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# The Dynamic Balance and Intervention Strategies between Neural Damage and Repair in Traumatic Brain Injury

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**Abstract:**

Traumatic brain injury (TBI) is one of the leading causes of disability and death worldwide, with a significant epidemiological burden and marked clinical heterogeneity. Recent studies have revealed that neural injury and repair are dynamically interactive processes, exhibiting a bidirectional pattern of "injury and repair in parallel" across different stages. This review systematically summarizes the pathophysiological changes of TBI during the acute, subacute, and chronic phases, focusing on the roles of neuroinflammation, cell death, glial scar formation, and neural plasticity in the progression and recovery of neural damage. Furthermore, we discuss recent advances in multitarget, multimodal, and phase-specific interventions, as well as integrated evaluation strategies involving neuroimaging, biomarkers, electrophysiological measures, and digital phenotypes. Looking forward, immune–metabolic–inflammatory network regulation, exosome and liquid biopsy technologies, and data-driven precision interventions hold great promise for achieving individualized treatment and functional recovery in TBI.

**Keywords:** Traumatic brain injury; Secondary injury; Neural repair; Multimodal intervention; Precision medicine.

## 1.Introdcution

Traumatic Brain Injury (TBI) is a leading cause of disability and mortality worldwide[1] and is recognized as one of the most critical public health challenges of the 21st century[2]. Epidemiological data from different countries reveal an annual incidence ranging from 200 to 500 per 100,000 people in developed nations, while in certain low- and middle-income countries, the rate can exceed 800 per 100,000[3]. These variations are largely attributed to factors such as traffic accidents, physical violence, and occupational exposures[4]. Beyond causing acute death and disability, TBI can give rise to long-term multidimensional impairments, including cognitive deficits, emotional and behavioral disturbances, as well as neurodegenerative changes, all of which significantly affect patients' quality of life and impose substantial socioeconomic burdens [5-7]. This review systematically examines the dynamic processes of neural damage and repair following TBI from a pathophysiological perspective, clarifies key molecular mechanisms involved, and summarizes recent advances in multimodal interventions and precision therapeutic strategies (see Table 1).

**Table 1: Epidemiological Investigation of Traumatic Brain Injury**

| Indicator | Global Overview | Regional Variations | Age Distribution | Gender Differences | Primary Causes |
|---|---|---|---|---|---|
| Annual Incidence | Approx. 800 per 100,000 population | Higher in high-income countries compared to low- and middle-income countries | Highest among individuals aged ≥55, especially prominent in aging societies | About 2 times higher in males than in females | Motor vehicle accidents, falls, violence, sports injuries |
| Annual Mortality | Approx. 8–15 per 100,000 population | Elevated in certain regions of Asia and Africa | Significantly increased in the elderly | Markedly higher in males | Severe head trauma, traffic accidents |
| Disability Rate | 40–60% of survivors experience long-term functional impairment | Higher in areas with limited rehabilitation resources | Poorer recovery in older patients | Long-term quality of life impact more pronounced in females | Motor deficits, cognitive impairment, epilepsy |

| | | | | | |
|---|---|---|---|---|---|
| Economic Burden | Tens of billions of US dollars globally annually | High-income countries: dominated by medical costs; low-income countries: dominated by productivity loss | Notable workforce loss among young and middle-aged patients | More prominent productivity loss in males | Rehabilitation and long-term care expenses |

## 2. Classification and Pathological Changes of TBI

### 2.1 Classification of TBI

TBI exhibits considerable clinical heterogeneity. Based on the Glasgow Coma Scale (GCS), it is classified into mild (13–15 points), moderate (9–12 points), and severe (≤8 points) types [8]. Mild TBI (e.g., concussion) accounts for approximately 70%–80% of all cases, while moderate and severe TBI together constitute about 20%–30%[9] . Mechanistically, TBI can be divided into closed and penetrating injuries. The former, often resulting from traffic accidents, falls, or impacts, differs significantly from the latter—typically caused by gunshot wounds or sharp object penetration—in terms of pathological basis, clinical presentation, and prognosis [10] . Variations in type and severity lead to distinct pathological mechanisms, injury extent, and repair potential, resulting in diverse outcomes and treatment responses. This heterogeneity presents a major challenge for both basic and clinical TBI research.

