Ca²⁺ Signal Through Inositol Trisphosphate Receptors for Cardiovascular Development and Pathophysiology of Pulmonary Arterial Hypertension

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Keywords

Inositol trisphosphate receptor · Calcium signaling · Cardiovascular system
Pulmonary arterial hypertension

Inositol triphosphate receptor (IP₃R) is an intracellular Ca²⁺ release channel located on the membrane of the sarco/endoplasmic reticulum (SR/ER), a major intracellular storage site for Ca²⁺. There are three subtypes of IP₃R (IP₃R1, 2, and 3), each of which is known to have versatile roles in the pathophysiology of many organs [1].

In the cardiovascular system, all subtypes of IP₃Rs are expressed from embryonic to postnatal periods. We previously reported that IP₃R1-IP₃R2 or IP₃R1-IP₃R3 double-knockout (DKO) mice died around embryonic day (E) 11.5 due to disorder of cardiovascular development (Fig. 13.1). IP₃R1-IP₃R2 DKO mice showed developmental defects of the myocardium and endocardial cushion, resulting from the disturbance of calcineurin/NFAT signaling [2]. IP₃R1-IP₃R3 DKO mice demonstrated hypoplasia of the outflow tract and the right ventricle of embryonic heart

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Fig. 13.1 The role of IP₃Rs for cardiogenesis, extra-embryonic vascularization, and suppression of pulmonary arterial hypertension. RV right ventricle, OFT outflow tract, PA pulmonary artery

with reduced expression levels of molecular markers for the second heart field [3]. In addition, IP₃R1-IP₃R3 DKO embryos exhibited defects in the vasculature of the labyrinth layers of the placenta, allantois, and yolk sac. Therefore, this suggests the essential redundant roles of endothelial IP₃R1 and 3 for angiogenesis during embryonic and extra-embryonic vascular development [4].

Recently, we found the specific expression of IP₃R in the pulmonary artery smooth muscle cells (PASMCs) of murine lungs. Although there are some reports that implicated IP₃R1 in vasoconstriction or remodeling in vascular smooth muscle cells [5], the precise role of IP₃Rs in PASMCs remains unknown. Since intracellular Ca²⁺ signaling in PASMCs is a major regulator for pulmonary vasoconstriction and remodeling, its dysregulation leads to the progression of pulmonary arterial hypertension (PAH). It was reported that store-operated Ca²⁺ (SOC) entry was upregulated in PASMCs with PAH patients. Our results suggest that intracellular Ca²⁺ depletion through Ca²⁺ release by IP₃R from the SR/ER may lead to the opening of SOC channels, a mechanism potentially involved in the pathophysiology of PAH (Fig. 13.1) [6].

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