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Suppression of HIF2 signalling attenuates the initiation of hypoxia-induced pulmonary hypertension

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Activation of HIF2 by hypoxia initiates vascular cell proliferation and recruitment of inflammatory cells at early stages of PH development through HIF2-dependent transcription of genes involved in these pathways in pulmonary vascular cells http://bit.ly/2lFwTGM

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ABSTRACT Most published studies addressing the role of hypoxia inducible factors (HIFs) in hypoxia-induced pulmonary hypertension development employ models that may not recapitulate the clinical setting, including the use of animals with pre-existing lung/vascular defects secondary to embryonic HIF ablation or activation. Furthermore, critical questions including how and when HIF signalling contributes to hypoxia-induced pulmonary hypertension remain unanswered.

Normal adult rodents in which global HIF1 or HIF2 was inhibited by inducible gene deletion or pharmacological inhibition (antisense oligonucleotides (ASO) and small molecule inhibitors) were exposed to short-term (4 days) or chronic (4–5 weeks) hypoxia. Haemodynamic studies were performed, the animals euthanised, and lungs and hearts obtained for pathological and transcriptomic analysis. Cell-type-specific HIF signals for pulmonary hypertension initiation were determined in normal pulmonary vascular cells *in vitro* and in mice (using cell-type-specific HIF deletion).

Global *Hif1a* deletion in mice did not prevent hypoxia-induced pulmonary hypertension at 5 weeks. Mice with global *Hif2a* deletion did not survive long-term hypoxia. Partial *Hif2a* deletion or *Hif2*-ASO (but not *Hif1*-ASO) reduced vessel muscularisation, increases in pulmonary arterial pressures and right ventricular hypertrophy in mice exposed to 4–5 weeks of hypoxia. A small molecule HIF2 inhibitor (PT2567) significantly attenuated early events (monocyte recruitment and vascular cell proliferation) in rats exposed to 4 days of hypoxia, as well as vessel muscularisation, tenascin C accumulation and pulmonary hypertension development in rats exposed to 5 weeks of hypoxia. *In vitro*, HIF2 induced a distinct set of genes in normal human pulmonary vascular endothelial cells, mediating inflammation and proliferation of endothelial cells and smooth muscle cells. Endothelial *Hif2a* knockout prevented hypoxia-induced pulmonary hypertension in mice.

Inhibition of HIF2 (but not HIF1) can provide a therapeutic approach to prevent the development of hypoxia-induced pulmonary hypertension. Future studies are needed to investigate the role of HIFs in pulmonary hypertension progression and reversal.