years in those without COPD. After adjusting for confounding by sex and stratifying for age, survival was shorter after 1st MI in patients with COPD; HR 1.37 (1.23 to 1.52, p<0.001) in those with COPD compared to those without COPD (Abstract S96 figure 1). Survival was shorter in those (n=96) who exacerbated within 6 months of their 1st MI; HR 1.72 (1.13 to 2.60, p=0.01).

Conclusions Survival is shorter after an "unanticipated" MI in patients with COPD and patients who exacerbate within 6 months of their MI have an even higher mortality rate.

BMP signalling in pulmonary hypertension

S97 BMPR2 R899X KNOCK-IN MICE DEVELOPED AGE-RELATED PULMONARY HYPERTENSION

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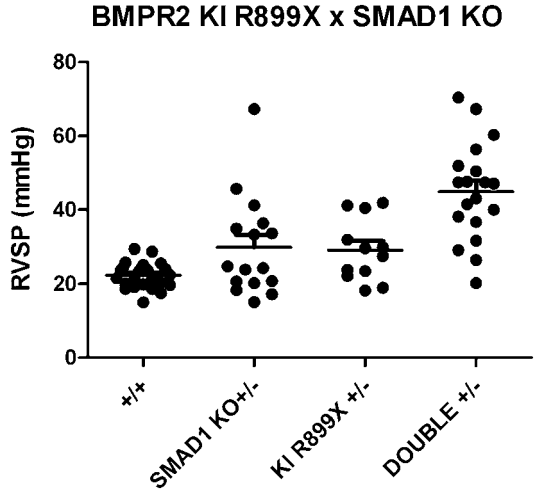
Background Heterozygous germline mutations in the gene encoding the bone morphogenetic protein type II receptor (*BMPR2*) underlie the majority (>70%) of cases of heritable pulmonary arterial hypertension (hPAH) and a variable proportion of idiopathic PAH (15%–40%). There are also reports of PAH in patients with mutations in the downstream Smad signalling proteins. However, to date there is no mouse model that mimics the genetic mutations in human disease.

Methods We developed a knock-in mouse harbouring a heterozygous (±) human disease causing mutation in BMPR-II: a nonsense mutation in the cytoplasmic tail (R899X) to determine the in vivo physiologic consequences of this *BMPR2* mutation. In addition, we crossed this animal with Smad1± knockout mice to determine the effect of additional loss of signalling via this pathway. Haemodynamic, and morphometric data were collected at 3 months and 6 months of age.

Results At 3 months of age pulmonary haemodynamics and vascular morphometry of R899X± and Smad1± mice were similar to wild-type littermate controls. In contrast, at 6 months of age R899X± and Smad1± mice developed mild pulmonary hypertension with pulmonary vascular remodelling compared with wild-types. Pulmonary artery smooth muscle cells from R899X± mice were hyperproliferative in serum and exhibited defects in Smad signalling in response to BMPs. When R899X± mice were crossed with Smad1± animals, double heterozygous mice had significantly higher right ventricular systolic pressures than single heterozygous mice.

Conclusion These findings demonstrate that knockin of a human disease causing BMPR-II mutation causes age-related pulmonary hypertension in mice. In addition, we show that the accumulation of defects in the BMP/Smad signalling pathway increases the susceptibility to pulmonary hypertension, highlighting the central role of this pathway in disease.



Abstract S97 Figure 1

S98 BMPR-II MUTATIONS DO NOT PREDISPOSE TO PULMONARY ARTERIAL HYPERTENSION IN A MOUSE MODEL OF SCHISTOSOMIASIS

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Schistosomiasis is the worldwide leading cause of pulmonary arterial hypertension (PAH) and is particularly prevalent in the third-world. More than 80% of patients with PAH in the western world have a mutation in bone morphogenetic protein type-II receptor (BMPR-II), which is a member of the transforming growth receptor-β (TGF-b) superfamily and is important in cell proliferation and differentiation. The aim of the study was to determine if mice with a heterozygous null mutation in BMPR-II are more susceptible to schistosomiasis–induced PAH, compared to wild-type littermates.

Methods Wild-type and mutant C56/BL6 mice were infected percutaneously with a low dose of *S mansoni*. At 17 weeks post-infection right ventricular systolic pressure (RVSP) and right ventricular (RV) hypertrophy, liver and lung egg counts and body weight were measured. Pulmonary vascular remodelling was assessed by morphometry, following immunohistochemistry. Human and mouse pulmonary arterial smooth muscle cells (PASMC) were cultured with *S mansoni* eggs for 24 h. At 24 h the expression of cytokines in PASMC were measured by qPCR and cytokine levels in the cell supernatant were measured by ELISA.

Measurements and Main results At 17 weeks post-infection there was no significant difference in RVSP, the degree of RV hypertrophy, liver weight or body weight between wild-type or mutant mice. However, 33% of the mutant mice died prematurely. After 24 h co-culture with eggs both mouse and human PASMC showed an increase in cytokine expression and cytokine release. More specifically we saw an increase in IL-6, Kc (mouse homologue of IL-8) and IL-13 expression and an increase in IL-6 and Kc secretion. We also saw an increase in PASMC proliferation, determined by Ki67. There was a suggestion that PASMC from mutant mice may display an increase in cytokine response to egg stimulation.

Conclusions This study has shown that BMPR-II mutations do not predispose to schistosomiasis-induced PAH. We have also shown that PASMC respond to *S mansoni* eggs by an increase in expression and release of inflammatory cytokines. These may play a part in inducing pulmonary vascular remodelling by stimulating PASMC proliferation. However, this affect was not significantly enhanced by BMPR-II mutations.

S99 THE ANTI-MALARIAL DRUG AND LYSOSOMAL INHIBITOR, CHLOROQUINE, INCREASES CELL SURFACE EXPRESSION OF BMPR-II

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Bone morphogenetic protein receptor type II (BMPR-II) is a member of the transforming growth factor ß (TGFß) receptor superfamily.