

Epigenetic reprogramming in traumatic brain injury

Zeyuan Lu, Jian Sima (✉)

Laboratory of Aging Neuroscience and Neuropharmacology, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing 210009, China

Received: 22 January 2026 | Revised: 5 February 2026 | Accepted: 8 February 2026

ABSTRACT

Traumatic brain injury (TBI) initiates a cascade of secondary molecular and cellular events that drive long-term neurological dysfunction. Increasing evidence positions epigenetic regulation as a central integrative mechanism through which acute injury-related signals are translated into sustained alterations in gene expression, cell state, and circuit function. Epigenetic mechanisms—including DNA methylation, histone modifications, and non-coding RNAs—act in a coordinated, cell type-specific manner to shape transcriptional programs underlying neuroinflammation, synaptic remodeling, and behavioral outcomes after TBI. Recent advances in epigenomic and transcriptomic profiling, particularly single-cell, spatial, and integrative multi-omics approaches, have enabled systems-level interrogation of injury-induced regulatory networks across neurons, glia, and the neurovascular unit. Beyond mechanistic insight, epigenetic reprogramming provides a conceptual framework for biomarker discovery and therapeutic development, given the accessibility and reversibility of epigenetic states. This review synthesizes current evidence to highlight how epigenetic mechanisms link acute brain injury to chronic neurological sequelae and discusses emerging opportunities for epigenetically informed precision medicine in TBI.

KEYWORDS

traumatic brain injury (TBI), epigenetic reprogramming, multiomics, precision medicine

1 Introduction

Traumatic brain injury (TBI) remains a leading cause of disability and mortality worldwide. Its pathogenesis reflects a complex interplay between the initial mechanical insult and secondary cascades involving metabolic dysfunction, inflammatory amplification, and disruption of neural circuits. Clinically and pathologically, TBI is broadly classified into focal and diffuse injuries [1]. Focal injuries typically arise from direct impact and are characterized by contusion and hemorrhage, whereas diffuse injuries—common in falls and vehicular accidents [2]—result from rapid acceleration–deceleration or rotational forces that induce widespread axonal deformation.

Beyond structural damage, accumulating evidence indicates that TBI induces profound and sustained epigenetic reprogramming. These alterations emerge in the acute phase but may persist for months or years, exerting lasting effects on neuroplasticity, immune responses, and functional recovery. Epigenetic remodeling encompasses multiple regulatory layers, including DNA methylation and hydroxymethylation, histone modifications, chromatin remodeling and nucleosome

positioning, and non-coding RNA regulation (including microRNAs, long non-coding RNAs, and circular RNAs) [3]. Importantly, the epigenetic landscape after TBI is highly dynamic and reversible, exhibiting pronounced cell type-specific, temporal, and spatial heterogeneity. This complexity helps explain why conventional morphological, biochemical, or electrophysiological measures fail to account for the striking interindividual variability in cognitive, emotional, and neurodegenerative outcomes among patients with comparable structural injuries. Although early research largely focused on inflammation, apoptosis, and axonal degeneration, recent epigenomic and multi-omics studies have revealed far more intricate regulatory architectures underlying TBI pathology. Reductionist analyses centered on individual molecules or pathways are insufficient to capture the multisystem, multicellular interactions that drive injury progression and recovery. The emergence of multi-omics technologies now provides a powerful system-level framework. Integration of methylome profiling, chromatin accessibility assays (ATAC-seq), histone modification mapping (ChIP-seq or CUT&Tag), transcriptomics (bulk, single-cell, and spatial RNA sequencing), together with proteomic and metabolomic

analyses, enables reconstruction of causal relationships linking epigenetic alterations to transcriptional outputs and functional phenotypes.

TBI is inherently heterogeneous, with disease trajectories shaped by age, genetic background, comorbidities, injury mechanism, and immune status [4]. Growing evidence suggests that much of this heterogeneity is encoded at the epigenetic and multi-omic level, giving rise to distinct inflammatory profiles, neuroplastic responses, repair capacities, and vulnerabilities to long-term cognitive or affective disorders [5]. These insights position epigenetics at the core of emerging precision medicine approaches for TBI. Epigenetic and multi-omic signatures hold promise not only for patient stratification and subtype classification, but also for prognostic prediction, longitudinal monitoring, and the identification of therapeutic windows. Such a framework shifts TBI management away from a “one-size-fits-all” paradigm toward molecularly informed, individualized interventions tailored to specific populations, including children, older adults, and patients across injury severities.

In this review, we integrate multi-layered epigenetic remodeling after TBI—including DNA methylation and hydroxymethylation, histone modifications, chromatin accessibility, three-dimensional genome organization, and non-coding RNA regulation—within a multicellular, spatiotemporal framework. Following a “heterogeneity–network modules–translatable targets” conceptual pathway, we highlight how integrative multi-omics approaches reconstruct causal chains from regulatory elements to transcriptional programs and functional outcomes. We further discuss translational avenues for patient stratification, outcome prediction, and therapeutic development, and identify key challenges and opportunities for future progress, including multimodal single-cell and spatial analyses and cross-cohort validation. Together, this synthesis aims to provide a roadmap for mechanism-driven precision medicine in TBI.

2 Epigenetic basis and multi-omics framework in TBI

TBI arises from cascades of interconnected molecular and cellular responses triggered by mechanical damage rather than a single pathway abnormality [6]. These responses drive dynamic remodeling across neurons, glial cells, endothelial cells, and infiltrating immune populations. Increasing evidence identifies epigenetic regulation as a central mechanism linking acute injury cues to persistent transcriptional and phenotypic alterations (Fig. 1). Advances in multi-omics technologies have therefore become essential for systematically dissecting epigenetic reprogramming and its functional consequences after TBI.

2.1 Epigenetic regulatory networks

Epigenetic mechanisms modulate transcriptional states by regulating chromatin structure and gene accessibility without altering DNA sequence. In TBI, multiple regulatory layers act in concert. DNA methylation at CpG dinucleotides influences transcription factor binding and gene expression [7, 8]. Injury-induced inflammatory and stress signals drive global and locus-specific methylation remodeling, generating differentially methylated regions that exert long-lasting effects on neuronal plasticity, synaptic function, and neuroinflammatory gene programs [9–11]. Histone modifications further regulate chromatin accessibility by altering nucleosome organization and the recruitment of transcriptional regulators [12]. In parallel, non-coding RNAs provide a complementary regulatory layer. MicroRNAs modulate mRNA stability and translation, influencing neuronal survival, glial activation, and blood–brain barrier (BBB) function [13, 14]. Long non-coding RNAs coordinate chromatin-modifying complexes and transcription factors, whereas circular RNAs, owing to their stability, have emerged as candidate regulators and biomarkers in TBI [15, 16]. Together, these epigenetic mechanisms form interconnected regulatory networks that shape cell fate decisions after injury.

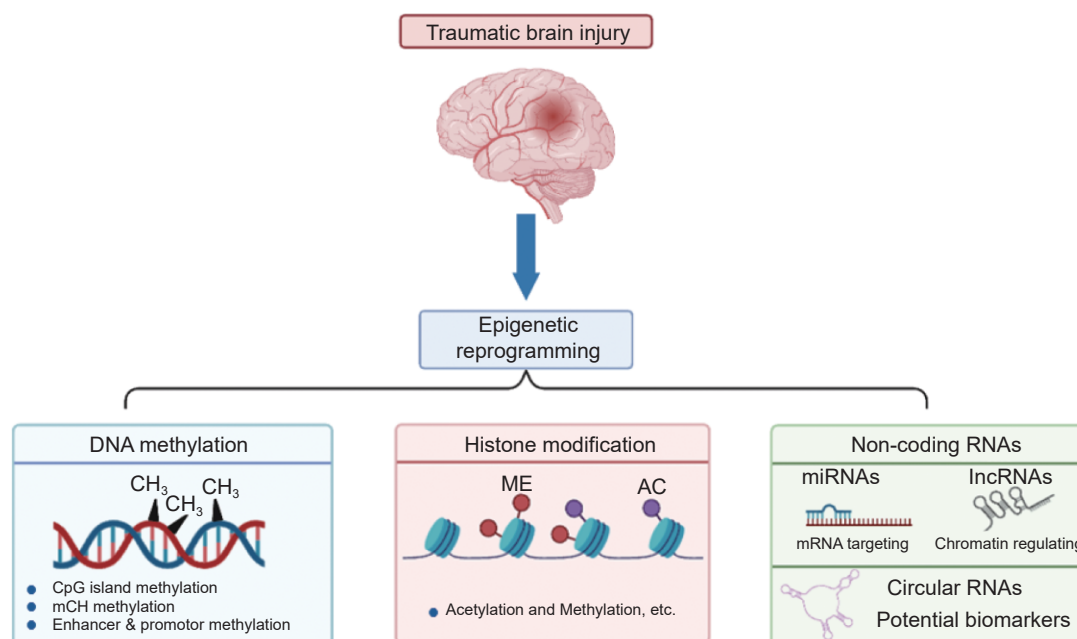


Figure 1 TBI induces extensive epigenetic reprogramming. TBI triggers widespread and persistent epigenetic reprogramming in the injured brain, which involves coordinated alterations across multiple epigenetic layers, including DNA methylation, histone modifications, and non-coding RNAs.

