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Neural-Respiratory Inflammasome Axis in Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality. Approximately 20-25 percent of TBI subjects develop Acute Lung Injury (ALI), but the pathomechanisms of TBI-induced ALI remain poorly defined. Currently, mechanical ventilation is the only therapeutic intervention for TBI-induced lung injury. Our recent studies have shown that the inflammasome plays an important role in the systemic inflammatory response leading to lung injury-post TBI. Here, we outline the role of the extracellular vesicle (EV)-mediated inflammasome signaling in the etiology of TBI-induced ALI. Furthermore, we evaluate the efficacy of a low molecular weight heparin (Enoxaparin, a blocker of EV uptake) and a monoclonal antibody against apoptosis speck-like staining protein containing a caspase recruitment domain (anti-ASC) as therapeutics for TBI-induced lung injury. We demonstrate that activation of an EV-mediated Neural-Respiratory Inflammasome Axis plays an essential role in TBI-induced lung injury and disruption of this axis has therapeutic potential as a treatment strategy.

Introduction

Traumatic Brain Injury (TBI) disrupts the normal function of the brain and is caused by a bump, blow, or jolt to the head, as well as rapid acceleration or deceleration of the calvarium, or a penetrating head injury (1). TBI is a major public health concern and is a leading cause of mortality and morbidity throughout the world (2). In the United States, the Centers for Disease Control report that 1.7 million individuals sustain a TBI annually and that 5.3 million individuals live with TBI-related disabilities (3). Nearly one-third of all injury related deaths in the US have at least one diagnosis of TBI (4). The leading causes of non-fatal TBI in the United States are falls (35%), motor-vehicle accidents (17%), sports injuries (17%), and strikes or blows to the head from an outside object (1). The leading cause of TBI-related deaths is motor vehicle accidents.

A major factor that contributes to the heterogeneity in the severe TBI population is the cause of injury that directly relates to the underlying pathophysiology. In critical care medicine, severe TBIs are classified as either polytrauma cases or isolated head trauma. For example,

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individuals involved in motor vehicle accidents, including car accidents and motorcycle accidents are often polytrauma cases and their injuries involve a number of extremities and organs, in addition to trauma to the head (5). Isolated severe TBI patients are a distinct population within the trauma setting. Most often, they are classified as patients with a GCS of 3-8 (classifying them as severe) (6). Common examples of isolated TBIs include penetrating injuries due to gunshot wounds or knives and other sharp implements and blast injuries (7). Penetrating brain injuries are less common than closed head trauma, but often carry a worse prognosis (8). Gunshot wounds to the head are one of the most common penetrating injuries and account for 1.5% of TBI incidents and are the most lethal (42% of TBI deaths) (9).

In this review we cover a brief overview of the role of Extracellular Vesicle (EV)-mediated inflammasome activation in the systemic inflammatory response that is seen after TBI. We discuss the development of pulmonary dysfunction after TBI, with a specific focus on the TBI-induced Acute Lung Injury (ALI). We also look at possible therapeutic interventions that may be used to inhibit EV-mediated inflammasome signaling in systemic complications after TBI.

TBI and Inflammation

TBI triggers a neuroinflammatory response, which contributes to secondary injury mechanisms. Initially, the inflammatory reaction to TBI was thought to occur solely through peripheral immune mediators entering through a disrupted blood brain-barrier (BBB), it is now recognized as a more complex interaction between central and peripheral cellular components (10). These mechanisms are influenced by factors such as patient age, sex, mechanism and severity of injury, and genetic variability (10). Immediately after TBI, there is an activation of resident microglia and peripheral neutrophil recruitment, which is then followed by infiltration of lymphocytes and monocyte-derived macrophages (11). In addition, during this early phase after TBI, anti- and pro-inflammatory cytokines are released to promote and terminate the post-traumatic neuroinflammatory response (10) (12).

