



Review Article

Post-traumatic dementia: Advances in understanding neurodegenerative mechanisms

Xiao-Jie He^a, Hui Wang^{b,*}, Yi Zhang^a

^a Department of Neurosurgery, Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

^b Department of Neurosurgery, Shaanxi Nuclear Industry 215 Hospital, Xianyang 712000, Shaanxi, China

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ABSTRACT

Traumatic brain injury can trigger long-term neurodegenerative diseases beyond its devastating acute effects. This narrative review summarizes current understanding of the neurodegenerative mechanisms underlying post-traumatic dementia. Core mechanisms involve multiple pathophysiological processes: long-term dysfunction of the blood-brain barrier, which impairs the clearance of toxic proteins; diffuse axonal injury, leading to persistent disruption of axonal transport, dysregulation of calcium homeostasis, and Wallerian-like degeneration; and the abnormal deposition of key pathological proteins such as amyloid- β , hyperphosphorylation and propagation of tau protein, and dysfunctional TAR DNA-binding protein-43, all of which disrupt protein homeostasis. In addition, chronic neuroinflammation mediated by microglia and astrocytes acts as a critical link, continuously exacerbating synaptic damage and neurodegeneration through the release of pro-inflammatory factors. Genetic factors, such as the *APOE4* allele, can significantly amplify these pathological processes. Collectively, this evidence indicates that traumatic brain injury is not an isolated acute event but rather initiates and accelerates a long-term, multifactorial neurodegenerative cascade, ultimately resulting in cognitive dysfunction. These insights provide important targets for the development of targeted intervention strategies.

1. Introduction

Traumatic brain injury (TBI) is a major public health challenge worldwide. According to data from the 2021 Global Burden of Disease Study, there were approximately 20.8 million new TBI cases that year. The resulting death, disability, and long-term functional impairment impose a heavy disease burden on society and healthcare systems.¹

TBI, which is primarily caused by falls, road traffic accidents, and sports participation, is defined by pathological alterations in brain function resulting from external mechanical forces.² In recent years, relevant studies have continuously challenged traditional perceptions—TBI is no longer regarded as a transient injury, and its pathophysiological processes (e.g., axonal degeneration and astrogliosis) can persist beyond the resolution of clinical symptoms, along with prolonged biomarker abnormalities and cumulative risk of neuropsychiatric comorbidities.³ These findings further indicate that TBI is one of the significant risk factors for the development of dementia.

Dementia is a clinical syndrome characterized by acquired and progressive cognitive decline, whose key neuropathological hallmarks are the aberrant deposition of hyperphosphorylated tau and amyloid- β ($A\beta$) in the brain.^{4,5} Recent studies have further suggested that TBI can dis-

rupt neurodegenerative processes, serving as a significant risk factor for the development of late-onset dementia.⁶ Evidence indicates that post-traumatic biomarkers [e.g., neurofilament light chain (NFL) protein, tau protein, etc.] remain elevated for over a decade post-injury.⁷ As demonstrated in many retrospective and prospective studies, brain injury may persist and exacerbate neurodegenerative pathological processes, thereby significantly increasing the risk of developing dementia in later life.

This narrative review summarizes recent research advances in post-traumatic dementia (PTD), integrating epidemiological and pathological evidence regarding the increased risk of all-cause dementia and specific neurodegenerative diseases [e.g., Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE)] following TBI. We synthesized key findings from seminal foundational studies, recent landmark clinical trials, and cutting-edge basic science investigations. Literature during the period from January 2005 to December 2025 was searched from PubMed, Web of Science, and Google Scholar databases using keywords such as “traumatic brain injury”, “dementia”, “neurodegeneration”, “blood-brain-barrier”, “tau”, and “neuroinflammation”. We prioritized high-impact, peer-reviewed articles deemed most relevant to elucidating the pathophysiological continuum linking TBI to long-term cognitive decline.

* Corresponding author.

E-mail: xy215wh2660@163.com (H. Wang).

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2. Epidemiology, diagnosis and pathology

2.1. Epidemiological evidence

Multiple large-scale clinical studies have confirmed that TBI exposure is significantly associated with an increased risk of dementia. In patients with moderate-to-severe TBI, the hazard ratio (HR) for all-cause dementia ranges from 1.35 to 3.77^{8–11} and the HR for AD can reach 2.3–4.5.¹² In populations with mild TBI (mTBI), further studies have shown that the risk of dementia increases by approximately 2.4-fold in patients without loss of consciousness (LOC), while it rises to 3.2 times in those with LOC.^{11,12}

2.2. Definition and clinical features of PTD

PTD refers to a clinical syndrome resulting from single or repeated¹³ external force(s) applied to the head, directly or indirectly causing brain tissue damage, and ultimately leading to persistent cognitive decline as its core feature. The diagnosis of PTD requires patient being in a state of clear consciousness, with core symptoms including acquired impairments in episodic memory, attention, and executive functions.¹⁴ Additionally, the course of the related cognitive impairment must persist for at least 4 months.