2.2 Multi-omics integration framework

Single-omics approaches are insufficient to capture the complexity of TBI pathology, necessitating integrative multi-omics strategies [17]. Methylome profiling identifies injury-associated DNA methylation changes, which, when integrated with transcriptomic data, link regulatory alterations to functional gene expression outcomes [18, 19]. Chromatin accessibility assays reveal dynamic, cell type-specific remodeling of regulatory elements following injury [20], while histone modification mapping defines shifts in active and repressive chromatin states at enhancers and promoters [21]. These data help define changes in active enhancers and promoters after TBI, linking regulatory elements to target genes. At the functional level, bulk and single-cell transcriptomics connect epigenetic remodeling to biological processes in defined cell populations [22]. Proteomic and metabolomic analyses further map these transcriptional changes to signaling pathways, metabolic states, and oxidative stress responses [23, 24]. Spatial omics technologies add anatomical context, enabling the resolution of epigenetic and transcriptional heterogeneity across brain regions and cellular niches after TBI [25, 26].

2.3 Three-dimensional genome organization and regulatory rewiring

Beyond linear genomic features, three-dimensional genome architecture plays a key role in gene regulation after TBI. Enhancer–promoter interactions, the stability of topologically associated domains, and insulation mediated by architectural proteins collectively determine transcriptional specificity [27]. Injury-associated DNA damage, metabolic stress, and inflammatory signaling remodel this spatial architecture, reconnecting or reinforcing regulatory contacts. Such regulatory “rewiring” provides a mechanistic basis for the long-term consequences of TBI. Stabilized three-dimensional interactions involving neuroplasticity- or immune-related genes can sustain maladaptive transcriptional programs even after acute injury resolution, contributing to chronic neuroinflammation, impaired synaptic remodeling, and persistent cognitive or affective dysfunction [28, 29]. Within this context, individual epigenetic layers can be examined not in isolation, but as components of coordinated regulatory programs shaping post-injury trajectories.

3 DNA methylation alterations in TBI

DNA methylation is one of the most extensively studied epigenetic mechanisms in TBI [30]. Injury-associated inflammation, oxidative stress, and metabolic disturbance rapidly modulate DNA methyltransferase and demethylation pathways, reshaping genome-wide methylation landscapes across acute and chronic phases (Fig. 2). These alterations contribute not only to immediate stress and inflammatory responses but also to persistent epigenetic reprogramming that may underlie long-term neurological dysfunction.

3.1 Genome-wide DNA methylation signatures after TBI

Genome-wide methylation studies consistently show that genes involved in neuronal plasticity, axon guidance, and inflammation undergo substantial remodeling after TBI.

Methylation changes at promoters and enhancers of neurotrophic genes, such as *BDNF*, are closely linked to neuronal survival and synaptic remodeling [31, 32]. In pediatric TBI, reduced brain-derived neurotrophic factor (BDNF) promoter methylation is observed acutely, with a subset of CpG sites remaining altered up to one year post-injury, suggesting durable epigenetic modification of neurotrophic pathways during recovery [33].

Epigenome-wide association studies have further identified aberrant methylation of axon guidance regulators, including repulsive guidance molecule A (RGMA), with specific CpG hypomethylation associated with intracranial hypertension and injury severity [34]. In parallel, neurodegeneration-related genes such as genes coding amyloid precursor protein (*APP*) and microtubule-associated protein tau (*MAPT*), as well as cytoskeletal and myelination-associated genes, exhibit differential methylation across experimental and clinical TBI cohorts [35, 36]. These findings provide molecular links between TBI, impaired structural remodeling, and increased vulnerability to long-term cognitive and motor deficits. Temporally, DNA methylation changes display phase-dependent features. Acute injury is characterized by rapid and partially reversible methylation shifts, whereas chronic neuroinflammatory states are associated with more stable methylation signatures linked to brain atrophy and cognitive decline [37, 38]. This pattern supports the concept that TBI can induce persistent epigenetic “imprints” that predispose to chronic neurological impairment and neurodegenerative processes.

3.2 Cell type-specific DNA methylation remodeling

Advances in single-cell methylome profiling have revealed pronounced cell type-specific methylation heterogeneity following TBI. Differentially methylated regions are frequently enriched at enhancers and non-CpG sites, underscoring regulatory complexity that is obscured in bulk tissue analyses [39]. Inflammatory and immune-related methylation changes are predominantly observed in non-neuronal populations, particularly microglia and astrocytes, implicating glial epigenetic reprogramming as a driver of sustained neuroinflammation [40]. By contrast, neuronal methylation changes preferentially affect distal regulatory elements controlling synaptic function, plasticity, and behavior, highlighting enhancer-centered regulation as a key mechanism linking TBI to long-term circuit dysfunction [41].

3.3 DNA methylation and clinical outcomes

Importantly, TBI-associated DNA methylation changes are also detectable in peripheral blood, providing a translational avenue for biomarker development [42]. Methylation states at specific loci correlate with injury severity, recovery trajectories, and neuropsychiatric outcomes, supporting their potential use in prognosis and patient stratification [43]. Pediatric TBI displays distinct methylation signatures compared with adult injury, reflecting disruption of developmentally programmed epigenetic trajectories and underscoring the need for age-specific frameworks when interpreting epigenetic biomarkers and therapeutic targets [44]. These observations indicate that DNA methylation changes after TBI are dynamic, context-dependent, and tightly linked to both cellular identity and clinical outcome. At the same time, their functional impact is inseparable from higher-order

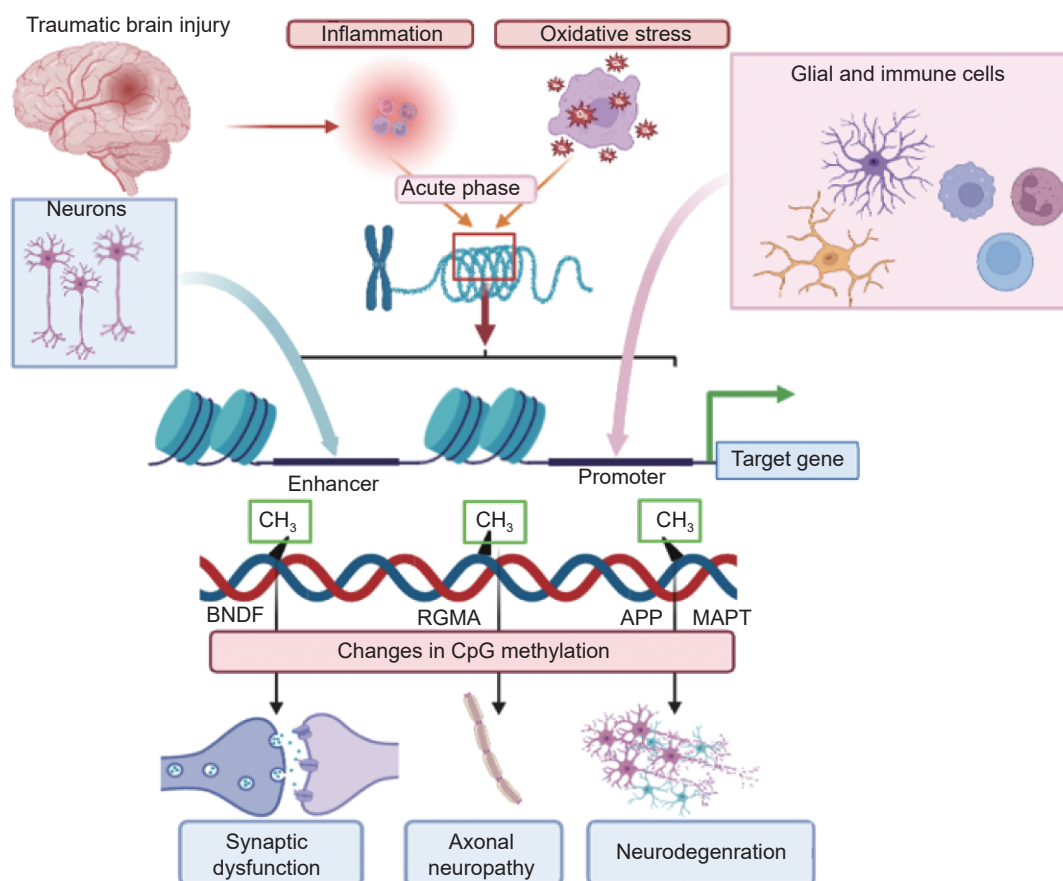


Figure 2 Acute TBI induces DNA methylation remodeling that shapes neuropathological trajectories. Following TBI, acute inflammatory signaling and oxidative stress rapidly drive cell type-specific epigenetic reprogramming. Neurons predominantly exhibit enhancer-associated DNA methylation changes, whereas glial and immune cells show promoter-centered methylation remodeling. During the acute post-injury phase, these pathological cues also disrupt chromatin architecture, leading to aberrant CpG methylation at genes governing synaptic dysfunction, axonal injury, and neurodegenerative progression.

chromatin organization and additional regulatory mechanisms that jointly determine transcriptional states.

