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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 ($[Ca^{2+}]_i$) 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 hypertension and other related diseases.

Phospholipase C (PLC) is a key enzyme family for numerous physiological and pathological cellular responses in the cardiovascular system. On activation, PLC hydrolyses the plasma membrane-bound phosphatidylinositol bisphosphate (PIP_2) into inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 opens IP_3 receptors (IP_3Rs) on the Sarcoplasmic Reticulum (SR) membrane to induce Ca^{2+} release. DAG activates protein kinase C to lead Ca^{2+}-dependent cellular responses. Among all known isoforms, PLCγ1 has shown to be highly expressed in the lungs [4], and involved in reactive oxygen species (ROS)-evoked increase in $[Ca^{2+}]_i$ 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 $[Ca^{2+}]_i$ in PAMSCs [1,8]. Taken together, it was conjectured that PLCγ1 would be a major regulator in the hypoxic increase in $[Ca^{2+}]_i$ 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 $[Ca^{2+}]_i$ in PASMCs and HPV [9]. It is interesting to note that PLCγ1 enhances survival of MEF cells [10] and cardiomycytes during oxidative stress [11]. Patterson and coworkers have reported that PLCγ is required for agonist-induced Ca^{2+} entry in PC12 and A7r5 cells by controlling TRPC3 trafficking and expression on the plasma membrane [12,13]. Homozygous PLCγ1 gene knockout mice show the early embryonic lethality [14], further reinforcing the functional importance of PLCγ1.

Our very recent studies have further unveiled that acute hypoxic exposure causes significant phosphorylation of PLCγ1 at tyrosine 783, which is regarded as vital for activation of PLCγ1 [15], in PASMCs [9]. Gene silencing of Rieske Iron-Sulfur Protein (RISP) to inhibit ROS generation at the mitochondrial complex III [8] fully abolishes the acute hypoxic phosphorylation of PLCγ1 [9]. Similarly, treatment with the mitochondrial complex III inhibitor myxothiazol to block ROS generation [16-18] completely inhibits the hypoxic response as well. Collectively, the hypoxic activation of PLCγ1 in PASMCs is mediated by RISP-dependent mitochondrial ROS production. Whether or not hypoxic activation of PLCγ1 is directly dependent on ROS or ROS mediated interplay molecules is a matter of further investigation. Nevertheless, targeting PLCγ1 on the plasma membrane may provide a viable and important approach in developing new and more effective therapeutic strategies for hypoxic pulmonary artery hypertension and other related diseases.

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***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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