### 2.2 Time-Dependent Pathological Progression of TBI

The processes of neural damage and repair following Traumatic Brain Injury (TBI) unfold in a distinct temporal sequence, broadly categorized into three phases: acute (minutes to days), subacute (days to weeks), and chronic (months to years or lifelong) [12].

(1) Acute Phase: This stage is characterized by primary mechanical injury and early secondary responses. Directly affected tissues include areas of parenchymal disruption, vascular damage, and diffuse axonal injury [13]. A rapid secondary cascade is triggered, involving increased blood-brain barrier permeability, excitotoxicity, ionic imbalance, mitochondrial dysfunction, and oxidative stress. These events precipitate an energy crisis within cells and contribute to early neuronal apoptosis [14-16].

(2) Subacute Phase: Secondary injury processes intensify, and inflammatory responses become pronounced. This period features glial cell activation, elevated release of pro-inflammatory cytokines (e.g., IL-1β, TNF-α), exacerbated apoptosis and necrosis, accompanied by cerebral edema and elevated intracranial pressure [17, 18]. Concurrently, certain reparative mechanisms are initiated, such as angiogenesis, enhanced neuroplasticity, and the onset of neurogenesis. However, these beneficial processes are often hampered by persistent inflammation and the formation of glial scars. (3) Chronic Phase: This long-term stage is defined by neural network remodeling, impeded axonal regeneration, and sustained chronic inflammation [19] . Some patients may experience seizures, cognitive decline, mood disorders, and progressive neurodegenerative changes, typified by conditions like Chronic Traumatic Encephalopathy (CTE) [20] .

In summary, TBI is not an isolated acute event but rather a continuous, dynamic continuum encompassing primary injury, secondary pathological reactions, and long-term repair and remodeling. Throughout its course, the nervous system endures assaults from detrimental factors like excitotoxicity, inflammation, blood-brain barrier disruption, and apoptosis, while also mobilizing endogenous repair responses such as angiogenesis, neurogenesis, synaptic reorganization, and functional compensation. A central challenge in contemporary TBI research lies in modulating this balance between "damage and repair" to minimize early neuronal loss and promote long-term functional recovery [21] [22]. Consequently, clinical interventions should be tailored to the specific temporal and pathological characteristics of the injury, adopting phased and targeted comprehensive strategies to optimize neural repair. This review, from the perspective of TBI's overall pathological progression, systematically elaborates on the interactions among inflammatory responses, cell death, glial scarring, and neuroplasticity across different stages. It further summarizes research advances and future directions for stage-specific therapeutic interventions.

## 3. Pathophysiological Mechanisms of Neural Injury

### 3.1. Network of Primary and Secondary Injury

Following traumatic brain injury, damage to the nervous system occurs at multiple levels—cellular, tissue, and systemic—with tissue and systemic injuries being most prominent. Primary injury results directly from the external force applied to the cranium and includes: (1) Contusions and lacerations: Local mechanical forces cause parenchymal destruction, hematoma formation, and tissue necrosis;

(2) Diffuse Axonal Injury (DAI): Characterized by widespread axonal shearing in the white matter and disrupted signal transmission, serving as a key pathological substrate for impaired consciousness and cognitive deficits; (3) Vascular shear and microhemorrhages: Mechanical stretching leads to rupture of small vessels. The resultant local ischemia and hypoxia exacerbate alterations in blood-brain barrier (BBB) permeability, thereby amplifying secondary damage. Primary injury occurs rapidly and is irreversible, typically within seconds to minutes post-trauma, establishing the pathological foundation for subsequent secondary injury processes [13, 23] .