4 Histone modifications and chromatin remodeling in TBI

4.1 Dynamic changes in active and repressive histone marks

TBI induces pronounced alterations in histone modifications associated with transcriptional activation, most notably acetylation of histone H3 residues. At inflammation-related genes, active histone marks become enriched at promoters and enhancers, coinciding with increased chromatin accessibility and sustained expression of pro-inflammatory mediators. In experimental TBI models, changes in histone H3 acetylation—such as at H3K9—correlate with pain sensitization and neurological dysfunction [45]. Pharmacological inhibition of histone deacetylases (HDACs) increases histone acetylation and attenuates microglia-driven inflammatory responses, highlighting histone acetylation as a dynamic regulator of both injury amplification and repair processes [46]. Genome-wide profiling of active enhancer marks, including H3K27ac, further demonstrates that injury or regeneration paradigms can reactivate developmental and repair-associated transcriptional programs through enhancer remodeling. This epigenetic reactivation drives coordinated

upregulation of gene modules involved in neural regeneration and functional recovery [47] (Fig. 3).

4.2 Chromatin remodeling complexes

Beyond covalent histone modifications, ATP-dependent chromatin remodeling complexes regulate gene accessibility by repositioning nucleosomes. Major remodeling families—including SWI/SNF, ISWI, CHD, and INO80/SWR—play essential roles in neuronal differentiation, synaptic plasticity, inflammatory responses, and DNA damage repair [48, 49] (Fig. 3). In neuroimmune contexts, polycomb repressive complex 2 (PRC2) maintains transcriptional repression through H3K27me₃, whereas disruption of PRC2 activity promotes microglial activation, implicating chromatin silencing mechanisms in injury-related inflammation [50]. Although these regulatory systems are well characterized in neurobiology, their specific roles and dynamics in TBI remain incompletely understood, representing an important area for future investigation.

4.3 Therapeutic targeting of histone modifications

The reversibility of histone modifications has positioned histone-modifying enzymes as promising therapeutic targets in TBI. In animal models, HDAC inhibitors consistently enhance histone acetylation, reduce neuroinflammation, promote neural plasticity, and improve behavioral outcomes. Agents such as DMA-PB and valproic acid increase histone

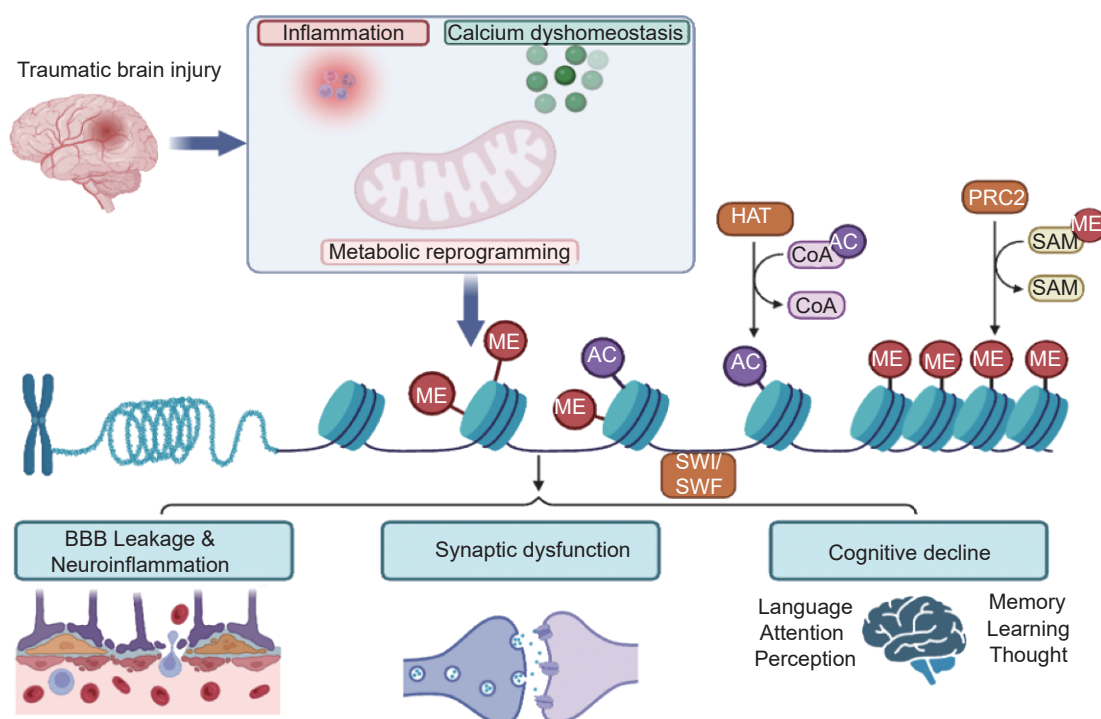


Figure 3 TBI-induced histone modification changes shape neuropathological outcomes. TBI elicits inflammation, calcium imbalance, and metabolic stress, which collectively remodel histone modification patterns. This epigenetic reprogramming alters gene expression, contributing to blood–brain barrier disruption, neuroinflammation, synaptic dysfunction, and cognitive deficits.

H3 and H4 acetylation in injury-vulnerable brain regions, attenuate microglial activation, reduce tissue damage, and improve cognitive and motor recovery [51, 52]. These findings support the concept that restoring transcriptional accessibility facilitates post-injury repair. More recently, attention has shifted toward modulating histone acetyltransferase (HAT) activity and histone metabolic pathways to achieve greater regulatory specificity (Fig. 3). Targeted HAT activators and related small molecules may selectively reinforce neuroprotective and repair-associated transcriptional programs while minimizing off-target effects associated with broad epigenetic modulation [53–55]. Collectively, alterations in histone marks and chromatin remodeling complexes highlight the plasticity of the post-injury chromatin landscape and its capacity to sustain both maladaptive and reparative transcriptional programs. Such chromatin-based regulation operates in concert with post-transcriptional control mechanisms that further refine injury responses. In addition to chromatin modifications, non-coding RNAs also play a role in the epigenetics of TBI.

5 Roles of non-coding RNAs in TBI

5.1 MicroRNAs: biomarkers for acute diagnosis and prognosis

MicroRNAs (miRNAs) are the most extensively studied ncRNAs in TBI. Injury consistently alters miR-124, miR-21, miR-9, and miR-155, among others. miR-124 is linked to neuronal homeostasis and anti-inflammatory phenotypes, with downregulation indicating neuronal injury and glial activation [56]. In contrast, miR-21 and miR-155 modulate inflammatory amplification and immune responses, with expression levels correlating with injury severity and clinical outcomes [57, 58]. Temporally, miR-21 and miR-155 change

rapidly in the acute phase, suggesting utility as early diagnostic biomarkers, whereas sustained dysregulation of miR-9-5p and miR-423-3p is associated with chronic cognitive and affective impairments, highlighting prognostic potential [59] (Fig. 4). Exosome-derived miRNAs are particularly promising for non-invasive detection due to their stability and ability to cross the blood–brain barrier [60].

5.2 Long non-coding RNAs: regulators of neuroinflammation and cell fate

Long non-coding RNAs (lncRNAs) modulate transcriptional networks, miRNA activity, and chromatin states, exerting cell-type-specific regulation after TBI (Fig. 4). For example, MALAT1 functions as a molecular sponge for miR-139-5p, influencing the CXCR4/NF- κ B axis and microglial activation [61], while NEAT1 regulates apoptosis and inflammatory pathways to support functional recovery [62]. Transcriptome analyses reveal extensive lncRNA dysregulation in the peripheral blood of TBI patients, enriched in immune and inflammatory pathways [63]. Certain lncRNAs also regulate apoptosis in neurons and oligodendrocytes, underscoring their role in long-term injury responses. Compared with miRNAs, lncRNAs provide more refined and context-specific control, albeit with greater mechanistic complexity.

5.3 Circular RNAs: modulators of hippocampal plasticity

Circular RNAs (circRNAs), covalently closed and highly stable, are abundantly expressed in the CNS. Following TBI, numerous circRNAs are altered in memory-related regions such as the hippocampus, correlating with impaired neural plasticity [64]. Functionally, circRNAs often act as miRNA sponges within circRNA–miRNA–mRNA networks, modulating downstream gene expression and contributing to

