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.

Irene Fernández-Ruiz

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)

PULMONARY HYPERTENSION

Treatment of PAH with a PPARγ agonist

Activation of peroxisome proliferator-activated receptor-γ (PPARγ) with pioglitazone reverses metabolic changes that occur with pulmonary arterial hypertension (PAH). These findings reveal a potential therapy to prevent the development of right ventricular failure, which is the leading cause of death in patients with PAH.

PPARγ is an important metabolic regulator in vascular cells, but its role in the heart is uncertain. Investigators now show that deletion of *Pparg*, which encodes PPARγ, specifically in cardiomyocytes of mice led to biventricular systolic dysfunction and intramyocellular lipid accumulation.

In a rat model of severe PAH, oral treatment with the PPARγ agonist pioglitazone completely reversed the PAH and vascular remodelling and prevented the development of right ventricular failure. The cardiomyocyte lipotoxicity and mitochondrial disarray observed in the rat model of PAH were prevented by pioglitazone. A series of microRNA (miRNA) arrays, mRNA sequencing, and lipid metabolism studies revealed dysregulation of cardiac hypertrophy, myocardial contractility, fibrosis, and fatty acid transport and oxidation. In particular, pre-miR-197 and pre-miR-146b were upregulated in the right ventricles of rats with PAH. These miRNAs repress genes (*Cpt1b* and *Fabp4*) that drive fatty acid oxidation in cardiomyocytes, and were downregulated with pioglitazone. Of note, levels of these miRNAs were also upregulated in the pressure-overloaded right ventricles of patients with end-stage PAH.

"PPARγ activation can normalize epigenetic and transcriptional regulation primarily related to disturbed lipid metabolism and mitochondrial morphology [and] function in the failing right ventricle and the hypertensive pulmonary vasculature, representing a therapeutic approach for PAH," conclude the researchers.

Gregory B. Lim

ORIGINAL ARTICLE Legchenko, E. et al. PPARγ agonist pioglitazone reverses pulmonary hypertension and prevents right heart failure via fatty acid oxidation. *Sci. Transl Med.* **10**, eaao0303 (2018)
FURTHER READING Lau, E. M. T. et al. Epidemiology and treatment of pulmonary arterial hypertension. *Nat. Rev. Cardiol.* **14**, 603–614 (2017)

HYPERTENSION

Ambulatory versus clinic BP values

Ambulatory blood-pressure (BP) measurements are a stronger predictor of all-cause and cardiovascular mortality than clinic BP measurements, according to a Spanish registry study published in *NEJM*. Of note, masked hypertension was associated with a greater risk of death than sustained hypertension, and white-coat hypertension was also associated with an increased risk of death.

The multicentre, national cohort included 63,910 adults recruited between 2004 and 2014 in Spain. Individuals were categorized as having sustained hypertension (elevated 24-h ambulatory and elevated clinic BP), white-coat hypertension (normal 24-h ambulatory and elevated clinic BP), masked hypertension (elevated 24-h ambulatory and normal clinic BP), or normotension (normal 24-h ambulatory and normal clinic BP).

During follow-up (median 4.7 years), 3,808 patients died, and 1,295 of those patients died from cardiovascular causes. Analyses showed that a 1 s.d. increase in 24-h systolic BP was more strongly associated with all-cause mortality (HR 1.58, 95% CI 1.56–1.60) than a 1 s.d. increase in clinic systolic BP (HR 1.02, 95% CI 1.00–1.04). The corresponding risks associated with night-time ambulatory systolic pressure (HR 1.55, 95% CI 1.53–1.57) and daytime ambulatory systolic pressure (HR 1.54, 95% CI 1.52–1.56) were similar to the risk associated with 24-h systolic BP. The findings were consistent when patients were stratified according to age, sex, and other factors. Results for cardiovascular mortality were similar to those for all-cause mortality.

Importantly, masked hypertension was more strongly associated with all-cause mortality (HR 2.83, 95% CI 2.12–3.79) than sustained hypertension (HR 1.80, 95% CI 1.41–2.31). Moreover, the presence of white-coat hypertension was not benign (HR 1.79, 95% CI 1.38–2.32). "Ambulatory BP monitoring provides the best confirmation of the presence of hypertension detected in the office setting," comments Raymond Townsend in an associated editorial.

Gregory B. Lim

ORIGINAL ARTICLE Banegas, J. R. et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N. Engl. J. Med.* **378**, 1509–1520 (2018)
FURTHER READING Ruiz-Hurtado, G. et al. Has the SPRINT trial introduced a new blood-pressure goal in hypertension? *Nat. Rev. Cardiol.* **14**, 560–566 (2017)