

Brain–lung axis and neuroimmune crosstalk in acute brain injury

Yanrui Jia · Min Liu · Ziren Tang · Yuanqing Xu

Received: 3 June 2026 / Accepted: 19 August 2026

© The Author(s) 2026

Abstract

Acute brain injury (ABI) frequently coexists with pulmonary complications, creating bidirectional interactions that can amplify secondary organ injury. This review reframes ABI-associated brain–lung crosstalk as a sequential neuroimmune relay—from generation and peripheral egress of CNS-derived signals, through systemic immune amplification and pulmonary effector injury, to reciprocal lung-to-brain feedback—and explicitly distinguishes directly supported mechanisms from emerging hypotheses. Following ABI, autonomic activation, damage-associated molecular patterns, extracellular vesicles, and peripheral immune responses may contribute to pulmonary endothelial dysfunction, innate immune activation, and alveolar-capillary barrier injury. Glymphatic and lymphatic clearance pathways are discussed as potential routes of CNS-to-systemic molecular transport, but direct evidence linking glymphatic-derived signals to pulmonary injury remains lacking. Conversely, acute pulmonary complications relevant to neurocritical illness—including ALI/ARDS, mechanical ventilation-associated injury, and pulmonary infection—may aggravate the vulnerable brain through systemic inflammation, impaired gas exchange, blood–brain barrier dysfunction, and neuroinflammatory signaling. We further evaluate candidate circulating biomarkers according to their biological source, specificity, and clinical readiness, emphasizing that currently available markers primarily reflect neural injury, endothelial dysfunction, or systemic inflammation rather than brain–lung axis injury itself. Therapeutic strategies targeting inflammation, autonomic regulation, immune modulation, microbiome-related pathways, and extracellular vesicles are assessed according to their mechanistic evidence and translational stage. By integrating directionality, evidence strength, and translational maturity, this review provides an ABI-centered framework for identifying experimentally testable relay points and priorities for future brain–lung research.

Keywords Brain–lung axis · Acute brain injury · Neuroinflammation · Neuroimmune relay · Glymphatic system · NLRP3 inflammasome · Evidence strength · Biomarkers · Extracellular vesicles

This Article in Press is shared early to give you faster access to new research. It is citable and carries a permanent DOI. The final edited version will replace it automatically.

Yanrui Jia and Min Liu are co-first authors.



Introduction

ABI remains a leading cause of death and disability worldwide. A critical challenge in managing ABI lies in the intricate brain-lung axis, where therapeutic strategies for one organ can adversely affect the other. For instance, lung-protective ventilation for ARDS may elevate intracranial pressure, while neuroprotective interventions can worsen pulmonary function. This double-hit phenomenon contributes to poor outcomes in patients with severe neurocritical illness.

Experimental and clinical studies have implicated glymphatic and lymphatic clearance systems in the peripheral appearance of CNS-derived molecules after brain injury [1, 2]. However, whether altered glymphatic transport directly delivers pathogenic DAMPs to the lung remains unknown. Accordingly, in this review, glymphatic dysfunction is considered a candidate route of CNS-to-systemic signal egress rather than an established mechanism of secondary pulmonary injury.

Pulmonary complications after ABI, including neurogenic pulmonary edema, ALI/ARDS, mechanical ventilation-associated injury, and pulmonary infection, may subsequently feed back to the vulnerable brain. We therefore narrow the lung-to-brain discussion to acute neurocritical illness rather than chronic pulmonary diseases or long-COVID syndromes, which are clinically important but outside the revised scope of this ABI-centered review.

Several recent reviews have highlighted the rapidly expanding landscape of brain–lung communication. Vilalba et al. focused on pulmonary infection-driven systemic inflammation, circulating mediators, and blood-brain barrier dysfunction, whereas Wang et al. examined pulmonary diseases and environmental exposures as contributors to neurological disorders. Yang et al. provided a broad framework of bidirectional brain–lung communication through neural, immune, microbial, and metabolic pathways, while Mascia et al. emphasized brain–lung interactions in critically ill patients, particularly acute brain injury, ARDS, and mechanical ventilation [3–6]. Against this background, the present review focuses specifically on acute brain injury as the initiating insult and addresses a more mechanistically defined question: how are injury signals generated within the injured CNS, released into the peripheral compartment, amplified by systemic immune networks, and translated into pulmonary injury, and how does subsequent lung injury feed back to the vulnerable brain? We therefore organize the evidence as a sequential neuroimmune relay, encompassing CNS signal generation and egress, systemic immune amplification, pulmonary effector injury, and reciprocal lung-to-brain feedback. Within this framework, emerging pathways such as glymphatic dysfunction are considered according to the strength of available evidence rather than presented as established mechanisms. By linking individual relay nodes to biomarkers, therapeutic targets, and major evidence gaps, this review aims to provide an ABI-centered framework for mechanistic investigation and translational development.

Pathophysiological mechanisms of the brain–lung axis: a neuroimmune perspective

Neural pathways as immune regulators

The autonomic nervous system, particularly the vagus nerve, regulates bidirectional immune signaling between the brain and lungs. The cholinergic anti-inflammatory pathway (CAP) is central to this regulation. Vagal efferent fibers release acetylcholine, which binds to $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChR) on pulmonary macrophages and suppresses TNF- α , IL-1 β , and IL-6 production, thereby limiting acute lung inflammation [7–9]. Conversely, sympathetic overactivation after ABI can increase circulating catecholamines, damage the pulmonary endothelial glycocalyx, increase vascular permeability, and prime immune cells for exaggerated inflammatory responses [10, 11]. The hypothalamic–pituitary–adrenal axis further modulates systemic inflammation through glucocorticoid signaling [12]. Pulmonary afferent inputs are integrated in the nucleus tractus solitarius and can influence descending autonomic and immune-regulatory responses [9, 13].

Immune pathways

Following ABI, injured neural, glial, endothelial, and immune compartments release heterogeneous damage-associated molecular patterns (DAMPs), including HMGB1, S100 proteins, extracellular ATP, cell-free nucleic acids, histones, and mitochondrial components [14–20]. These signals may reach cerebrospinal fluid or the systemic circulation through blood–brain barrier disruption, meningeal lymphatic drainage, or other clearance routes. Once present in the circulation, DAMPs can activate Toll-like receptor and inflammasome-associated pathways in neutrophils, monocytes, and alveolar macrophages. Pulmonary activation promotes IL-1 β and IL-18 maturation, reactive oxygen species generation, protease release, and alveolar-capillary barrier failure. However, direct organ-of-origin tracing remains limited, so individual circulating DAMPs should not be assumed to arise exclusively from the injured CNS.

Peripheral myeloid responses provide a more directly testable cellular bridge. In experimental TBI, IL-1-dependent emergency myelopoiesis expands inflammatory monocytes that infiltrate both the brain and lungs and amplify secondary injury [21]. Neutrophils can further injure cerebral and pulmonary barriers through reactive oxygen species, proteases, and neutrophil extracellular traps (NETs). In TBI-associated acute lung injury, inhibition of S100B-mediated NET formation reduced pulmonary damage, while DNase I-mediated NET degradation attenuated neurogenic pulmonary edema after experimental subarachnoid hemorrhage [22, 23]. Border-associated macrophages in the meninges, perivascular spaces, and choroid plexus regulate immune surveillance at CNS interfaces, although their specific contribution to remote pulmonary injury remains uncertain [24].

Adaptive immunity may influence the persistence and resolution of this relay. Blood–brain barrier disruption and antigen release after ABI can recruit CD4⁺ and CD8⁺ T cells. Th17-derived IL-17 A may promote endothelial activation and neutrophil recruitment, whereas regulatory T cells can restrain microglial and macrophage activation through IL-10 and TGF- β . CD8⁺ T cells may aggravate neuronal and endothelial injury, and B cells may contribute through antigen presentation, cytokine production, or autoantibody formation. Immune checkpoints such as PD-1/PD-L1 may further regulate the balance between tissue-protective resolution and persistent neuroinflammation. These functions are supported in brain-injury models, but their direct roles in ABI-associated brain–lung crosstalk remain incompletely defined [25–28].

The repertoire of DAMPs potentially involved in inter-organ signaling extends beyond HMGB1, S100 proteins, and extracellular ATP. Mitochondrial DAMPs (mtDAMPs) are of particular interest because mitochondria contain evolutionarily conserved immunostimulatory molecules, including mitochondrial DNA (mtDNA) and N-formyl peptides. In patients with TBI or aneurysmal subarachnoid hemorrhage, circulating cell-free mtDNA has been detected at increased concentrations in both cerebrospinal fluid and serum within the early phase after injury, with CSF mtDNA levels associated with injury severity and the IL-6 response [15]. Outside the isolated ABI setting, circulating mtDNA can activate TLR9-dependent innate immune signaling, whereas mitochondrial N-formyl peptides signal through formyl peptide receptor 1 (FPR1); experimental and human studies implicate both pathways in systemic inflammation and acute pulmonary injury [16].

Cell-free nuclear DNA and extracellular histones represent another class of injury-associated signals. Plasma cell-free DNA is increased after severe TBI and has been associated with injury severity and mortality [17]. Extracellular histones released during major tissue injury can exert direct cytotoxic and pro-inflammatory effects on the pulmonary endothelium and have been implicated experimentally in trauma-associated lung injury [18]. Heat-shock proteins, particularly extracellular HSP70, may also function as stress-associated signals: circulating HSP70 increases after severe TBI, and extracellular HSP70 has been reported to engage CD14/TLR2/TLR4-associated inflammatory signaling, although this extracellular HSP70 signaling literature remains mechanistically debated [19–20].

However, the relevance of these DAMPs to ABI-associated brain–lung crosstalk remains incompletely defined. Current evidence generally demonstrates either their release after brain injury or their capacity to promote systemic or pulmonary inflammation in other injury models, rather than direct trafficking of brain-derived mtDNA,

nuclear DNA, histones, or HSPs from the injured CNS to the lung. These molecules should therefore be regarded as candidate inter-organ mediators rather than established brain-to-lung signals.

Sex-related differences in neuroimmune signaling are considered in Sect. “[Sex as a biological modifier of neuroimmune crosstalk](#)”.

Microbial pathways

The microbiome modulates the brain–lung axis through metabolic, immune, and neural signals, forming a gut–lung–brain triad.

Intestinal barrier disruption and bacterial translocation ABI can disrupt intestinal tight-junction integrity and permit microbial products such as lipopolysaccharide (LPS) and peptidoglycan to enter the circulation, where they may prime peripheral and pulmonary macrophages through TLR4-associated signaling [29, 30]. A more specific gut–immune–brain pathway has been demonstrated after cardiac arrest and cardiopulmonary resuscitation. Early *Enterobacter* expansion increased intestinal LPS exposure, activated TLR4 and triggering receptor expressed on myeloid cells 1 (TREM-1) in small-intestinal macrophages, and promoted the migration of TREM-1-positive gut-derived macrophages into the injured brain [31]. Related post-stroke and cerebral ischemia–reperfusion studies connect dysbiosis and barrier disruption with LPS exposure, intestinal TLR4 signaling, blood–brain barrier impairment, and microglial activation [32, 33]. These findings support gut-derived immune amplification, but they do not establish a complete gut-to-lung-to-brain causal chain in ABI.