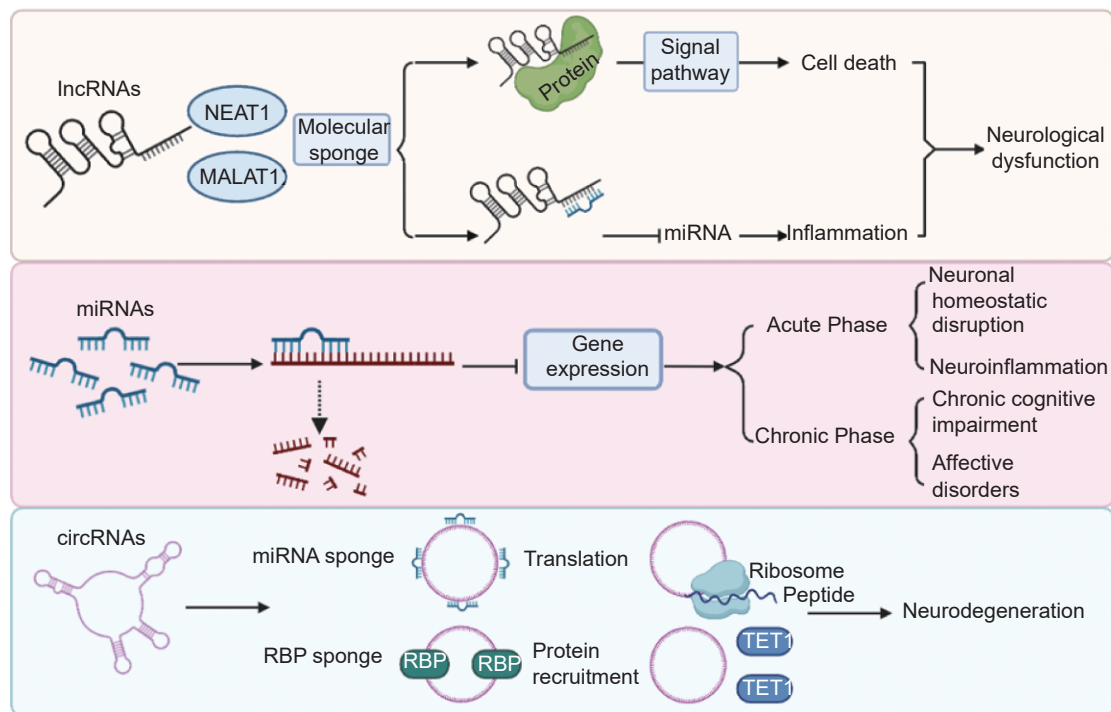


Figure 4 Distinct regulatory roles of non-coding RNAs in TBI-induced neuropathology. lncRNAs act as molecular scaffolds or sponges, modulating transcriptional networks, signaling pathways, and miRNA activity to influence neuroinflammation, cell survival, and functional recovery. miRNAs fine-tune post-transcriptional gene expression, contributing to acute neuronal and glial responses as well as chronic cognitive and affective impairments. circRNAs, through miRNA and protein interactions, regulate gene expression and synaptic plasticity, promoting long-term neurodegenerative processes.

synaptic remodeling deficits and memory dysfunction [65, 66] (Fig. 4). For example, circHtra1 promotes neuronal apoptosis and neuroinflammatory responses after experimental TBI by sponging miR-3960 and derepressing GRB10 signaling, leading to worsened neurological outcomes [67]. Similarly, circIgfbp2 regulates synaptic and mitochondrial dysfunction through a circIgfbp2–miR-370-3p–BACH1 axis, with demonstrated relevance to post-injury cognitive and affective phenotypes. In addition to miRNA-mediated regulation, emerging evidence indicates that circRNAs can interact with RNA-binding proteins (RBPs) and influence epigenetic regulators such as TET1, thereby linking post-injury transcriptomic remodeling to neurodegeneration-associated pathways [68, 69]. High-throughput and network-based analyses have systematically identified circRNAs implicated in plasticity and long-term cognitive outcomes, revealing their potential as both mechanistic targets and biomarkers [70, 71]. Taken together, non-coding RNAs add an additional layer of regulatory precision, fine-tuning gene expression programs across acute and chronic phases of injury. These molecular adjustments ultimately converge with chromatin-level remodeling to shape cellular behavior and neural circuit function. We can then link epigenetic alterations to the heterogeneous functional phenotypes of TBI.

6 From epigenetic remodeling to functional phenotypes in TBI

6.1 Linking molecular remodeling to cellular and circuit-level dysfunction

Epigenetic changes after TBI propagate across multiple regulatory layers—chromatin remodeling, transcriptional

reprogramming, protein expression, and cellular function—ultimately impacting neural circuits and behavior. Integrated methylome and transcriptome analyses in rodent models reveal disrupted molecular networks involving inflammatory, metabolic, and synaptic pathways, with key regulatory hubs driving system-level outcomes [42]. DNA methylation and histone modifications reshape chromatin accessibility at promoters and enhancers, sustaining activation or repression of transcriptional programs that influence synaptic architecture, signal transduction, and cellular metabolic states. Multi-omics integration—including methylome, ATAC-seq, transcriptome, and proteome—enables identification of core regulatory modules comprising transcription factors, chromatin remodelers, and downstream gene networks, many of which display conserved or cell type-specific activation patterns [72, 73]. For example, post-TBI hippocampal neural stem cells (NSCs) exhibit altered fate decisions, favoring neurogenesis over astrocyte generation, illustrating how molecular remodeling shapes lineage outcomes [74].

6.2 Epigenetic mechanisms of neuroinflammation and glial activation

Neuroinflammation is a central driver of TBI pathology, with epigenetic reprogramming orchestrating glial responses. Microglia transition from homeostatic to pro-inflammatory or reparative states, characterized by type I interferon signaling and major histocompatibility complex (MHC) class I pathway activation [75–77]. Astrocytes undergo reactive changes regulated by DNA methylation and histone modifications, which influence proliferation, scar formation, and neurotrophic support, correlating with clinical markers such as BBB disruption [78–80]. Microglia and astrocytes interact dynamically: microglial cytokines (IL-1 α , TNF- α , and

C1q) induce neurotoxic astrocytic phenotypes, while astrocyte-derived exosomal miRNAs (e.g., miR-873a-5p) suppress pro-inflammatory microglial states, forming stage-dependent bidirectional feedback loops [81, 82]. This coordinated network underlies the temporal evolution of post-TBI neuroinflammation.

6.3 Epigenetic alterations and long-term brain disease risk

Persistent epigenetic remodeling may link TBI to chronic neurodegenerative disorders. DNA methylation and chromatin states can remain altered for months to years post-injury, with enrichment in neuroinflammation, synaptic, and proteostasis pathways [83, 84]. In chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD), tau-related chromatin alterations correlate with sustained inflammation and synaptic dysfunction [85, 86]. Epidemiological and neuropathological studies indicate that acute TBI can trigger early amyloid- β accumulation and impaired APP processing, establishing a molecular cascade that predisposes to late-life AD [87]. These findings support a model in which TBI establishes stable epigenetic “memory” effects, reshaping neural networks and increasing susceptibility to long-term cognitive decline and neurodegeneration. These multi-layered regulatory processes illustrate how epigenetic remodeling propagates across biological scales, linking molecular alterations to cellular dysfunction, circuit reorganization, and long-term behavioral outcomes. This convergence of mechanisms provides a conceptual bridge between experimental observations and clinical relevance.

7 Clinical translation: epigenetic biomarkers and therapeutic strategies

7.1 Peripheral and CSF biomarkers

Peripheral blood and cerebrospinal fluid (CSF) provide accessible windows into TBI-induced epigenetic remodeling. Specific miRNA signatures in plasma, serum, or CSF are reproducibly altered after injury and correlate with severity, imaging features, and functional outcomes [88]. miRNA panels also outperform single-molecule markers in reproducibility and predictive accuracy [89]. DNA methylation signatures similarly offer prognostic potential, with acute-phase alterations reflecting injury severity and chronic-phase marks predicting long-term cognitive and neuropsychiatric sequelae [62].

7.2 Epigenetic therapeutics

The reversibility of epigenetic modifications enables targeted interventions. HDAC inhibitors enhance histone acetylation, promote neural plasticity, and attenuate neuroinflammation [90, 91], while DNA methyltransferase (DNMT) inhibitors modulate aberrant DNA methylation, though their safety and efficacy in TBI remain under investigation [92]. miRNA mimics and inhibitors offer precision modulation of neuroinflammatory and apoptotic pathways, but in vivo stability and targeted delivery remain challenges [93]. Nanoparticle- and exosome-based platforms,

including intranasal exosome delivery, have shown promise in directing epigenetic therapies to injured brain regions, reducing systemic effects, and improving functional outcomes [94]. Despite strong preclinical evidence that HDAC inhibitors improve synaptic plasticity and reduce neuroinflammation after TBI, clinical translation remains limited, with most agents still at early Phase I/II stages and no large-scale trials completed to date [95]. In contrast, DNMT-targeting strategies have shown beneficial effects in experimental settings but lack corresponding human clinical data, reflecting ongoing challenges in safety and translational development.

7.3 Multi-omics integration for precision medicine

Integrating DNA methylation, ncRNA profiles, transcriptomics, metabolomics, and clinical variables enables predictive models that surpass traditional injury-based classifications [96]. Prospective studies demonstrate that combining multi-omics data with clinical scoring can identify molecular subtypes and predict outcomes in children with severe TBI [97]. Successful translation requires attention to sampling time windows, therapeutic interventions, and peripheral immune status, with external validation and cross-platform reproducibility as critical prerequisites. Multi-omics integration thus offers a path toward mechanism-driven, individualized TBI management, enabling patient stratification, prognostic prediction, and targeted epigenetic or immune-modulatory therapies. Together, these translational efforts underscore both the promise and the current limitations of leveraging epigenetic information in clinical contexts. Realizing their full potential will depend on continued integration of molecular insight with longitudinal, patient-centered, and mechanistically informed approaches.

8 Conclusion and perspectives

Traumatic brain injury is increasingly recognized as a dynamic and heterogeneous disorder in which long-lasting functional outcomes are shaped not only by the initial mechanical insult but also by sustained epigenetic and transcriptional reprogramming. Accumulating evidence demonstrates that DNA methylation, histone modifications, chromatin accessibility, three-dimensional genome organization, and non-coding RNA regulation act in a coordinated manner to reshape gene regulatory networks across neurons, glial cells, vascular components, and infiltrating immune populations. These multilayered epigenetic alterations link acute injury signals to persistent changes in neuroinflammation, synaptic plasticity, cellular metabolism, and circuit function, thereby providing a mechanistic framework for the marked interindividual variability observed in cognitive, emotional, and neurodegenerative outcomes after TBI.