3. Pathological injury mechanisms of PTD following TBI

Multiple studies have demonstrated that long-term cognitive dysfunction following TBI is characterized by the coexistence of multiple pathologies.¹⁵ TBI can directly initiate or accelerate neurodegenerative processes through mechanisms involving blood–brain barrier (BBB) disruption, axonal injury, proteostatic dysfunction, and neuroinflammation.¹⁶ Most notably, TBI exacerbates pathological hallmarks of dementia, driving sustained elevations in NFL, total tau, the A β 42/A β 40 ratio, and pathologically hyperphosphorylated tau levels,^{3,17} as well as sustained accumulation of alpha-synuclein and TAR DNA-binding protein 43 (TDP-43). These aberrant expressions of neurodegeneration-related proteins provide a neuropathological basis for the overlap in clinical manifestations between TBI and dementia, and support TBI as an independent risk factor for dementia.¹⁸

Autopsy studies have shown that TBI leads to upregulated expression of amyloid precursor protein (APP) and hyperphosphorylation of tau protein in the brain,^{17,19} and their elevated levels are associated with poor patient prognosis.^{20,21} A systematic review of animal models further reveals that TBI-induced pathological changes related to hyperphosphorylated tau protein (p-tau) are widely present, including neuronal loss (23%), axonal injury (43%), microglial activation and astrogliosis (each 50%), and A β protein deposition (29%), providing solid pathological evidence for the development of PTD.²²

In studies related to CTE,²³ approximately 69% of patients exhibited cognitive symptoms, primarily manifesting as memory impairment (86%), executive dysfunction (76%), and language impairment (53%). The severity of cognitive impairment positively correlates with the severity of CTE pathology.²⁴

The pathological mechanisms of dementia following TBI are closely related to secondary and delayed neurochemical alterations and neurodegenerative processes.²⁵ Although prior reviews have comprehensively cataloged the individual pathological features of PTD, such a reductionist perspective fails to capture the dynamic interplay among these processes. To address this gap, we propose an integrated spatiotemporal-causal model (Fig. 1) that unifies vascular, mechanical, biochemical, and immunological insults into a single progressive cascade. This model posits BBB disruption as the primary upstream trigger, initiating a self-propagating cycle of neurodegeneration.

The cascade is initiated when acute biomechanical forces disrupt BBB endothelial integrity,^{15,26} thereby increasing vascular permeability and promoting the extravasation of serum proteins and

peripheral immune cells. Subsequently, this altered microenvironment—characterized by edema and oxidative stress—renders axons vulnerable, precipitating diffuse axonal injury (DAI), a process further exacerbated by the loss of endothelial metabolic support. Axonal transection then facilitates the mislocalization and accumulation of axoplasmic proteins, particularly tau, while BBB leakage promotes A β deposition. Concurrently, compromised proteostatic networks fail to clear these toxic aggregates. The resulting buildup of cellular debris and misfolded proteins triggers persistent microglial activation and neuroinflammation. Crucially, this chronic inflammation further compromises BBB integrity, thereby closing the loop and driving the transition from acute injury to chronic neurodegeneration (Fig. 2).

Neurovascular dysfunction accelerates the production and deposition of A β , thereby exacerbating neuroinflammation and neuronal degeneration²⁷ and promoting DAI.²⁸ Consistent with the finding that tau protein is the main component of NFTs in AD, studies have confirmed that TBI can induce abnormal aggregation of multiple tau-phosphorylating kinases in axons,²⁸ which mutually promote with persistent neuroinflammation and jointly drive cognitive decline.²⁹ These new evidence further reveals the pathological overlap between TBI and AD, providing support for the biological mechanisms underlying their association.¹¹

3.1. BBB dysfunction

BBB is a selectively permeable barrier that plays a critical role in maintaining brain homeostasis by regulating the passage of molecules and protecting the central nervous system (CNS) from harmful substances.³⁰ The integrity of the BBB is essential for normal brain function, and its dysfunction has been implicated in various neurological disorders including TBI and AD. Both TBI and AD are characterized by BBB dysfunction, which may exacerbate neuroinflammation, disrupt neural function, and promote the accumulation and aggregation of neurotoxic proteins.¹⁵

BBB is primarily composed of brain endothelial cells, which are interconnected via junctional proteins to form a selective barrier that regulates the passage of molecules into the brain. This selective permeability is reinforced by pericytes, astrocytic end-feet, and the basal lamina, collectively known as the neurovascular unit.³⁰ BBB permeability serves as a key indicator of its integrity, reflecting both paracellular and transcellular transport.³¹ Paracellular transport is regulated by tight and adherens junctions, which form seals between endothelial cells, whereas transcellular transport depends on specialized transporter proteins governing molecular exchange in the brain.³⁰ Degeneration or contraction of brain endothelial cells, coupled with downregulation, degradation, and mislocalization of tight junction proteins, disrupts paracellular transport. Similarly, impaired expression or function of TBI-associated receptors and transporter proteins leads to dysregulation of transcellular transport. TBI-related dysfunction may also involve other components of the neurovascular unit, including pericyte degeneration or reduced coverage, basal lamina degradation, and swelling or detachment of astrocytic end-feet.³¹

