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Targeting peptidyl-prolyl isomerase 1 in experimental pulmonary arterial hypertension

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Abstract

Background Pulmonary arterial hypertension (PAH) is a progressive disease characterised by pro-proliferative and anti-apoptotic phenotype in vascular cells, leading to pulmonary vascular remodelling and right heart failure. Peptidyl-prolyl *cis*/*trans* isomerase, NIMA interacting 1 (Pin1), a highly conserved enzyme, which binds to and catalyses the isomerisation of specific phosphorylated Ser/Thr-Pro motifs, acts as a molecular switch in multiple coordinated cellular processes. We hypothesised that Pin1 plays a substantial role in PAH, and its inhibition with a natural organic compound, Juglone, would reverse experimental pulmonary hypertension.

Results We demonstrated that the expression of Pin1 was markedly elevated in experimental pulmonary hypertension (*i.e.* hypoxia-induced mouse and Sugen/hypoxia-induced rat models) and pulmonary arterial smooth muscle cells of patients with clinical PAH. *In vitro* Pin1 inhibition by either Juglone treatment or short interfering RNA knockdown resulted in an induction of apoptosis and decrease in proliferation of human pulmonary vascular cells. Stimulation with growth factors induced Pin1 expression, while its inhibition reduced the activity of numerous PAH-related transcription factors, such as hypoxia-inducible factor (HIF)-α and signal transducer and activator of transcription (STAT). Juglone administration lowered pulmonary vascular resistance, enhanced right ventribular function, improved pulmonary vascular and cardiac remodelling in the Sugen/hypoxia rat model of PAH and the chronic hypoxia-induced pulmonary hypertension model in mice.

Conclusion Our study demonstrates that targeting of Pin1 with small molecule inhibitor, Juglone, might be an attractive future therapeutic strategy for PAH and right heart disease secondary to PAH.

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