The neuroinflammatory response following TBI activates the innate immune system. The inflammasome is an important component of the innate immune system and has been implicated in the pro-inflammatory response post-TBI (13). The inflammasome is a multiprotein complex that plays a role in the activation of caspase-1 and the processing of IL-1 β and IL-18. Disruption of the cellular membrane as a result of the primary mechanical insult causes the release of intracellular Damage Associated Molecular Patterns (DAMPs) that trigger inflammasome activation (10). DAMPs include High Mobility Group Box Protein 1 (HMGB1), S-100 proteins, adenosine triphosphate, uric acid, DNA (deoxyribonucleic acid), among others (11). DAMPs bind to inflammasomes and induce processing of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), interleukin-18 (IL-18), and an increase in production of Tumor Necrosis Factor α (TNF α), and interleukin-6 (IL-6) by glial cells and infiltrating immune cells (14).

The inflammatory cascade associated with the release of these pro-inflammatory cytokines may ultimately lead to cell death by a variety of mechanisms. For example, cell death via

programmed necrosis may be initiated via TNF α -mediated RIP (Receptor-Interacting Protein) kinase activation that may lead to further DAMP release resulting in additional waves of necrosis (15). Necrosis takes place during the first phase of cell death and also may be initiated by irreversible metabolic disturbances and excitotoxicity after TBI (16). The second wave of cell death involves apoptosis (17). Neuronal apoptosis may be a caspase-dependent mechanism or a caspase-independent mechanism (17). Lastly, pyroptosis, an inflammasome dependent programmed cell death mechanism, has also identified as a form of secondary cell death after TBI (18).

A variety of therapeutic strategies have been attempted to block and/or reverse the secondary injury cascade (19). These include: calcium channel blockers, corticosteroids, excitatory amino acids inhibitors, NMDA receptor antagonists, anti-inflammatory drugs, free radical scavengers, magnesium sulfate, and growth factors (20). Because of the complexity of secondary injury mechanisms, treatment options must be multi-faceted and have the ability to simultaneously modulate different cellular changes (21). The use of hypothermia and temperature management protocols has also proven to be successful in the reduction of secondary injury mechanisms after severe TBI (22). While critical care management of TBI patients has improved, there are still no FDA approved pharmaceutical agents that target multiple secondary injury mechanisms.

Systemic Complications after TBI

In 1992, Piek et al., performed a clinical study where they were able to identify the high incidence of systemic complications in patients with severe TBI (23) (Figure1). Examples of systemic complications include pneumonia, sepsis, and multiple organ dysfunction syndrome and they are the leading causes of morbidity and mortality in many types of brain damage (24). Even with no extracranial organ injuries, 89% of severe TBI patients show signs of non-neurological organ dysfunction, which is independently associated with worse outcome (25). The organ systems that are most commonly damaged after severe TBI include are the respiratory (81%), cardiovascular (52%), coagulation (17%), renal (8%), and hepatic (7%) (26).

The current consensus is that there are two main pathways, which can contribute to the development of extracranial organ failure after TBI. The first involves the “catecholamine surge” that is driven by the hypothalamic pituitary axis, which increases the release of epinephrine and norepinephrine and thus activates the adrenal glands (27). This sympathetic-excited catecholamine release causes the vasoconstriction of peripheral vessels, which then elevates systemic arterial pressure (24). Cardiorespiratory complications are the most common non-neurological organ issues that are seen after TBI. In 1997, the first clinical evidence was shown that severe TBI can lead to a critical care disorder known as Acute Lung Injury (ALI) (28). The systemic vasoconstriction that is observed after TBI may eventually lead to non-neurological organ complications in the cardiorespiratory system, including cardiogenic pulmonary edema, cardiac injury, and Neurogenic Pulmonary Edema (27) (29). Furthermore, TBI leads to an increase in intracranial pressure (ICP), which can also result in increased sympathetic activation leading to cardiorespiratory complications (30).

The second pathway that is involved in the development of extracranial organ dysfunction is the systemic inflammatory response that is seen after TBI. The early, delayed, and systemic effects of severe TBI are the result of inflammatory mediators that initiate Systemic Inflammatory Response Syndrome (SIRS) (31). SIRS is an initial hyperinflammatory response to trauma, resulting in increased levels of inflammatory mediators in the circulation which cause damage to end organs (31). Examples of inflammatory mediators that are found in the systemic circulation after TBI are DAMPs, cytokines, chemokines, coagulation factors, growth factors, and nitric oxide (31). Cytokines are the largest group of mediators and some of the common ones that are found in the circulation after TBI include: IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-11 and TNF-alpha (29, 31). However, it remains unclear as to which of these cytokines primarily affect distal organs, but some of the proposed mechanisms are cytokine release, HMGB1 release, and involvement of the lymphatic system (29). It is clear that the systemic immune response initiated after TBI leads to cardiorespiratory complications such as myocardial tissue injury and Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS) (29). Therefore, it appears that there is communication between the brain and other organs, despite the concept that the brain is an immunologically privileged site due to the presence of the BBB (32).