BBB dysfunction is a direct consequence of TBI¹⁶ and often persists into the chronic phase,^{16,32} affecting both acute pathology and long-term outcomes. Following the traumatic impact of TBI, microvascular shear, hemorrhage, and hemodynamic dysregulation occur,³³ leading to rapid BBB disruption. Plasma proteins breach the barrier and enter the brain, triggering astrogliopathy and impairing astrocytic function. These astrocytes lose expression of homeostatic proteins, hindering BBB repair and neuronal recovery. Studies have found that chronic degeneration of mural cell and reduced expression of caveolin-1 (cav-1) and LDL receptor-related protein 1 (LRP1)³⁴ may underlie persistent TBI-related dysfunction. Cav-1 is crucial for vesicle formation and endothelial transcytosis,^{34,35} while LRP1 facilitates the clearance of AD-associated A β and tau at TBI sites.³⁶ These changes disrupt the ability of TBI to elim-

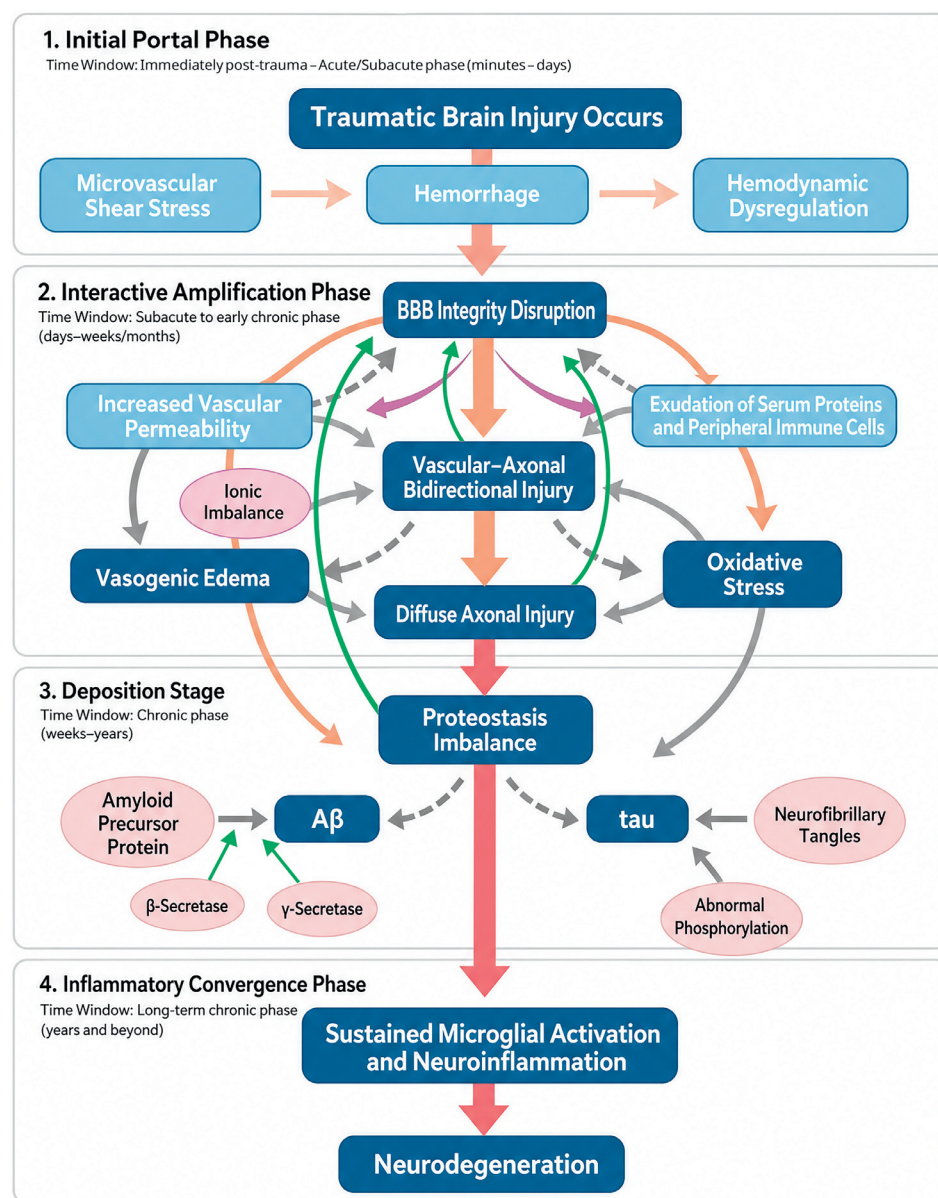


Fig. 1. A temporal-causal model of post-traumatic dementia pathogenesis.

inate extracellular $A\beta$ and tau via transport pathways, reducing their clearance distance from the cerebrovascular system.

