Introduction and objectives Mutations in the bone morphogenetic protein type II receptor (BMPR-II) are responsible for the majority of cases of heritable pulmonary arterial hypertension (PAH). Mutations lead to reduced Smad1/5-driven expression of inhibitor of DNA binding protein 1 (Id1) and loss of the growth suppressive effects of BMPs. The impact of existing PAH therapies on BMP signalling is lacking. Because prostanolycin analogues are effective treatments for clinical PAH, we hypothesised that these agents enhance Smad1/Id1 signalling.

Methods Iloprost alone induced Id1 expression in human pulmonary artery smooth muscle cells (PASMCs), an effect that was independent of Smad1/5 activation but dependent on a cAMP-responsive element in the Id1 promoter. In addition, iloprost and treprostinil enhanced BMP-induced phosphorylation of Smad1/5 and Id1 expression in a cAMP-dependent manner. The mechanism involved suppression of inhibitory Smad, Smad6. Furthermore, iloprost rescued the deficit in Smad1/5 phosphorylation and Id1 gene expression in PASMCs harbouring mutations in BMPR-II and restored growth suppression to BMP4 in mutant PASMCs.

Results We confirmed a critical role for Id1 in PASMC proliferation. Reduced expression of Id1 was observed in concentric intimal lesions of heritable PAH cases. In the monocrotaline rat model of PAH, associated with reduced BMPR-II expression, we confirmed that treprostinil inhibited smooth muscle cell proliferation and prevented progression of PAH while enhancing Smad1/5 phosphorylation and Id1 gene expression.

Conclusions Prostacyclin analogues enhance Id1 expression in vitro and in vivo and restore deficient BMP signalling in BMPR-II mutant PASMCs.

Cell signalling and cell responses in pulmonary vascular disease

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SMAAD-DEPENDENT AND SMAAD-INDEPENDENT INDUCTION OF ID1 BY PROSTACYCLIN ANALOGUES INHIBITS PROLIFERATION OF PULMONARY ARTERY SMOOTH MUSCLE CELLS IN VITRO AND IN VIVO

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Jun Yang, Xiaoli Li, Rafia S Al-Lamki, Mark Southwood, Jing Zhao, Andrew M Lever, Friedrich Grimminger, Ralph T Schemuly, Nicholas W Morrell. University of Cambridge, Cambridge, UK

Background Pulmonary arterial hypertension (PAH) associated with pulmonary vascular inflammation and dysregulated bone morphogenetic protein receptor type 2 (BMPR2) signalling in both human and experimental PAH. We evaluated the effects of dexamethasone on established monocrotaline-induced PAH in rats for potential reversal of PAH, at time points when pulmonary vascular remodelling has already developed (from day 14 after a single injection of monocrotaline at day 0), and for the effects on pulmonary IL6 and BMPR2 expression.

Methods Saline-treated controls, monocrotaline-exposed, monocrotaline-exposed and dexamethasone-treated rats (5 mg/kg/day, 1.25 mg/kg, and 2.5 mg/kg/4 h given from day 14–28 and day 21–35) were evaluated at day 28 and day 35 following monocrotaline for potential reversal of PAH, at time points when pulmonary vascular remodelling has already developed (from day 14 after a single injection of monocrotaline at day 0), and for the effects on pulmonary IL6 and BMPR2 expression.

Results Dexamethasone significantly improved pulmonary haemodynamics and morphometric indices of pulmonary vascular remodelling, reversing PAH when given at day 14–28, day 21–35 following monocrotaline, as well as improving survival in monocrotaline-exposed rats compared to controls (log rank p<0.0001). Dexamethasone reduced both monocrotaline-induced whole lung IL-6 and BMPR2 expression by quantitative real-time PCR (qRT-PCR).

Conclusions TRAIL is a critical mediator in disease pathogenesis of PAH in the diet-induced murine model of PAH. Targeting TRAIL could provide a novel therapeutic approach to the treatment of PAH. Work is ongoing to determine if this approach can stabilise or reverse established disease, in both this, and rat, experimental models of PAH.

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DEXAMETHASONE REVERSES ESTABLISHED MONOCROTALINE-INDUCED PULMONARY HYPERTENSION IN RATS AND INCREASES PULMONARY BMPR2 EXPRESSION

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1 C Price, 1 S J Wort, 2 D Montani, 2 C Tcherakian, 2 P Dorfmuller, 2 R Souza, 2 D Shao, 2 G Simonneau, 1 L S Howard, 1 A Adcock, 1 M Humbert, 2 P Perros. 1National Heart & Lung Institute, Royal Brompton Hospital, London, UK; 2Centre National de Référence de l’HypertensionPulmonaireSevère, Hôpital Antoine Béclère, Clamart, F-92140, France; Université Paris-Sud, Paris, France; 3Hammersmith Hospital, Imperial College Healthcare NHS Trust, Du Cane Road, London, UK

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S150 Smad-dependent and Smad-independent induction of Id1 by prostacyclin analogues inhibits proliferation of pulmonary artery smooth muscle cells in vitro and in vivo

Jun Yang, Xiaohui Li, Rafia S Al-Lamki, Mark Southwood, Jing Zhao, Andrew M Lever, Friedrich Grimminger, Ralph T Schermuly and Nicholas W Morrell

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