Short-chain fatty acids (SCFAs) as immunomodulators Butyrate, a major SCFA produced by commensal bacteria, can modulate inflammatory responses. In experimental LPS-induced acute lung injury, sodium butyrate attenuated pulmonary inflammation and injury [34]. Related GPR43 and β -arrestin-2/NF- κ B pathways have been studied in vascular remodeling and inflammatory organ-injury models [35–36]. These data support SCFA-related immunomodulation as a plausible but indirect pathway in ABI-associated brain–lung crosstalk.

Pulmonary dysbiosis Mechanical ventilation and aspiration can disrupt the respiratory microbiome in patients with ABI and promote colonization by pathogenic bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This dysbiosis may amplify pulmonary inflammation and increase the risk of ARDS, which can subsequently worsen neurological outcomes [37, 38]. ABI-associated autonomic dysregulation and immunosuppression further increase susceptibility to pulmonary infection and reinforce a bidirectional cycle of organ injury [39].

Neurovascular unit dysfunction and vascular remodeling

The neurovascular unit comprises endothelial cells, pericytes, astrocytic endfeet, neurons, and extracellular-matrix components that jointly regulate blood–brain barrier integrity and vascular signaling. Experimental CNS-injury studies show that altered pericyte–endothelial interactions and microRNA-dependent pathways can modify neuroinflammation, angiogenesis, and functional recovery. Pericyte-specific deletion of miR-15a/16–1 promoted cerebral angiogenesis and recovery after ischemic stroke, while inhibition or deletion of the same microRNA cluster reduced neuroinflammation and improved outcomes after experimental TBI [40, 41]. These findings identify the neurovascular unit as a plausible regulator of systemic signal release and lung-to-brain susceptibility. Direct evidence that neurovascular-unit dysfunction independently causes remote pulmonary injury, however, remains limited.

Sex as a biological modifier of neuroimmune crosstalk

Biological sex modifies neurovascular and immune responses after acute CNS injury. Experimental studies report sex- and age-dependent differences in cytokine expression, astrocyte–vessel interactions, cerebrospinal-fluid inflammation, microglial states, and responses to miR-15a/16–1 inhibition [42–45]. Pulmonary inflammation

and vascular responses during critical illness may also differ by sex, although associations with outcomes are inconsistent. Sex should therefore be treated as a context-dependent biological modifier rather than a fixed determinant. Brain–lung studies should report sex-disaggregated results and test sex-by-injury or sex-by-treatment interactions when adequately powered.

Collectively, neural, immune, microbial, and clearance-related pathways form an integrated but unevenly supported neuroimmune network. The revised framework therefore distinguishes established mechanisms from candidate or hypothesized relay routes, and it links each pathway to evidence strength, major limitations, and translational relevance.

Mechanisms of lung injury after acute brain injury

Sympathetic storm and neurogenic pulmonary edema

Severe ABI can evoke a marked sympathoadrenal response, although catecholamine magnitude and timing vary by injury type, severity, and model. In a feline fluid-percussion TBI model, plasma norepinephrine and epinephrine rose transiently by up to approximately 100-fold and 500-fold, respectively, within seconds of injury [46]. In clinical ABI, sympathetic overactivation is better interpreted as a context-dependent contributor to pulmonary vascular stress than as a uniform quantitative response. High shear stress and catecholamine excess can damage the pulmonary endothelial glycocalyx, alter endothelial tight-junction proteins, and increase vascular permeability. In a rat controlled cortical-impact model, cervical sympathetic trunk transection restrained sympathetic and cardiac overactivation and preserved the endothelial glycocalyx and tight-junction proteins. The intervention also reduced Evans blue extravasation, the lung wet-to-dry ratio, and bronchoalveolar-lavage protein levels [11]. Together, these findings support sympathetic activation as an important brain-to-lung effector pathway while retaining clear model-specific boundaries.

Potential sex-related modification of pulmonary responses is considered together with neurovascular and immune effects in Sect. “[Sex as a biological modifier of neuroimmune crosstalk](#)”.

Inflammasomes and DAMP-driven lung injury

Candidate CNS- or injury-associated DAMPs, including eNAMPT, S100A8/A9, HMGB1, ATP, cell-free nucleic acids, and mitochondrial components, engage overlapping innate-sensing pathways [14–20, 47]. NLRP3 activation promotes caspase-1-dependent maturation of IL-1 β and IL-18 and gasdermin D-mediated pyroptosis. Clinical biomarker studies in TBI and ARDS support inflammatory and vascular activation, but they do not establish the CNS origin or brain–lung specificity of every circulating DAMP [48]. In addition to NLRP3, AIM2 can detect cytosolic double-stranded DNA, cGAS–STING can induce type I interferon and NF- κ B-dependent responses to cytosolic DNA, and NAIP–NLRC4 senses bacterial flagellin and type III secretion-system components [49–52]. These pathways may operate in parallel or interact with NLRP3-associated pyroptosis. Their direct involvement in sterile ABI-associated lung injury, especially that of NLRC4, remains substantially less established than that of NLRP3.

Disease-relevant models support a contribution of pulmonary NLRP3 signaling to secondary lung injury after ABI. NLRP3 deletion attenuated pulmonary inflammation after experimental cerebral ischemia, while the selective small-molecule inhibitor MCC950 provides proof of direct pharmacological NLRP3 inhibition in experimental systems [49, 53]. Pharmacologically distinct agents modulate this pathway indirectly. In a rat free-fall TBI model, fingolimod reduced pulmonary NLRP3, ASC, and caspase-1 activation, oxidative stress, IL-1 β release, capillary leakage, edema, and histopathological injury [54]. In a rat lateral fluid-percussion model, the TREM-1 inhibitor LP17 reduced NLRP3 activation, pyroptosis, lung pathology, edema, and bronchoalveolar-lavage protein. Ondansetron produced similar protection and was associated with suppression of TREM-1/NLRP3-related signaling [55]. In a mouse controlled cortical-impact model, remimazolam suppressed ATF3-dependent NLRP3

activation, reduced alveolar epithelial pyroptosis, and preserved ZO-1, E-cadherin, and blood–air barrier integrity [56]. Fingolimod and remimazolam should therefore be described as indirect modulators rather than direct NLRP3 inhibitors.

Glymphatic dysfunction as a hypothesized route of CNS-to-systemic signal egress

The glymphatic system facilitates perivascular exchange between cerebrospinal fluid and interstitial fluid and contributes to the clearance of solutes from the brain. Experimental brain-injury studies provide evidence that this pathway can influence the appearance of CNS-derived molecules in the peripheral circulation. In a mouse model of traumatic brain injury, manipulation of glymphatic function markedly altered circulating concentrations of brain injury biomarkers, supporting a role for glymphatic transport in brain-to-blood molecular clearance [2]. Glymphatic dysfunction has also been demonstrated after subarachnoid hemorrhage. Experimental restoration or preservation of glymphatic function, including treatment with nimodipine, has been associated with reduced early brain injury [1]. Importantly, however, these studies primarily evaluated intracranial glymphatic function and neurological injury and did not establish pulmonary consequences of glymphatic modulation. Thus, the proposed sequence of brain injury, altered glymphatic/lymphatic transport, systemic release of CNS-derived DAMPs, pulmonary accumulation, and lung injury currently represents a biologically plausible but unproven pathway. The principal brain-to-lung mechanisms are summarized in Fig. 1. Experimentally supported pathways

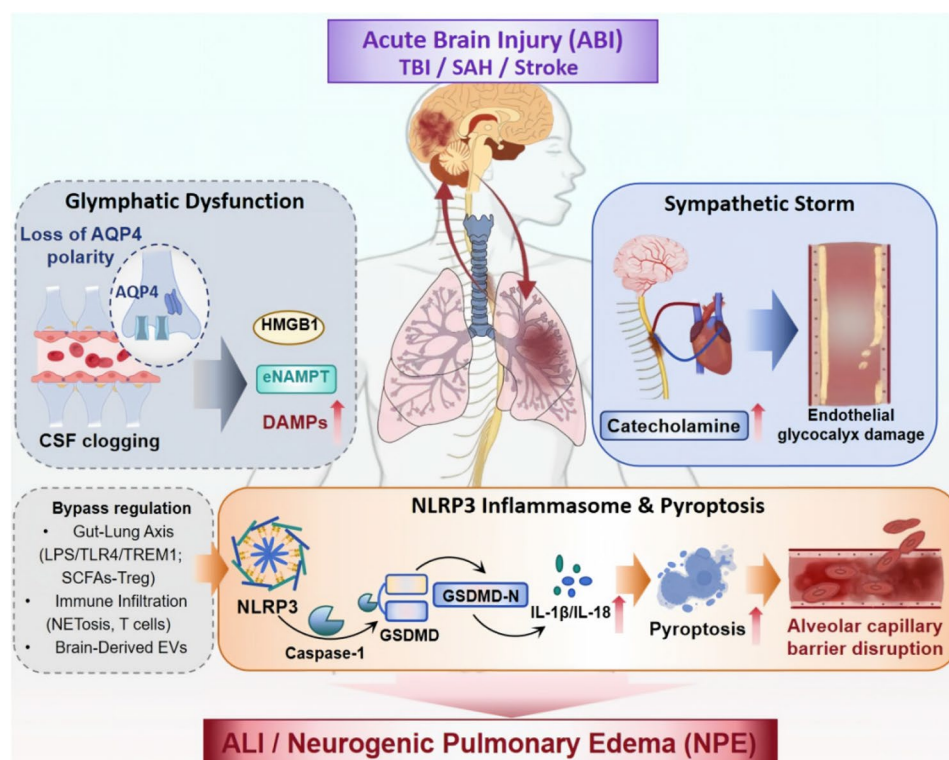


Fig. 1 Proposed brain-to-lung neuroimmune relay after acute brain injury. Acute brain injury, including traumatic brain injury, subarachnoid hemorrhage and stroke, may promote pulmonary injury through interacting autonomic, innate-immune and barrier pathways. Disease-relevant preclinical evidence supports sympathetic overactivation and catecholamine-associated pulmonary endothelial glycocalyx injury, as well as pulmonary NLRP3 activation, caspase-1-dependent cleavage of GSDMD, IL-1 β /IL-18 release, pyroptosis and alveolar-capillary barrier disruption. Glymphatic dysfunction with loss of AQP4 polarity is shown as a proposed route that may increase systemic exposure to DAMPs such as HMGB1 and eNAMPT; direct tracing from glymphatic clearance to lung injury has not yet been established. Gut-lung signaling, infiltrating immune cells and brain-derived EVs are depicted as potential auxiliary routes

include sympathetic overactivation, pulmonary NLRP3 inflammasome activation, pyroptosis, and alveolar-capillary barrier disruption, whereas the proposed glymphatic/lymphatic-to-lung route remains hypothetical.

Reciprocal lung-to-brain injury in acute neurocritical illness

Pulmonary complications arising after acute brain injury can subsequently feed back to the vulnerable brain. This reciprocal phase of brain–lung crosstalk is particularly relevant in patients who develop ALI/ARDS, neurogenic pulmonary edema, prolonged mechanical ventilation, or pulmonary infection. Rather than representing an independent primary neurological insult, these pulmonary complications may aggravate secondary brain injury through systemic inflammation, impaired gas exchange, blood–brain barrier (BBB) dysfunction, and ventilation-associated neuroinflammatory signaling.

