, ATAC-seq, and DNA methylation sequencing—primarily rely on postmortem specimens. This inherent limitation prevents real-time monitoring of epigenetic modification dynamics within living organisms (*in vivo*). Furthermore, the intricate three-dimensional architecture and marked cellular heterogeneity of neural tissue present significant technical barriers to achieving high-sensitivity *in situ* detection at single-cell or subcellular resolutions. Recent advances in *in situ* imaging techniques, particularly those utilizing CRISPR/dCas9 systems coupled with fluorescent reporters, show promise for tracking specific epigenetic marks. Nevertheless, these approaches still face limitations in signal-to-noise ratio, target specificity, and capacity for long-term dynamic tracking [102,103]. Consequently, there is an urgent need to develop more sensitive, real-time *in situ* monitoring platforms capable of

Table 2. Age-adapted precision intervention strategies for TBI repair. con.

Strategy type	Pediatric applications	Adult applications	Mechanism	Evidence level & Key support
Molecular Delivery	Exosomal miR-133b	CRISPR/dCas9-BDNF editing	Neuronal differentiation/Epigenetic regulation	Preclinical [87]
Physical Stimulation	Electroacupuncture	Electroacupuncture	BDNF-miRNA axis modulation	Preclinical [91,92,94]
Growth Factors	IGF-1 enhancement *	Not Recommended †	Neurogenesis promotion	Preclinical (Hypoxia model) [99]
Natural Compounds	Ganglioside GM1	Curcumin	Anti-inflammatory & BDNF modulation	Preclinical [96]
Cross-system Modulators	Probiotics (*Bifidobacterium*)	SCFA supplementation	Gut-brain axis metabolic reprogramming	Hypothesized [66,69] ‡

Evidence Limitations:

* The evidence for IGF-1 is derived exclusively from the neonatal hypoxia model [99], and the extrapolation of these findings to TBI in children requires further validation.

† **Not Recommended for Adults**: Direct IGF-1 enhancement is not advised due to a lack of supportive evidence in adult TBI, potential suppression by miRNAs like miR-129, and age-associated risks such as increased tumor promotion concerns.

‡ **Hypothesized Mechanism**: The gut-brain axis role is a compelling hypothesis derived from correlative and preliminary experimental data. Its precise mechanistic role in TBI repair and efficacy as a therapeutic target require further validation in age-stratified animal models and clinical studies.

distinguishing distinct cellular subpopulations. Such platforms would be instrumental in comprehensively elucidating the mechanisms governing epigenetic states in brain tissue across developmental stages and would provide crucial technical support for precision interventions in neural injury repair.

The multifaceted roles of miRNA regulatory networks in neural repair and their therapeutic potential have attracted significant attention. However, two major challenges hinder the clinical translation of miRNA-based therapeutics. First, as short, freely circulating nucleic acids, miRNAs are highly susceptible to degradation by nucleases in the bloodstream. The BBB further substantially restricts their delivery to the central nervous system. Although delivery platforms such as nanoparticles, liposomes, and viral vectors have improved the *in vivo* stability and delivery efficiency of miRNAs to some extent, overcoming the BBB and achieving effective targeting to lesion sites remains a pivotal technical hurdle [104,105]. Second, miRNAs typically regulate multiple target genes—a characteristic that enables them to form multi-layered regulatory networks but also introduces substantial off-target risks. Non-specific gene modulation may lead to unintended cellular dysfunction or other unforeseen adverse effects. Several studies advocate for establishing high-throughput, high-precision evaluation systems to proactively assess and mitigate potential off-target effects of miRNAs. There is also a clear need to develop more precise regulatory models tailored to different cellular subpopulations [100,101]. Therefore, optimizing miRNA-targeted delivery systems and gaining deeper insights into miRNA expression profiles and multi-target effects within neural cells are paramount for developing safe and effective miRNA therapeutics.

