Kidney-lung cross talk during ARDS: mitochondrial DAMPs join the conversation

Jack Varon and Joshua A. Englert

Division of Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts and Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio

Acute respiratory distress syndrome (ARDS) is characterized by hypoxemia and bilateral radiographic lung infiltrates in response to a local or systemic insult. Infection is the most common cause of ARDS, including viral infection with SARS-CoV2. The ongoing COVID19 pandemic has highlighted the lethality and morbidity of ARDS. Although some patients with ARDS die from refractory hypoxemia and inadequate oxygenation, a larger percentage die of progressive multiorgan failure (1). Injurious cross talk between organs contributes to multiorgan failure in patients with ARDS, though the mechanisms by which this occurs remain incompletely understood.

Kidney injury is common in patients with ARDS and associated with increased mortality (2). The mainstay of therapy for ARDS is supportive care with mechanical ventilation. Unfortunately, mechanical ventilation can cause kidney injury, and patients requiring mechanical ventilation with acute kidney injury (AKI) have higher mortality compared with those without kidney injury (3). Although AKI is most often thought to be a sequela of lung injury during ARDS, the cross talk between these organs is bidirectional and lung injury can develop as a complication of AKI. Pulmonary edema from volume overload is the most recognizable pulmonary complication of renal dysfunction, but in recent years it has become clear that there are other mechanisms that contribute to lung injury following AKI (4). Prior studies have used unbiased approaches, such as transcriptomic profiling of lung tissue, to explore the mechanisms of AKI-induced lung injury (4); however, our understanding of how lung injury develops following AKI remains incomplete.

In this issue of the Journal, Hepokoski et al. (5) build upon this literature and examine mechanisms of lung injury following AKI using untargeted metabolomics in a model of renal ischemia-reperfusion (I/R) injury. They performed metabolomic profiling of the lung, kidney, and plasma following the induction of lung injury from ischemic AKI and found an increase in metabolites related to fatty acid oxidation (FAO) in both organs and the plasma. These findings suggest that mitochondrial function is impaired in the lung and plasma following renal I/R. These metabolic alterations are accompanied by the accumulation of mitochondrial damage-associated molecular patterns (mtDAMPs) including mitochondrial DNA (mtDNA) and mitochondrial transcription factor A (TFAM) in the plasma and bronchoalveolar lavage. Interestingly, when mtDAMPs isolated from ischemic kidneys were administered to uninjured mice, similar increases in FAO metabolites were seen in the lung. These data identify a potential novel mechanism by which primary ischemic injury of the kidney leads to the release of mitochondrial DAMPs, which in turn, contribute to the development of lung injury.

The mechanisms of kidney-lung cross talk during AKI have been investigated previously using preclinical models. Given that I/R and other forms of kidney injury are associated with local and systemic inflammation, several groups have studied how circulating proinflammatory cytokines can lead to lung injury. Plasma interleukin-6 (IL-6) levels are increased in patients with AKI and ARDS and in several preclinical models of AKI. Klein et al. (6) showed that IL-6-knockout mice were protected from lung injury following AKI due to ischemia or bilateral nephrectomy. Other groups have shown that neutrophil chemokines such as KC/IL-8 are increased in murine models of ischemic AKI and patients with AKI (4). Another mechanism by which injury to one organ can lead to remote injury of another is by the release of molecules known as damage-associated molecular patterns (DAMPs). Most often these molecules are intracellular proteins that lead to an inflammatory response when they are released into the extracellular space following tissue damage. Extracellular mitochondrial proteins and nucleic acids (i.e., mtDAMPs) are known to play a role in the pathogenesis of AKI from sepsis (7). Hepokoski and colleagues are the first to show that mtDAMPs from the injured kidney are released into the circulation and contribute to the development of lung injury.

Metabolic dysfunction, including impaired FAO, has been demonstrated in patients with ARDS (8). However, it is unclear if the metabolic derangements observed by Hepokoski and colleagues are the proximate cause of lung injury from mtDAMPs or a consequence of that injury. The distinction is important in that it may inform which strategies are most likely to prevent kidney-induced lung injury. Cui and colleagues (9) recently found that mice exposed to intratracheal endotoxin had impaired FAO in alveolar epithelial cells and that treatment with a therapy that upregulates FAO (i.e., fenofibrate) was protective. Their work suggests that certain metabolic derangements may be the proximate cause of...
lung injury and that treatment with drugs that restore FAO may be a viable strategy to prevent lung injury in the setting of AKI. As an alternative strategy, Hepokoski et al. suggest directly targeting mtDNA using DNase to interrupt the harmful communication between the kidney and lung. At this point it is not clear whether targeting the dangerous communication or the metabolic derangements will be a more effective strategy to prevent lung injury due to AKI.

