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Diagnostic and prognostic significance of serum levels of selenoprotein P in patients with pulmonary arterial hypertension

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Background: Despite the recent progress in upfront combination therapy for pulmonary arterial hypertension (PAH), a useful biomarker for the disorder still remains to be developed. Selenoprotein P (SeP) is a glycoprotein secreted mainly from hepatocytes but also from other various kinds of cells, including pulmonary artery smooth muscle cells (PASMCs), to maintain selenium homeostasis and cellular energy metabolism. We have recently demonstrated that SeP expression in PASMCs is markedly up-regulated in PAH patients and plays crucial roles in the pathogenesis of the disorder. In this study, we thus examined whether serum levels of SeP could be a useful biomarker for the disorder.

Methods: In the experimental study, we performed gene expression microarray and in silico analyses to identify a novel therapeutic target for PAH. We also used the lung, serum, and cultured PAMSCs derived from patients with PAH for mechanistic experiments. In the clinical study, we enrolled a total of 65 consecutive patients with PAH who underwent right heart catheterization for hemodynamic assessment. We measured serum SeP levels and evaluated their prognostic impacts during follow-up (mean 1,520 days, IQR: 1,393-1,804 days). Serum SeP level was measured using a newly developed sol particle homogeneous immunoassay. As controls, we collected serum samples from 20 controls without any known cardiac disorders evaluated by hematological examination, echocardiography, and coronary angiography. In PAH patients, we examined the relationship between baseline SeP levels and composite endpoint of all-cause death and lung transplantation. The correlation between the absolute changes in SeP and those in hemodynamic parameters during follow-up were also examined.

Results: In the experimental study, SeP promoted PASMC proliferation through increased oxidative stress and mitochondrial metabolic dysfunction, which were associated with activated HIF-1a and dysregulated glutathione metabolism. In the clinical study, PAH patients showed significantly higher levels of serum SeP compared with controls (3.07±0.57 vs. 2.43±0.25 mg/L, P<0.0001). Higher SeP levels (cut-off point, 3.47 mg/L) were significantly associated with the composite endpoint of all-cause death and lung transplantation in PAH patients [HR: 4.85 (1.42 to 16.6), P<0.01]. Importantly, we found that absolute changes in SeP levels in PAH patients significantly correlated with those in mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac index in response to PAH-specific therapy (R=0.78, 0.76, and -0.71, respectively, all P<0.0001). Furthermore, the increases in SeP levels during follow-up predicted the poor outcome in PAH patients [Figure, HR: 4.29 (1.27 to 14.4), P<0.05].

Conclusions: These results indicate that SeP is a novel therapeutic target of PAH and that serum SeP levels are a novel biomarker for diagnosis and assessment of treatment efficacy and long-term prognosis in PAH patients.
Event-free survival (death or lung transplantation) in patients with PAH

Hazard ratio, 4.29 (95% CI, 1.27-14.4)  
\( P<0.05 \)