3.2. Axonal injury

An axon is a long, thin neuronal process responsible for ensuring information transmission from the cell body to the nerve terminals.³⁷ In the CNS, axons are classified into unmyelinated axons and myelinated axons, and the latter are covered by myelin sheaths formed by oligodendrocytes in the CNS.³⁸ In neuroelectrophysiological processes, axons primarily perform four main functions: action potential initiation, action potential conduction, excitation-release coupling, and integration. Action potentials are generated within the axon initial segment and subsequently propagate toward nerve terminals that release neurotransmitters.³⁹ Axonal microtubules serve as structural support tracks for motor proteins, neurofilaments provide tensile strength, and actin filaments—arranged in repeating ring-like structures along the axon—assist in protein linkage and cross-linking, thereby providing membrane stability.⁴⁰ These structures undergo anterograde transport driven by kinesin, which transports mitochondria and proteins required for growth

from the cell body along the axon to the axon terminals, and simultaneously undergo retrograde transport driven by dynein, which transports cellular waste from the axon terminals back to the cell body.³⁷ Further studies in primary neuronal cultures have revealed that pathological protein forms such as tau protein, alpha-synuclein, $A\beta$, and mutant huntingtin protein can be transported along axons,^{41,42} suggesting that axonal injury may lead to disruption of cargo transport, thereby potentially causing $A\beta$ deposition at the injury site. On the other hand, axons undergo various pathological changes and play a critical role in neurological disorders such as axonal transport deficits, axonal swelling, axonal degeneration, as well as axonal regeneration impairment or demyelination.

DAI is the most common neuropathology in closed head injury,⁴³ reflecting the selective vulnerability of white matter axons to mechanical load injury during rapid head acceleration. After TBI, axonal degeneration caused by DAI is generally considered to progress as disruption of axonal transport leads to axonal swelling, followed by secondary disconnection, and ultimately the advancement of Wallerian degeneration. Traditionally, this process was thought to be limited to the acute and subacute phases post-injury. However, recent evidence has identified

