Piezo1 in the Lung: At Last!

The search for a mechanosensitive ion channel that accounts for flow-induced vasoactivity led to the recent identification of Piezo1, a homotrimeric membrane-spanning protein complex that responds directly to mechanical distortion of the plasma membrane. In mice with endothelium-specific *Piezo1* knockout (*Piezo1ΔEC*), embryonic lethality occurs around embryonic day 9.5–11.5, the age that corresponds to the formation of the circulatory system, identifying this endothelial channel as a major determinant of vascular development (1). In *Piezo1*-transfected kidney cells, shear rates as low as 5–10 dyn/cm^2 (a range relevant to shear rates in lung microvessels) induced Piezo1-dependent endothelial Ca^{2+} increases, revealing the channel's shear-sensitive properties. Taken together, these and similar findings (2) have supported the hypothesis that endothelial Piezo1 plays a central role in the mechanotransduction of vascular shear (3).

The story, however, becomes complicated when we consider Piezo1's role as a regulator of organ perfusion. The channel is permissive to nonspecific cation transport, allowing cellular entry of divalent ions such as Ca^{2+}, as well as monovalent ions such as Na^+. Because Ca^{2+}-dependent nitric oxide (NO) production causes vasorelaxation (4), and cellular depolarization after Na^+ entry causes vasoconstriction (5), the net vascular outcome in terms of organ perfusion depends on the balance between these opposing effects of nonspecific ion entry.

In a study by Rode and colleagues (5), increases of flow in isolated mesenteric arteries induced vasoconstriction, an effect that was absent in the arteries of *Piezo1ΔEC* mice, implicating Piezo1 in the effect. Endothelial cells isolated from the arteries displayed flow-induced, Piezo1-dependent membrane depolarization, consistent with the notion that flow induces an inward current through the channel. The authors showed that because of endothelial–smooth muscle coupling, the endothelial depolarization caused voltage-gated Ca^{2+} entry in smooth muscle, which therefore caused the vasoconstriction. They proposed the fascinating hypothesis that this Piezo1 mechanism optimizes exercise performance by redistributing blood flow away from vasoconstricted nonmuscle beds, such as the mesentery, to skeletal muscle.

By contrast, Wang and colleagues, who also studied responses in isolated, precontracted mesenteric arteries, found the opposite, namely, that flow caused Piezo1-induced vasorelaxation, and that the effect was absent in arteries obtained from *Piezo1ΔEC* mice (6). Thus, unlike Rode and colleagues, Wang and colleagues implicated Ca^{2+} entry through endothelial Piezo1 as the critical mechanism underlying the vasorelaxation. Wang and colleagues showed that the vasodilatation results from a mechanistic sequence initiated by Ca^{2+}-induced release of endothelial ATP, which then signals through the P2Y2 receptor to cause Akt-induced endothelial NO synthase activation, and hence NO release. Interestingly, induced deletion of endothelial *Piezo1* caused systemic hypertension and decreased endothelial NO synthase phosphorylation at serine 1176, implicating Piezo1 as the critical mechanism that prevents systemic hypertension through constitutive NO release.

Other studies have also implicated Piezo1 in blood pressure maintenance, as the channel is the pressure sensor of baroreceptors and thereby determines pressure regulation through the baroreflex (7). Despite these exciting findings, the conflicting results of Rode and colleagues and Wang and colleagues suggest that interpretations derived from studies in isolated vessels and cells—approaches used by these authors and other groups—may complicate our understanding of physiological blood flow regulation.

Given the burgeoning excitement about the involvement of Piezo1 in systemic vascular beds, as detailed above, as well as in multiple other aspects of systemic regulation (8–10), the absence of information regarding the role of Piezo1 in the pulmonary circulation stands out. The report by Lhomme and colleagues in this issue of the *Journal* (pp. 650–658) now rectifies this omission (11). The authors ask whether Piezo1 is involved in hypoxia-induced pulmonary vasoconstriction. They demonstrate that Piezo1 is well expressed in endothelium of mouse intrapulmonary arteries (IPAs), and that pharmacological activation of Piezo1 with the agonist Yoda1 (12) induces Ca^{2+} increases and NO production in endothelial cells, and relaxes precontracted IPAs. In agreement with responses reported in mesenteric arteries (6), the relaxation is blocked in IPAs from *Piezo1ΔEC* mice, thereby affirming Piezo1's role as a lung vasodilator.

A surprising finding in Lhomme and colleagues's study came when they questioned the disease relevance of Piezo1 in the setting of chronic hypoxia (CH). Their findings indicate that CH did not alter lung endothelial Piezo1 expression, nor did it abrogate Yoda1's ability to induce pulmonary artery relaxation, as revealed through the IPA model and by measurements of right ventricular pressure. Accordingly, it was reasonable to expect that through its vasodilatory effect, Piezo1 would inhibit pulmonary vasoconstriction, and that in the absence of Piezo1 the vasoconstriction and right ventricular hypertrophy (RVH) would both be more severe. However, these expectations did not bear out, as the CH-induced RVH was similar in wild-type and *Piezo1ΔEC* mice. This negative effect of Piezo1 on RVH is an important finding because it leaves open the question as to what extent mechanisms induced by Piezo1 might modulate the onset of pulmonary hypertension.

Clearly, further studies are warranted to better understand Piezo1's function in the lung. For example, the extent to which Piezo1 regulates acute hypoxic vasoconstriction requires clarification. The significance here could relate to Piezo1's distribution in the pulmonary arterial bed, as the distribution could be a determinant of ventilation/perfusion ratios in the setting of hypoxia-inducing diseases. Furthermore, pulmonary Piezo1 may have more than one

class of effects. Thus, as Lhomme and colleagues point out, its pharmacologically accessible vasodilatory effect may have therapeutic potential. There may also be a chronic and perhaps subtler Piezo1 effect whereby long-term depolarization in endothelium and smooth muscle sets up the vascular remodeling mechanisms seen in many lung diseases. Because gain-of-function mutations in the human *Piezo1* cause autosomal-recessive congenital lymphatic dysplasia (13), the role of Piezo1 in lung lymphatic biology needs to be addressed. Evidently, Piezo1 has a future in the lung—one that is likely to be promising and exciting. ■

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