Secondary injury encompasses a complex cascade of molecular and cellular events, including excitotoxicity, ionic imbalance, mitochondrial dysfunction, oxidative stress, and inflammatory responses. A pivotal early event is excitotoxicity and ionic dyshomeostasis. Massive glutamate release leads to overactivation of NMDA and AMPA receptors, triggering calcium overload and $Na^+/K^+$-ATPase pump failure, which disrupts membrane potential. Concurrently, opening of the mitochondrial permeability transition pore (mPTP) and excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) create an energy crisis, inducing cell apoptosis or necrosis [24-26]. BBB disruption and impairment of the neurovascular unit (NVU) further precipitate cerebral edema and infiltration of inflammatory cells, forming a vicious cycle [27].

Neuroinflammation is recognized as a central driver of secondary injury. Post-trauma, microglia dynamically shift along a spectrum between M1 (pro-inflammatory) and M2 (anti-inflammatory/reparative) polarization states, their activation regulated by cytokines and signaling pathways. In the chronic phase, persistently overactivated glial cells continually release inflammatory mediators, contributing to neuronal damage and glial scar formation. Furthermore, peripheral immune cells (e.g., monocytes, T cells) and the complement system participate in amplifying the inflammatory response, collectively shaping an aberrant neural microenvironment after TBI [28-31].

The progression of secondary injury involves the parallel and interconnected activation of multiple cell death pathways, including necrosis, necroptosis, apoptosis, pyroptosis, ferroptosis, and dysregulated autophagy. These processes collectively reduce the number of neurons and glial cells, leading to axonal degeneration, demyelination, synaptic loss, and disruption of neural networks [32, 33]. Consequently, secondary injury in TBI should be viewed as a multidimensional, networked pathological process. Its prevention and treatment require comprehensive strategies that employ

multi-target, systems-level interventions (see Table 2).

Table 2: Pathophysiological Injury Network of Traumatic Brain Injury
(This table outlines the primary injury mechanisms, typical manifestations, and their interrelationships in TBI.)

| Injury Category | Primary Mechanisms | Typical Manifestations | Relationship with Secondary Injury |
|---|---|---|---|
| Primary Injury | Direct mechanical damage (impact, acceleration-deceleration, rotational forces) Contusions, vascular rupture, diffuse axonal injury | Direct disruption of brain tissue, vascular injury, hemorrhage, skull fractures | Establishes the pathological foundation for secondary injury and initiates the cascade response |
| Secondary Injury: Excitotoxicity | Massive glutamate release, overactivation of NMDA/AMPA receptors | $Ca^{2+}$ overload, $Na^{+}$ influx, cellular swelling | Exacerbates cellular damage and triggers apoptosis/necrosis |
| Secondary Injury: Ionic Imbalance | Dysregulation of $Ca^{2+}$, $Na^{+}$, $K^{+}$; ATP deficiency | Membrane depolarization, mitochondrial damage | Interacts with and amplifies excitotoxicity and oxidative stress |
| Secondary Injury: Mitochondrial Dysfunction | Excessive ROS/RNS production, impaired energy metabolism | ATP depletion, cell death | Closely linked to oxidative stress and apoptosis |
| Secondary Injury: Blood-Brain Barrier Disruption | Endothelial damage, basement membrane degradation, MMP activation | Cerebral edema, leukocyte infiltration | Facilitates inflammation and immune cell activation |
| Secondary Injury: Inflammatory Response | Activation of microglia/astrocytes; release of inflammatory cytokines (IL-1β, TNF-α) | Neuronal damage, glial scar formation | Forms a vicious cycle with BBB disruption and cell death |
| Secondary Injury: Cell Death Pathways | Apoptosis (Caspase-dependent), necrosis, ferroptosis, necroptosis | Neuronal loss, functional deficits | Driven by excitotoxicity, oxidative stress, and inflammation |

