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HYPERTENSION

Selenoprotein P — a new player in PAH

Selenoprotein P, an extracellular protein involved in cellular metabolism, promotes the development of pulmonary arterial hypertension (PAH) and might be a useful biomarker and therapeutic target for PAH.

Using microarray analysis, Kikuchi et al. found that the gene encoding selenoprotein P had a 32-fold increased expression in pulmonary artery smooth muscle cells (PASMCs) from patients with PAH compared with PASMCs from healthy individuals. Selenoprotein P levels were also elevated in lung and serum samples from patients with PAH, and high serum selenoprotein P levels predicted a poor outcome in these patients. Assays in five strains of genetically modified mice showed that selenoprotein P deficiency prevented the development of hypoxia-induced pulmonary hypertension. Compared with wild-type mice, *Selenop*$^{-/-}$ mice exposed to chronic hypoxia had lower right ventricular systolic pressure, right ventricular hypertrophy, and pulmonary artery remodelling, whereas mice with systemic *Selenop* overexpression had increases in pulmonary hypertension parameters. PASMC-specific selenoprotein P deficiency, but not liver-specific selenoprotein P deficiency or liver-specific *Selenop* overexpression, reduced hypoxia-induced pulmonary hypertension compared with control mice. Mechanistically, selenoprotein P promoted proliferation and apoptosis resistance in PASMCs through increased oxidative stress and mitochondrial dysfunction, which were associated with activation of hypoxia-inducible factor 1α and dysregulation of glutathione metabolism.

Finally, high-throughput screening of 3,336 low-molecular-weight compounds identified sanguinarine, an orally active plant alkaloid, as a potential therapeutic agent. Sanguinarine reduced *SELENOP* expression and proliferation in human PASMCs, and ameliorated hypoxia-induced pulmonary hypertension in mouse and rat models.

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ORIGINAL ARTICLE Kikuchi, N. et al. Selenoprotein P promotes the development of pulmonary arterial hypertension: a possible novel therapeutic target. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.117.033113 (2018)
FURTHER READING Lau, E. M. T. et al. Epidemiology and treatment of pulmonary arterial hypertension. *Nat. Rev. Cardiol.* **14**, 603–614 (2017)