BMPR-II mutations promote pulmonary arterial hypertension via a hyperinflammatory response

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Aims

Pulmonary arterial hypertension (PAH) is a collective term for diseases characterised by increased pulmonary artery pressures, which lead to fulminant right heart failure and death if left untreated. Mutations in the bone morphogenetic protein type II receptor (BMPR-II) underlie most cases of heritable pulmonary arterial hypertension. However, disease penetrance is only 20–30%, suggesting a requirement for additional triggers. Inflammation is emerging as a key factor in PAH, but to date there is no clear mechanism linking BMPR-II deficiency and inflammation. There is also very little in the way of treatment modalities for PAH other than vasodilators. Therefore, we sought to establish a direct link between BMPR-II deficiency and a heightened inflammatory response, and to see whether anti-inflammatory therapies would prevent development of PAH.

Methods

We employed mouse pulmonary artery smooth muscle cells (PASMCs) heterozygous for a null mutation in *Bmpr2* (*Bmpr*2+/–), human PASMCs from patients with a mutation in BMPR2 and corresponding wild-type controls. For *in vivo* studies, we employed the heterozygous null *Bmpr2* mouse (*Bmpr*2+/–) and wild-type littermate controls.

Results

Acute exposure to lipopolysaccharide (LPS) increased levels of IL-6 and KC (IL-8 analogue) levels in *Bmpr*2+/– mice to a greater extent than wild-type controls. Similarly, PASMCs from *Bmpr*2+/– mice and patients with BMPR2 mutations produced higher levels of IL-6 and KC/IL-8 following LPS stimulation than controls. BMPR-II deficiency in mouse and human PASMCs was associated with increased superoxide levels and loss of extracellular superoxide dismutase. Chronic LPS administration caused pulmonary hypertension in *Bmpr*2+/– mice, but not in wild-type littermates. Co-administration of tempol, a superoxide dismutase mimetic, ameliorated the exaggerated inflammatory response and prevented development of PAH.

Conclusions

This study demonstrates that BMPR-II deficiency promotes an exaggerated inflammatory response *in vitro* and *in vivo*, which instigates the development of pulmonary hypertension. It also suggests that anticytokine and antioxidant approaches may be novel therapeutic targets in the treatment of this deadly disease.

Conflict of interest statement

The authors have no conflict of interest with regard to this abstract. ■

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