The integration of epigenomics with transcriptomic, proteomic, metabolomic, and spatially resolved data has enabled a shift from reductionist pathway analyses toward network-based models of TBI pathophysiology. Such multi-omics approaches reveal that injury-induced regulatory rewiring occurs in a cell type-specific and spatiotemporally structured manner, generating stable molecular states that can persist long after the resolution of acute pathology. Importantly, these epigenetic “memory” effects offer a

unifying explanation for the transition from acute injury to chronic neuroinflammation, impaired repair, and increased susceptibility to late-life neurodegenerative disease. Together, current findings position epigenetic regulation as a central organizing principle of TBI biology and a critical interface between molecular mechanisms and clinical phenotypes.

Looking forward, several challenges must be addressed to translate these insights into clinical impact. Greater resolution will be required through multimodal single-cell and spatial multi-omics to disentangle cell type-specific regulatory programs and their anatomical context. Causal inference frameworks integrating longitudinal data and targeted epigenetic perturbations will be essential to identify driver regulatory modules and actionable targets. Finally, rigorous cross-cohort validation is needed to establish robust epigenetic biomarkers and to guide the development of precise, cell type-directed epigenetic therapies. Continued integration of epigenetic mechanisms within a systems-level, precision medicine framework holds promise for transforming TBI management from injury-based classification to mechanism-informed, individualized intervention.

Author contributions

Z.L. collected the data and wrote the manuscript; J.S. supervised and revised this work.

Conflict of interests

The authors declare no conflict of interests.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82173804) and the Postgraduate Research & Practice Innovation Program of Jiangsu Province (Nos. KYCX23_0865 and SJCX24_0253).

References

- [1] Wong, V. S., Langley, B. Epigenetic changes following traumatic brain injury and their implications for outcome, recovery and therapy. *Neuroscience Letters*, **2016**, 625: 26–33. <https://doi.org/10.1016/j.neulet.2016.04.009>
- [2] Taylor, C. A., Bell, J. M., Breiding, M. J., Xu, L. K. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United states, 2007 and 2013. *MMWR Surveillance Summaries*, **2017**, 66(9): 1–16. <https://doi.org/10.15585/mmwr.ss6609a1>
- [3] Antrobus, M. R., Desai, T., Young, D., Machado, L., Ribbans, W. J., El Khoury, L. Y., Brazier, J. Epigenetics of concussion: A systematic review. *Gene*, **2025**, 935: 149046. <https://doi.org/10.1016/j.gene.2024.149046>
- [4] Swaro, A., Bristow, B. N., Anwer, M., Zhang, A. A., Kraus, L., Gandhi, R. K., Erwin, S. R., Stach, T. R., Sullivan, K. E., Fan, J. J. et al. Widespread and cell-type-specific transcriptomic reorganization following mild traumatic brain injury. *Cell Reports*, **2025**, 44(6): 115795. <https://doi.org/10.1016/j.celrep.2025.115795>
- [5] Kocheril, P. A., Moore, S. C., Lenz, K. D., Mukundan, H., Lilley, L. M. Progress toward a multiomic understanding of traumatic brain injury: A review. *Biomarker Insights*, **2022**, 17: 11772719221105145. <https://doi.org/10.1177/11772719221105145>
- [6] Maze, I., Noh, K. M., Soshnev, A. A., Allis, C. D. Every amino acid matters: Essential contributions of histone variants to mammalian development and disease. *Nature Reviews Genetics*, **2014**, 15(4): 259–271. <https://doi.org/10.1038/nrg3673>
- [7] Holliday, R., Pugh, J. E. DNA modification mechanisms and gene activity during development. *Science*, **1975**, 187(4173): 226–232.
- [8] Meissner, A., Mikkelsen, T. S., Gu, H. C., Wernig, M., Hanna, J., Sivachenko, A., Zhang, X. L., Bernstein, B. E., Nusbaum, C., Jaffe, D. B. et al. Genome-scale DNA methylation maps of pluripotent and differentiated cells. *Nature*, **2008**, 454(7205): 766–770. <https://doi.org/10.1038/nature07107>
- [9] Schober, M. E., Ke, X. R., Xing, B. H., Block, B. P., Requena, D. F., McKnight, R., Lane, R. H. Traumatic brain injury increased IGF-1B mRNA and altered IGF-1 exon 5 and promoter region epigenetic characteristics in the rat pup hippocampus. *Journal of Neurotrauma*, **2012**, 29(11): 2075–2085. <https://doi.org/10.1089/neu.2011.2276>
- [10] Zhang, Z. Y., Zhang, Z. R., Fauser, U., Schluesener, H. J. Global hypomethylation defines a sub-population of reactive microglia/macrophages in experimental traumatic brain injury. *Neuroscience Letters*, **2007**, 429(1): 1–6. <https://doi.org/10.1016/j.neulet.2007.09.061>
- [11] Haghighi, F., Ge, Y. C., Chen, S. A., Xin, Y. R., Umali, M. U., De Gasperi, R., Gama Sosa, M. A., Ahlers, S. T., Elder, G. A. Neuronal DNA methylation profiling of blast-related traumatic brain injury. *Journal of Neurotrauma*, **2015**, 32(16): 1200–1209. <https://doi.org/10.1089/neu.2014.3640>
- [12] Kouzarides, T. Chromatin modifications and their function. *Cell*, **2007**, 128(4): 693–705. <https://doi.org/10.1016/j.cell.2007.02.005>
- [13] Zhang, J. D., Li, A., Gu, R. Z., Tong, Y. Y., Cheng, J. B. Role and regulatory mechanism of microRNA mediated neuroinflammation in neuronal system diseases. *Frontiers in Immunology*, **2023**, 14: 1238930. <https://doi.org/10.3389/fimmu.2023.1238930>
- [14] Wang, H., Fan, X. L., Zhang, Y. H., Ma, N., Li, L., Lu, Q., Wang, Q., Yu, B. Y., Li, X., Gao, J. H. The application of microRNAs in traumatic brain injury: Mechanism elucidation and clinical translation. *Molecular Neurobiology*, **2025**, 62(6): 7846–7863. <https://doi.org/10.1007/s12035-025-04737-4>
- [15] Zhang, L., Li, Z. X., Mao, L., Wang, H. D. Circular RNA in acute central nervous system injuries: A new target for therapeutic intervention. *Frontiers in Molecular Neuroscience*, **2022**, 15: 816182. <https://doi.org/10.3389/fnmol.2022.816182>
- [16] Dong, X. J., Bai, Y. F., Liao, Z. X., Gritsch, D., Liu, X. L., Wang, T., Borges-Monroy, R., Ehrlich, A., Serrano, G. E., Feany, M. B. et al. Circular RNAs in the human brain are tailored to neuron identity and neuropsychiatric disease. *Nature Communications*, **2023**, 14: 5327. <https://doi.org/10.1038/s41467-023-40348-0>
- [17] Hasin, Y., Seldin, M., Lusis, A. Multi-omics approaches to disease. *Genome Biology*, **2017**, 18: 83. <https://doi.org/10.1186/s13059-017-1215-1>
- [18] Laird, P. W. Principles and challenges of genome-wide DNA methylation analysis. *Nature Reviews Genetics*, **2010**, 11(3): 191–203. <https://doi.org/10.1038/nrg2732>
- [19] Consortium, R. E., Kundaje, A., Meuleman, W., Ernst, J., Bilenky, M., Yen, A., Heravi-Moussavi, A., Kheradpour, P., Zhang, Z. Z., Wang, J. R. et al. Integrative analysis of 111 reference human epigenomes. *Nature*, **2015**, 518(7539): 317–330. <https://doi.org/10.1038/nature14248>
- [20] Buenrostro, J. D., Wu, B. J., Chang, H. Y., Greenleaf, W. J. ATAC-seq: A method for assaying chromatin accessibility genome-wide. *Current Protocols in Molecular Biology*, **2015**, 109(1): 693–705. <https://doi.org/10.1002/0471142727.mb2129s109>
- [21] Barski, A., Cuddapah, S., Cui, K. R., Roh, T. Y., Schones, D. E., Wang, Z. B., Wei, G., Chepelev, I., Zhao, K. J. High-resolution profiling of histone methylations in the human genome. *Cell*, **2007**, 129(4): 823–837. <https://doi.org/10.1016/j.cell.2007.05.009>
- [22] Stuart, T., Satija, R. Integrative single-cell analysis. *Nature Reviews Genetics*, **2019**, 20(5): 257–272. <https://doi.org/10.1038/s41576-019-0093-7>
- [23] Aebersold, R., Mann, M. Mass spectrometry-based proteomics. *Nature*, **2003**, 422(6928): 198–207. <https://doi.org/10.1038/nature01511>