ALI/ARDS: systemic inflammation, BBB dysfunction, and secondary brain injury

ALI and ARDS are frequently accompanied by acute neurological dysfunction and may be followed by persistent cognitive impairment. Clinical studies support cognitive sequelae after ARDS. Experimental lung-injury models implicate circulating IL-6, TNF- α , DAMPs, and extracellular vesicles in blood–brain barrier disruption, neurovascular dysfunction, glial activation, and neuronal injury [57–61]. These mediators provide plausible routes of lung-to-brain signaling, although their relative contributions in patients with pre-existing ABI remain uncertain.

This interaction may be particularly important in patients with ABI because the blood–brain barrier, neurovascular unit, and cerebral autoregulation are already vulnerable. Pulmonary edema and impaired gas exchange can produce hypoxemia and carbon dioxide disturbances that aggravate secondary cerebral injury. Lung-derived cytokines, DAMPs, and extracellular-vesicle cargoes may promote pro-inflammatory microglial and astrocytic programs through TLR4/NF- κ B, inflammasome, and related signaling. Conversely, IL-10, TGF- β , α 7nAChR signaling, and reparative extracellular-vesicle cargoes may favor inflammatory resolution and tissue repair. The common M1-like/M2-like terminology provides a simplified comparison, but in vivo glial responses form a context- and time-dependent continuum. Direct evidence linking individual lung-derived signals to defined glial states after ABI remains limited.

Long-term cognitive impairment reported among ARDS survivors further suggests that neurological consequences of an acute pulmonary insult can persist beyond the critical illness itself [57–58]. These clinical observations support the relevance of lung-to-brain signaling, although they do not by themselves establish the contribution of individual inflammatory pathways.

Mechanical ventilation and ventilator-associated brain injury

Mechanical ventilation is frequently required in patients with severe ABI and pulmonary complications. Although essential for gas exchange, injurious ventilation can generate systemic signals that affect the brain. Preclinical ventilation models implicate circulating extracellular vesicles, IL-6, ATP–P2Y1 signaling, blood–brain barrier dysfunction, microglial activation, and neuronal injury [59, 60, 62]. In experimental ventilator-induced lung injury, inhibition of IL-6 reduced neuronal injury, supporting a pathway-specific inflammatory contribution [60]. The clinical magnitude of these mechanisms in ventilated patients with ABI nevertheless remains uncertain.

Additional experimental work has implicated ATP production, P2Y1 receptor signaling, and altered dopaminergic activity in ventilation-associated brain injury. However, these pathways have primarily been demonstrated in animal models and their contribution to neurological injury in mechanically ventilated patients remains uncertain. Accordingly, they should be regarded as candidate mechanisms rather than established clinical pathways.

Pulmonary infection and ventilator-associated pneumonia

Patients with severe ABI are particularly susceptible to pulmonary infection because of impaired airway protection, aspiration, mechanical ventilation, and ABI-associated immune dysfunction. Ventilator-associated pneumonia is common in neurocritical patients and can amplify systemic inflammation and worsen respiratory dysfunction, creating conditions that may aggravate secondary brain injury [39, 63].

Lung-to-brain effects during pulmonary infection are likely multifactorial. Systemic cytokines, microbial products, extracellular vesicles, hypoxemia, and altered cerebral oxygen delivery may further disrupt an already vulnerable blood–brain barrier and activate glial inflammatory responses. However, direct tracing of specific infection-derived mediators from the lung to secondary neuronal injury in ABI remains limited. Pulmonary infection should therefore be considered a clinically important amplifier of the reciprocal relay rather than a fully resolved molecular pathway. The principal lung-to-brain feedback pathways are summarized in Fig. 2. Pulmonary inflammatory mediators, hypoxemia, and lung-derived extracellular vesicles may converge on blood–brain barrier disruption, pro-inflammatory microglial activation, and secondary neuronal injury. Evidence levels, experimental models, and major limitations of the representative brain–lung mechanisms are summarized in Table 1.

Candidate biomarkers of biological processes involved in brain–lung crosstalk

Circulating biomarkers may provide complementary information about the biological processes participating in brain–lung crosstalk; however, no currently available biomarker has been validated as specific for brain–lung axis injury. Existing Critical Illness Lung–Brain Axis Biomarker (CILBA) data and related critical-illness biomarker studies support overlapping inflammatory, vascular, and neurotrauma-associated signals in TBI and ARDS, but not an axis-specific diagnostic signature [48].

Candidate biomarkers can be broadly categorized into markers of systemic innate immune activation and DAMP signaling (e.g., eNAMPT and S100A8/A9), endothelial activation and vascular injury (e.g., Ang-2 and PSGL-1), and neural tissue injury (e.g., GFAP, NfL, and tau). The first two categories are particularly vulnerable to confounding by sepsis, shock, mechanical ventilation, and multiorgan failure, whereas neural biomarkers may provide greater tissue specificity but cannot determine whether neurological injury is primary or secondary to pulmonary dysfunction.

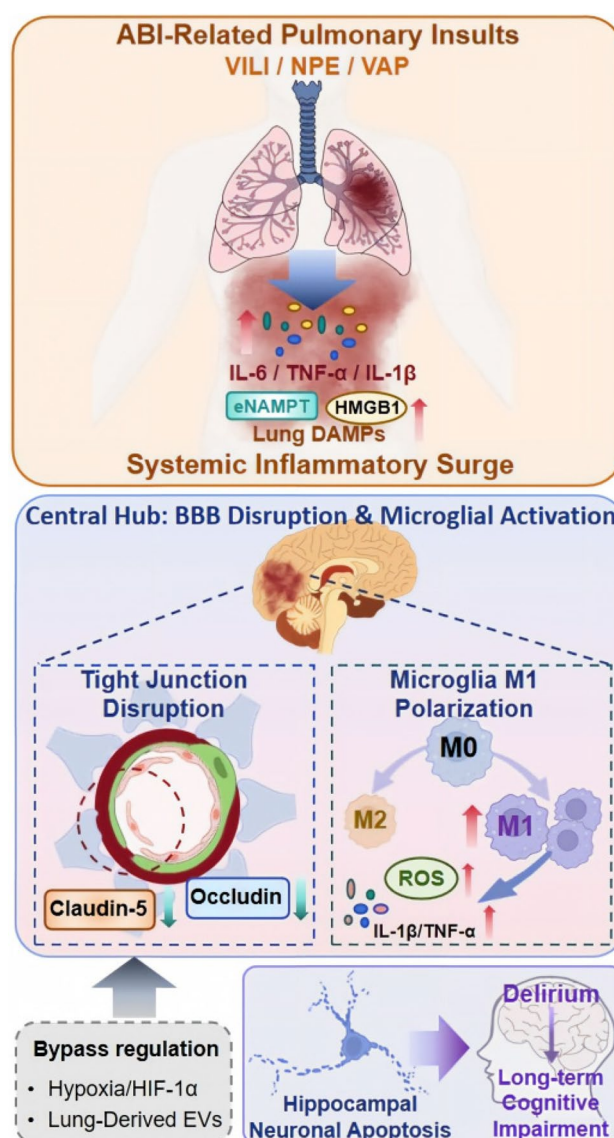
An exploratory clinical study using a CILBA panel reported overlapping elevations of inflammatory, vascular, and neurotrauma-associated biomarkers in patients with TBI and ARDS, with additional elevations among mechanically ventilated patients [48]. Although these observations support shared biological responses across neurological and pulmonary critical illness, they do not establish a biomarker signature that distinguishes brain–lung crosstalk from generalized critical illness.

Among the individual neural injury markers, GFAP, UCH-L1, NfL, and S100B differ in cellular origin and intended clinical use. GFAP is enriched in astroglial tissue, whereas UCH-L1 reflects neuronal cell-body injury; their combined measurement has received regulatory clearance to aid the detection of intracranial lesions in selected patients with mild TBI. NfL primarily reflects neuroaxonal injury and may provide prognostic information over a longer temporal window. S100B has also been used to support CT decision-making, but extracranial sources limit its brain specificity. These markers therefore indicate distinct aspects of neural injury, but none can determine whether neurological injury is primary or secondary to ARDS, hypoxemia, or systemic inflammation. Moreover, none of these biomarkers is specific for brain–lung axis injury [64].

Conversely, eNAMPT, S100A8/A9, Ang-2, and PSGL-1 predominantly reflect inflammatory, endothelial, or leukocyte activation. Although these processes are biologically relevant to brain–lung crosstalk, they are also prominent features of sepsis, ARDS, shock, and other forms of critical illness, substantially limiting their diagnostic specificity.

Future biomarker studies should move beyond individual circulating proteins and test temporally resolved multimarker profiles in prospectively phenotyped ABI populations. One strategy would combine CNS-enriched

Fig. 2 Proposed lung-to-brain feedback following pulmonary complications of acute brain injury. Ventilator-induced lung injury, neurogenic pulmonary edema and ventilator-associated pneumonia can generate a systemic inflammatory surge containing cytokines and pulmonary DAMPs. These signals, together with hypoxia/HIF-1 α and lung-derived EVs, may reduce claudin-5 and occludin expression, disrupt the BBB and shift microglia towards pro-inflammatory states, with increased ROS, IL-1 β and TNF- α . Microglia are depicted using simplified M0/M1/M2 labels; in vivo states exist on a continuum and are better interpreted as pro-inflammatory and reparative phenotypes. These changes may contribute to hippocampal neuronal apoptosis, delirium and long-term cognitive impairment. Direct tracing of lung-derived signals to these neurological endpoints remains limited, and the pathway should be interpreted as a mechanistic framework rather than an established causal sequence



injury markers with pulmonary, endothelial, and systemic immune indicators and determine whether their temporal trajectories track secondary pulmonary or neurological injury. Cell-of-origin-defined extracellular vesicles may extend this approach because their protein and regulatory non-coding RNA cargoes, including microRNAs, long non-coding RNAs, and circular RNAs, can reflect inflammatory, endothelial, and repair-related states. However, vesicle heterogeneity, isolation methods, cargo normalization, and limited human brain–lung validation currently constrain specificity [65]. All composite approaches require comparison with isolated ABI, isolated ARDS, sepsis, and other critical-illness controls before they can be interpreted as biomarkers of brain–lung-axis injury.

Sex should also be considered when evaluating candidate biomarkers and therapeutic interventions. Sex-dependent differences in immune, endothelial, and neural injury responses may influence circulating biomarker concentrations and pharmacological effects. Future biomarker studies and interventional experiments should therefore report sex-disaggregated results and, where adequately powered, assess sex-by-treatment or sex-by-biomarker interactions rather than treating sex solely as an adjustment covariate. The biological sources, supporting evidence, major confounders, and clinical readiness of the principal candidate biomarkers are summarized in Table 2.