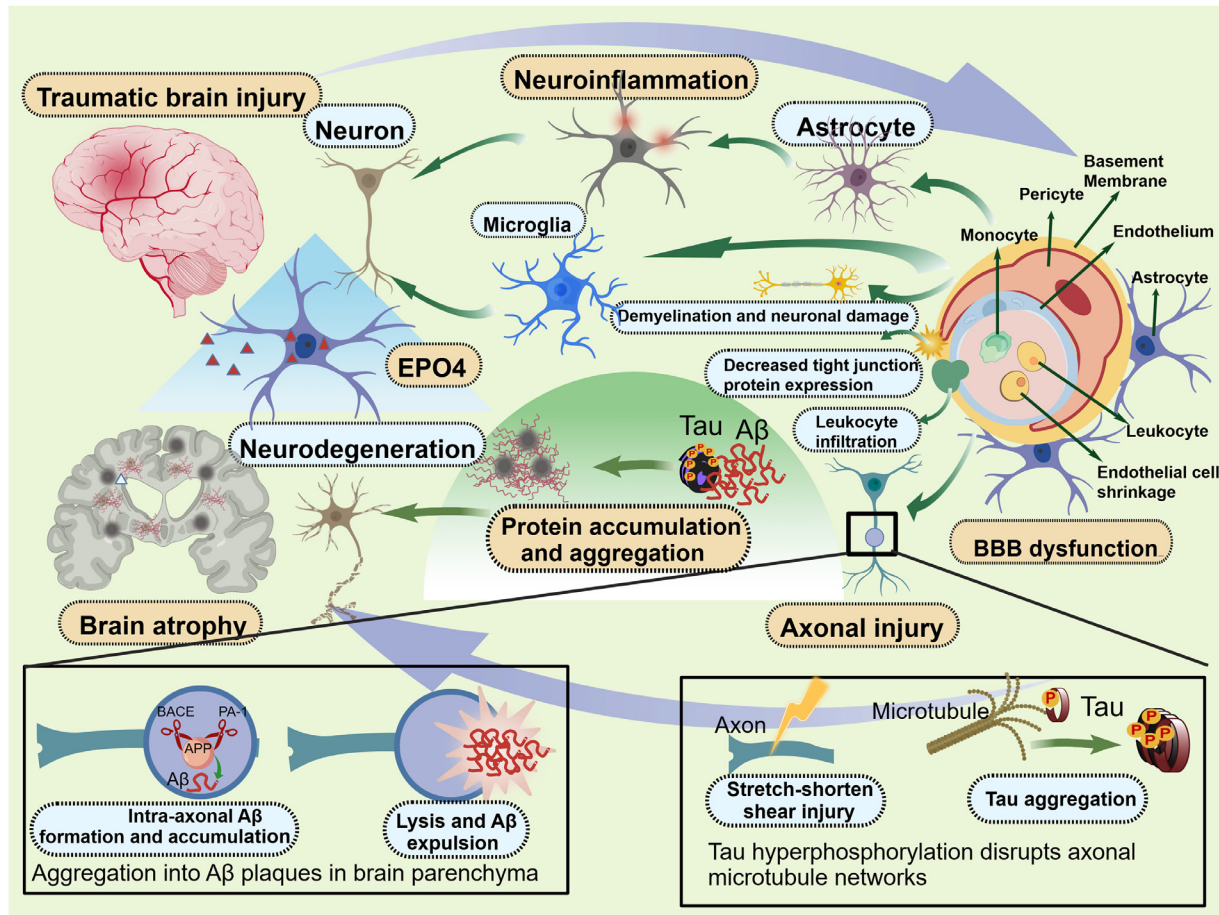


Fig. 2. Pathological injury mechanisms of post-traumatic dementia.

axonal degeneration in brain material years after human brain injury, indicating that TBI may trigger a progressive, long-term neurodegenerative process, partially reflected in axonal degeneration.⁴⁴ Notably, mild TBI, due to its lower inertial force intensity and lack of complete primary axonal transection, can still cause partial axonal injury, trigger molecular pathways, and lead to what is now referred to as secondary axonal transection.⁴⁵ Secondary axonal transection is an inflammatory and apoptotic event, and treatment targeting axonal microtubules (MTs) within hours post-injury represents a potential therapeutic window.⁴⁰ Studies have shown that axonal pathology may play a role in the development of Alzheimer-like pathology during both the acute phase post-injury and long-term survival.^{3,27,37,43,44}

After TBI, the initial injury combined with secondary pathological events leads to neuronal death, DAI, dendritic degeneration, and widespread synaptic loss, damaging neural circuits beyond the injury focus and resulting in further neuronal dysfunction and death.⁴³ Intracerebral hemorrhage increases intracranial pressure and causes tissue damage, while mitochondrial damage leads to ATP depletion, triggering neuronal death. Disruption of ionic homeostasis impairs neuronal signal transmission and exacerbates injury, whereas axonal degeneration disrupts neural connections. Furthermore, microglia and astrocytes may exacerbate inflammatory responses while clearing debris⁴⁶ whereas the release of Aβ and tau proteins induces neurotoxicity and promotes neurodegeneration.²⁷ Among these, the mechanism of ionic imbalance following axonal injury is considered a core link in axonal degeneration and persistent functional impairment. Initial mechanical injury leads to membrane perforation and opening of ion exchange channels, causing an influx of calcium ions and further activating calpains. Activated calpains degrade structural proteins, leading to morpholog-

ical changes such as post-traumatic axonal swelling.⁴⁷ Additional experiments have shown that cerebral demyelination following TBI is significantly correlated with memory consolidation and cognitive function performance,^{48,49} suggesting that intact myelin is crucial for memory and cognition.⁵⁰ A hypoxic white matter model has confirmed pathological sodium influx in axonal channels,⁵¹ revealing that this sodium influx elevates intracellular calcium concentration,^{52,53} inducing harmful activation of proteases such as calpains, caspases, cysteine proteases, and phosphatases, which mediate cytoskeleton destruction.⁵⁴ Furthermore, activated calpains degrade inactivated sodium channel proteins, which reciprocally promotes increased sodium influx.³⁷

Studies on synaptic plasticity in the brain have shown that synaptic pruning is significantly involved in the formation of precise neural circuits and synaptic plasticity during development.⁵⁵ This process involves complement signals (C1q, C3, and CR3) or signaling pathways [CD47 and signal regulatory protein α (SIRP α)].^{2,56,57} Among these, the C1q-dependent complement pathway plays a crucial role in synaptic elimination by microglia, while CD55, as an inhibitor of the complement pathway, can disrupt microglial functions related to memory storage in engram cells.⁵⁸ Another cell surface receptor on microglia that promotes synaptic pruning—TREM2—interacts with phosphatidylserine (PS) to regulate synaptic pruning in the hippocampus and dorsal lateral geniculate nucleus.^{59,60} In studies using high-frequency head impact (HF-HI) models, HF-HI induces acute synaptic changes, thereby impairing synaptic plasticity, with glutamatergic synapses emerging as a significantly affected pathway in KEGG pathways.⁶¹ In research on light flicker intervention for cognitive impairment following TBI, it is commonly observed that hippocampal long-term potentiation is impaired, spontaneous synaptic transmission is reduced, and the intrinsic excitability

of CA1 pyramidal neurons is decreased. It has been suggested that light flicker intervention may potentially affect the aforementioned mechanisms.⁶²

3.3. Proteostasis dysregulation

The current prevailing view holds that long-term neurodegenerative diseases induced by TBI are closely associated with proteostasis dysregulation of proteins such as $A\beta$, tau, and TDP-43. Following axonal injury, $A\beta$ plaque deposition, accumulation and spread of pathologically hyperphosphorylated tau, and dysfunction in TDP-43 transcription and expression are induced. These proteostasis dysregulation events are regarded as key pathological mechanisms underlying the development of PTD.

