

Essential Role of Phospholipase C- γ 1 in Hypoxia-Induced Pulmonary Vasoconstriction and Hypertension

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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_3 Rs) 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, $PLC\gamma$ 1 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 $PLC\gamma$ 1 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 $PLC\gamma$ 1 is activated in pulmonary arteries following acute hypoxic exposure. Equally importantly, lentiviral shRNA-mediated knock-down of $PLC\gamma$ 1 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 $PLC\gamma$ 1 enhances survival of MEF cells [10] and cardiomyocytes during oxidative stress [11]. Patterson and coworkers have reported that $PLC\gamma$ 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 $PLC\gamma$ 1 gene knockout mice show the early embryonic lethality [14], further reinforcing the functional importance of $PLC\gamma$ 1.

Our very recent studies have further unveiled that acute hypoxic exposure causes significant phosphorylation of $PLC\gamma$ 1 at tyrosine 783, which is regarded as vital for activation of $PLC\gamma$ 1 [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 $PLC\gamma$ 1 [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 $PLC\gamma$ 1 in PASMCs is mediated by RISP-dependent mitochondrial ROS production. Whether or not hypoxic activation of $PLC\gamma$ 1 is directly dependent on ROS or ROS mediated interplay molecules is a matter of further investigation. Nevertheless, targeting $PLC\gamma$ 1 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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