Table 1 Evidence grading of representative mechanisms in the brain–lung axis

Mechanism	Model	Evidence level	Reference
Sympathetic activation-mediated pulmonary endothelial glycocalyx injury and increased vascular permeability	Rat controlled cortical impact model; cervical sympathetic trunk transection and endothelial shear-stress experiments	Direct preclinical evidence from a disease-relevant model	[11]
Pulmonary NLRP3 activation and pyroptosis after traumatic brain injury	Rat free-fall TBI model; pharmacological intervention with fingolimod	Direct preclinical evidence	[54]
TREM-1-mediated amplification of NLRP3 activation and pulmonary pyroptosis	Rat lateral fluid-percussion TBI model; LP17 and ondansetron interventions	Direct preclinical evidence	[55]
Gut LPS-TLR4-TREM1 signaling and inflammatory macrophage trafficking	Cardiac arrest/cardiopulmonary resuscitation model with photoconversion-based lineage tracing	Direct evidence for gut-to-brain signaling; indirect evidence for ABI-related brain–lung injury	[31]
Glymphatic dysfunction, increased systemic DAMP exposure, and secondary pulmonary injury	Mouse SAH glymphatic model and mechanistic perspective	Emerging hypothesis; direct brain-to-lung tracing evidence is lacking	[1, 2]
Extracellular vesicle-mediated inter-organ inflammatory signaling	Experimental ALI and ventilation-induced lung injury models	Supportive preclinical evidence	[59]

Evidence levels describe the proximity of the cited experiments to the proposed acute-brain-injury brain–lung mechanism and are not formal certainty scores. ‘Direct’ denotes pathway interrogation in a disease-relevant preclinical model; ‘indirect’ denotes mechanistic support from a related organ-to-organ model; and ‘emerging hypothesis’ denotes a plausible route that lacks direct brain-to-lung tracing. Reference numbers correspond to the manuscript reference list

ABI acute brain injury, *ALI* acute lung injury, *DAMP* damage-associated molecular pattern, *LPS* lipopolysaccharide, *LP17* a peptide TREM-1 inhibitor, *NLRP3* NOD-, LRR- and pyrin domain-containing protein 3, *SAH* subarachnoid hemorrhage, *TBI* traumatic brain injury, *TLR4* Toll-like receptor 4, *TREM-1* triggering receptor expressed on myeloid cells 1

Intervention strategies targeting the neuroimmune axis

Anti-inflammatory and immune modulation

Targeting DAMP and NLRP3-associated signaling represents a potential strategy for ABI-associated lung injury. MCC950 directly inhibits NLRP3 in experimental systems, whereas fingolimod and remimazolam act through broader upstream pathways and should not be classified as direct NLRP3 inhibitors [53, 54, 56]. Extracellular NAMPT functions as a DAMP and TLR4 ligand. Neutralizing eNAMPT can suppress NF- κ B signaling, inflammatory-cell recruitment, and pulmonary vascular injury in preclinical ALI/ARDS models, although direct evidence in TBI-associated lung injury remains limited [66, 67]. TREM-1 expressed on pulmonary myeloid cells amplifies DAMP-induced signaling through DAP12/SYK and NF- κ B/MAPK, thereby promoting NLRP3 priming and pyroptosis. In experimental TBI-associated lung injury, LP17 and ondansetron reduced TREM-1/NLRP3-associated signaling, pyroptosis, edema, and barrier injury [55].

Vagus nerve regulation

Vagus nerve stimulation (VNS) activates efferent vagal pathways and the CAP. Acetylcholine engages $\alpha 7$ nAChR on splenic and pulmonary macrophages and microglia, suppressing NF- κ B and NLRP3 activation and reducing TNF- α , IL-1 β , and IL-6 release [7–9]. In experimental lung inflammation, vagal signaling reduces pulmonary macrophage activation, inflammatory mediator release, and pulmonary edema. In experimental stroke and TBI, VNS attenuates neurological deficits, cerebral edema, oxidative stress, and neuronal apoptosis through $\alpha 7$ nAChR-associated NF- κ B/NLRP3 regulation [68, 69]. Standardized cognitive outcomes have not been assessed consistently in the relevant TBI studies, so VNS should not be described as having established cognitive benefits. Transcutaneous auricular VNS has shown cytokine-lowering effects in experimental inflammation and early clinical critical-illness studies, but direct dual-organ efficacy in ABI remains to be tested [70, 71].

Table 2 Evidence and translational characteristics of candidate biomarkers for brain–lung axis injury

Panel A. Disease setting, study model, and key findings			Key findings	Reference
Biomarker	Disease condition	Experimental/clinical model		
eNAMPT	TBI, ARDS, trauma, and critical illness	Human TBI/ARDS biomarker cohorts and preclinical ALI models; no validated brain–lung axis diagnostic model.	Circulating eNAMPT increases in critical illness. It is associated with mechanical-ventilation exposure and adverse clinical burden, while neutralization attenuates inflammatory signaling and lung injury in preclinical models.	[48, 66, 67]
S100A8/A9 (calprotectin)	ARDS and systemic inflammation	Human critical-illness cohorts and S100A9-deficient LPS-induced ALI models.	Reflects myeloid activation. S100A9 amplifies TLR4/MyD88/NF- κ B signaling, macrophage polarization, and pyroptosis in experimental ALI.	[47, 48]
HMGB1	SAH, ALI, and neurogenic pulmonary edema	Clinical association studies after SAH and experimental ALI models; no direct lymphatic-to-lung tracing model.	Associated with poor outcome after SAH and promotes inflammatory signaling and macrophage polarization in ALI. Its brain-to-lung route remains unproven.	[14, 47]
IL-6, IL-1 β , TNF- α , and IL-1Ra	TBI and ARDS	Human TBI/ARDS serum biomarker cohorts, including mechanically ventilated patients.	Reflect systemic and neuroinflammatory activation; IL-1Ra may represent a compensatory anti-inflammatory response. Values overlap substantially with ordinary critical illness.	[48]
Angiopoiectin-2 and PSGL-1	ARDS, sepsis-associated endothelial dysfunction, and ALI	Prospective human sepsis/ARDS cohorts for Angiopoiectin-2 and experimental ALI models for PSGL-1-related adhesion.	Angiopoiectin-2 is prognostic for ARDS and mortality in sepsis; PSGL-1 participates in leukocyte adhesion and experimental lung injury. Direct ABI-linked clinical evidence is limited.	[48]
CILBA composite panel	TBI and ARDS	Cross-sectional serum study of 97 TBI patients, 39 ARDS patients, and 46 healthy controls.	Most panel markers increased in both disease groups; PSGL-1 increased only in ARDS and GFAP only in TBI. Mechanical ventilation was associated with broader biomarker elevations.	[48]
GFAP	TBI and acute brain injury	Multicenter clinical TBI cohorts and post-acute neurological cohorts.	An established astrocytic-injury marker that supports CNS injury assessment, but does not demonstrate pulmonary involvement or brain–lung directionality.	[48, 64]
UCH-L1	TBI and intracranial injury	Multicenter observational TBI cohort used to predict the absence of intracranial injury on CT.	Complements GFAP in blood-based TBI assessment. Evidence for pulmonary involvement or inter-organ signaling is absent.	[64]
NfL	TBI, critical illness, and secondary neuroaxonal injury	Human neurological and critical-illness association studies; no validated brain–lung axis-specific model.	Reflects axonal injury and may provide prognostic information. Its slower kinetics may complement acute markers such as GFAP and UCH-L1.	[48, 64]
Tau protein	ARDS, critical illness, and secondary neuroaxonal injury	Human cross-sectional biomarker cohorts; limited direct mechanistic validation for lung-to-brain injury.	Indicates neuronal or axonal injury, but does not identify the cause or direction of organ crosstalk.	[48]
S100B	TBI, ALI, and general CNS injury	Clinical and experimental ALI studies, including experimental TBI-associated lung injury.	Increases after TBI and ALI. S100B-related neutrophil extracellular trap formation has been linked to pulmonary injury in experimental TBI-associated ALI.	[22, 61]
Brain-derived and lung-derived extracellular vesicles/exosomes	ABI, ARDS, and experimental inter-organ signaling	Neuronal–microglial communication models, human stroke serum-exosome studies, and airway EV-to-microglia models.	Selected EV cargoes may reflect neuroinflammatory status or influence recipient cells, but human brain–lung axis validation and assay standardization remain limited.	[59, 65]

Table 2 (continued)

Panel B. Biological source, evidence, specificity, and clinical readiness				
Biomarker	Predominant source	Evidence in brain–lung axis injury	Specificity and major confounders	Clinical readiness
eNAMPT	Activated leukocytes, endothelial cells, adipocytes, and injured tissues; extracellular NAMPT can act as a DAMP.	Elevated circulating eNAMPT has been associated with trauma, critical illness, and ARDS. Neutralization reduces preclinical lung injury through modulation of TLR4/NF- κ B and Akt/mTORC2 signaling, but TBI-specific evidence remains limited.	Low. It is not brain-derived or lung-specific and is also increased in sepsis, trauma, pancreatitis, and other systemic inflammatory states.	Translational biomarker and therapeutic candidate. No validated cutoff or prospective test exists for brain–lung axis injury. [48, 66, 67]
S100A8/A9 (calprotectin)	Activated neutrophils, monocytes, and other myeloid cells.	Calprotectin and S100A9 signaling are associated with critical illness and experimental ALI. S100A9 can amplify TLR4/MyD88/NF- κ B signaling, macrophage polarization, and pyroptosis.	Low. It primarily reports myeloid activation and can be elevated in infection, sepsis, COVID-19, and non-neurological lung inflammation.	Research-stage prognostic candidate. Not validated for distinguishing ABI-associated lung injury from ordinary critical illness. [47, 48]
HMGB1	Necrotic or stressed cells and activated innate immune cells; tissue of origin is not organ-specific in plasma.	HMGB1 is associated with poor outcome after SAH and participates in experimental ALI through inflammatory signaling and macrophage polarization. A direct glymphatic-to-lung route is unproven.	Low. It is a broad alarmin increased in trauma, sepsis, infection, ischemia, and tissue necrosis.	Investigational. No brain–lung axis-specific assay, cutoff, or prospective clinical validation. [14, 47]
IL-6, IL-1 β , TNF- α , and IL-1Ra	Leukocytes, endothelial cells, epithelial cells, and injured tissues across organs.	These cytokines reflect systemic and neuroinflammatory activation in TBI and ARDS. IL-1Ra may indicate a compensatory anti-inflammatory response, but the group is not organ-specific.	Very low. Levels are strongly affected by sepsis, infection, mechanical ventilation, sedation, surgery, and general critical illness.	Routine clinical assays exist for several members, but none is clinically ready to diagnose brain–lung axis injury. [48]
Angiopoietin-2 and PSGL-1	Angiopoietin-2: activated endothelial cells and Weibel-Palade bodies. PSGL-1: circulating leukocytes and platelet-leukocyte interfaces.	Angiopoietin-2 is prognostic for ARDS and mortality in critically ill patients with sepsis. PSGL-1 participates in leukocyte adhesion and experimental ALI; direct ABI-linked clinical evidence is limited.	Low. Angiopoietin-2 reflects generalized endothelial activation, whereas PSGL-1 reflects leukocyte adhesion. Both are confounded by sepsis and vascular injury.	Angiopoietin-2 is an early translational prognostic candidate. PSGL-1 remains preclinical or exploratory. Neither is validated for the brain–lung axis. [48]
CILBA composite panel	A serum panel integrating DAMPs, cytokines, vascular markers, and neurotrauma markers; no single cellular source.	A cross-sectional study compared 97 TBI patients, 39 ARDS patients, and 46 healthy controls. Most markers increased in both disease groups; PSGL-1 increased only in ARDS and GFAP only in TBI. Mechanical ventilation was associated with broader biomarker elevations.	Limited. Overlap between TBI and ARDS and sensitivity to mechanical ventilation reduce attribution. Healthy controls do not establish discrimination from sepsis or other critical illnesses.	Early clinical discovery stage. External validation, longitudinal sampling, diagnostic performance metrics, and clinically usable cutoffs are required. [48]
GFAP	Astrocytes and astrocytic processes.	Serum GFAP is an established marker of astrocytic injury and supports CNS injury assessment after TBI. It provides anatomical information that inflammatory markers lack, but does not demonstrate lung involvement.	Moderate-to-high for astrocytic/CNS injury, but low for brain–lung axis injury. It can be affected by injury severity and extracranial factors.	Clinically available for selected TBI assessment. Not prospectively validated as a brain–lung axis biomarker. [48, 64]
UCH-L1	Neuronal cell bodies and axons.	UCH-L1 complements GFAP in blood-based assessment of intracranial injury and prediction of CT findings after TBI. Evidence for pulmonary involvement or inter-organ signaling is absent.	Moderate for neuronal injury, but not specific for ABI etiology or brain–lung axis injury.	Clinically available in selected TBI testing contexts. No brain–lung axis-specific validation. [64]