ALI/ARDS and TBI

ALI/ARDS is a significant contributor to morbidity and mortality in trauma patients. The incidence of ALI in the United States is quoted to be between 78.9 in every 100,000 patients (33). ALI/ARDS was first described in 1967, and it was not until 1994 that the American European Consensus Conference (AECC), provided the first consistent definition (34). However, alterations to the definition have been made and the current version of the disease is based on criteria known as the Berlin Definition (Table 2) (35). This is comprised of the following criteria: (a) Acute onset within in 7 days, (b) Bilateral pulmonary infiltrates on chest x-ray or CT scan, (c) The presence of lung edema, without including a pulmonary capillary pressure wedge cutoff, (d) The standardization of hypoxemia calculated with a Positive Expiratory End Pressure (PEEP) of less than or equal to 5cm H₂O and (e) the categorization of lung injury into three grades of severity according to the PaO₂/FiO₂ ratio with a necessary minimum amount of PEEP (5cm H₂O) (36). This ratio is a measure of the partial pressure of oxygen over the fraction of inspired oxygen. Since 1994, the AECC defined the ALI class of lung injury as condition of a PaO₂/FiO₂ ratio less than or equal to 300 mmHg or ARDS as a ratio of less than or equal to 200 mmHg (36). ALI/ARDS has been well described in patients who survive the initial insult to the brain (34). The worldwide incidence of ALI/ARDS in severe TBI patients ranges from 20-30% and mortality rates range from 28-38% (34).

Mechanisms of TBI-induced lung injury

Since the lungs are more vulnerable and susceptible to injury after TBI, it is important that treatment strategies do not interfere with lung function. The various physiological changes that occur after TBI also put the lungs at risk of developing injury. Mechanical ventilation is currently the only treatment for patients with ALI/ARDS. Even though mechanical ventilation is the only clinical treatment for stroke, it may have a detrimental effect on the

lung. Adequate oxygenation is crucial during mechanical ventilation, which may require high FiO_2 concentration. Therefore, it is important that FiO_2 should be reduced to 40% to prevent hyperoxic lung injury (37).

In TBI-induced lung injury patients, mechanical ventilation can present several challenges and the specific guidelines for treatment strategies in these patients come into conflict with what is considered the best ventilator practice (38). In a randomized control trial on the prevention of secondary ischemic insults after severe TBI, it was shown that patients with a higher cerebral perfusion pressure (70 vs. 50 mmHg) were five times more likely to develop ALI/ARDS (39). Due to the tight interactions between cerebral blood flow and lung mechanics, mechanical ventilation may have an effect on cerebral perfusion and allow for risk of a potential secondary brain damage (38). Thus various mechanisms that are used during mechanical ventilation may have a harmful effect on the brain in TBI patients. For example, PEEP, which is commonly used during mechanical ventilation in ALI/ARDS, may reduce cerebral blood flow. This is due to the fact that increased intra-alveolar pressure secondary to PEEP may reduce cerebral venous return and consequently increase intracranial pressure (ICP) (38). During mechanical ventilation in TBI patients, PEEP is adjusted to an optimal level (optimal PEEP), which is adequate to maintain ideal intra-alveolar pressure and lung volume, as will oxygenation (40). Therefore, it is important to further understand the pathomechanisms underlying TBI-induced lung injury in order to develop better treatment options and strategies.

Recent studies have suggested that there is crosstalk between the brain and lungs in TBI patients and that this signaling leads to development of lung TBI-induced lung injury are the (a) the involvement of the autonomic system through sympathetic activation and (b) the involvement of the innate immune system (41). The sympathetic response is mainly a result of the increased ICP that is seen after severe TBI (42). TBI leads to stimulation of the adrenal glands and this allows for the release of epinephrine and norepinephrine (29). Subsequently, increased systemic vascular resistance is seen and leads to increased fluid pressure and alveolar leakage (29). This phenomenon has become widely known as the “blast injury theory”. The blast theory suggests that the sympathetic storm, which follows the sudden increase in ICP induces a transient increase in intravascular pressure and the disruption of the alveolar-capillary membrane (43). This mechanism is associated more with Neurogenic Pulmonary Edema, but still has consequences that are involved with development of ALI/ARDS after severe TBI.