- [24] Chakraborty, P., Mukherjee, C. The interplay of metabolic and epigenetic players in disease development. *Biochemical and Biophysical Research Communications*, **2024**, 734: 150621. <https://doi.org/10.1016/j.bbrc.2024.150621>
- [25] Rao, A., Barkley, D., França, G. S., Yanai, I. Exploring tissue architecture using spatial transcriptomics. *Nature*, **2021**, 596(7871): 211–220. <https://doi.org/10.1038/s41586-021-03634-9>
- [26] Han, B., Zhou, S. H., Zhang, Y., Chen, S. N., Xi, W., Liu, C. C., Zhou, X., Yuan, M. Q., Yu, X. Y., Li, L. et al. Integrating spatial and single-cell transcriptomics to characterize the molecular and cellular architecture of the ischemic mouse brain. *Science Translational Medicine*, **2024**, 16(733): eadg1323. <https://doi.org/10.1126/scitranslmed.adg1323>
- [27] Fujita, Y., Pather, S. R., Ming, G. L., Song, H. J. 3D spatial genome organization in the nervous system: From development and plasticity to disease. *Neuron*, **2022**, 110(18): 2902–2915. <https://doi.org/10.1016/j.neuron.2022.06.004>
- [28] Lu, L. N., Liu, X. X., Huang, W. K., Giusti-Rodríguez, P., Cui, J., Zhang, S. S., Xu, W. Y., Wen, Z. X., Ma, S. F., Rosen, J. D. et al. Robust hi-C maps of enhancer-promoter interactions reveal the function of non-coding genome in neural development and diseases. *Molecular Cell*, **2020**, 79(3): 521–534.e15. <https://doi.org/10.1016/j.molcel.2020.06.007>
- [29] Hu, B. X., Won, H., Mah, W., Park, R. B., Kassim, B., Spiess, K., Kozlenkov, A., Crowley, C. A., Pochareddy, S., Li, Y. et al. Neuronal and glial 3D chromatin architecture informs the cellular etiology of brain disorders. *Nature Communications*, **2021**, 12: 3968. <https://doi.org/10.1038/s41467-021-24243-0>
- [30] Nagalakshmi, B., Sagarkar, S., Sakharkar, A. J. Epigenetic mechanisms of traumatic brain injuries. In: *Epigenetics and Psychiatric Disease*. Amsterdam: Elsevier, **2018**: 263–298. <https://doi.org/10.1016/bs.pmbts.2017.12.013>
- [31] Gustafsson, D., Klang, A., Thams, S., Rostami, E. The role of BDNF in experimental and clinical traumatic brain injury. *International Journal of Molecular Sciences*, **2021**, 22(7): 3582. <https://doi.org/10.3390/ijms22073582>
- [32] Tao, X., Finkbeiner, S., Arnold, D. B., Shaywitz, A. J., Greenberg, M. E. Ca^{2+} influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron*, **1998**, 20(4): 709–726. [https://doi.org/10.1016/S0896-6273\(00\)81010-7](https://doi.org/10.1016/S0896-6273(00)81010-7)
- [33] Heinsberg, L. W., Kesbhat, A., Petersen, B., Kaseman, L., Stec, Z., Anton, N., Kochanek, P. M., Yeates, K. O., Weeks, D. E., Conley, Y. P. et al. Differential DNA methylation of the brain-derived neurotrophic factor gene is observed after pediatric traumatic brain injury compared with orthopedic injury. *Journal of Neurotrauma*, **2025**: 08977151251400737. <https://doi.org/10.1177/08977151251400737>
- [34] Liu, D. J., Zusman, B. E., Shaffer, J. R., Li, Y. Q., Arockiaraj, A. I., Liu, S. W., Weeks, D. E., Desai, S. M., Kochanek, P. M., Puccio, A. M. et al. Decreased DNA methylation of RGMA is associated with intracranial hypertension after severe traumatic brain injury: An exploratory epigenome-wide association study. *Neurocritical Care*, **2022**, 37(1): 26–37. <https://doi.org/10.1007/s12028-021-01424-9>
- [35] Abu Hamdeh, S., Ciuculete, D. M., Sarkisyan, D., Bakalkin, G., Ingelsson, M., Schiöth, H. B., Marklund, N. Differential DNA methylation of the genes for amyloid precursor protein, tau, and neurofilaments in human traumatic brain injury. *Journal of Neurotrauma*, **2021**, 38(12): 1679–1688. <https://doi.org/10.1089/neu.2020.7283>
- [36] Tiane, A., Schepers, M., Reijnders, R. A., van Veggel, L., Chenine, S., Rombaut, B., Dempster, E., Verfaillie, C., Wasner, K., Grünwald, A. et al. From methylation to myelination: Epigenomic and transcriptomic profiling of chronic inactive demyelinated multiple sclerosis lesions. *Acta Neuropathologica*, **2023**, 146(2): 283–299. <https://doi.org/10.1007/s00401-023-02596-8>
- [37] Treble-Barna, A., Heinsberg, L. W., Puccio, A. M., Shaffer, J. R., Okonkwo, D. O., Beers, S. R., Weeks, D. E., Conley, Y. P. Acute Brain-derived neurotrophic factor DNA methylation trajectories in cerebrospinal fluid and associations with outcomes following severe traumatic brain injury in adults. *Neurorehabilitation and Neural Repair*, **2021**, 35(9): 790–800. <https://doi.org/10.1177/15459683211028245>
- [38] Conole, E. L. S., Stevenson, A. J., Muñoz Maniega, S., Harris, S. E., Green, C., Valdés Hernández, M. D. C., Harris, M. A., Bastin, M. E., Wardlaw, J. M., Deary, I. J. et al. DNA methylation and protein markers of chronic inflammation and their associations with brain and cognitive aging. *Neurology*, **2021**, 97(23): e2340–e2352. <https://doi.org/10.1212/wnl.00000000000012997>
- [39] Luo, C. Y., Keown, C. L., Kurihara, L., Zhou, J. T., He, Y. P., Li, J. H., Castanon, R., Lucero, J., Nery, J. R., Sandoval, J. P. et al. Single-cell methylomes identify neuronal subtypes and regulatory elements in mammalian cortex. *Science*, **2017**, 357(6351): 600–604. <https://doi.org/10.1126/science.aan3351>
- [40] Nott, A., Holtman, I. R., Coufal, N. G., Schlachetzki, J. C. M., Yu, M., Hu, R., Han, C. Z., Pena, M., Xiao, J. Y., Wu, Y. et al. Brain cell type-specific enhancer–promoter interactome maps and disease-risk association. *Science*, **2019**, 366(6469): 1134–1139. <https://doi.org/10.1126/science.aay0793>
- [41] Lister, R., Mukamel, E. A., Nery, J. R., Urich, M., Puddifoot, C. A., Johnson, N. D., Lucero, J., Huang, Y., Dwork, A. J., Schultz, M. D. et al. Global epigenomic reconfiguration during mammalian brain development. *Science*, **2013**, 341(6146): 1237905. <https://doi.org/10.1126/science.1237905>
- [42] Meng, Q. Y., Zhuang, Y. M., Ying, Z., Agrawal, R., Yang, X., Gomez-Pinilla, F. Traumatic brain injury induces genome-wide transcriptomic, methylomic, and network perturbations in brain and blood predicting neurological disorders. *EBioMedicine*, **2017**, 16: 184–194. <https://doi.org/10.1016/j.ebiom.2017.01.046>
- [43] Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., de los Santos, R., Goldmann, E., Galea, S. Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proceedings of the National Academy of Sciences of the United States of America*, **2010**, 107(20): 9470–9475. <https://doi.org/10.1073/pnas.0910794107>
- [44] Duan, K. K., Mayer, A. R., Shaff, N. A., Chen, J. Y., Lin, D. D., Calhoun, V. D., Jensen, D. M., Liu, J. Y. DNA methylation under the major depression pathway predicts pediatric quality of life four-month post-pediatric mild traumatic brain injury. *Clinical Epigenetics*, **2021**, 13: 140. <https://doi.org/10.1186/s13148-021-01128-z>
- [45] Liang, D. Y., Sahbaie, P., Sun, Y., Irvine, K. A., Shi, X. Y., Meidahl, A., Liu, P., Guo, T. Z., Yeomans, D. C., Clark, J. D. TBI-induced nociceptive sensitization is regulated by histone acetylation. *IBRO Reports*, **2017**, 2: 14–23. <https://doi.org/10.1016/j.ibror.2016.12.001>
- [46] Zhao, Y. F., Mu, H. F., Huang, Y. C., Li, S. C., Wang, Y. F., Stetler, R. A., Bennett, M. V. L., Dixon, C. E., Chen, J., Shi, Y. J. Microglia-specific deletion of histone deacetylase 3 promotes inflammation resolution, white matter integrity, and functional recovery in a mouse model of traumatic brain injury. *Journal of Neuroinflammation*, **2022**, 19: 201. <https://doi.org/10.1186/s12974-022-02563-2>
- [47] Chang, C. Y., Hung, J. H., Huang, L. W., Li, J., Fung, K. S., Kao, C. F., Chen, L. Y. Epigenetic regulation of WNT3A enhancer during regeneration of injured cortical neurons. *International Journal of Molecular Sciences*, **2020**, 21(5): 1891. <https://doi.org/10.3390/ijms21051891>
- [48] Jiang, D. F., Li, T. T., Guo, C. X., Tang, T. S., Liu, H. M. Small molecule modulators of chromatin remodeling: From neurodevelopment to neurodegeneration. *Cell & Bioscience*, **2023**, 13: 10. <https://doi.org/10.1186/s13578-023-00953-4>
- [49] Sokpor, G., Xie, Y. B., Rosenbusch, J., Tuoc, T. Chromatin remodeling BAF (SWI/SNF) complexes in neural development and disorders. *Frontiers in Molecular Neuroscience*, **2017**, 10: 243. <https://doi.org/10.3389/fnmol.2017.00243>
- [50] Ayata, P., Badimon, A., Strasburger, H. J., Duff, M. K., Montgomery, S. E., Loh, Y. E., Ebert, A., Pimenova, A. A., Ramirez, B. R., Chan, A. T. et al. Epigenetic regulation of brain region-specific microglia clearance activity. *Nature Neuroscience*, **2018**, 21(8):

