

Brain injury requires lung protection

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Abstract: The paper entitled “The high-mobility group protein B1-Receptor for advanced glycation endproducts (HMGB1-RAGE) axis mediates traumatic brain injury (TBI)-induced pulmonary dysfunction in lung transplantation” published recently in *Science Translational Medicine* links lung failure after transplantation with alterations in the axis HMGB1-RAGE after TBI, opening a new field for exploring indicators for the early detection of patients at risk of developing acute lung injury (ALI). The lung is one of the organs most vulnerable to the inflammatory cascade triggered by TBI. HMGB1 is an alarm in that can be released from activated immune cells in response to tissue injury. Increased systemic HMGB1 concentration correlates with poor lung function before and after lung transplant, confirming its role in acute ALI after TBI. HMGB1 exerts its influence by interacting with several receptors, including the RAGE receptor. RAGE also plays an important role in the onset of innate immune inflammatory responses, and systemic levels of RAGE are strongly associated with ALI and clinical outcomes in ventilator-induced lung injury. RAGE ligation to HMGB1 triggers the amplification of the inflammatory cascade involving nuclear factor- κ B (NF- κ B) activation. Identifying early biomarkers that mediate pulmonary dysfunction will improve outcomes not only in lung transplantation, but also in other scenarios. These novel findings show that upregulation of the HMGB1-RAGE axis plays an important role in brain-lung crosstalk.

Keywords: Traumatic brain injury (TBI); acute lung injury (ALI); HMGB1; RAGE; inflammation; lung transplantation

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Traditionally, the management of patients with acute brain injury focused on monitoring brain function and improving neurological recovery. However, patients with severe acute brain injury are at risk of developing dysfunction of other organs, especially of the lung. Thus, outcome in patients with acute brain injury depends on more than just neurological recovery. A recent observational multicenter study (1) carried out in 198 intensive care units (ICUs) in 24 European countries showed that neurological patients developed ICU-acquired sepsis and respiratory failure more frequently than other patients, and acute respiratory distress syndrome was independently associated with a higher risk of death in the ICU.

Brain injury seems to increase lung vulnerability and treatments that are essential to sustain lung function or

adequate hemodynamics might further aggravate vulnerable lungs. In a randomized controlled trial on the prevention of secondary ischemic insults after severe head injury, Robertson *et al.* (2) found that patients managed with higher cerebral perfusion pressure (70 *vs.* 50 mmHg) were five times more likely to develop ARDS. High pulmonary vascular flows might exacerbate ventilator-induced lung injury by deforming endothelial cells, raising cytoskeletal tension, and promoting vascular stress failure, and these effects are independent of the effects of high flows on pulmonary vascular pressures (3). At the transcriptional level, shear stress activates nuclear factor- κ B (NF- κ B) translocation with the consequent activation of NF- κ B promoters (4).

Several experimental studies have shown that lung injury

occurs shortly after brain injury. Ultrastructural changes in type II pneumocytes such as mitochondrial edema and chromatin disintegration in the nucleus have been observed within 2 hours of traumatic brain injury (TBI) (5). Within 3 hours, TBI triggers an inflammatory response in the lungs similar to that induced by direct injury through high tidal volume ventilation; interestingly, these phenomena occur in the context of relatively normal lung function without evidence of important structural changes (6). However, brain injury not only damages healthy lungs, but also exacerbates the damage in lungs with preexisting lesions (7). Massive brain injury predisposes to lung injury, and this effect occurs earlier during injurious mechanical ventilation (8).

Physiologic measurements commonly used at bedside to monitor hemodynamic and respiratory system mechanics fail to identify early lung deterioration. This is particularly important in the setting of human lung transplantation. A recent study demonstrated that a lung protective strategy in potential organ donors resulted in a higher number of eligible donors and harvested lungs compared with a conventional strategy (9); interestingly, however, ventilation strategy (conventional or protective) had no effect on the number of harvested hearts, livers, and kidneys (9). Recent studies have also found that lung protection is an independent predictor of outcome in patients with acute brain injury (10). Exposure to high tidal volume ventilation is an important risk factor for development of ARDS after intubation for intracerebral hemorrhage (10). Lastly, intact brains can control and inhibit cytokine release via neural pathways through the vagus nerve (11), and stimulation of the anti-inflammatory cholinergic pathway mitigates mechanical injury caused by repetitive cyclic stretch associated with ventilator-induced lung injury (12). However, it is not known whether these effects are preserved in injured brains.