Another proposed mechanism leading to TBI-induced lung injury is the role of the innate immune response as part of the systemic inflammatory changes. Within 3 hours after brain injury an inflammatory response is triggered, which is similar to that induced by direct injury through high tidal volume ventilation (41). Clinical studies in brain-injured patients suggest that there is an increased intracranial production and eventual release of pro-inflammatory mediators into the systemic circulation, which allows for the activation of various inflammatory cascades (43). In the brain, these pro-inflammatory mediators are most likely produced in microglia and astrocytes. Once the BBB is disrupted, these mediators may reach peripheral organs, such as the lungs (43). Pro-inflammatory cytokines have been found in the broncho-alveolar lavage fluid (BAL), in patients that suffered a fatal TBI (44).

Fisher et al., also reported that increased levels of interleukin-8 in BAL of TBI-lung donors correlated with early graft dysfunction and recipient mortality (44).

Several experimental studies have reported that the innate systemic immune response plays a critical role in TBI-induced lung injury. In 2007, Kalostra et al. detected a significant migration of immune cells such as neutrophils and macrophages into the lungs 24 hrs after severe brain injury (45). Other important pro-inflammatory mediators including TNF- α , IL-1 β , IL-6, S-100B, E-Selectin, and caspase-1 have been found in a porcine and rodent model of TBI-induced lung injury (43).

In 2014, Weber et al., used a mouse model of TBI-induced acute lung injury to study the role of the HMGB1 (High Mobility Group Box 1) -RAGE (Receptor for advanced glycation end products) axis in pulmonary dysfunction after TBI (46). HMGB1 is one of the most widely studied DAMPs that is known to be quickly released into the cytoplasm following stress, injury, or disease and can also be passively released into the extracellular space (46). Alternatively, HMGB1 may be actively released by cells in the immune and nervous systems following injury, inflammation, or disease (47). HMGB1 has been shown to bind to TLRs (Toll-like receptors), but typically it binds to RAGE (46). In the Weber study, TBI animals developed systemic hypoxia, acute lung injury, and decreased lung compliance compared to control animals and that this response was attenuated in RAGE $-/-$ mice (46). They also found that delivery of an HMGB1 neutralizing antibody prior to TBI reversed hypoxia and also improved lung compliance (46). Thus, it appears that the HMGB1-RAGE axis plays an important role in initiation of the innate immune response in TBI-induced pulmonary dysfunction.

The Inflammasome and TBI/ALI

The inflammasome was first described in 2002 (48) as a group of multimeric protein complexes that consist of the inflammasome sensor molecule, the adaptor protein apoptosis-speck like protein containing a caspase-activating recruitment domain protein (ASC), and caspase-1 (49). Several Nod-like Receptors (NLR) have been shown to form inflammasomes as well as the Absent in Melanoma 2 protein (AIM2) (49) (50). The NLRP 1, 2, 3, NLRC4 inflammasome as well as the AIM2 inflammasome have recently been studied in TBI and CNS (Central Nervous System) disease. The NLRP1 inflammasome is present in neurons (13), the NLRP2 in astrocytes (51), the NLRP3 in microglia (52), and the AIM2 inflammasome in neurons (53).

Fan et al., were the first to show evidence of an increase IL-1 β expression after experimental brain injury. (54) The NLRP 1, 2, 3, NLRC4, and AIM2 inflammasomes have all been implicated to play a role in TBI (50). The NLRP1 inflammasome is preassembled in neurons and may facilitate the rapid activation of the innate immune response after trauma (50). An increase in activated NLRP1, ASC, caspase-1 and IL-1 β are present in brain and spinal cord motor neurons after injury (55, 56). TBI also leads to NLRP3 inflammasome activation, and NLRP3 knockdown reduces brain damage in rodent models (57). In addition, levels of caspase-1, NLRP1, ASC, and the AIM2 inflammasome have been shown to be elevated in CSF of TBI patients and increased levels of these proteins have been associated with poor

prognosis (58) (53). Thus, inflammasome proteins may serve as potential biomarkers for assessing severity and outcome of TBI. In the case of cerebral ischemia, activated NLRP3 and AIM2 inflammasome leads to an increase of infarct size and neurovascular damage (59). Therefore, these data indicate a critical role of inflammasomes in TBI pathophysiology and suggest that inhibition of inflammasome signaling after trauma offers a therapeutic potential to decrease damage in the acute phase after TBI.