Table 2 (continued)

Panel B. Biological source, evidence, specificity, and clinical readiness				
Biomarker	Predominant source	Evidence in brain–lung axis injury	Specificity and major confounders	Clinical readiness
NfL	Axonal cytoskeleton of neurons in the CNS.	NfL reflects neuroaxonal injury and may provide prognostic information after TBI and critical illness. Its slower kinetics may complement acute markers such as GFAP and UCH-L1.	Moderate for neuroaxonal injury, but low for brain–lung axis attribution. Age, neurodegeneration, renal dysfunction, and critical illness can confound levels.	Translational and early clinical use in neurological disease. No validated cutoff for brain–lung axis injury or ARDS-associated neuroaxonal damage.
Tau protein	Neurons and axons; circulating levels reflect neuronal/axonal damage rather than a specific organ-to-organ pathway.	Tau has been associated with secondary neuroaxonal injury in ARDS and other critical illnesses, but the evidence is less specific than for direct CNS injury markers.	Low-to-moderate for neuronal injury and low for brain–lung axis attribution. Age, neurodegeneration, and critical illness are important confounders.	Research-stage for this application. No brain–lung axis-specific clinical validation.
S100B	Astrocytes, Schwann cells, adipocytes, and other extracerebral tissues.	S100B rises after TBI and has also been reported after ALI. In experimental TBI-associated ALI, S100B-related NET formation has been linked to pulmonary injury.	Low-to-moderate for CNS injury and low for brain–lung axis specificity because extracerebral expression and blood–brain barrier disruption confound interpretation.	Clinically used as an adjunctive injury marker in some settings, but not validated for brain–lung axis diagnosis or prognosis.
Brain-derived and lung-derived extracellular vesicles/exosomes	Cell-of-origin dependent; neuronal, glial, pulmonary epithelial, endothelial, and immune-cell vesicles may carry distinct proteins and non-coding RNAs.	Experimental studies support EV-mediated inter-organ communication and show that selected cargoes may reflect neuroinflammatory status or influence recipient cells. Human brain–lung axis validation remains limited.	Potentially higher if cell-of-origin and cargo are rigorously defined, but currently uncertain because EV heterogeneity and isolation methods affect specificity.	Preclinical or early translational liquid-biopsy research. No standardized assay, cutoff, or prospective clinical readiness for brain–lung axis injury.

Panels A and B summarize the disease context, study model, biological source, major findings, specificity, confounders and translational readiness of candidate biomarkers. These markers report neural injury, systemic inflammation, vascular or leukocyte activation, or extracellular-vesicle biology; none has been validated as specific for brain–lung-axis injury. Evidence ranges from human association studies to preclinical models and does not by itself establish organ of origin or directionality. Reference numbers correspond to the manuscript reference list

ABI acute brain injury, *Akt* protein kinase B, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *CILBA* Critical Illness Lung-Brain Axis Biomarker, *CNS* central nervous system, *COVID-19* coronavirus disease 2019, *CT* computed tomography, *DAMP* damage-associated molecular pattern, *eNAMPT* extracellular nicotinamide phosphoribosyltransferase, *EV* extracellular vesicles, *GFAP* glial fibrillary acidic protein, *HMGBl* high-mobility group box 1, *IL* interleukin, *IL-1Ra* interleukin-1 receptor antagonist, *LPS* lipopolysaccharide, *mTORC2* mechanistic target of rapamycin complex 2, *MyD88* myeloid differentiation primary response 88, *NET* neutrophil extracellular trap, *NF-κB* nuclear factor-κB, *NfL* neurofilament light chain, *PSGL-1* P-selectin glycoprotein ligand 1, *SAH* subarachnoid hemorrhage, *S100B* S100 calcium-binding protein B, *S100A8/A9* S100 calcium-binding proteins A8 and A9, *TBI* traumatic brain injury, *TLR4* Toll-like receptor 4, *TNF-α* tumor necrosis factor-α, *UCH-L1* ubiquitin C-terminal hydrolase L1

Microbiome and glymphatic system interventions

Microbiome-targeted interventions, including probiotics and fecal microbiota transplantation, may alter systemic immune tone through microbial products and short-chain fatty acids, but direct ABI-associated brain–lung evidence remains limited [29, 30, 34]. Glymphatic-preserving interventions have shown intracranial benefit in experimental brain injury. Nimodipine improved glymphatic function and attenuated early brain injury after experimental subarachnoid hemorrhage [1]. Whether microbiome manipulation or glymphatic preservation reduces secondary pulmonary injury has not been directly tested, so both strategies remain hypothesis-generating in this context.

Stem cell/exosome therapy

Mesenchymal stromal cells (MSCs) and extracellular-vesicle-based therapies can modulate immune-cell phenotypes, endothelial injury, and repair pathways. Preclinical neurological models support anti-inflammatory and tissue-repair effects of MSC secretome and MSC-derived extracellular vesicles [72–78]. Regulatory cargoes such as miR-146a can influence NF- κ B-associated signaling in non-neurological injury models, but these findings cannot be assumed to demonstrate brain-to-lung delivery or dual-organ efficacy. Future studies should define vesicle source, cargo, biodistribution, dose, and organ-specific outcomes before considering MSC-derived extracellular vesicles as established brain–lung interventions. The mechanisms of action, disease settings, experimental models, reported outcomes, and translational limitations of the principal therapeutic interventions are summarized in Table 3. An integrated overview of the principal biomarker classes and therapeutic strategies is presented in Fig. 3. The figure emphasizes the relative tissue specificity of candidate biomarkers and distinguishes direct therapeutic targets from indirect or emerging interventions.

Conclusion

The brain–lung axis provides a useful framework for understanding ABI as a systemic neuroimmune disorder rather than an isolated CNS event. The evidence is most coherently organized as a sequential relay comprising CNS signal generation and egress, systemic immune amplification, pulmonary effector injury, and reciprocal lung-to-brain feedback. Sympathetic activation, peripheral myeloid responses, NLRP3-associated signaling, endothelial dysfunction, ventilation-associated inflammation, and pulmonary infection have varying degrees of mechanistic support. Adaptive immune responses, border-associated macrophages, NET formation, neurovascular regulation, and sex-dependent effects extend this framework but remain unevenly characterized. Glymphatic and meningeal lymphatic pathways may influence the peripheral availability of CNS-derived signals, yet direct evidence linking glymphatic transport to pulmonary DAMP accumulation and lung injury is still lacking. Current biomarkers mainly report neural injury, endothelial dysfunction, or systemic inflammation rather than brain–lung-axis injury itself, and most candidate interventions remain preclinical. Future studies should prioritize organ-of-origin molecular tracing, pathway-specific manipulation in clinically relevant ABI models, appropriate critical-illness controls, sex-disaggregated analyses, and prospective biomarker and therapeutic validation. By linking directionality, evidence strength, and translational maturity, this ABI-centered framework identifies testable relay points without overstating causal relationships.

Table 3 Therapeutic interventions targeting the neuroimmune axis

Therapeutic agent/intervention	Mechanism of action	Disease setting	Preclinical/clinical model	Main outcome	Reference
Anti-eNAMPT monoclonal antibody	Neutralizes extracellular NAMPT and attenuates DAMP-mediated inflammatory responses	Experimental ALI/ARDS; proposed application to TBI-associated ALI	Preclinical ALI/ARDS models; no direct TBI-associated ALI model was identified in the cited studies	Reduced pulmonary edema and inflammatory-cell infiltration	[66, 67]
Fingolimod	S1P-receptor modulator reported to suppress NLRP3 inflammasome activation, IL-1 β /IL-18 maturation, and pyroptosis	TBI-induced ALI	Animal model of TBI-induced ALI	Attenuated pulmonary inflammation and lung injury	[54]
Remimazolam	Benzodiazepine anesthetic reported to suppress ATF3-dependent NLRP3 activation and pulmonary epithelial pyroptosis	TBI-induced ALI	Mouse controlled cortical impact (CCI) model	Reported to attenuate inflammasome-related lung injury	[56, 79]
TREM-1 inhibitor	Suppresses TREM-1-mediated inflammatory amplification and NLRP3 activation	TBI-induced ALI	Animal model of TBI-induced ALI	Reduced NLRP3 activation and pyroptosis	[55]
Ondansetron (5-HT3 receptor antagonist)	Suppresses 5-HT3-mediated inflammatory signaling and NLRP3 activation	TBI-induced ALI	Animal model of TBI-induced ALI	Reduced inflammasome activation and pulmonary inflammation	[55]
Dexamethasone	Inhibits NF- κ B signaling and the production of pro-inflammatory cytokines	Acute brain injury, including stroke and TBI	Systematic review and meta-analysis of corticosteroid use in stroke and TBI	May reduce inflammation; however, its use remains controversial because it may interfere with neural repair	—
Anakinra (recombinant IL-1 receptor antagonist)	Blocks IL-1-mediated inflammatory signaling	COVID-19-associated ARDS	Clinical cohort and meta-analytic evidence in severe COVID-19; no direct ABI-associated lung-injury model	Reduced mortality in patients with COVID-19-associated ARDS; its application in ABI requires further investigation	—
Vagus nerve stimulation (VNS)	Activates the cholinergic anti-inflammatory pathway through α 7nAChR and reduces TNF- α and IL-6 release	Experimental lung inflammation; ischemic stroke and TBI	Rodent LPS-induced ALI/lung-inflammation, ischemic stroke, and TBI models	Reduced pulmonary macrophage activation, inflammatory mediator release, and pulmonary edema in lung-inflammation models; attenuated neurological deficits, cerebral edema, oxidative stress, and neuronal apoptosis in stroke/TBI models.	[7, 9, 68, 69]
Transcutaneous auricular vagus nerve stimulation (taVNS)	Reduces systemic inflammatory responses through non-invasive vagal modulation	ARDS or systemic acute inflammation	Mouse model of LPS-induced acute inflammation; clinical evidence is also available in sepsis	Reduced circulating cytokine levels and demonstrated feasibility in critically ill patients	[70, 71]
Probiotics and fecal microbiota transplantation (FMT)	Restore intestinal microbial balance and reduce bacterial translocation and systemic inflammation	COPD-associated inflammation; proposed for SAH-associated neurogenic pulmonary edema (NPE)	Gut microbiota and pulmonary disease models; no direct SAH-NPE validation model is currently available	May reduce systemic inflammation and potentially attenuate neuroinflammation and NPE	[29, 30, 34]

Table 3 (continued)

