Stretching to Understand How Proteostasis and the Unfolded Protein Response Regulate Lung Injury

The alveolocapillary barrier in the lung permits gas exchange during normal breathing and is largely impermeable to solute flux. During infections or excessive stretch, the barrier is disrupted, leading to increased permeability that can lead to pulmonary edema accumulation and impaired edema clearance, which are hallmarks of the acute respiratory distress syndrome (ARDS) (1–4). Mechanical ventilation, although often lifesaving in patients with respiratory failure, may cause ventilator-induced lung injury (VILI) and worsen preexisting lung injury, and thereby increase the mortality of patients with ARDS (5–8).

Proteome homeostasis (proteostasis) is a biological process that regulates protein folding, processing, trafficking, and timely degradation to maintain cell and tissue homeostasis (9). The integrated stress response and unfolded protein response (UPR) are evolutionarily conserved pathways to restore cellular homeostasis when endoplasmic reticulum (ER) stress leads to activation of the integrated stress response via three main sensors in the ER membrane: PERK, IRE1, and ATF6 (10, 11). These signals promote the synthesis of new proteins to cope with stress while inhibiting general protein translation (9, 11). A role for proteostasis in inflammatory airway stress diseases such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis, as well as alpha-1 antitrypsin deficiency, has been described (9). However, there are no reports on the role of the UPR pathway in epithelial stretch-induced injury and VILI, which is the focus of the report in this issue of the *Journal* by Dolinay and colleagues (pp. 193–203) (12).

Dolinay and colleagues (12) describe differentially expressed genes that are relevant to the integrated stress response pathway in stretched alveolar epithelial cells and in a lung injury model (13, 14). *In vitro* experiments in rat alveolar epithelial cells revealed that the PERK/ATF4/CHOP signaling was activated during high levels of stretch that induced cell death and increased epithelial barrier permeability (15). Interestingly, the investigators show that an inhibitor of PERK prevents epithelial barrier permeability and cell death *in vitro*. Importantly, they also report that pretreatment with the PERK inhibitor GSK2606414 improved markers of lung injury in an *in vivo* rodent model of VILI. Administration of the PERK inhibitor GSK2606414 to rats before mechanical ventilation decreased the UPR response and improved the alveolocapillary barrier permeability and lung injury score. Moreover, administration of the PERK inhibitor was associated with lower levels of interleukin 18 in bronchoalveolar lavage fluid and serum of mechanically ventilated rats.

A previous report relevant to ARDS pathophysiology suggested that during hypoxic conditions, UPR is activated via the PERK/ATF4/CHOP pathway (14). The current study by Dolinay and colleagues is important because it is the first to implicate the unfolded protein response in the pathophysiology of VILI or ventilator-associated lung injury, which is of biologic importance, clinical relevance, and significant interest to this field. Although the investigators did not explore whether PERK activation was directly responsible for cell death and increased permeability, nor the specific mechanisms by which the PERK inhibitor prevented injury in this model, the results alleviating the lung injury in the *in vivo* model of VILI are striking. The study has some limitations. The data on cytokine production are limited, so further research regarding the interplay of integrated stress response-cytokines and VILI are warranted. Many studies have detected high levels of cytokines during high tidal volume ventilation in animal models and patients. The high cytokine levels during VILI have been implicated in amplifying lung injury and inducing multiorgan failure in patients with ARDS (16). Thus, it is surprising to find that the PERK inhibitor mostly affects the levels of IL-18. The investigators articulate a rationale to focus on the PERK/ATF4/CHOP pathway; however, it would be of interest to explore whether the ATF6 pathway plays a role or is also involved in the stretch-induced lung injury.

Although the report does not explore it in detail, it suggests a role for epithelial-derived cytokines, particularly IL-18, during cyclic stretch. It also invites future studies exploring whether the epithelium-released cytokines prime the release of cytokines by macrophages; such studies could shed light on the complexity of the systemic effects of VILI/VALI and multiorgan dysfunction in ARDS.

The findings of Dolinay and colleagues are novel and important, as they may lead to new translational approaches in patients with VILI and to identification of new targets of therapy in mechanically ventilated patients with ARDS. They also stimulate inquiry on the paradigm shift in focus toward prevention, rather than treatment, of VILI and ARDS. The current standard-of-care ventilation strategy to prevent VILI/ventilator-associated lung injury attempts to reduce alveolar overdistension and minimize recruitment–derecruitment by lowering tidal volumes to 6 ml/kg combined with optimal positive end-expiratory pressure (7). The potential strategy of modulating proteostasis and, more specifically, the unfolded protein response in models of lung injury and patients at risk for ARDS could represent a new paradigm to aid in preventing lung injury in mechanically ventilated patients. ■

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