A fundamental challenge in validating the "Divergent Adaptation" theory lies in the translational gap between existing models and human pathophysiology. While developmental-stage-matched animal models remain indispensable, they often fail to fully recapitulate the complexity of human brain development and aging. To this end, future research must aggressively incorporate human-based model systems. Brain organoids derived from human induced pluripotent stem cells (iPSCs) represent a particularly promising avenue [106]. By generating organoids that capture distinct developmental stages [107] (e.g., pediatric-like vs. adult-like), researchers could create human-specific platforms to directly test the age-dependent functions of the BDNF-miRNA network and the efficacy of proposed interventions in a controlled, ethically feasible manner. Combining these *in vitro* human models with *in vivo* animal studies will create a powerful complementary framework for deciphering age-stratified repair mechanisms and accelerating the development of precision therapies.

6. Conclusion

As illustrated in Fig. 1, this review systematically examines the central roles of neurotrophic factors—particularly BDNF and IGF-1—and microRNAs, along with their complex interactive networks, in neural repair following TBI across different age groups. Through integrative analysis of extensive animal studies and clinical evidence, we have proposed and elaborated the "Divergent Adaptation" theoretical framework. The core premise of

Table 3. Critical research gaps and future directions in age-stratified TBI repair.

Challenge domain	Current limitations	Proposed solutions	Expected outcomes
Pediatric Data Scarcity	Limited access to brain tissue/CSF samples (ethical constraints)	Multicenter collaboration: Organoid models + Non-invasive biomarker development	Pediatric TBI molecular atlas
Cross-system Mechanisms	Unclear interactions between gut-brain axis/CSF dynamics and BDNF networks	Humanized murine models + Gnotobiotic animal studies	Age-dependent weight of systemic modulation
Intervention Translation	Low miRNA delivery efficiency (<5% CNS penetration due to BBB)	Engineered nanocarriers (exosome-liposome hybrids)	Enhanced CNS-targeted delivery specificity
Age-stratified Efficacy	Lack of clinical trial designs adapted to developmental stages	Staggered dosing trials (pediatric-first → adult expansion)	Precision therapeutic windows

Footnotes:
BBB, Blood-brain barrier; CSF, Cerebrospinal fluid; CNS, Central nervous system.
Evidence Support:
All content derived from *Section 5: Limitations and Future Perspectives* (Original analysis).
Key quantitative claims (e.g., miRNA delivery <5%) sourced to [100,101].

this framework is that pediatric and adult brains respond to TBI not through a simple dichotomy of superior versus inferior repair capacity, but by developing distinct molecular adaptation strategies specifically tailored to their respective developmental stages, physiological characteristics, and requirements.

Neural repair following childhood TBI primarily leverages the inherent heightened plasticity of the developing brain. This manifests through elevated expression of neurotrophic factors like BDNF and IGF-1, actively dynamic miRNA regulatory networks (e.g., neurogenesis-promoting miR-124 and inflammation-modulating miR-9), and greater epigenetic flexibility. Collectively, these mechanisms drive robust neural circuit reorganization, enabling functional compensation through bilateral cortical recruitment. However, this high-plasticity strategy carries inherent risks, including aberrant circuit formation, malignant edema due to immature cerebrovascular regulation, and significant impact on subsequent neurodevelopment, leading to cognitive and behavioral sequelae along with elevated risk of upper cervical injuries.

In contrast, repair mechanisms in adulthood prioritize stability maintenance and localized restoration within established neural pathways. In the mature brain, neurotrophic factor expression is constrained by age-related promoter hypermethylation (e.g., BDNF) and miRNA-mediated suppression (e.g., miR-129 targeting IGF-1). Key miRNAs such as miR-21 shift their function toward apoptosis inhibition and glial scar regulation—sometimes excessively promoting scar formation. While this stability-focused strategy offers protective benefits, its reduced plasticity can limit functional restoration and lead to complications such as maladaptive scar formation.