3.3.1. Abnormal metabolism of $A\beta$

$A\beta$ pathology is a core pathological hallmark of AD¹⁹ and is closely associated with the progression of dementia. After sequential cleavage of APP by β -secretase and γ -secretase,⁶³ aberrant protein fragments prone to aggregation— $A\beta$ —are generated, which subsequently deposit abnormally in the brain to form plaques.²⁷ These plaques are morphologically classified into two main types: diffuse plaques and neuritic plaques. Among these, neuritic plaques are dense argyrophilic aggregates of $A\beta$, containing NFTs, dystrophic neurites, and a dense amyloid core.⁶⁴ Such plaques can lead to synaptic dysfunction and neuronal injury, and are significantly correlated with the degree of cognitive impairment in patients.^{19,65}

Existing studies have shown that TBI can cause mechanical injury to brain tissue, triggering DAI and BBB dysfunction.²⁷ Under this pathological state, the distribution and metabolism of APP become dysregulated. Through sequential cleavage by β -secretase and γ -secretase, APP generates $A\beta$ prone to aggregation, particularly dominated by the $A\beta$ 42 subtype, which is closely associated with AD.^{65,66} These aberrantly generated $A\beta$ can further aggregate into amyloid fibrils and deposit as amyloid plaques,⁶⁷ with regions of increased deposition primarily concentrated in the cingulate gyrus and the cuneus/precuneus.²⁰ Among $A\beta$ subtypes, $A\beta$ 42 and $A\beta$ 40 are the main forms constituting plaques,⁶⁶ and studies have confirmed that the elevated $A\beta$ 42/ $A\beta$ 40 ratio in cerebrospinal fluid (CSF) or imaging biomarkers of patients after TBI can persist for up to 8–9 years.⁷

3.3.2. Hyperphosphorylation of tau protein

NFTs, composed of filamentous tau protein, are a typical pathological hallmark of AD.⁶⁴ Tau protein is involved in regulating the assembly and disassembly of axonal microtubules. Its post-translational modifications appear to be a prelude to the development of tauopathies in the brain. These modifications primarily include: (1) hyperphosphorylation mediated by multiple kinases; (2) proteolysis induced by calpains and caspases; and (3) oxidative modifications. Hyperphosphorylated and abnormally folded tau protein, compared to unbound normal tau protein, loses its ability to normally bind to and stabilize axonal microtubules.⁶⁸ Due to its enhanced aggregation propensity, it forms paired helical filaments (PHFs) and gradually aggregates into the main component of NFTs.²⁸ The deposition of tau and its subsequent spread are characteristic of a class of neurodegenerative diseases called “tauopathies.” The correlation between its lesions and patient cognitive impairment is more significant than that of amyloid deposition.^{3,7}

Multiple studies have reported that pathologically hyperphosphorylated tau accumulates and spreads after TBI, with the ratio of phosphorylated tau to total tau in plasma serving as a peripheral biomarker for acute and chronic TBI.²⁸ Longitudinal studies have also confirmed that blood biomarkers can remain abnormal after TBI: in adult patients, NFL and tau protein remain elevated for nearly a decade post-injury, and elevated concentrations of AD-related biomarkers [($A\beta$ 42/ $A\beta$ 40 ratio and p-tau181) persist for 8–9 years.^{3,7} These findings suggest that brain in-

jury may accelerate the neurodegenerative process and interact with it, thereby increasing the risk of late-life dementia.

It has been proposed that mechanical stress exceeding certain thresholds after TBI disrupts the microtubule network within axons, leading to DAI, tau release, hyperphosphorylation, and extracellular accumulation.⁶⁹ Evidence has shown that elevated tau is most pronounced in the medial temporal lobe, entorhinal cortex, precuneus, as well as the frontal, temporal, parietal, and occipital lobes.²⁰ In NFTs in neurodegenerative diseases, phosphorylation at the Ser262 site is commonly observed.⁷⁰ Proline-directed protein kinases are most commonly associated with tau phosphorylation, including mitogen-activated protein kinase (MAPK),⁷¹ glycogen synthase kinase-3 β (GSK3- β), cyclin-dependent kinase (CDK), integrin-linked kinase (ILK), and stress-activated protein kinase (SAPK).⁷² Animal model studies have confirmed that acceleration/deceleration injury induces tau to undergo phosphorylation, misfolding, aggregation, and cleavage, generating neurotoxic tau peptide fragments.⁷³ Furthermore, studies have shown that the mere accumulation of tau can induce chronic dysfunction of cerebral blood vessels, contributing to the development of neurodegenerative diseases.^{11,74}