- 1049–1060. <https://doi.org/10.1038/s41593-018-0192-3>
- [51] Chen, X. R., Wang, H. D., Zhou, M. L., Li, X., Fang, Z. N., Gao, H. Z., Li, Y. S., Hu, W. P. Valproic acid attenuates traumatic brain injury-induced inflammation *in vivo*: Involvement of autophagy and the Nrf2/ARE signaling pathway. *Frontiers in Molecular Neuroscience*, **2018**, 11: 117. <https://doi.org/10.3389/fnmol.2018.00117>
 - [52] Dash, P. K., Orsi, S. A., Zhang, M., Grill, R. J., Pati, S., Zhao, J., Moore, A. N. Valproate administered after traumatic brain injury provides neuroprotection and improves cognitive function in rats. *PLoS One*, **2010**, 5(6): e11383. <https://doi.org/10.1371/journal.pone.0011383>
 - [53] Gaub, P., Joshi, Y., Wuttke, A., Naumann, U., Schnichels, S., Heiduschka, P., Di Giovanni, S. The histone acetyltransferase p300 promotes intrinsic axonal regeneration. *Brain*, **2011**, 134(7): 2134–2148. <https://doi.org/10.1093/brain/awr142>
 - [54] Hutson, T. H., Kathe, C., Palmisano, I., Bartholdi, K., Hervera, A., De Virgiliis, F., McLachlan, E., Zhou, L. M., Kong, G. P., Barraud, Q. et al. Cbp-dependent histone acetylation mediates axon regeneration induced by environmental enrichment in rodent spinal cord injury models. *Science Translational Medicine*, **2019**, 11(487): eaaw2064. <https://doi.org/10.1126/scitranslmed.aaw2064>
 - [55] Chatterjee, S., Cassel, R., Schneider-Anthony, A., Merienne, K., Cosquer, B., Tzeplaff, L., Halder Sinha, S., Kumar, M., Chaturbedy, P., Eswaramoorthy, M. et al. Reinstating plasticity and memory in a tauopathy mouse model with an acetyltransferase activator. *EMBO Molecular Medicine*, **2018**, 10(11): e8587. <https://doi.org/10.15252/emmm.201708587>
 - [56] Yang, Y. X., Ye, Y. Q., Fan, K. X., Luo, J. N., Yang, Y. J., Ma, Y. miR-124 reduced neuroinflammation after traumatic brain injury by inhibiting TRAF6. *Neuroimmunomodulation*, **2023**, 30(1): 55–68. <https://doi.org/10.1159/000528502>
 - [57] Ge, X. T., Lei, P., Wang, H. C., Zhang, A. L., Han, Z. L., Chen, X., Li, S. H., Jiang, R. C., Kang, C. S., Zhang, J. N. miR-21 improves the neurological outcome after traumatic brain injury in rats. *Scientific Reports*, **2014**, 4: 6718. <https://doi.org/10.1038/srep06718>
 - [58] Di Pietro, V., Ragusa, M., Davies, D., Su, Z. J., Hazeldine, J., Lazzarino, G., Hill, L. J., Crombie, N., Foster, M., Purrello, M. et al. microRNAs as novel biomarkers for the diagnosis and prognosis of mild and severe traumatic brain injury. *Journal of Neurotrauma*, **2017**, 34(11): 1948–1956. <https://doi.org/10.1089/neu.2016.4857>
 - [59] Schindler, C. R., Woschek, M., Vollrath, J. T., Konradowitz, K., Lustenberger, T., Störmann, P., Marzi, I., Henrich, D. MiR-142-3p expression is predictive for severe traumatic brain injury (TBI) in trauma patients. *International Journal of Molecular Sciences*, **2020**, 21(15): 5381. <https://doi.org/10.3390/ijms21155381>
 - [60] O'Connell, G. C., Smothers, C. G., Winkelman, C. Bioinformatic analysis of brain-specific miRNAs for identification of candidate traumatic brain injury blood biomarkers. *Brain Injury*, **2020**, 34(7): 965–974. <https://doi.org/10.1080/02699052.2020.1764102>
 - [61] Dong, Q., Chen, P. Y., Qiu, W. Q., Yang, Z. J., Li, Y. T., Zhou, Y. H., Guo, L. L., Zou, D., Xu, R. X., Gao, M. Long non-coding RNA Malat1 modulates CXCR4 expression to regulate the interaction between induced neural stem cells and microglia following closed head injury. *Stem Cell Research & Therapy*, **2025**, 16: 31. <https://doi.org/10.1186/s13287-024-04116-1>
 - [62] Zhong, J. J., Jiang, L., Huang, Z. J., Zhang, H. R., Cheng, C. J., Liu, H., He, J. C., Wu, J. C., Darwazeh, R., Wu, Y. et al. The long non-coding RNA Neat1 is an important mediator of the therapeutic effect of bexarotene on traumatic brain injury in mice. *Brain, Behavior, and Immunity*, **2017**, 65: 183–194. <https://doi.org/10.1016/j.bbi.2017.05.001>
 - [63] Ren, D. B., Chen, W., Cao, K., Wang, Z. H., Zheng, P. Expression profiles of long non-coding RNA and messenger RNA in human traumatic brain injury. *Molecular Therapy Nucleic Acids*, **2020**, 22: 99–113. <https://doi.org/10.1016/j.omtn.2020.08.012>
 - [64] Xie, B. S., Wang, Y. Q., Lin, Y., Zhao, C. C., Mao, Q., Feng, J. F., Cao, J. Y., Gao, G. Y., Jiang, J. Y. Circular RNA expression profiles alter significantly after traumatic brain injury in rats. *Journal of Neurotrauma*, **2018**, 35(14): 1659–1666. <https://doi.org/10.1089/neu.2017.5468>
 - [65] Du, M. R., Wu, C. R., Yu, R. Q., Cheng, Y. Q., Tang, Z. H., Wu, B. Y., Fu, J., Tan, W. L., Zhou, Q., Zhu, Z. Y. et al. A novel circular RNA, circIgf2bp2, links neural plasticity and anxiety through targeting mitochondrial dysfunction and oxidative stress-induced synapse dysfunction after traumatic brain injury. *Molecular Psychiatry*, **2022**, 27(11): 4575–4589. <https://doi.org/10.1038/s41380-022-01711-7>
 - [66] Memczak, S., Jens, M., Elefsinioti, A., Torti, F., Krueger, J., Rybak, A., Maier, L., Mackowiak, S. D., Gregersen, L. H., Munschauer, M. et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature*, **2013**, 495(7441): 333–338. <https://doi.org/10.1038/nature11928>
 - [67] Zheng, P., Shu, L., Ren, D. B., Kuang, Z. C., Zhang, Y. S., Wan, J. circHtra1/miR-3960/GRB10 axis promotes neuronal loss and immune deficiency in traumatic brain injury. *Oxidative Medicine and Cellular Longevity*, **2022**, 2022: 3522492. <https://doi.org/10.1155/2022/3522492>
 - [68] Kristensen, L. S., Andersen, M. S., Stagsted, L. V. W., Ebbesen, K. K., Hansen, T. B., Kjems, J. The biogenesis, biology and characterization of circular RNAs. *Nature Reviews Genetics*, **2019**, 20(11): 675–691. <https://doi.org/10.1038/s41576-019-0158-7>
 - [69] Prasanth, M. I., Sivamaruthi, B. S., Cheong, C. S. Y., Verma, K., Tencomnao, T., Brimson, J. M., Prasansuklab, A. Role of epigenetic modulation in neurodegenerative diseases: Implications of phytochemical interventions. *Antioxidants*, **2024**, 13(5): 606. <https://doi.org/10.3390/antiox13050606>
 - [70] Li, Z. X., Lin, Y. X., Mao, L., Zhang, L. Expression characteristics of circular RNA in human traumatic brain injury. *Frontiers in Neurology*, **2023**, 13: 1086553. <https://doi.org/10.3389/fneur.2022.1086553>
 - [71] Zhao, R. T., Zhou, J., Dong, X. L., Bi, C. W., Jiang, R. C., Dong, J. F., Tian, Y., Yuan, H. J., Zhang, J. N. Circular ribonucleic acid expression alteration in exosomes from the brain extracellular space after traumatic brain injury in mice. *Journal of Neurotrauma*, **2018**, 35(17): 2056–2066. <https://doi.org/10.1089/neu.2017.5502>
 - [72] Su, Q., Chen, Q. L., Li, Z. G., Zhao, J., Li, L. Y., Xu, L. Y., Yang, B., Liu, C. Multi-omics analysis reveals GABAergic dysfunction after traumatic brainstem injury in rats. *Frontiers in Neuroscience*, **2022**, 16: 1003300. <https://doi.org/10.3389/fnins.2022.1003300>
 - [73] Li, L. M., Kodosaki, E., Heslegrave, A., Zetterberg, H., Graham, N., Zimmerman, K., Soreq, E., Parker, T., Garbero, E., Moro, F. et al. High-dimensional proteomic analysis for pathophysiological classification of traumatic brain injury. *Brain*, **2025**, 148(3): 1015–1030. <https://doi.org/10.1093/brain/awae305>
 - [74] Bielefeld, P., Martirosyan, A., Martín-Suárez, S., Apresyan, A., Meerhoff, G. F., Pestana, F., Poovathingal, S., Reijner, N., Koning, W., Clement, R. A. et al. Traumatic brain injury promotes neurogenesis at the cost of astroglialogenesis in the adult hippocampus of male mice. *Nature Communications*, **2024**, 15: 5222. <https://doi.org/10.1038/s41467-024-49299-6>
 - [75] Jassam, Y. N., Izzy, S., Whalen, M., McGavern, D. B., El Khoury, J. Neuroimmunology of traumatic brain injury: Time for a paradigm shift. *Neuron*, **2017**, 95(6): 1246–1265. <https://doi.org/10.1016/j.neuron.2017.07.010>
 - [76] Grovola, M. R., von Reyn, C., Loane, D. J., Cullen, D. K. Understanding microglial responses in large animal models of traumatic brain injury: An underutilized resource for preclinical and translational research. *Journal of Neuroinflammation*, **2023**, 20: 67. <https://doi.org/10.1186/s12974-023-02730-z>
 - [77] Todd, B. P., Chimenti, M. S., Luo, Z. L., Ferguson, P. J., Bassuk, A. G., Newell, E. A. Traumatic brain injury results in unique microglial and astrocyte transcriptomes enriched for type I interferon response. *Journal of Neuroinflammation*, **2021**, 18: 151. <https://doi.org/10.1186/s12974-021-02197-w>
 - [78] Myer, D. J., Gurkoff, G. G., Lee, S. M., Hovda, D. A., Sofroniew, M. V. Essential protective roles of reactive astrocytes in traumatic brain injury. *Brain*, **2006**, 129(10): 2761–2772. <https://doi.org/10.1093/brain/awl165>