### 3.2. Structural and Functional Alterations at the Tissue and System Levels

TBI can lead to extensive reorganization of both the structure and function of neural networks. Neuroimaging studies, such as diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (rs-fMRI), reveal impairments in the structural connectome of both gray and white matter. These impairments manifest as reduced integrity of axonal tracts and abnormal

functional connectivity between distant brain regions[34, 35]. Emerging research indicates that white matter hyperintensities (WMH) disrupt long-range white matter tracts, thereby affecting the underlying structural connectivity within large-scale brain networks[36]. This compromised structural connectivity, in turn, disrupts functional connectivity, impairs information transfer between distal brain regions, and ultimately contributes to the development of cognitive deficits [37] .

## 4. Endogenous Repair Mechanisms and Translational Interventions

### 4.1. Neuroregeneration and Vascular Self-Repair

Despite the extensive and complex neural damage inflicted by Traumatic Brain Injury (TBI), the central nervous system (CNS) retains a degree of regenerative and network-reorganizing capacity. Structurally, neural stem cells and progenitor cells can be activated in regions such as the subventricular zone (SVZ) and the hippocampal dentate gyrus (DG), contributing to neurogenesis and the migration of new neurons [38].

Angiogenesis and the reconstruction of the neurovascular unit (NVU) are also crucial for repair. While the cerebral vasculature in adults is typically stable, it can be activated under pathological conditions, including injury [39]. Adult vascular remodeling involves angiogenesis through mature endothelial cells (sprouting from pre-existing vessels) and endothelial progenitor cells (EPCs). EPCs reside in the bone marrow and peripheral blood and are mobilized into the circulation after TBI. The induction of angiogenesis can be mediated by angiogenic factors such as Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and Angiopoietin (Ang). The NVU is a multicellular complex comprising endothelial cells, pericytes, neurons, glial cells, growth factors, and extracellular matrix proteins, all in close physical proximity to the endothelium[40, 41]. Within the NVU, newly generated immature neurons are intimately associated with the revascularizing system. This neovascularization promotes highly coupled neurorepair processes, including neurogenesis and synaptogenesis, which in turn lead to improved functional recovery [42, 43] .

### 4.2. Glial Cell Responses and Microenvironment Remodeling

Glial cells play a dual role in TBI repair. In the acute phase, reactive astrocytes can help confine the injury, clear debris, maintain ionic homeostasis, regulate inflammation, and support synaptic remodeling and circuit reorganization [44, 45] . However, excessive or persistent activation can lead to the formation of a glial scar, which inhibits axonal regeneration [46] , disrupts homeostatic

functions, exacerbates inflammation and edema, and may induce aberrant neural activity [47, 48].

Following brain injury, microglia activation results in diverse phenotypes, corresponding to either neurotoxic or neuroprotective states. Depending on the disease stage and chronicity, microglia receive different stimuli, leading to specific activation states characterized by changes in morphology, gene expression, and function[49]. Microglia regulate the neural microenvironment through polarization along a spectrum (from pro-inflammatory M1 to anti-inflammatory/reparative M2 phenotypes) and via immune-metabolic reprogramming. They interact with endothelial cells and pericytes, jointly participating in debris clearance and repair within the injury zone.M1-type microglia release pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, as well as reactive oxygen species (ROS) and nitric oxide (NO) [50, 51]. These factors further activate more glial cells, damage neurons and the blood-brain barrier, creating a self-reinforcing vicious cycle of neuroinflammation. Persistent inflammatory stimuli can lead to chronically activated microglia, whose harmful secretions damage healthy neurons and synapses, contributing to chronic neuroinflammation. This state is closely linked to long-term cognitive impairment, emotional disturbances, and increased risk of neurodegenerative diseases after TBI [52] [53] .

M2-type microglia exhibit phagocytic activity and release neurotrophic factors, promoting neuronal survival and synaptic plasticity, thereby accelerating tissue repair and inflammation resolution.

