

Title

Intracellular iron deficiency in pulmonary arterial smooth muscle cells induces pulmonary arterial hypertension in mice

Short title

Linking iron deficiency and pulmonary hypertension

Authors and affiliations

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Keywords

Iron

Ferroportin

Hepcidin

Endothelin-1

Pulmonary arterial hypertension

ABSTRACT

Iron deficiency augments hypoxic pulmonary arterial pressure in healthy individuals and exacerbates pulmonary arterial hypertension (PAH) in patients, even without anaemia. Conversely, iron supplementation has been shown to be beneficial in both settings. The mechanisms underlying the effects of iron availability are not known, due to lack of understanding of how cells of the pulmonary vasculature respond to changes in iron levels. The iron export protein ferroportin (FPN) and its antagonist peptide hepcidin control systemic iron levels by regulating release from the gut and spleen, the sites of absorption and recycling, respectively. We found FPN to be present in pulmonary arterial smooth muscle cells (PASMCs) and regulated by hepcidin cell-autonomously. To interrogate the importance of this regulation, we generated mice with smooth muscle-specific knock-in of the hepcidin-resistant isoform *fpn* C326Y. While retaining normal systemic iron levels, this model developed PAH and right heart failure as a consequence of intracellular iron deficiency and increased expression of the vasoconstrictor endothelin-1 (ET-1) within PASMCs. PAH was prevented and reversed by i.v iron and by the ET receptor antagonist BQ-123. The regulation of ET-1 by iron was also demonstrated in healthy humans exposed to hypoxia and in PASMCs from PAH patients with mutations in bone morphogenetic protein receptor type II. Such mutations were further associated with dysregulation of the HAMP/FPN axis in PASMCs. This study presents the first evidence that intracellular iron deficiency specifically within PASMCs alters pulmonary vascular function. It offers a mechanistic underpinning for the known effects of iron availability in humans.