Roles of Canonical Transient Receptor Potential 6 in Basal \([\text{Ca}^{2+}]_i\) Regulation in Pulmonary Venous Smooth Muscle Cells Under Chronic Hypoxia-Induced Hypertension

Takeo Itoh, PhD

**P**ulmonary hypertension is thought to result from a number of disorders, including left heart disease, lung disease, and chronic thromboembolic disease.\(^1\)\(^2\) It is characterized by progressive remodeling of the distal pulmonary arteries, such as medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening with moderate perivascular inflammatory infiltrates, and thrombotic lesions.\(^1\)\(^2\)\(^3\) Chronic hypoxia (CH) induces such vascular remodeling not only in the pulmonary artery but also in the pulmonary vein (that plays essential roles in regulating the recruitment of blood flow from alveolar wall capillaries). Although much progress has been made to clarify the mechanism underlying CH-induced pulmonary artery remodeling, less attention has been paid to that in pulmonary vein remodeling.

**Editorial**

In this issue of the Journal, Peng et al\(^5\) report that CH...
Roles of TRPC6 in PH

increases basal intracellular Ca²⁺ concentration ([Ca²⁺]i) in pulmonary vein smooth muscle cells (PVSMCs) and induces their proliferation, as found in pulmonary artery smooth muscle cells (PASMCs). An increase in SMC [Ca²⁺]i is thought to be an important signal for CH-induced pulmonary vascular remodeling and could result from activation of 2 pathways: Ca²⁺ influx from the extracellular space and Ca²⁺ release from the intracellular storage sites (Figure). The former is caused by activation of voltage-dependent L-type Ca²⁺ channels (VDCC), store-operated Ca²⁺ channels (SOCC) and receptor-operated Ca²⁺ channels (ROCC). As shown in Figure, SOCC mediates store-operated Ca²⁺ entry (SOCE), which is activated by depletion of the Ca²⁺ stores. ROCC mediates receptor-operated Ca²⁺ entry (ROCE). Canonical transient receptor potential (TRPC) proteins constitute a family of 7 nonselective cation channels and have been suggested as the molecular components of SOCC and ROCC. TRPC channels require the phospholipase C (PLC) pathway for activation, either directly by diacylglycerol (DAG), such as TRPC2, TRPC3, TRPC6, and TRPC7, or indirectly through an as yet unknown mechanism, such as TRPC1, TRPC4, and TRPC5. Peng et al. found in rat PVSMCs that (1) CH-induced basal [Ca²⁺]i increase was blocked by SKF-96365 (an inhibitor of ROCE and SOCE) but not by the VDCC blocker nifedipine; (2) CH enhanced ROCE [that is activated by 1-oleoyl-2-acetyl-sn-glycerol (a membrane-permeable DAG analog)], but it had no effect on SOCE; (3) CH increased expression of TRPC6 (but neither TRPC1 nor TRPC3); and (4) downregulation of TRPC6 (but not TRPC1) with siRNA attenuated the ROCE. The authors also found that (5) TRPC6 knockdown attenuated CH-induced PVSMC proliferation. All these findings support the hypothesis that CH enhances TRPC6 expression and induces basal [Ca²⁺]i increase mainly through activation of ROCE in PVSMCs.

The mechanism underlying CH-induced basal [Ca²⁺]i increase in pulmonary vascular SMCs may be different between artery and vein. For example, it was found that in rat PASMCs CH upregulates both TRPC1 and TRPC6 and elevates basal [Ca²⁺]i via activation of SOCE. These results provide a hint that SOCC and ROCC contribute to CH-induced basal [Ca²⁺]i elevation in PASMCs and PVSMCs, respectively. Furthermore, pivotal roles played by TRPC6 on basal [Ca²⁺]i regulation have been suggested in both vessels under such conditions. To develop better treatment for pulmonary hypertension, further research is required to clarify the mechanism underlying CH-induced pulmonary vascular remodeling in not only the artery but also the vein.

Acknowledgments

This work was partially supported by JSPS Kakenhi Grants numbers 25460655 and 25293295.

References