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<sup>−/−</sup> 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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