Therapeutic strategies targeting inflammasome assembly have shown promise in TBI. Inflammasome inhibition or the blocking of IL-1 β both significantly reduced neuronal cell death in the brains and spinal cords of ischemic animals (60). In addition, downregulation of NLRP1 and NLRP3 activation have been shown to have a protective role in TBI (50) (56). Inhibition of the inflammasome using neutralizing antibodies against inflammasome proteins, such as ASC, have been tested and had some success in preclinical models of TBI (50) (61). The mechanism behind antibody blocking of ASC is unclear, but one interpretation is that anti-ASC antibodies bind to ASC specks that are released into the extracellular space after inflammasome activation and ultimately prevents the extracellular activation of caspase-1 and IL-1 β (62).

Activation of the inflammasome ultimately leads to initiation of inflammatory death process known as pyroptosis (59). Unlike apoptosis, pyroptosis is a caspase-1 mediated form of cell death. Pyroptosis is a form of programmed cell death, but it is morphologically distinct from other forms of cell death processes. It is characterized by the activation of caspase-1 and the formation of the pyroptosome, which is a complex of oligomerized ASC molecules (62). Activated caspase-1 subsequently cleaves the amino terminus of Gasdermin-D, (GSDMD), a member of the gasdermin family of proteins (63). The N-terminal of GSDMD exhibits robust and specific binding to membrane lipids and oligomerizes to form pores with a diameter between 10 to 16 nm (63, 64). However, in the normal state GSDMD is inhibited by its' C-terminal portion (64). The pore formation disrupts the cellular osmotic potential and collapses the electrochemical gradient of the cell (65), which then causes the cell to swell and lyse and thus release intracellular contents (64). The diameter of the pore allows for the passage of mature IL-1 β and IL-18 (66). Gasdermin-D induced pyroptosis has been shown in the brain (67) as well as in the lungs (68) in preclinical TBI models.

The Inflammasome and ALI

Inflammasome-dependent excessive inflammation is involved in the pathogenesis of acute lung injury (59). Recent studies have shown that the inflammasome plays a role in the development of lung injury post-TBI (68). Trauma-related acute lung problems lead to the development of systemic and local NLRP3 activation (59). Other studies have reported an increase in caspase-1, IL-1 β , and IL-18 in peripheral blood of trauma patients with ARDS (69). Certain forms of trauma, such as hemorrhagic shock, lung contusion, burns, ventilator-induced lung injury, or transfusion-related acute lung injury have also been shown to activate the NLRP3 inflammasome in the lung, which is the most widely studied inflammasome in ALI/ARDS (59). Inhibition of the NLRP3 inflammasome reduces lung injury as evidenced by a decrease in histopathological damage, reduction in myeloperoxidase activity and reduction in inflammatory cytokines in lung tissue (59).

The Neural-Respiratory Inflammasome Axis

A recent study in our lab showed that extracellular vesicles (EVs), containing pro-inflammatory cytokines are released after experimental TBI and are taken up by lung cell and trigger inflammasome activation (68). EVs are lipid-bound vesicles ranging in size from 10 to 1000 nm, are secreted from almost all cell types, and are found in all bodily fluids and the extracellular matrix (70). The vesicle character depends on cellular origin, function and size (71). Exosomes, a type of EV, were first discovered from exfoliated membrane from neo-plastic cell lines (72) (Figure 1). EVs play important roles in intracellular communication, thus allowing cells to exchange proteins, lipids, and genetic material (73). They are important in cell-to-cell communication and induce a variety of effects on the target cells (73)