In recent years, exosomes and extracellular vesicles (EVs) have emerged as key mediators of intercellular communication. Capable of transporting bioactive molecules such as miRNAs and proteins, they modulate neurogenesis, synaptic plasticity, and immune responses, positioning them as critical biological agents in facilitating endogenous repair [54, 55].

It is therefore inaccurate to simply categorize glial cells as "good" or "bad." Future therapeutic strategies should not aim to suppress or activate them indiscriminately but should focus on modulating specific molecular pathways governing their responses. The goal is to steer them toward protective and reparative functions while inhibiting their detrimental effects.

**4.3 Axonal Remodeling and Metabolic Adaptation**

Post-TBI, the hippocampal dentate gyrus undergoes complex synaptic plasticity remodeling. On one hand, injury leads to widespread synaptic loss and a reduction in postsynaptic proteins (e.g., PSD95), which is believed to underlie cognitive deficits[1]. On the other hand, research reveals that

newborn granule cells generated through adult hippocampal neurogenesis possess unique reparative potential. By 60 days post-TBI, the long-term potentiation (LTP) capacity of the newborn neuron population is fully restored, while the plasticity of the mature neuron population progressively declines. This temporal pattern of recovery correlates with the restoration of spatial memory behavior. The high plasticity of newborn neurons stems from their intrinsically low LTP threshold and relative insensitivity to GABAergic inhibition, among other properties [56, 57]. Furthermore, diffuse axonal injury caused by TBI is not only a cause of acute dysfunction but may also contribute to long-term synaptic dysfunction and neurodegeneration through the production of pathological proteins like Aβ[58]. Thus, post-TBI synaptic plasticity reflects a dynamic interplay between injury and endogenous repair mechanisms at a cell-specific level. Targeting the integration and functional recovery of newborn neurons may offer novel strategies for promoting cognitive rehabilitation.

**4.4 Multi-Level Intervention Strategies and Translational Directions**

The treatment of TBI is progressively shifting from monotherapeutic drug approaches towards multi-level, systemic intervention models. Current major intervention avenues include pharmaceuticals and biologics, cell and gene therapies, tissue engineering, neuromodulation, and comprehensive rehabilitation.

Pharmaceuticals and Biologics: Research focuses on the combined use of neuroprotective and immunomodulatory agents. Calcium stabilizers and antioxidants can reduce apoptosis and oxidative stress damage [59-61]. Microglial polarization modulators may alleviate chronic inflammation [62]. Furthermore, delivery systems for neurotrophic factors (e.g., BDNF, NGF, GDNF) help sustain neuronal survival and synaptic plasticity [63].

Cell and Gene Therapy: Neural stem cells (NSCs) [64], induced pluripotent stem cell (iPSC)-derived neurons [65], and mesenchymal stem cells (MSCs) [66] are all being investigated for TBI repair, though challenges remain regarding cell homing, integration, and safety. Gene-editing technologies (e.g., CRISPR/Cas9) [67] and RNA-based intervention strategies (miRNA, siRNA, AAV vectors) offer precision modulation of inflammatory responses and neural circuit reconstruction at the molecular level [68-70].

Biomaterials and Tissue Engineering: These provide novel supportive platforms for TBI repair. Injectable hydrogels, guidance scaffolds, and controlled-release carriers can mimic the extracellular matrix (ECM) environment [71-73]. Bioactive materials themselves can promote recovery and repair,

or serve as delivery agents for factors aiding tissue regeneration, such as cells, ECM proteins, growth factors, angiogenic factors, anti-inflammatory cytokines, and antioxidants [74] [75]. Additionally, using biomaterials to deliver cells, combined with neurotrophic factors or ECM proteins, can appropriately guide stem cell differentiation and support tissue regeneration [76] .

Physical and Neuromodulatory Interventions: These are gaining prominence in multimodal TBI treatment. Hypothermia, hyperbaric oxygen therapy, and photobiomodulation can mitigate acute tissue damage [77-79] . Non-invasive brain stimulation techniques (e.g., rTMS, tDCS) [80] and invasive neuromodulation (e.g., VNS, DBS) can promote functional recovery by modulating brain plasticity [81, 82]. Brain-computer interfaces (BCIs) coupled with neurofeedback systems offer new avenues for cognitive and motor function reconstruction [83] .