The study by Hepokoski et al. has some limitations that are worth noting. Although the I/R model is directly relevant for renal injury observed after cardiac arrest or kidney transplantation, the authors acknowledge that complete cessation of renal blood flow is not frequently encountered in the intensive care unit (ICU). However, ischemia from kidney hypoperfusion during shock is one of the most common causes of AKI in ICU patients. It is also difficult to know if mtDAMPs play a role in the development of lung injury in patients with AKI since all of the data thus far are from a murine model. Along with the inflammatory effects from I/R, the mice studied also likely had impaired renal function, which may have contributed to the metabolic changes observed in the lung. Cell and organ metabolism are dynamic processes, and the authors investigated these changes at a single early timepoint. Finally, there is some evidence that metabolic derangements are observed after I/R of other tissue beds, suggesting that this phenomenon may not be specific to AKI-induced lung injury (10). We hope future studies will help answer these questions. Nevertheless, we commend the authors for contributing to our understanding of injurious cross talk between the kidney and lung during critical illness and believe that these findings represent an important step toward targeted therapy for ARDS.

**REFERENCES**

1. Ketcham SW, Sedhai YM, Miller HC, Bolig TC, Ludwig A, Co I, Claar D, McSparron JI, Prescott HC, Sjodin MW. Causes and characteristics of death in patients with acute hypoxic respiratory failure and acute respiratory distress syndrome: a retrospective cohort study. Crit Care 24: 391, 2020. doi:10.1186/s13054-020-03108-w.

2. McNicholas BA, Rezoagli E, Pham T, Madotto F, Giuaid E, Fanelli V, Bellani G, Griffin MD, Ranieri M, Laffey JG. Impact of early acute kidney injury on management and outcome in patients with acute respiratory distress syndrome: a secondary analysis of a multicenter observational study. Crit Care Med 47: 1216–1225, 2019. doi:10.1097/CCM.0000000000003832.

3. Hepokoski M, Engler JT, Baron RM, Crotty-Alexander LE, Fuster MM, Beittler JR, Malhotra A, Singh P. Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney. Am J Physiol Renal Physiol 312: F654–F660, 2017. doi:10.1152/ajprenal.00523.2016.

4. Fauvel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. Nat Rev Nephrol 12: 49–60, 2016. doi:10.1038/nrneph.2015.58.

5. Hepokoski M, Wang J, Li K, Li Y, Gupta P, Mai T, Moshensky A, Alotaibi M, Crotty-Alexander LE, Malhotra A, Singh P. Altered lung metabolism and mitochondrial DAMPs in lung injury due to acute kidney injury. Am J Physiol Lung Cell Mol Physiol. In press. doi:10.1152/ajplung.00578.2020.

6. Klein CL, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Fauvel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. Kidney Int 74: 901–909, 2008. doi:10.1038/ki.2008.314.

7. Tsuji N, Tsuji T, Ohashi N, Kato A, Fujigaki Y, Yasuda H. Role of mitochondrial DNA in septic AKI via toll-like receptor 9. J Am Soc Nephrol 27: 2009–2040, 2016. doi:10.1681/ASN.2015040376.

8. Siempos II, Ma KC, Imamura M, Baron RM, Fredenburg LE. Huh J-W, Moon J-S, Finkelstein EJ, Jones DS, Lizardi MT, Schenck EJ, Ryter SW, Nakahira K, Choi AM. RIPK3 mediates pathogenesis of experimental ventilator-induced lung injury. JCI Insight 3: e97102, 2018. doi:10.1172/jci.insight.97102.

9. Cui H, Xie N, Banerjee S, Ge J, Guo S, Liu G. Impairment of fatty acid oxidation in alveolar epithelial cells mediates acute lung injury. Am J Respir Cell Mol Biol 60: 167–178, 2019. doi:10.1165/rcmb.2018-0152OC.

10. Mansour Z, Charles AL, Kindo M, Pottecher J, Chamaraux-Tran TN, Lejay A, Zoli J, Mazzucotelli JP, Geny B. Remote effects of lower limb ischemia-reperfusion: impaired lung, unchanged liver, and stimulated kidney oxidative capacities. Biomed Res Int 2014: 392390, 2014. doi:10.1155/2014/392390.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

J.V. and J.A.E. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.