EVs are also carriers of PAMPs and DAMPs, cytokines, autoantigens, and tissue-degrading enzymes, such as proteases and glycosidases (74). Furthermore, EVs are vital for host defense against pathogens and communicate between infected cells (75). Various immune cells have been studied in EV-mediated IL-1 β release. EVs from monocytes activate endothelial cells and stimulate the production of IL-1 β from monocytes in autocrine fashion (76). Furthermore, upon stimulation macrophages and dendritic cells release vesicles containing inflammasome proteins (77). EV-mediated IL-1 β signaling has been studied in multiple systemic inflammatory disease conditions, including rheumatoid arthritis, systemic sclerosis, sepsis and, trauma-induced inflammatory complications. With regard to TBI, evidence shows that the circulating EV population increases and changes after injury (78). For example, an increase in inflammasome proteins was observed in the CSF of severe TBI patients (62). Increases in the levels of miR-21 in EVs (79) have also been reported, thus providing evidence that the composition of EVs is altered after injury.

We have recently shown an EV-mediated “Neural-Respiratory Inflammasome Axis” (68) (80). Specifically, we demonstrated that EV-mediated inflammasome signaling contributes to the pathomechanism of TBI-induced ALI. Results showed that EVs released into the peripheral circulation following TBI mediate inflammasome signaling in the lungs and therefore play a central role in the innate immune response after TBI (68). Previous studies have shown that EV uptake is inhibited *in vitro* using heparin and forms of low-molecular weight heparin, such as enoxaparin (81). Our data has shown that treatment with enoxaparin and an ASC monoclonal antibody reduce ALI after adoptive transfer of serum-derived EV from TBI injured mice (68). In addition, anti-ASC reduced inflammasome activation in the brain of mice after severe TBI and enoxaparin reduced inflammasome activation in both the brain and lungs of mice after severe TBI.

Another recent study from our lab provides further evidence on the role of EV-mediated inflammasome activation in TBI-induced lung injury by investigating serum-derived EV samples from severe TBI patients and by performing *in-vitro* studies looking at the mechanisms of TBI-induced lung injury at the cellular level(80). The origin and concentration of serum-derived EVs after TBI was evaluated, the particle size was characterized by size by NTA, and the levels of inflammasome signaling proteins were quantified in serum and EV preparations. Evidence is also provided that ASC is a reliable

serum biomarker for TBI (82) and TBI-induced lung injury as evidenced by analysis of receiver operator characteristic (ROC) with associated confidence intervals of EVs from serum samples of severe TBI patients with lung injury (80). Importantly, evidence is also provided that EVs from TBI subjects target human lung microvascular endothelial cells (HMVEC-L) and induce inflammasome activation leading to pyroptosis, thus providing a mechanistic basis for TBI-induced ALI.

HMGB1 and inflammasome activation

The inflammasome is activated in a response to both pathogen-associated molecular patterns (PAMPs) and DAMPs. Inflammasome activation occurs through binding of PAMPs and DAMPs to pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), nod-like receptors (NLRs), or RIG-like receptors (50). PAMPs initiate the immune response to infection, while DAMPs trigger “sterile inflammation” (48). Additionally, PAMPs are exogenous compounds of infectious origin and DAMPs are primarily endogenous substances released after alteration of cellular integrity (59). DAMPs have been more widely studied as inflammasome activators in the context of trauma. DAMPs are mainly classified based on their origin, e.g., mitochondrial, cytosolic, or nucleic (59). One of the most well studied DAMPs in the TBI and lung injury field is HMGB1.

HMGB1 is a 25 kD non-histone chromosomal protein that is released by damaged immune cells in response to inflammatory stimuli. It binds to DNA in a sequence-dependent manner and modifies DNA structure (83). HMGB1 has two DNA-binding domains, termed A and B box as well as a negatively charged C-terminal acidic region (31). After infection or disease HMGB1 is released into the extracellular space by dying cells, where it acts as a pro-inflammatory mediator and contributes to the pathogenesis of disease. HMGB1 has been well studied in trauma due to the fact that it responds to endogenous substances that are released from injured tissue to induce the production of inflammatory mediators (84). Extracellular HMGB1 signals through TLR4 receptors in macrophages to induce cytokine release and mediate cell migration by interacting with RAGE (85).