Therapeutic agent/intervention	Mechanism of action	Disease setting	Preclinical/clinical model	Main outcome	Reference
Glymphatic system restoration (nimodipine or AQP4-targeted approaches)	Restores AQP4 polarity or promotes cerebrospinal fluid flow, thereby accelerating DAMP clearance	SAH/ABI-associated lymphatic dysfunction; potential relevance to secondary lung injury remains unvalidated.	Mouse SAH model evaluating nimodipine-mediated preservation of lymphatic function; no direct ABI-associated lung injury model.	Preserved lymphatic function and attenuated early brain injury after SAH. Effects on systemic DAMP exposure and secondary pulmonary injury remain hypothetical and require direct experimental validation.	[1, 2]
Sleep optimization	Supports lymphatic function and neuroimmune homeostasis	ABI-associated brain–lung axis dysfunction	Evidence derived from general sleep and lymphatic research; no direct ABI brain–lung intervention model	May improve lymphatic clearance and restore brain–lung axis homeostasis	—
Mesenchymal stromal cells (MSCs)	Secrete IL-10 and TGF- β and promote macrophage polarization toward a tissue-repair phenotype	ABI/TBI with concomitant lung injury	Preclinical TBI models	Reduced cerebral and pulmonary edema and promoted tissue repair	[72, 73]
MSC-derived extracellular vesicles/exosomes	Deliver anti-inflammatory molecules, including miR-146a and miR-21, and inhibit NF- κ B signaling and apoptosis	TBI and ALI, including TBI-associated ALI	Rodent TBI and ALI models	Reduced neuroinflammation, pulmonary inflammation, alveolar epithelial-cell apoptosis, and neuronal apoptosis and improved neurological recovery	[74–78]

The interventions differ substantially in disease model, target proximity and translational maturity. The outcomes summarize the cited findings and should not be interpreted as uniform clinical efficacy in acute-brain-injury-associated lung injury. A dash indicates that no corresponding reference is provided in the manuscript reference list. Reference numbers correspond to that list

5-HT3 5-hydroxytryptamine receptor 3, α 7nAChR α 7 nicotinic acetylcholine receptor, ABI acute brain injury, ALI acute lung injury, AQP4 aquaporin-4, ARDS acute respiratory distress syndrome, ATF3 activating transcription factor 3, CCI controlled cortical impact, COPD chronic obstructive pulmonary disease, DAMP damage-associated molecular pattern, eNAMPT extracellular nicotinamide phosphoribosyltransferase, FMT fecal microbiota transplantation, IL interleukin, LPS lipopolysaccharide, miR microRNA, MSC mesenchymal stromal cell, NF- κ B nuclear factor- κ B, NLRP3 NOD-, LRR- and pyrin domain-containing protein 3, NPE neurogenic pulmonary edema, SAH subarachnoid hemorrhage, SIP sphingosine-1-phosphate, taVNS transcutaneous auricular vagus nerve stimulation, TBI traumatic brain injury, TGF- β transforming growth factor- β , TLR4 Toll-like receptor 4, TNF- α tumor necrosis factor- α , TREM-1 triggering receptor expressed on myeloid cells 1, VNS vagus nerve stimulation

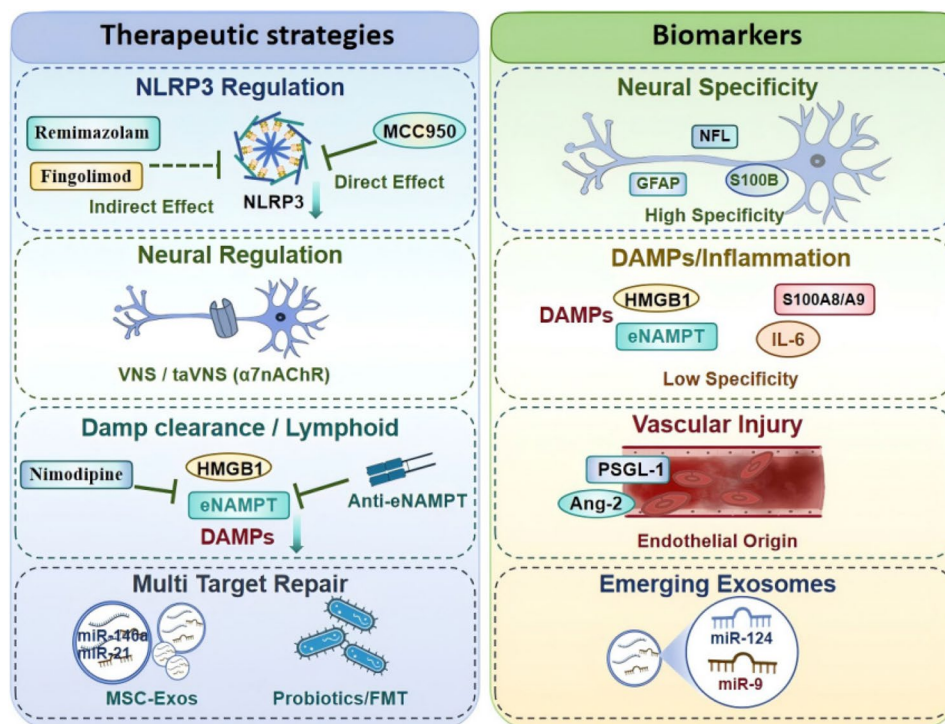


Fig. 3 Candidate therapeutic strategies and biomarkers for brain–lung–axis injury. Left, interventions are grouped by proposed target: direct NLRP3 inhibition by MCC950; indirect reduction of NLRP3 activation by remimazolam and fingolimod; vagal modulation through VNS or taVNS; hypothesis-generating approaches to DAMP clearance or neutralization using nimodipine or anti-eNAMPT; and multi-target repair approaches using MSC-derived exosomes or probiotics/FMT. Right, candidate biomarkers are grouped by biological process rather than axis specificity. GFAP, NfL and S100B indicate neural injury; HMGB1, eNAMPT, S100A8/A9 and IL-6 reflect systemic inflammation or DAMP activity; Ang-2 and PSGL-1 reflect endothelial or leukocyte activation; and exosomal miR-9 and miR-124 remain emerging candidates. Except for MCC950 as a direct NLRP3 inhibitor, the displayed interventions are indirect, predominantly preclinical or hypothesis-generating, and none has established clinical efficacy specifically for brain–lung–axis injury. None of the displayed biomarkers has been validated as brain–lung–axis-specific.

Abbreviations

ABI	Acute brain injury
CNS	Central nervous system
DAMP	Damage—associated molecular pattern
NLRP3	NLR family pyrin domain containing 3
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
BBB	Blood—brain barrier
eNAMPT	Extracellular nicotinamide phosphoribosyltransferase
IL	6—Interleukin—6
IL	1β—Interleukin—1β
MSC	Mesenchymal stromal cell
NPE	Neurogenic pulmonary edema
TNF	α—Tumor necrosis factor—α
TBI	Traumatic brain injury
SAH	Subarachnoid hemorrhage
ATP	Adenosine triphosphate

$\alpha 7$ nAChR	$\alpha 7$ nicotinic acetylcholine receptor
CSF	Cerebrospinal fluid
TLR2/4	Toll—like receptor 2/4
ROS	Reactive oxygen species
MMP	Matrix metalloproteinase
EVs	Extracellular vesicles
VNS	Vagus nerve stimulation
LPS	Lipopolysaccharide
SCFA	Short—chain fatty acid
Treg	Regulatory T cell
HDAC	Histone deacetylase
GPR41/43	G protein—coupled receptor 41/43
PI3K	Phosphatidylinositol 3—kinase
MAPK	Mitogen—activated protein kinase
GSDMD	Gasdermin D
TREM	1—Triggering receptor expressed on myeloid cells 1
AQP4	Aquaporin—4
GFAP	Glial fibrillary acidic protein
NfL	Neurofilament light chain
UCH	L1—Ubiquitin C—terminal hydrolase L1
S100B	S100 calcium—binding protein B
Ang	2—Angiopoietin—2
PSGL	1—P—selectin glycoprotein ligand—1
CILBA	Critical Illness Lung—Brain Axis Biomarker
JAK	STAT3—Janus kinase—signal transducer and activator of transcription 3
HIF	1 α —Hypoxia—inducible factor—1 α
ICU	Intensive care unit
FMT	Fecal microbiota transplantation
taVNS	Transcutaneous auricular vagus nerve stimulation
CAP	Cholinergic anti—inflammatory pathway
HMGB1	High—mobility group box 1
HPA	Hypothalamic—pituitary—adrenal
BAM	Border—associated macrophage
NET	Neutrophil extracellular trap
TGF	β —Transforming growth factor— β
cGAS	Cyclic GMP—AMP synthase
STING	Stimulator of interferon genes
NLRC4	NLR family CARD domain containing 4
AIM2	Absent in melanoma 2
NTS	Nucleus tractus solitarius
RVLM	Rostral ventrolateral medulla

Acknowledgements Not applicable.

Authors' contributions ZRT: Conceptualization, ML: Writing – original draft, YRJ, YQX, and ZRT: Writing – review and editing. All authors read and approved the final manuscript.

Funding (1) Beijing Hospitals Authority's Ascent Plan (DFL20240302), (2) Beijing Municipal Science & Technology

Commission, Administrative Commission of Zhongguancun Science Park (Z251100006025022), (3) Beijing Municipal Natural Science Foundation (7262045), (4) Prevention and Control of Emerging and Major Infectious Diseases-National Science and Technology Major Project (2026ZD01910300).

Data availability No datasets were generated or analysed during the current study.

Declarations

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Hou C, Liu Q, Zhang H, Wang W, Wang B, Cui X, et al. Nimodipine attenuates early brain injury by protecting the lymphatic system after subarachnoid hemorrhage in mice. *Neurochem Res.* 2022;47:701–12. <https://doi.org/10.1007/s11064-021-03478-9>.
2. Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, et al. Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. *J Neurosci.* 2015;35:518–26. <https://doi.org/10.1523/JNEUROSCI.3742-14.2015>.
3. Villalba N, Beard RS Jr, Yuan SY. Barrier breakdown: lung-brain crosstalk in systemic inflammation. *J Neuroinflammation.* 2026;23:164. <https://doi.org/10.1186/s12974-026-03807-1>.
4. Wang L, Wang F, Wang X, Chen X, Li C, Shan K, et al. The lung-brain axis: elucidating the mechanisms of pulmonary-driven neurological disorders. *J Neuroinflammation.* 2026;23:115. <https://doi.org/10.1186/s12974-026-03721-6>.
5. Yang W, Shi X, Xie L, Zhang H, Shen L, Pan L, et al. The brain-lung axis: bridging neurological and respiratory disorders via neural-immune-microbial dialogue. *Chin J Traumatol.* 2026;29:235–44. <https://doi.org/10.1016/j.cjtee.2025.10.006>.
6. Mascia L, D'Albo R, Cavalli I, Giaccari L, Della Giovampaola M, Donati B. Organ crosstalk: brain-lung interaction. *Front Med (Lausanne).* 2025;12:1655813. <https://doi.org/10.3389/fmed.2025.1655813>.
7. Huang Y, Dong S, Li X, Shi J, Zhang Y, Liu S, et al. VNS-mediated $\alpha 7$ nAChR signaling promotes SPM synthesis via regulation of netrin-1 expression during LPS-induced ALI. *FASEB J.* 2024;38:e9664. <https://doi.org/10.1096/fj.202301623R>.
8. Li Y, Ding S, Wang Y. Targeting the cholinergic anti-inflammatory pathway: an innovative strategy for treating diseases. *Mol Biol Rep.* 2025;52:199. <https://doi.org/10.1007/s11033-025-10288-7>.
9. Murray K, Cremin M, Tay E, Sanchez K, Schreiber S, Lloyd E, et al. Inhibition of acute lung inflammation by a neuroimmune circuit induced by vagal nerve stimulation. *Sci Adv.* 2025;11:eadw7080. <https://doi.org/10.1126/sciadv.adw7080>.
10. Hasegawa Y, Uchikawa H, Kajiwarra S, Morioka M. Central sympathetic nerve activation in subarachnoid hemorrhage. *J Neurochem.* 2022;160:34–50. <https://doi.org/10.1111/jnc.15511>.
11. Zhao N, Liu C, Tian X, Yang J, Wang T. Acute brain injury increases pulmonary capillary permeability via sympathetic activation-mediated high fluid shear stress and destruction of the endothelial glycocalyx layer. *Exp Cell Res.* 2024;434:113873. <https://doi.org/10.1016/j.yexcr.2023.113873>.
12. Knezevic E, Nenic K, Milanovic V, Knezevic NN. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. *Cells.* 2023;12:2726. <https://doi.org/10.3390/cells12232726>.
13. Katayama PL, Leirão IP, Kanashiro A, Luiz JPM, Cunha FQ, Navegantes LCC, et al. The carotid body detects circulating tumor necrosis factor- α to activate a sympathetic anti-inflammatory reflex. *Brain Behav Immun.* 2022;102:370–86. <https://doi.org/10.1016/j.bbi.2022.03.014>.