- [79] Zhou, Y. X., Shao, A. W., Yao, Y. H., Tu, S., Deng, Y. C., Zhang, J. M. Dual roles of astrocytes in plasticity and reconstruction after traumatic brain injury. *Cell Communication and Signaling*, **2020**, 18: 62. <https://doi.org/10.1186/s12964-020-00549-2>
- [80] Cui, W. X., Bai, H., Guo, C. X., Zhou, J. P., Feng, D. Y., Zhang, S. J., Gao, F., Han, L. Y., Tian, Y., Dong, J. Y. et al. Interferon regulatory factor-1-expressing astrocytes are epigenetically controlled and exacerbate TBI-associated pathology in mice. *Science Translational Medicine*, **2025**, 17(800): eadr5300. <https://doi.org/10.1126/scitranslmed.adr5300>
- [81] Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C. et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, **2017**, 541(7638): 481–487. <https://doi.org/10.1038/nature21029>
- [82] Long, X. B., Yao, X. L., Jiang, Q., Yang, Y. P., He, X. J., Tian, W. D., Zhao, K., Zhang, H. Q. Astrocyte-derived exosomes enriched with miR-873a-5p inhibit neuroinflammation via microglia phenotype modulation after traumatic brain injury. *Journal of Neuroinflammation*, **2020**, 17: 89. <https://doi.org/10.1186/s12974-020-01761-0>
- [83] Sagarkar, S., Bhamburkar, T., Shelkar, G., Choudhary, A., Kokare, D. M., Sakharkar, A. J. Minimal traumatic brain injury causes persistent changes in DNA methylation at BDNF gene promoters in rat amygdala: A possible role in anxiety-like behaviors. *Neurobiology of Disease*, **2017**, 106: 101–109. <https://doi.org/10.1016/j.nbd.2017.06.016>
- [84] Eskesen, T. O., Almstrup, K., Elgaard, L., Arleth, T., Lassen, M. L., Creutzburg, A., Jensen, A. H., Breindahl, N., Dinesen, F., Vang, M. et al. Severe traumatic injury is associated with profound changes in DNA methylation. *npj Genomic Medicine*, **2024**, 9: 53. <https://doi.org/10.1038/s41525-024-00438-4>
- [85] McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., Lee, H. S., Hall, G., Wojtowicz, S. M., Baugh, C. M. et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*, **2013**, 136(1): 43–64. <https://doi.org/10.1093/brain/aws307>
- [86] De Jager, P. L., Srivastava, G., Lunnon, K., Burgess, J., Schalkwyk, L. C., Yu, L., Eaton, M. L., Keenan, B. T., Ernst, J., McCabe, C. et al. Alzheimer's disease: Early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. *Nature Neuroscience*, **2014**, 17(9): 1156–1163. <https://doi.org/10.1038/nn.3786>
- [87] Johnson, V. E., Stewart, W., Smith, D. H. Traumatic brain injury and amyloid- β pathology: A link to Alzheimer's disease. *Nature Reviews Neuroscience*, **2010**, 11(5): 361–370. <https://doi.org/10.1038/nrn2808>
- [88] Magee, R., Shen, J. C., Walter, A. E., Schneider, A. L. C., Puccio, A. M., Lynch, C. E., Diaz-Arrastia, R., Sandsmark, D. K. microRNAs detected in whole blood following traumatic brain injury are associated with recovery 6 months after injury. *Neurotrauma Reports*, **2025**, 6(1): 903–914. <https://doi.org/10.1177/2689288x251380526>
- [89] Redell, J. B., Moore, A. N., Ward, N. H. III, Hergenroeder, G. W., Dash, P. K. Human traumatic brain injury alters plasma microRNA levels. *Journal of Neurotrauma*, **2010**, 27(12): 2147–2156. <https://doi.org/10.1089/neu.2010.1481>
- [90] Sada, N., Fujita, Y., Mizuta, N., Ueno, M., Furukawa, T., Yamashita, T. Inhibition of HDAC increases BDNF expression and promotes neuronal rewiring and functional recovery after brain injury. *Cell Death & Disease*, **2020**, 11(8): 655. <https://doi.org/10.1038/s41419-020-02897-w>
- [91] Xu, L. J., An, T. T., Jia, B. H., Wu, Q., Shen, J. G., Jin, J., Liu, J., Li, C. J. Histone deacetylase 3-specific inhibitor RGFP966 attenuates oxidative stress and inflammation after traumatic brain injury by activating the Nrf2 pathway. *Burns & Trauma*, **2024**, 12: tkad062. <https://doi.org/10.1093/burnst/tkad062>
- [92] Pappalardi, M. B., Keenan, K., Cockerill, M., Kellner, W. A., Stowell, A., Sherk, C., Wong, K., Pathuri, S., Briand, J., Steidel, M. et al. Discovery of a first-in-class reversible DNMT1-selective inhibitor with improved tolerability and efficacy in acute myeloid leukemia. *Nature Cancer*, **2021**, 2(10): 1002–1017. <https://doi.org/10.1038/s43018-021-00249-x>
- [93] Sun, P., Liu, D. Z., Jickling, G. C., Sharp, F. R., Yin, K. J. microRNA-based therapeutics in central nervous system injuries. *Journal of Cerebral Blood Flow & Metabolism*, **2018**, 38(7): 1125–1148. <https://doi.org/10.1177/0271678x18773871>
- [94] Li, P. T., Sun, S. S., Zhu, X. Y., Liu, X. Y., Yin, R., Chen, Y. H., Chang, J. B., Ye, L. G., Gao, J. X., Zhao, X. Y. et al. Intranasal delivery of engineered extracellular vesicles promotes neurofunctional recovery in traumatic brain injury. *Journal of Nanobiotechnology*, **2025**, 23: 229. <https://doi.org/10.1186/s12951-025-03181-9>
- [95] Visa, M. A., Liggett, M. R., Lashley, S., Bhatti, U., Dawood, Z. A., Anand, A., Gill, N. P., Scholtens, D. M., Wang, B. W., Alam, H. B. Valproic acid for treatment of traumatic brain injury: Study protocol for the VIBRANT prospective randomized trial. *Transfusion*, **2025**: trf.70029. <https://doi.org/10.1111/trf.70029>
- [96] Abu Hamdeh, S., Tenovuo, O., Peul, W., Marklund, N. "Omics" in traumatic brain injury: Novel approaches to a complex disease. *Acta Neurochirurgica*, **2021**, 163(9): 2581–2594. <https://doi.org/10.1007/s00701-021-04928-7>
- [97] Hussain, E., Prokop, J. W., Nonnemacher, E., Ashrafi, N., Yilmaz, A., Mimi, R. A., Khalid, A., Krinickis, K., Lomeikaite, V., Sanfilippo, L. et al. The molecular architecture of severe pediatric traumatic brain injury: Integrated omics reveal therapeutic pathways. *Critical Care*, **2026**, 30: 23. <https://doi.org/10.1186/s13054-025-05789-7>