Additionally, HMGB1 plays a role in inflammasome activation. Recent studies have shown that HMGB1 activates both the NLRP3 (83) and AIM2 inflammasomes (86). The AIM2 inflammasome functions as a DNA sensor and activates the inflammasome in response to cytoplasmic DNA (87). A recent study described a novel mechanism for the role of the HMGB1-DNA complex in activation of the AIM2 inflammasome and IL-1 β (86). On the other hand, HMGB1 release appears to be regulated by inflammasomes (31). For example, double-stranded RNA dependent protein kinase (PKR) regulates the releases of IL-1 β , IL-18 and HMGB1 through interaction with the NLR family of inflammasomes (85).

The HMGB1-RAGE axis has been implicated in TBI and TBI-induced lung injury (46). A recent clinical study showed that levels of HMGB1 in the plasma and CSF (Cerebrospinal Fluid) of TBI patients are increased and that higher levels of HMGB1 contributes to the pathogenesis of TBI and poor outcome (88). In another study, increased systemic levels of HMGB1 were associated with poor lung function and worsened outcomes due to acute lung

injury (89). Therefore, it appears that HMGB1 activation of inflammasomes might play an important role in regulation of inflammatory mechanisms in systemic complications of TBI.

Conclusion

In summary, recent findings suggest that a “Neural-Respiratory-Inflammasome Axis” contributes to systemic inflammation after brain injury, which affects the lungs. Moreover, this finding opens the possibility of developing potential pharmacological agents that may reduce TBI-induced lung damage (68). Both inflammasome inhibition and EV uptake inhibition have been studied as potential targets for therapeutic intervention strategies in various diseases. It has been shown that an anti-ASC antibody has potential as one therapeutic option for TBI and TBI-induced lung injury, which can block inflammasome activation and the subsequent prevention of pyroptosis (Fig 2). Additionally, inflammasome proteins can also be used as promising biomarkers for TBI severity and the development of TBI-induced lung injury. The other treatment used in this study was Enoxaparin (Fig 2.) that is not clinically indicated for TBI, but recent studies have shown that it reduced cerebral edema and neurological recovery after TBI (90). Enoxaparin is one of the preferred drugs for venous thrombotic events prophylaxis in trauma but is often not given to TBI patients due to the fear of possible intracranial hemorrhage from its anti-coagulant properties (90). However, in the last two decades, unexpected but potent anti-inflammatory properties of heparinoids have been reported (90). The anti-inflammatory properties of Enoxaparin along with its ability to block EV uptake can provide promising therapeutic benefits for EV-mediated inflammatory diseases. Therefore, novel findings from of an EV-mediated Neural-Respiratory Inflammasome Axis provide therapeutic intervention strategies than may be beneficial in treating TBI-induced systemic complications.

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Figure1.

Timeline: A history of milestones in TBI-induced lung injury research.

Fig. 2. Proposed model of EV-mediated inflammasome signaling and therapeutic intervention for TBI-induced ALI.

After TBI, the blood brain barrier is disrupted and EV's containing inflammasome cargo are released into the systemic circulation. EV containing inflammasomes are taken up by target cells (e.g. pulmonary endothelial cells) in the lungs. Enoxaparin prevents EV uptake into lung cells. Therefore, inflammasome activation, which mediates processing and release of mature IL-1 β and IL-18, is reduced due to blockage of EV uptake. This leads to the inhibition of pyroptosis and prevents the development of ALI/ARDS. Anti-ASC blocks inflammasome assembly, thus inhibiting capase-1 activation and the release of IL-1 β and IL-18 and pyroptosis in lung cells.

Table 1.

Systemic Complications after TBI

Organ System	Incidence of Organ Dysfunction (%)
Respiratory	81
Cardiovascular	52
Coagulation	17
Renal	8
Hepatic	7

(adapted from Zygun et al., 2005) (26)

Table 2.

Clinical Features of ALI/ARDS

	Definition of ALI/ARDS		
Onset	Within 7 days		
Radiography	Bilateral Pulmonary Infiltrates		
Edema	Presence of lung edema		
Hypoxemia	< 5cm H ₂ O		
PaO ₂ /FiO ₂	Mild 200 < PaO ₂ /FiO ₂ < 300	Moderate 100 < PaO ₂ /FiO ₂ < 200	Severe PaO ₂ /FiO ₂ < 100