Rehabilitation Interventions: These remain a cornerstone for functional recovery in TBI patients. Multimodal rehabilitation approaches—including task-oriented training, virtual reality, robot-assisted motor and cognitive training, and psychological interventions—facilitate neural network reorganization and functional compensation [84]. Developing individualized, phase-specific rehabilitation plans can significantly improve long-term prognosis and quality of life.

In summary, multi-target, multimodal, and time-phase-specific interventions represent promising new directions for both basic and clinical-translational research in TBI. However, there is still a lack of large-scale, multi-center randomized controlled trials with long-term follow-up. The efficacy and safety of these emerging strategies require further validation and optimization.

## 5. Assessment Tools and Outcome Measures

The prognostic evaluation of Traumatic Brain Injury (TBI) requires the integration of multidimensional information spanning structural, functional, and molecular levels to form a comprehensive multimodal system. This system aims to fully reflect the extent of neurological impairment and the trajectory of recovery in patients.

### 5.1. Neuroimaging Assessment

Neuroimaging serves as a cornerstone in TBI evaluation. Conventional imaging includes CT and MRI. CT is suitable for detecting acute hemorrhage and fractures, while MRI is superior for assessing soft tissue and microstructural changes. Modalities such as Susceptibility-Weighted Imaging (SWI) can visualize microhemorrhages, Diffusion Tensor Imaging (DTI) evaluates white matter integrity, and Arterial Spin Labeling (ASL) measures cerebral perfusion. Functional imaging

techniques (e.g., fMRI, MEG, PET) dynamically reflect brain network activity and metabolic changes, providing insights for predicting cognitive and motor recovery [85-87].

### 5.2. Biomarker Detection

Fluid biomarkers offer objective evidence for molecular-level assessment. Commonly used indicators include Glial Fibrillary Acidic Protein (GFAP), Ubiquitin C-terminal Hydrolase L1 (UCH-L1), Neurofilament Light Chain (NFL), Tau protein, and S100B. These can assist in diagnosing the presence of brain injury across varying severities and predicting outcomes [87]. Furthermore, exosomes/microvesicles and microRNAs represent emerging assessment avenues, demonstrating clinical value in predicting TBI severity and recovery potential [88, 89].

### 5.3 Clinical Function and Electrophysiological Assessment

Electrophysiological examinations, such as electroencephalography (EEG) and event-related potentials (ERP), along with network connectivity analysis, can be used to detect neural circuit reorganization and functional recovery [90, 91]. For clinical functional assessment, scales like the Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), and Functional Independence Measure (FIM) are commonly employed [92, 93]. In pediatric assessment, virtual reality (VR) technology provides an immersive and safe environment well-suited for children, enhancing their motivation to participate [94]. VR also offers high ecological validity, better simulating the cognitive demands of daily life [95].

### 5.4. Individual Variability and Precision Assessment

TBI exhibits significant clinical and pathological heterogeneity, with marked differences among patients in injury mechanisms, genetic backgrounds, and comorbid conditions. Research indicates that factors such as age, sex, APOE genotype, and metabolic comorbidities (e.g., diabetes, cardiovascular disease) influence the degree of neural damage, inflammatory response, and repair capacity [96]. Additionally, factors like mechanical stress intensity and secondary insults (e.g., reperfusion injury, infection) can exacerbate pathological damage. Therefore, establishing an individualized, stratified, and phase-specific assessment system is key to enabling precise intervention and predicting treatment efficacy.