14. Sun B, Zhang J, Li Z, Wang J, Zhao C, Xu X. Role of damage-associated molecular patterns in the pathogenesis and therapeutics of traumatic brain injury. *Burns Trauma*. 2025;13:tkaf043. <https://doi.org/10.1093/burnst/tkaf043>.
15. Kayhanian S, Glynos A, Mair R, Lakatos A, Hutchinson PJA, Helmy AE, et al. Cell-free mitochondrial DNA in acute brain injury. *Neurotrauma Rep*. 2022;3:415–20. <https://doi.org/10.1089/neur.2022.0032>.
16. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464:104–7. <https://doi.org/10.1038/nature08780>.
17. Rodrigues Filho EM, Simon D, Ikuta N, Klovian C, Dannebrock FA, Oliveira de Oliveira C, et al. Elevated cell-free plasma DNA level as an independent predictor of mortality in patients with severe traumatic brain injury. *J Neurotrauma*. 2014;31:1639–46. <https://doi.org/10.1089/neu.2013.3178>.
18. Abrams ST, Zhang N, Manson J, Liu T, Dart C, Baluwa F, et al. Circulating histones are mediators of trauma-associated lung injury. *Am J Respir Crit Care Med*. 2013;187:160–9. <https://doi.org/10.1164/rccm.201206-1037OC>.
19. da Rocha AB, Zanoni C, de Freitas GR, André C, Himelfarb S, Schneider RF, et al. Serum Hsp70 as an early predictor of fatal outcome after severe traumatic brain injury in males. *J Neurotrauma*. 2005;22:966–77. <https://doi.org/10.1089/neu.2005.22.966>.
20. Asea A, Rehli M, Kabingu E, Boch JA, Bare O, Auron PE, et al. Novel signal transduction pathway utilized by extracellular HSP70: role of toll-like receptor (TLR) 2 and TLR4. *J Biol Chem*. 2002;277:15028–34. <https://doi.org/10.1074/jbc.M200497200>.
21. Ma T, Liu J, Gao Z, Li Y, Lin J, Pang K, et al. Bone marrow-derived emergency monopoiesis drives brain-lung axis injury after traumatic brain injury via IL-1. *J Neuroinflammation*. 2025;22:262. <https://doi.org/10.1186/s12974-025-03589-y>.
22. Gu Z, Li L, Li Q, Tan H, Zou Z, Chen X, et al. Polydatin alleviates severe traumatic brain injury induced acute lung injury by inhibiting S100B mediated NETs formation. *Int Immunopharmacol*. 2021;98:107699. <https://doi.org/10.1016/j.intim.2021.107699>.
23. Wu X, Guo Y, Zeng H, Chen G. DNase-1 treatment exerts protective effects in neurogenic pulmonary edema via regulating the neutrophil extracellular traps after subarachnoid hemorrhage in mice. *J Clin Med*. 2022;11:4349. <https://doi.org/10.3390/jcm11154349>.
24. Sun R, Jiang H. Border-associated macrophages in the central nervous system. *J Neuroinflammation*. 2024;21:67. <https://doi.org/10.1186/s12974-024-03059-x>.
25. Alam A, Thelin EP, Tajsic T, Khan DZ, Khellaf A, Patani R, et al. Cellular infiltration in traumatic brain injury. *J Neuroinflammation*. 2020;17:328. <https://doi.org/10.1186/s12974-020-02005-x>.
26. Shan J, Shi R, Hazra R, Hu X. Regulatory T lymphocytes in traumatic brain injury. *Neurochem Int*. 2024;173:105660. <https://doi.org/10.1016/j.neuint.2023.105660>.
27. Izzy S, Yahya T, Albastaki O, Abou-El-Hassan H, Aronchik M, Cao T, et al. Nasal anti-CD3 monoclonal antibody ameliorates traumatic brain injury, enhances microglial phagocytosis and reduces neuroinflammation via IL-10-dependent Treg-microglia crosstalk. *Nat Neurosci*. 2025;28:499–516. <https://doi.org/10.1038/s41593-025-01877-7>.
28. Gao X, Li W, Syed F, Yuan F, Li P, Yu Q. PD-L1 signaling in reactive astrocytes counteracts neuroinflammation and ameliorates neuronal damage after traumatic brain injury. *J Neuroinflammation*. 2022;19:43. <https://doi.org/10.1186/s12974-022-02398-x>.
29. El Baassiri MG, Raouf Z, Badin S, Escobosa A, Sodhi CP, Nasr IW. Dysregulated brain-gut axis in the setting of traumatic brain injury: review of mechanisms and anti-inflammatory pharmacotherapies. *J Neuroinflammation*. 2024;21:124. <https://doi.org/10.1186/s12974-024-03118-3>.
30. Hanscom M, Loane DJ, Shea-Donohue T. Brain-gut axis dysfunction in the pathogenesis of traumatic brain injury. *J Clin Invest*. 2021;131:e143777. <https://doi.org/10.1172/JCI143777>.
31. Chang Y, Chen J, Peng Y, Zhang K, Zhang Y, Zhao X, et al. Gut-derived macrophages link intestinal damage to brain injury after cardiac arrest through TREM1 signaling. *Cell Mol Immunol*. 2025;22:437–55. <https://doi.org/10.1038/s41423-025-01263-0>.
32. Wang H, Zhang M, Li J, Liang J, Yang M, Xia G, et al. Gut microbiota is causally associated with poststroke cognitive impairment through lipopolysaccharide and butyrate. *J Neuroinflammation*. 2022;19:76. <https://doi.org/10.1186/s12974-022-02435-9>.
33. Zhang S, Chen Q, Jin M, Ren J, Sun X, Zhang Z, et al. Notoginsenoside R1 alleviates cerebral ischemia/reperfusion injury by inhibiting the TLR4/MyD88/NF- κ B signaling pathway through microbiota-gut-brain axis. *Phytomedicine*. 2024;128:155530. <https://doi.org/10.1016/j.phymed.2024.155530>.
34. Ni YF, Wang J, Yan XL, Tian F, Zhao JB, Wang YJ, et al. Histone deacetylase inhibitor, butyrate, attenuates lipopolysaccharide-induced acute lung injury in mice. *Respir Res*. 2010;11:33. <https://doi.org/10.1186/1465-9921-11-33>.
35. Castro PR, Bittencourt LFF, Larochelle S, Andrade SP, Mackay CR, Slevin M, et al. GPR43 regulates sodium butyrate-induced angiogenesis and matrix remodeling. *Am J Physiol Heart Circ Physiol*. 2021;320:H1066–79. <https://doi.org/10.1152/ajpheart.00515.2019>.
36. Luo QJ, Sun MX, Guo YW, Tan SW, Wu XY, Abassa KK, et al. Sodium butyrate protects against lipopolysaccharide-induced liver injury partially via the GPR43/ β -arrestin-2/NF- κ B network. *Gastroenterol Rep (Oxf)*. 2021;9:154–65. <https://doi.org/10.1093/gastro/goaa085>.