3.3.3. TDP-43 dysfunction

TDP-43 is a highly conserved protein widely expressed in multiple tissues, including the CNS. Its physiological functions may involve regulating multiple biological processes through its binding to DNA, RNA, and other proteins, including the regulation of nuclear transcription, RNA splicing, and metabolism.⁷⁵ The accumulation of TDP-43 is a pathological phenomenon observed in amyotrophic lateral sclerosis and frontotemporal dementia, with TDP-43 inclusions present in the spinal cord and cortex. In AD, TDP-43 immunoreactivity is primarily localized to the medial temporal lobe, except in late stages (e.g., Braak stages V or VI), where it may appear in the neocortex and basal ganglia.⁷⁶ In contrast, in reports on CTE, the widespread presence of TDP-43 immunoreactivity, along with TDP-43 pathology in autopsy neurons of CTE—manifested as nuclear loss and cytoplasmic inclusions—confirms that TDP-43 is also a common co-morbid pathology in AD.⁷⁷

TDP-43 dysfunction is a key driver of neuronal death after mechanical injury. TBI-induced neuroinflammation stimulates nuclear factor (NF)- κ B-mediated TDP-43 transcription and expression, which in turn promotes tau phosphorylation and $A\beta$ formation by activating GSK3- β phosphorylation and β -secretase 1 expression. Studies have shown that aberrant production of TDP-43 exacerbates neuropathology and triggers synaptic and cognitive decline after TBI.⁷⁸ Through single-cell RNA sequencing and histological validation, deep glutamatergic neurons exhibit more pronounced TDP-43 dysfunction after TBI compared to superficial neurons.⁷⁹ Other studies have proposed that axonal shearing caused by head impacts after TBI may be associated with further degeneration influenced by the accumulation of p-tau and TDP-43.^{78,80}

3.4. Initiation and amplification of neuroinflammation

Neuroinflammation is a prominent feature of many neurodegenerative diseases^{81,82} and is increasingly recognized as a key pathophysiological mechanism underlying chronic neurodegeneration following TBI.^{83,84} Resident macrophages (microglia) in the brain parenchyma and infiltrating immune cells from the peripheral immune system, including monocytes and monocyte-derived macrophages,⁸⁵ play a critical role in neuroinflammation and secondary injury after TBI.

3.4.1. Microglia

As resident innate immune cells in the CNS, microglia play a critical role in neuroinflammation and secondary injury following TBI. A growing body of research supports that microglia exhibit functional duality in injured brain and spinal cord environments: they may either participate in neurorepair and tissue remodeling or promote sustained neuroinflammation and degenerative pathologies. Microglia remove cellular debris

via phagocytosis, release neurotrophic factors and anti-inflammatory cytokines, prevent neuronal damage, and restore tissue integrity in the injured brain. However, unrestrained and hyper-reactive microglial activation leads to the release of high levels of pro-inflammatory and cytotoxic mediators, thereby inducing neurological dysfunction and cell death.⁸⁶

It has been reported that microglia and macrophages possess the ability to polarize into “M1-like” and “M2-like” activation phenotypes.⁸⁷ They respond to pro-inflammatory molecules (such as bacterial lipopolysaccharide or the TH1 cytokine interferon- γ) to form the “classical” M1-like phenotype, producing high levels of pro-inflammatory cytokines [IL-1 β , IL-12, and tumor necrosis factor- α (TNF α)], chemokines (CCL2, CXCL9, and CXCL10), and reactive oxygen species (ROS), which are crucial for host defense.^{88,89} Markers of the M1-like phenotype include CD16, CD32, CD86, MHCII, and inducible nitric oxide synthase (iNOS). M1-like activation is associated with phagocytosis, the ability to kill pathogens via iron restriction, phagosomal acidification, and release of reactive oxygen species.^{88,89} In many contexts, the M1-like response is protective and downregulated after injury or clearance of pathogens; however, dysregulated or excessive M1-like activation in the brain may induce neurotoxicity by releasing pro-inflammatory factors and neurotoxic mediators, thereby triggering a microglia-mediated vicious cycle of neurodegeneration.⁹⁰ Microglia and macrophages can also respond to TH2 cytokines such as IL-4 and IL-13, polarizing into an “alternative” M2a-like state,⁸⁸ which is associated with anti-parasitic immunity, Th2 cell recruitment, tissue repair, and growth stimulation.^{88,89} In addition to producing anti-inflammatory cytokines (e.g., IL-10), M2a-polarized cells upregulate various phenotypic markers (e.g., arginase 1, CD206, Ym1, Fizz1), inhibit NF- κ B subtypes, and increase the production of scavenger receptors to enhance phagocytic function.^{88,89}

