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Oral Sessions

Inhibition of excessive cell proliferation by Rho kinase 2 (ROCK2) in idiopathic pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a progressive and fatal disease that is characterized by the irreversible remodeling of the pulmonary artery. Although several PAH drugs have been developed, additional drugs are needed. Rho kinases (ROCKs) are involved in the pathogenesis of PAH, and thus, their inhibitors may prevent the development of PAH. However, the therapeutic benefits of ROCK isoform-specific inhibitors for PAH remain largely unknown. The in vitro and in vivo effects of the ROCK2-specific inhibitor, KD025, were examined herein using pulmonary arterial smooth muscle cells (PASMCs) from idiopathic pulmonary arterial hypertension (IPAH) patients and monocrotaline (MCT)-induced pulmonary hypertensive (PH) rats. The expression of ROCK1 was similar between normal- and IPAH-PASMCs, whereas that of ROCK2 was markedly higher in IPAH-PASMCs than in normal-PASMCs. KD025 inhibited the accelerated proliferation of IPAH-PASMCs in a concentration-dependent manner ($IC_{50} = 289$ nM). Accelerated proliferation was also reduced by the siRNA knockdown of ROCK2. In MCT-PH rats, the expression of ROCK2 was up-regulated in PASMCs. Elevated right ventricular systolic pressure in MCT-PH rats was attenuated by KD025 (1 mg/kg/day). These results strongly suggest that enhanced ROCK2 signaling is involved in the pathogenic mechanism underlying the development of PAH, including accelerated PASMC proliferation and vascular remodeling in patients with PAH. Therefore, ROCK2 may be a novel therapeutic target for the treatment of PAH.