37. Zhou X, Bates AH, Hoffer A. Challenges in pulmonary management after traumatic brain and spinal cord injury. *Neurosurg Clin N Am*. 2025;36:355–64. <https://doi.org/10.1016/j.nec.2025.03.004>.
38. Huang S, Zhou Y, Ji H, Zhang T, Liu S, Ma L, et al. Decoding mechanisms and protein markers in lung-brain axis. *Respir Res*. 2025;26:190. <https://doi.org/10.1186/s12931-025-03272-z>.
39. Rodríguez A, Claverias L, Martín-Loeches I, Bertomeu FG, Picó Plana E, Rosich S, et al. Ventilator-associated pneumonia (VAP) in neurocritical patients: the hidden dialog of brain and infection. *Biomedicines*. 2025;13:3112. <https://doi.org/10.3390/biomedicines13123112>.
40. Sun P, Xu Y, Xiong T, Li S, Qiu N, Zhou C, et al. Genetic deletion of microRNA-15a/16–1 in pericytes stimulates cerebral angiogenesis and promotes functional recovery after ischemic stroke. *Angiogenesis*. 2025;28:35. <https://doi.org/10.1007/s10456-025-09987-3>.
41. Zhou C, Li S, Qiu N, Sun P, Hamblin MH, Dixon CE, et al. Loss of microRNA-15a/16–1 function promotes neuropathological and functional recovery in experimental traumatic brain injury. *JCI Insight*. 2024;9:e178650. <https://doi.org/10.1172/jci.insight.178650>.
42. Huang X, Li S, Qiu N, Ni A, Xiong T, Xue J, et al. Sex- and age-dependent effects of miR-15a/16–1 antagomir on ischemic stroke outcomes. *Int J Mol Sci*. 2024;25:11765. <https://doi.org/10.3390/ijms252111765>.
43. Sabetta Z, Krishna G, Curry-Koski T, Lopez M, Adelson PD, Thomas TC. Sex-dependent temporal changes in astrocyte-vessel interactions following diffuse traumatic brain injury in rats. *Front Physiol*. 2024;15:1469073. <https://doi.org/10.3389/fphys.2024.1469073>.
44. Karam J, Ashfaq N, Benitez C, Morales V, Partida E, Hernandez M, et al. Minimally invasive serial collection of cerebrospinal fluid reveals sex-dependent differences in neuroinflammation in a rat model of mild traumatic brain injury. *Brain Behav Immun*. 2025;124:237–52. <https://doi.org/10.1016/j.bbi.2024.11.015>.
45. Datta Roy PM, Cuba J, Milligan KS, Shi W, Wang D, LaPlaca MC. Sex dimorphism influences cortical microglial morphological and phenotypic marker profile after closed-head mild traumatic brain injury in rats. *Neurotrauma Rep*. 2025;6:790–803. <https://doi.org/10.1177/2689288X251377030>.
46. Rosner MJ, Newsome HH, Becker DP. Mechanical brain injury: the sympathoadrenal response. *J Neurosurg*. 1984;61:76–86. <https://doi.org/10.3171/jns.1984.61.1.0076>.
47. Wang J, Li LL, Zhao ZA, Niu CY, Zhao ZG. NLRP3 inflammasome-mediated pyroptosis in acute lung injury: roles of main lung cell types and therapeutic perspectives. *Int Immunopharmacol*. 2025;154:114560. <https://doi.org/10.1016/j.intimp.2025.114560>.
48. Johnson NH, Casanova NG, White SP, Canizales J, Camp SM, Barcena JP, et al. Lung-brain axis-generated inflammatory biomarkers in traumatic brain injury and acute respiratory distress syndrome: role of mechanical ventilation/stress. *Adv Biomark Sci Technol*. 2025;7:238–47. <https://doi.org/10.1016/j.abst.2025.08.002>.
49. Xu Q, Ye Y, Wang Z, Zhu H, Li Y, Wang J, et al. NLRP3 knockout protects against lung injury induced by cerebral ischemia-reperfusion. *Oxid Med Cell Longev*. 2022;2022:6260102. <https://doi.org/10.1155/2022/6260102>.
50. Zhao Y, Yang J, Shi J, Gong YN, Lu Q, Xu H, et al. The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus. *Nature*. 2011;477:596–600. <https://doi.org/10.1038/nature10510>.
51. Hu X, Zhang H, Zhang Q, Yao X, Ni W, Zhou K. Emerging role of STING signalling in CNS injury: inflammation, autophagy, necroptosis, ferroptosis and pyroptosis. *J Neuroinflammation*. 2022;19:242. <https://doi.org/10.1186/s12974-022-02602-y>.
52. Kong L, Li W, Chang E, Wang W, Shen N, Xu X, et al. mtDNA-STING axis mediates microglial polarization via IRF3/NF- κ B signaling after ischemic stroke. *Front Immunol*. 2022;13:860977. <https://doi.org/10.3389/fimmu.2022.860977>.
53. Coll RC, Robertson AA, Chae JJ, Higgins SC, Muñoz-Planillo R, Inerra MC, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nat Med*. 2015;21:248–55. <https://doi.org/10.1038/nm.3806>.
54. Shi Q, Hu T, Xu L, Fu J, Fang Y, Lan Y, et al. Fingolimod suppresses NLRP3 inflammasome activation and alleviates oxidative stress in traumatic brain injury-induced acute lung injury. *J Inflamm Res*. 2025;18:2229–45. <https://doi.org/10.2147/JIR.S503428>.
55. Li F, Qin N, Yu Y, Dong R, Li X, Gong S, et al. TREM-1 inhibition or ondansetron administration ameliorates NLRP3 inflammasome and pyroptosis in traumatic brain injury-induced acute lung injury. *Arch Med Sci*. 2024;20:984–96. <https://doi.org/10.5114/aoms/174264>.
56. Sun C, Zhang Y, Wang J, Wang B, Gu A, Wang Y, et al. Remimazolam attenuates traumatic brain injury-induced acute lung injury by suppressing pulmonary epithelial pyroptosis. *J Neuroinflammation*. 2026;23:16. <https://doi.org/10.1186/s12974-025-03653-7>.
57. Pohl R, Wolff D, Özkan E, Sprenger AA, Hasenpusch C, Wesenberg J, et al. Prevalence and incidence of cognitive impairment following acute respiratory distress syndrome of any cause: a systematic review and meta-analysis. *Crit Care*. 2025;29:164. <https://doi.org/10.1186/s13054-025-05375-x>.
58. Peach BC, Cooney S, Richards S. Prominent cognitive impairment sequelae in adult survivors of acute respiratory distress syndrome. *Rehabil Nurs*. 2022;47:72–81. <https://doi.org/10.1097/RNJ.0000000000000351>.

59. Chavez L, Meguro J, Chen S, de Paiva VN, Zambrano R, Eterno JM, et al. Circulating extracellular vesicles activate the pyroptosis pathway in the brain following ventilation-induced lung injury. *J Neuroinflammation*. 2021;18:310. <https://doi.org/10.1186/s12974-021-02364-z>.
60. Sparrow NA, Anwar F, Covarrubias AE, Rajput PS, Rashid MH, Nisson PL, et al. IL-6 inhibition reduces neuronal injury in a murine model of ventilator-induced lung injury. *Am J Respir Cell Mol Biol*. 2021;65:403–12. <https://doi.org/10.1165/rmb.2021-0072OC>.
61. Raabe A, Wissing H, Zwissler B. Brain cell damage and S-100B increase after acute lung injury. *Anesthesiology*. 2005;102:713–4. <https://doi.org/10.1097/0000542-200504000-00003>.
62. Wei W, Sun Z, He S, Zhang W, Chen S, Cao YN, et al. Mechanical ventilation induces lung and brain injury through ATP production, P2Y1 receptor activation and dopamine release. *Bioengineered*. 2022;13:2346–59. <https://doi.org/10.1080/21655979.2021.2022269>.
63. Ferreira AMS, Castro LVG, Ferreira-Costa M, Gonçalves-de-Albuquerque CF, Silva AR. Glial cells as central players in neuroinflammation and neuronal damage caused by bacterial pneumonia. *Neuroimmunomodulation*. 2026;33:89–100. <https://doi.org/10.1159/000550709>.
64. Hossain I, Marklund N, Czeiter E, Hutchinson P, Buki A. Blood biomarkers for traumatic brain injury: a narrative review of current evidence. *Brain Spine*. 2024;4:102735. <https://doi.org/10.1016/j.bas.2023.102735>.
65. Li S, Qiu N, Ni A, Hamblin MH, Yin KJ. Role of regulatory non-coding RNAs in traumatic brain injury. *Neurochem Int*. 2024;172:105643. <https://doi.org/10.1016/j.neuint.2023.105643>.
66. Bermudez T, Sammani S, Song JH, Hernon VR, Kempf CL, Garcia AN, et al. eNAMPT neutralization reduces preclinical ARDS severity via rectified NFκB and Akt/mTORC2 signaling. *Sci Rep*. 2022;12:696. <https://doi.org/10.1038/s41598-021-04444-9>.
67. Quijada H, Bermudez T, Kempf CL, Valera DG, Garcia AN, Camp SM, et al. Endothelial eNAMPT amplifies pre-clinical acute lung injury: efficacy of an eNAMPT-neutralising monoclonal antibody. *Eur Respir J*. 2021;57:2002536. <https://doi.org/10.1183/13993003.02536-2020>.
68. Xia XM, Duan Y, Wang YP, Han RX, Dong YF, Jiang SY, et al. Vagus nerve stimulation as a promising neuroprotection for ischemic stroke via α7nAChR-dependent inactivation of microglial NLRP3 inflammasome. *Acta Pharmacol Sin*. 2024;45:1349–65. <https://doi.org/10.1038/s41401-024-01245-4>.
69. Tang Y, Dong X, Chen G, Ye W, Kang J, Tang Y, et al. Vagus nerve stimulation attenuates early traumatic brain injury by regulating the NF-κB/NLRP3 signaling pathway. *Neurorehabil Neural Repair*. 2020;34:831–43. <https://doi.org/10.1177/1545968320948065>.
70. Go YY, Ju WM, Lee CM, Chae SW, Song JJ. Different transcutaneous auricular vagus nerve stimulation parameters modulate the anti-inflammatory effects on lipopolysaccharide-induced acute inflammation in mice. *Biomedicines*. 2022;10:247. <https://doi.org/10.3390/biomedicines10020247>.
71. Wu Z, Zhang X, Cai T, Li Y, Guo X, Zhao X, et al. Transcutaneous auricular vagus nerve stimulation reduces cytokine production in sepsis: an open double-blind, sham-controlled, pilot study. *Brain Stimul*. 2023;16:507–14. <https://doi.org/10.1016/j.brs.2023.02.008>.
72. Pischiutta F, Caruso E, Cavaleiro H, Salgado AJ, Loane DJ, Zanier ER. Mesenchymal stromal cell secretome for traumatic brain injury: focus on immunomodulatory action. *Exp Neurol*. 2022;357:114199. <https://doi.org/10.1016/j.expneurol.2022.114199>.
73. Wang D, Zhang S, Ge X, Yin Z, Li M, Guo M, et al. Mesenchymal stromal cell treatment attenuates repetitive mild traumatic brain injury-induced persistent cognitive deficits via suppressing ferroptosis. *J Neuroinflammation*. 2022;19:185. <https://doi.org/10.1186/s12974-022-02550-7>.
74. Xiong Y, Tang R, Xu J, Jiang W, Gong Z, Zhang L, et al. Tongxinluo-pretreated mesenchymal stem cells facilitate cardiac repair via exosomal transfer of miR-146a-5p targeting IRAK1/NF-κB p65 pathway. *Stem Cell Res Ther*. 2022;13:289. <https://doi.org/10.1186/s13287-022-02969-y>.
75. Chen J, Chen J, Li Q, Hu M, Zhong X, Yu L, et al. Astragaloside promotes the secretion of MSC-derived exosomal miR-146a-5p by regulating TRAF6/NF-κB pathway to attenuate inflammation in high glucose-impaired endothelial cells. *Vitro Cell Dev Biol Anim*. 2025;61:93–106. <https://doi.org/10.1007/s11626-024-00984-2>.
76. Yang Z, Liang Z, Rao J, Lin F, Lin Y, Xu X, et al. Mesenchymal stem cell-derived extracellular vesicles therapy in traumatic central nervous system diseases: a systematic review and meta-analysis. *Neural Regen Res*. 2023;18:2406–12. <https://doi.org/10.4103/1673-5374.371376>.
77. Dumbrava DA, Surugiu R, Börger V, Ruscu M, Tertel T, Giebel B, et al. Mesenchymal stromal cell-derived small extracellular vesicles promote neurological recovery and brain remodeling after distal middle cerebral artery occlusion in aged rats. *Geroscience*. 2022;44:293–310. <https://doi.org/10.1007/s11357-021-00483-2>.
78. Wang C, Börger V, Sardari M, Murke F, Skuljec J, Pul R, et al. Mesenchymal stromal cell-derived small extracellular vesicles induce ischemic neuroprotection by modulating leukocytes and specifically neutrophils. *Stroke*. 2020;51:1825–34. <https://doi.org/10.1161/STROKEAHA.119.028012>.
79. Kim KM. Remimazolam: pharmacological characteristics and clinical applications in anesthesiology. *Anesth Pain Med (Seoul)*. 2022;17:1–11. <https://doi.org/10.17085/apm.21115>.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Yanrui Jia¹ · Min Liu² · Ziren Tang² · Yuanqing Xu³

✉ Ziren Tang
tangziren1970@163.com

✉ Yuanqing Xu
bitxyq@bit.edu.cn

¹ Department of Nursing, Beijing Key Laboratory of Multimodal Intelligent Diagnosis and Treatment System for Respiratory Diseases, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital Affiliated to Capital Medical University, Beijing, China

² Beijing Key Laboratory of Cardiopulmonary-Cerebral Resuscitation Innovation and Translation, Beijing Chaoyang Hospital Emergency Medical Center Affiliated to Capital Medical University, Beijing, China

³ School of Medical Science and Engineering, Beijing Institute of Technology, Beijing, China