INVESTIGATING THE ROLE OF GCN2 IN THE PATHOGENESIS OF PULMONARY HYPERTENSION

Soon, Crosby, Southwood, Moore, Ron, Marciniak, NW Morrell.

University of Cambridge, Cambridge, UK; Papworth Hospital NHS Trust, Cambridge, UK.

10.1136/thoraxjnl-2016-209333.89

Background Mutations in the bone morphogenetic protein type II receptor (BMPR-II) underlie the majority (>80%) of familial and up to 25% of sporadic cases of idiopathic pulmonary arterial hypertension (PAH). Recently, homozygous recessive mutations in GCN2 (also known as EIF2AK4) were identified as causative in a rare cause of PAH, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH). The mechanisms by which GCN2 deficiency contributes to the development of PAH remain unknown. GCN2 is a serine/threonine protein kinase, one of a family of 4 kinases that phosphorylate the α-subunit of the translation initiation factor eIF2α. Phosphorylation of eIF2α at serine 51 results in an inhibition of eIF2B (the eIF2 guanine nucleotide exchange factor), which ultimately leads to loss of eIF2α function. This results in inhibition of protein synthesis while enhancing the translation of a small number of mRNAs encoding proteins involved in the response to cellular stress.

Methods We characterised the pulmonary vascular phenotype of the homozygous null Gcn2 (Gcn2−/−) and wild-type controls at 6 months of age. This mouse was chosen because it mimics the homozygous loss-of-function genotype of patients with familial PVOD/PCH. In addition, we investigated the phenotype of Gcn2−/− mice crossed with bmpr2-deficient mice. In complementary in vitro studies, pulmonary artery smooth muscle cells (PASMCs) were extracted from patients with PVOD and idiopathic/heritable PAH and studied with wild-type controls.

Findings The Gcn2−/− mouse displayed mild pulmonary hypertension. Mean right ventricular systolic pressure (RVSP) was 28.3 ± 1.2 mmHg in Gcn2−/− mice compared with 24.7 ± 1.1 mmHg in wild-type mice. GCN2−/− mice crossed with bmpr2-deficient mice demonstrated a further increase in RVSP (32.8 ± 4.1 mmHg). Exposure of human PASMCs derived from a PVOD patient, and patients with mutations in BMPR2, to L-histidinol, which increases the phosphorylation of eIF2α, resulted in proliferation of these cells but had no effect on control PASMCs.

Conclusions GCN2 deficiency promotes the development of pulmonary hypertension in mice, an effect that is exaggerated by BMPR2 deficiency. Increased phosphorylation of eIF2α resulted in PASMC proliferation. Further elucidation of these mechanisms may reveal new treatments for this devastating disease.

IDENTIFICATION OF MIR-124A AS A MAJOR REGULATOR OF ENHANCED ENDOTHELIAL CELL GLYCOLYSIS IN PULMONARY ARTERIAL HYPERTENSION

Caruso, Dunmore, Schlosser, Schoors, Dos Santos, Perez-Iratxeta, Lavoie, Long, Hurst, Ormiston, Hata, DJ Stewart, NW Morrell, University of Cambridge, Cambridge, UK; Ottawa Hospital Research Institute and the University of Ottawa, Ottawa, Canada; Laboratory of Angiogenesis and Neurovascular Link, Vesalius Research Centre, Leuven, Belgium; Queen’s University, Kingston, Canada; Cardiovascular Research Institute, University of California, San Francisco, USA.

10.1136/thoraxjnl-2016-209333.90

Introduction Pulmonary arterial hypertension (PAH) is a rare disease characterised by profound vascular abnormalities in the peripheral arteries of the lung, leading to a progressive increase in pulmonary vascular resistance, right heart failure and death. The disease exists in several forms including a heritable form (HPAH) caused primarily by mutations in bone morphogenetic protein receptor type 2 (BMPR2) and an idiopathic form (IPAH). Endothelial cell (EC) dysfunction is considered a critical initiating factor in the pathobiology of PAH, manifested by increased...