In light of all this evidence, management of brain-injured patients now aims to both improve neurologic outcome and prevent respiratory failure by adjusting modifiable risk factors or modulating brain-induced inflammation of distant organs.

In a recent attempt to elucidate the mechanisms involved in the link between TBI and acute lung injury (ALI), Weber *et al.* (13) used a mouse model to explore the role of the HMGB1-RAGE axis in lung dysfunction after TBI. Mice with TBI developed ALI and had higher systemic levels of HMGB1 (13). TBI promoted lung dysfunction

through decreasing lung compliance and impairing gas exchange. The RAGE receptor played an important role in ALI secondary to TBI. Moreover, the authors contrasted HMGB1 blood levels in lung donor patients with the derangement in oxygenation capabilities and lung function in the lungs before and after lung transplantation, linking lung failure after transplantation with the alterations observed in the HMGB1-RAGE axis after TBI (13).

Several authors have noted the importance of brain-lung crosstalk. The brain orchestrates the homeostatic equilibrium of the whole body through regulatory processes involving the autonomic, endocrine, and immune systems (11,14,15). For this reason, brain derangements can have deleterious consequences in other organs. In the study discussed here, Weber *et al.* (13) found that TBI, an extrapulmonary clinical condition, predisposes healthy lungs to ALI.

The lung is one of the organs most vulnerable to the inflammatory cascade triggered by TBI or other acute or chronic conditions, and the inflammatory cascade can compromise pulmonary function. After TBI, mice in Weber *et al.*'s study (13) developed alterations in lung architecture, such as alveolar hemorrhage, proteinaceous debris, and neutrophilic infiltration, that contribute to deranged gas exchange and respiratory system compliance. These authors found that the response to TBI courses through a nontraditional pathophysiological inflammatory response involving HMGB1.

HMGB1 is an alarm in that can be released from activated immune cells and from stressed and/or necrotic cells in response to tissue injury. After TBI, HMGB1 is released into the extracellular space and its systemic concentration increases. Weber *et al.* (13) found that elevated serum concentration of HMGB1 correlated with poor blood oxygenation before and after lung transplant, confirming its role in ALI. Thus, evaluating HMGB1 in lung donors could help predict lung function after transplant and clinical outcome.

HMGB1 exerts its influence by interacting with several receptors, such as RAGE and some toll-like receptors (TLR). RAGE and TLR4 transmembrane receptors are highly expressed in the lung and play an important role in innate immune inflammatory responses. Emerging evidence points to RAGE as a strong candidate molecule linked to the pathogenesis of ALI. Systemic levels of RAGE are strongly associated with clinical outcomes in ventilator-induced lung injury (16). RAGE ligation promotes increased

RAGE expression and amplification of the inflammatory signal. RAGE is promising as a biomarker of type I alveolar cell injury, because plasma RAGE concentrations are higher in patients with ALI than in healthy controls or patients with hydrostatic edema (17). Interestingly, Weber *et al.* (13) found high expression of RAGE in lung tissue. Moreover, they found enhanced translocation of NF- κ B p65 and p50 from the cytoplasm to the nucleus in alveolar type 2 cells, indicators of NF- κ B activation 24 hours after stimulation with HMGB1. In this sense, these authors demonstrated that blocking the HMGB1-RAGE axis improved lung function in this murine model of TBI by reducing hypoxia and increasing lung compliance. RAGE may be an indicator of disease severity and will help the early detection of patients at risk of developing ALI.

Furthermore, it is important to note that TBI is frequently associated with altered blood-brain barrier (BBB) integrity, resulting in the systemic release of different factors that can be used as molecular biomarkers of TBI, including glial fibrillary acidic protein, neuron specific enolase, and in particular S100B, which in turn is also a RAGE-ligand participating in different pathologies (18). Stabilization of the BBB after TBI could be a promising strategy to limit neuronal inflammation and secondary damage.

Identifying early biomarkers or common pathways mediating pulmonary dysfunction may be crucial to attain better outcomes not only in the field of lung transplantation, but also in other clinical scenarios leading to ALI in patients with other diseases. These novel findings suggest that upregulation of the HMGB1-RAGE axis plays an important role in augmenting lung injury through brain-lung crosstalk mechanisms. Modulation of HMGB1 and RAGE may provide a novel and effective therapeutic approach to mitigate TBI-induced lung inflammation.

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