Essential Role of Phospholipase C-γ1 in Hypoxia-Induced Pulmonary Vasoconstriction and Hypertension

Vishal R Yadav, Yun-Min Zheng and Yong-Xiao Wang*

Center for Cardiovascular Sciences, Albany Medical College, Albany, New York, USA

Hypoxia-induced Pulmonary Vasoconstriction (HPV) is an essential physiological process which ensures proper ventilation-perfusion matching in pulmonary circulation with the ultimate aim of optimizing systemic oxygen delivery. However, this cellular response can become a key pathological process leading to pulmonary artery hypertension and right heart failure. An increase in intracellular calcium concentration ([Ca²⁺]) in Pulmonary Artery Smooth Muscle Cells (PASMCs) plays a crucial role in producing HPV. However, the underlying signaling mechanisms are not completely understood [1-3]. Thus, the identification of the molecular players involved in HPV is imperative for a deeper and broader understanding of hypoxic pulmonary artery vasoconstriction and other related diseases.

Phospholipase C (PLC) is a key enzyme family for numerous physiological and pathological cellular responses in the cardiovascular system. Upon activation, PLC hydrolyses the plasma membrane-bound phosphatidylinositol bisphosphate (PIP₂) into inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG). IP₃ opens IP₃ receptors (IP₃Rs) on the Sarcoplasmic Reticulum (SR) membrane to induce Ca²⁺ release. DAG activates protein kinase C to lead Ca²⁺-dependent cellular responses. Among all known isoforms, PLCγ1 has been shown to be highly expressed in the lungs [4], and involved in reactive oxygen species (ROS)-evoked increase in [Ca²⁺]i in PC-12 cell line [5], cultured human venous SMCs [6] and cultured rat astrocytes [7]. ROS are known to be critical for the hypoxic increase in [Ca²⁺]i in PASMCs [1,8]. Taken together, it was conjectured that PLCγ1 would be a major regulator in the hypoxic increase in [Ca²⁺]i, in PASMCs and HPV.

We conducted a series of experiments to test the aforementioned exciting assumption. Our data have revealed that PLCγ1 is activated in pulmonary arteries following acute hypoxic exposure. Equally importantly, lentiviral shRNA-mediated knock-down of PLCγ1 or pharmacological inhibition of PLC significantly reduces hypoxia-induced increase in [Ca²⁺]i in PASMCs and HPV [9]. It is interesting to note that PLCγ1 enhances survival of MEF cells [10] and cardiomyocytes during oxidative stress [11]. Patterson and coworkers have reported that PLCγ is required for agonist-induced Ca²⁺ entry in PC12 and A7r5 cells by controlling TRPC3 trafficking and expression on the plasma membrane [12,13]. Homozygous PLCγ1 gene knockout mice show a viable and important approach in developing new and more effective therapeutic strategies for hypoxic pulmonary artery hypertension and other related diseases.

References

*Corresponding author: Dr. Yong-Xiao Wang, Center for Cardiovascular Sciences, Albany Medical College, Albany, New York, USA. E-mail: wangy@mail.amc.edu

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