Disruption of GCN2 aggravates vascular and parenchymal remodeling during pulmonary fibrosis.

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Background: GCN2, a major stress regulator, was recently implicated in pulmonary veno-occlusive disease (Eyries M, et al. Nat Genet 2014 and Perros F, et al. Circulation 2015). This study aims to explore the involvement of the GCN2/eIF2α signalling pathway in the development of pulmonary hypertension (PH) during idiopathic pulmonary fibrosis (IPF), in both human disease and in an experimental animal model.

Methods: Lung tissue from IPF patients (n=19) with or w/o PH were collected at the time of lung transplantation, and controls (CTR, n=11) were obtained from tumour resection surgery. Experimental lung disease was induced in male SD rats, randomly receiving a single intratracheal instillation of bleomycin (BM, 7.5U/Kg) or saline (SL). Echocardiographic and haemodynamic studies, as well as organ collection were performed 3 weeks post-instillation. Only significant results ($p<0.05$) are given.

Results: In total IPF lung tissue, GCN2 protein expression was decreased, when compared with CTR. GCN2 expression was reduced in $CD31^+$ endothelial cells, regardless the presence of PH. Rats treated with BM showed increased parenchymal fibrosis (hydroxyproline levels) and vascular remodelling (media wall thickness) as well as increased mean pulmonary artery pressure and impaired right ventricular function. In line with human data, GCN2 protein expression was decreased in the lung of BM rats when compared with SL.

Conclusion: Our data show that GCN2 is dysregulated in both human IPF and in an animal model of combined IPF+PH. The possibility of a causative implication of GCN2 dysregulation in IPF and/or PH development will be further studied.