### 5.5. Big Data and Artificial Intelligence in Assessment

With advancements in multi-omics technologies and machine learning methods, predictive models that integrate clinical, imaging, and molecular features are becoming a significant direction in TBI

precision medicine. Artificial intelligence (AI)-based deep learning algorithms can extract features from imaging, electrophysiological, and biomarker data to forecast prognosis and treatment response [97]. Large-scale, multi-center databases (e.g., TRACK-TBI, CENTER-TBI) already provide data support for individualized decision-making [98, 99]. In the future, AI-driven multimodal integrated assessment systems will form a crucial foundation for precise intervention in TBI.

### 5.6. Experimental Models and Translational Research

Research into TBI mechanisms relies on standardized experimental models. *In vitro* models (e.g., neuron-glia co-culture systems, neurovascular unit-on-a-chip) are useful for analyzing cellular-level injury, inflammation, and drug responses but lack the complexity of the *in vivo* environment. Animal models (e.g., Controlled Cortical Impact (CCI), Weight Drop (WD), blast injury, and penetrating injury models) can better simulate the pathological features of different TBI types and are essential tools for validating interventions . These models vary in injury location, severity, and reproducibility; researchers must select and standardize their use appropriately based on experimental objectives.

To enhance the reproducibility and generalizability of TBI animal studies, it is crucial to rigorously control experimental design, ensure adequate sample sizes, and employ practices like pre-registration. Strengthening multi-center collaboration and data sharing, along with establishing unified model evaluation standards, will help increase the translational value of experimental results. This approach will better bridge the gap between animal research and clinical translation, providing a reliable basis for future clinical trials.

## 6. Summary and Future Perspectives

Despite significant advancements in basic and clinical research on Traumatic Brain Injury (TBI) in recent years, translating laboratory findings into clinical practice remains challenging. The numerous negative clinical trial outcomes suggest that factors such as the therapeutic time window, dosage selection, and endpoint assessment significantly impact efficacy. Furthermore, the limited reproducibility of animal studies and the substantial clinical heterogeneity among patients constrain the generalizability of preclinical results. The intricate pathological network underlying TBI makes single-target therapies unlikely to achieve ideal outcomes. Consequently, future research is progressively moving towards multi-target combination therapies, network-level regulation, and multimodal integrated approaches. Composite strategies combining neuroprotection,

immunomodulation, rehabilitation training, and neuromodulation hold promise for achieving more efficient repair.

Future TBI research should focus on multi-level precision interventions and innovations in translational medicine: (1) The immune-metabolic-mitochondrial-inflammation axis is recognized as a core component of secondary injury; deciphering its dynamic network relationships will help identify novel therapeutic targets. (2) Regarding glial cell responses, the approach should shift from indiscriminate "inhibition" to precise "modulation." The goal is to preserve their acute protective functions while steering microglial polarization towards reparative phenotypes and reducing the formation of inhibitory scars in the chronic phase. (3) Extracellular vesicles (EVs) and liquid biopsy can serve not only as biomarkers for monitoring neural damage but also as efficient delivery vehicles for drugs or nucleic acids, offering novel tools for repair. (4) Leveraging real-world data (RWD) and digital phenotyping, combined with AI algorithms to design adaptive clinical trials, has the potential to realize personalized treatment and optimize therapeutic efficacy.

Additionally, strengthening interdisciplinary collaboration is crucial. Deep integration of neuroscience, immunology, metabolomics, engineering, and artificial intelligence is needed to construct multimodal prediction and intervention systems. Promoting multi-center clinical studies and long-term follow-up can establish a closed loop of verification from mechanistic exploration to clinical translation, thereby fostering the continuous refinement of precision medicine and rehabilitation frameworks for TBI.

In summary, the prevention and treatment of TBI urgently require a multi-target, multimodal, and individualized approach. By integrating molecular mechanistic insights with robust clinical evidence to dynamically balance injury and repair processes, we can ultimately improve long-term patient outcomes and quality of life.

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**Author Contributions**

Yongmei Li conceived and supervised the study. Yufan Wang was responsible for original draft preparation. Hongyu Quan, Wenyuan Wang and Lihua Jin reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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