Prevention of progression of pulmonary hypertension by the Nur77 agonist 6-mercaptopurine: role of BMP signalling

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Pharmacological activation of Nur77 with 6-mercaptopurine reduces the progression of pulmonary hypertension by enhancing BMP signalling


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ABSTRACT Pulmonary arterial hypertension (PAH) is a progressive fatal disease characterised by abnormal remodelling of pulmonary vessels, leading to increased vascular resistance and right ventricle failure. This abnormal vascular remodelling is associated with endothelial cell dysfunction, increased proliferation of smooth muscle cells, inflammation and impaired bone morphogenetic protein (BMP) signalling. Orphan nuclear receptor Nur77 is a key regulator of proliferation and inflammation in vascular cells, but its role in impaired BMP signalling and vascular remodelling in PAH is unknown.

We hypothesised that activation of Nur77 by 6-mercaptopurine (6-MP) would improve PAH by inhibiting endothelial cell dysfunction and vascular remodelling.

Nur77 expression is decreased in cultured pulmonary microvascular endothelial cells (MVECs) and lungs of PAH patients. Nur77 significantly increased BMP signalling and strongly decreased proliferation and inflammation in MVECs. In addition, conditioned medium from PAH MVECs overexpressing Nur77 inhibited the growth of healthy smooth muscle cells. Pharmacological activation of Nur77 by 6-MP markedly restored MVEC function by normalising proliferation, inflammation and BMP signalling. Finally, 6-MP prevented and reversed abnormal vascular remodelling and right ventricle hypertrophy in the Sugen/hypoxia rat model of severe angioproliferative PAH.

Our data demonstrate that Nur77 is a critical modulator in PAH by inhibiting vascular remodelling and increasing BMP signalling, and activation of Nur77 could be a promising option for the treatment of PAH.