6.1 Significance of This Work

The primary significance of this review lies in implementing the "Divergent Adaptation" framework, which moves beyond the simplistic debate about relative repair superiority between age groups. Instead, it provides a comprehensive perspective integrating molecular networks (BDNF-miRNA), microenvironmental regulation (cerebrospinal fluid dynamics), and trans-system mechanisms (gut-brain axis) to understand age-dependent disparities in post-TBI repair. Furthermore, this work offers detailed analysis of the BDNF-miRNA network's central role, clarifying its dynamic differences and functional priorities across developmental stages. For instance, BDNF/TrkB signaling more readily facilitates widespread reorganization in the developing brain, while being oriented toward localized repair and stability maintenance in adults.

The review also highlights emerging trans-system mechanisms, including the unique physical properties of pediatric CSF environments and the "developmental window effect" of gut-brain axis metabolic reprogramming, as valuable explanatory factors for repair heterogeneity. Examination of localized synaptic regulation by miRNAs and integrative actions of neurotrophic factors with diverse signaling systems deepens understanding of brain injury complexity while suggesting promising molecular targets.

From a clinical translation perspective, we emphasize the necessity of age-appropriate intervention strategies. For example, IGF-1 supplementation may effectively promote

neurogenesis during development but demonstrate limited efficacy or even carry risks in the aged brain. This insight provides a crucial theoretical foundation for developing precision therapies based on developmental chronobiology, including exosome-mediated miRNA delivery, electroacupuncture modulation of the BDNF-miRNA axis, and multi-target interventions using traditional Chinese medicine formulations.

6.2 Limitations and Future Directions

This study has several limitations requiring focused attention in future research:

A critical limitation is the scarcity of high-quality pediatric evidence. Ethical and practical constraints severely limit the availability of molecular studies involving longitudinal dynamic monitoring of brain tissue and cerebrospinal fluid in children. Consequently, some inferences regarding child-specific mechanisms—particularly direct comparisons with adults—remain largely prospective. There is an urgent need for validation through innovative approaches, including brain organoids, advanced imaging biomarkers, and large-scale multicenter cohorts.

Second, reliance on non-TBI models creates a significant translational gap. Current understanding of the BDNF-miRNA network, particularly miRNA functions, predominantly derives from studies using non-TBI models (e.g., stroke, neurodegenerative diseases, *in vitro* systems) or specific animal models (e.g., rodents, zebrafish). Translating these findings to human TBI pathophysiology, especially in children, involves inherent uncertainties due to species differences (e.g., human-specific miRNA regulation) and variations in injury modeling.

Third, deeper mechanistic investigation and integration are needed. The specific molecular pathways, intercellular communication, and quantitative contributions of proposed trans-system mechanisms—such as how CSF hydrodynamics precisely influences neural stem/progenitor cell migration, or how gut-brain axis signaling modulates the central BDNF-miRNA network—require further elucidation across age groups. Additionally, current limitations in epigenetic monitoring technologies hinder real-time, *in situ* resolution of age-related regulatory mechanisms.

Finally, proposed intervention strategies require further development. While the concept of age-appropriate interventions is established, most specific approaches (e.g., miRNA therapies, exosome-targeted delivery, CRISPR/dCas9-based epigenetic editing) remain preclinical. Their clinical translation faces substantial challenges including delivery efficiency across the blood-brain barrier, target specificity, long-term safety, and the need for rigorous age-stratified efficacy and safety evaluations.

In summary, sustained investigation into neurotrophic factor-miRNA regulatory networks and their age-dependent characteristics holds significant promise. Such research will not only elucidate unified mechanisms governing nervous system development, injury response, and neurodegeneration—thereby validating and refining the "Divergent Adaptation" theory—but also establish a solid foundation for developing safe, effective precision neural regeneration strategies. Overcoming current limitations, particularly bridging the pediatric TBI research gap, represents a crucial step toward achieving developmentally staged, precision interventions for TBI repair.

Author Contributions

Study concept and design: LP, HS, SY, XC. Searching the literature: TY, YM, SY. Data collection: SY, LP. Critical revision of the manuscript for important intellectual content: XC, HS, LP. Supervision: XC, HS. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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