Chronic microglial activation has been reported in patients with moderate-to-severe TBI and is observable in white matter and distant regions for years after the initial brain injury.⁸⁴ In rodents, microglia can remain activated for up to 1 year after experimental brain injury, leading to chronic neurodegeneration and cognitive impairments.⁹¹ Therefore, a chronic inflammatory state accompanied by widespread microglial activation is a defining feature of moderate-to-severe TBI and an important potentially treatable secondary injury mechanism.⁹²

3.4.2. Astrocytes

Astrocytes are the most abundant glial cells in the brain.⁹³ They play active and critical roles in maintaining brain homeostasis.⁹⁴ Astrocytes regulate blood flow, maintain the BBB, provide energy metabolites to neurons, modulate synaptic activity, control neurotrophic factor secretion, clear dead cells, regulate the balance of extracellular ions, fluids, and neurotransmitters, and contribute to scar formation.^{93,94} Currently, glial fibrillary acidic protein (GFAP), S100B, YKL404, and D-serine have been evaluated as CSF biomarkers, with GFAP and S100B serving as blood biomarkers,⁹⁵ and are significantly correlated with cognitive performance.⁹⁶

Similar to microglia, astrocytes possess pro-inflammatory and neuroprotective (immunomodulatory) subpopulations upon injury response. Pro-inflammatory reactive astrocytes can upregulate multiple genes (e.g., complement cascade genes) and induce pro-inflammatory factors (such as IL-1 β , TNF α , and NO).^{82,97} In contrast, neuroprotective reactive astrocytes upregulate various neurotrophic factors and thrombospondins, exerting neurosupportive and reparative effects.⁹⁷ Studies have confirmed that anti-inflammatory cytokines, such as IL-4, IL-13, and IL-10, may induce the neuroprotective activation of astrocytes, and these alternatively activated astrocytes can release regulatory factors like IL-4, IL-10, and transforming growth factor-beta (TGF- β).⁹⁴

Apolipoprotein E (APOE) is a major genetic risk factor for AD and is produced by astrocytes.⁹⁵ Human APOE has three isoforms: APOE2, APOE3, and APOE4. Studies have confirmed that APOE4 is the strongest genetic risk factor for both early-onset and late-onset AD⁹⁸ and is also the best-known genetic risk factor for poor prognosis after TBI. In APOE4

knockout mouse models, APOE4 was found to induce neuroinflammation, impair cerebrovascular integrity, and exacerbate A β and tau pathologies,⁹⁹ suggesting that APOE4 may contribute to the pathological process of PTD through the aforementioned mechanisms.

4. Conclusions and therapeutic perspectives

This review redefines PTD not as a linear sequence of events, but as a hierarchical cascade initiated by BBB disruption. We identify BBB breakdown as the primary upstream trigger that initiates and sustains a self-amplifying vicious cycle involving axonal injury, proteostatic collapse, and neuroinflammation.

4.1. Integrated mechanistic framework

The proposed model emphasizes dynamic bidirectional interactions rather than isolated pathological changes. BBB breakdown permits the infiltration of neurotoxic blood components and immune cells into the parenchyma, sparking inflammation that exacerbates axonal shearing. Conversely, axonal damage reciprocally worsens vascular leakage. Simultaneously, the accumulation of misfolded proteins—including A β and tau—engages in a vicious cycle with microglial activation, effectively lowering the threshold for subsequent inflammatory insults. This integrated perspective addresses the translational gap left by prior reviews that focused narrowly on singular pathways.

4.2. Critical knowledge gaps

Current understanding is constrained by the paucity of longitudinal human data and an over-reliance on rodent models, which fail to recapitulate the full etiological heterogeneity of human TBI. Furthermore, the precise molecular triggers driving the conversion of acute tau phosphorylation into chronic insoluble tangles remain elusive. Notably, analyses addressing sex-specific differences in BBB integrity are critically lacking.

4.3. Future directions and therapeutic strategies

Future investigations should prioritize multi-omics integration, utilizing serial CSF sampling to map the spatiotemporal evolution of PTD. Therapeutically, strategies must extend beyond single-target interventions such as isolated A β reduction. Promising avenues include leveraging focused ultrasound to induce transient, reversible BBB opening for enhanced drug delivery, alongside precision targeting of the APOE4-CypA-MMP-9 axis to restore barrier integrity. Ultimately, combination therapies that concurrently address vascular stability and protein clearance, tailored to specific temporal windows and biomarker profiles, offer the most viable path toward effective clinical translation.

Authors' contributions

He XJ: methodology, investigation, data curation, writing – original draft, visualization; Wang H: supervision, conceptualization, and writing – review & editing, validation; Zhang Y: project administration, resources, and writing – review & editing. All authors read and approved the final version of the manuscript to be published.

Declaration of generative AI and AI-assisted technologies use

During the preparation of this work, the authors used large language models to assist with language editing, translation, and figure formatting. After using this tool/service, the authors closely reviewed and edited the content as needed and take full responsibility for the final content of the publication.

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Conflict of interests

The authors declare no conflict of interest.

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