A Cation Channel Protects the Stretched Lung

Overdistension of the lung causes ventilator-induced lung injury (VILI), and VILI is a severe consequence of mechanical ventilation (1). Yet, it is unclear why not every patient develops VILI under conditions such as high-volume mechanical ventilation and unequal ventilation distribution (1). One potential explanation is a difference in signaling mechanisms within the alveolar-capillary unit, which is comprised of lung alveolar epithelium and alveolar-capillary endothelium, separated by a thin basement membrane (2). Changes in ventilation pressure are directly reflected in the alveolar pressure, and increased alveolar pressure leads to enhanced stretch of the alveolar epithelium and endothelium. Various signaling pathways have been shown to be induced by cyclic stretch in pulmonary endothelial cells (ECs). Both edemagenic agents (e.g., thrombin and histamine) and proinflammatory cytokines (e.g., IL-8 and TNF-α) contribute to the vascular leakage observed in VILI (3, 4). In addition to these signals, stretch-activated channels are important sensors of mechanical loading cues in ECs (5). Piezo1 is a nonselective cation channel that allows for the influx of calcium and sodium into ECs (5).

In this issue of the *Journal*, Zhong and coworkers (pp. 168–177) identify a protective role for Piezo1 in adherens junctions and lung vascular barrier function in alveolar capillary ECs (6). The authors examined Piezo1 and vascular endothelial (VE)-cadherin expression in explanted human lungs from patients undergoing short-term or long-term mechanical ventilation. Piezo1 and the adherens junction component VE-cadherin were both downregulated in long-term mechanically ventilated samples. Endothelial Piezo1 deficiency caused increased endothelial permeability *in vivo* and augmented permeability in response to mechanical loading *in vitro*. In this study, the authors further identified the cysteine protease calpain as a downstream mediator of the protective effects of Piezo1. They found that calpain cleaved Src kinase in response to mechanical loading, thus preventing disassembly of the adherens junctions and thereby stabilizing the endothelial barrier. *In vivo*, pharmacological activation of calpain caused Src cleavage and restored lung endothelial barrier in endothelium-specific Piezo1 knockout mice undergoing high-volume ventilation.

The study by Zhong and colleagues raises a number of interesting questions about the basic mechanotransduction of Piezo1 in the pulmonary endothelium. The authors show that Piezo1 only plays a role during overdistension or prolonged distension of the endothelium. The pulmonary endothelium is constantly exposed to limited cyclical stretch during normal breathing and appears to be independent of Piezo1 for the maintenance of barrier function under physiological conditions. These findings are similar to previous observations regarding other endothelial mechanotransductive proteins that are upregulated under pathological cyclic stretch, such as guanine nucleotide exchange factor H1 (7) and VE growth factor receptor 2 (8). Zhong and colleagues point to Piezo1 as a protective mechanotransducer that functions only during injury, which makes it a more attractive therapeutic target.

It is difficult to parse the role of the individual mechanical contributions of shear stress, stretch, and pressure in the pulmonary vasculature, as all three of these mechanical stimuli are present at the same time during both physiological and pathological ventilation, albeit at different levels. The authors note that in the current study, they found that activation of calpain normalized lung barrier function in a high tidal mechanical ventilation model, whereas previous work from their group showed that Piezo1 mediated the degradation of VE-cadherin and catenin proteins in an elevated hydrostatic pressure model (9). This contrast highlights the importance of the changes that occur in both the magnitude and direction of mechanical force in pulmonary EC signaling. These are encouraging results that indicate that Piezo1 may be a clinically relevant target in the future.

Although targeting Piezo1 is an exciting possibility, further studies will be required to examine the role of the underlying conditions of patients undergoing mechanical ventilation. For example, the inflammatory environment plays a role in the mechanosensitivity of Piezo1 in astrocytes and adipocytes (10, 11). Therefore, it will be intriguing to examine two-hit rodent mechanical ventilation models with a closer look into the role of Piezo1 in a proinflammatory environment before and during increased stretch due to mechanical ventilation.

To move forward from benchside results to clinical-translational applications, it will be necessary to develop specific therapeutic approaches to target the Piezo1 channel. Such approaches could include restoring Piezo1 expression and promoting the activity of existing Piezo1 channel molecules, for example, by using Yoda1, which stabilizes the open state of the Piezo1 channel and hence increases activation (12). One alternative approach based on the current study would be to improve endothelial barrier function by activating the Piezo1 downstream mediator calpain. Based on the study by Zhong and colleagues, as well as previous studies in the literature, promoting Piezo1 activity and expression may be a valuable treatment option not only for acute respiratory distress syndrome/VILI but also for pulmonary hypertension, as Piezo1 reduces pulmonary vasoconstriction via increased nitric oxide and calcium influx (5). With more and more data showing a protective effect of Piezo1, it will be important to demonstrate the relationship between the timing of the channel opening of Piezo1 and its protective effects to facilitate the design of therapeutic approaches with optimized pharmacokinetics.

In summary, we commend Zhong and colleagues for advancing our understanding of the protective mechanism of Piezo1 in the alveolar-capillary barrier. ■

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