hyperproliferation observed. Hyperproliferation in response to hypoxia in WT cells could be blocked by addition of IL-33. IL-33 stimulation also decreased the phosphorylation of p38 MAP kinase. There was no effect of IL-33 on ST2−/− cells.

Conclusions Mouse pulmonary artery fibroblasts hyperproliferate in response to hypoxia and in the absence of the ST2 receptor. This hyperproliferation involves phosphorylation of p38 MAP kinase. This phosphorylation and excessive cell proliferation can be blocked by ST2/IL-33 signalling. ST2 may be a potentially novel therapeutic target in the PAH.

S156 CHLORIDE INTRACELLULAR CHANNEL PROTEIN 4 (CLIC4) IN THE REGULATION OF HUMAN PULMONARY ENDOTHELIAL RESPONSES TO HYPOXIA

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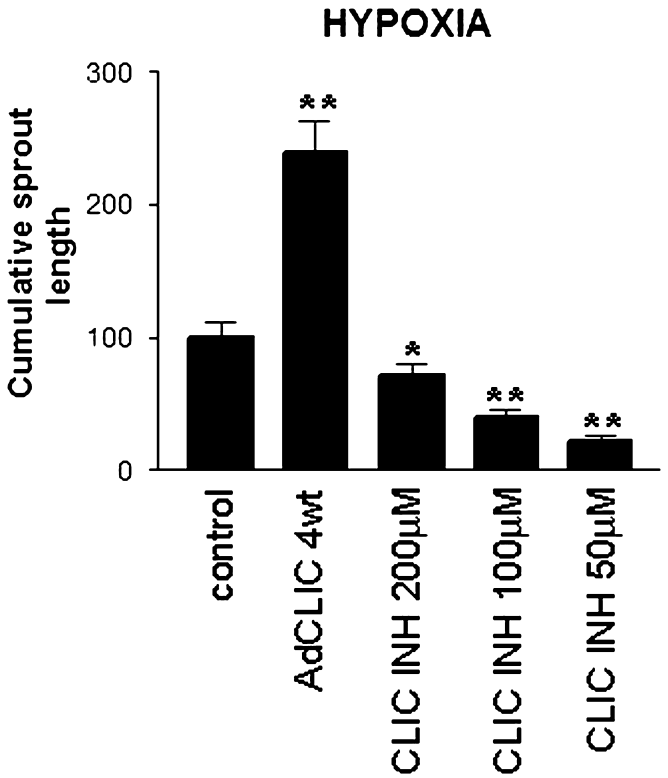
Introduction and Objectives CLIC-4 belongs to the family of chloride intracellular channels, proteins structurally homologous to glutathione transferases. CLIC4 has been implicated in tumour angiogenesis and signalling pathways important in the pathogenesis of pulmonary arterial hypertension (PAH). We have previously demonstrated increased CLIC4 protein expression in whole lung samples from patients with PAH and animals with chronic hypoxia- and monocrotaline-induced PH. CLIC4 is particularly abundant in pulmonary endothelium of patients with PAH. In this project we aimed to establish a role of CLIC4 plays in the regulation of pulmonary endothelial cell responses to hypoxia.



Abstract S156 Figure 1 Endothelial spheroids were left untreated, were infected with adenoviruses to overexpress wtCLIC4, or were treated with NPPB, as indicated. The spheroids were then left in normoxia (not shown) or placed in hypoxia (2% O_2, 5% CO_2, 93% N_2) for 24 h. The cumulative sprout length was studied with image analysis software (Image J). *P<0.05; **P<0.01; n=4.

Methods Human pulmonary artery endothelial cells (HPAECs) were cultured in normoxic conditions or were exposed to hypoxia (2% O_2, 5% CO_2, 93% N_2) for 1–24 h. CLIC4 expression and localisation was studied by Western blotting, immunofluorescence and confocal microscopy. The wildtype and nuclear-targetted CLIC4 were overexpressed via adenoviral gene transfer while chloride channel inhibitor NPPB (5-Nitro-2-(3-phenylpropylamino)benzoic acid) was used to inhibit CLIC4 activity. We studied the effects of CLIC4 on endothelial permeability, angiogenesis and proliferation.

Results Overexpression of the wildtype CLIC4 in HPAECs increased pulmonary endothelial proliferation, compromised barrier function and increased angiogenic responses to chronic hypoxia in vitro (Abstract S156 Figure 1). These effects were prevented by chloride channel inhibitor NPPB. In normoxic HPAECs CLIC4 was localised predominantly to the cell nucleus and cytoplasm. Upon stimulation with hypoxia, CLIC-4 translocated to the cell periphery, localising in particular to membrane protrusions (filopodia and lamellipodia), the effect mimicked by overexpression of CLIC4.

Conclusions Hypoxia induces translocation of CLIC-4 to the membrane of HPAECs. This behaviour has been linked to increased motility and malignant phenotype in other cell types. CLIC-4 overexpression in HPAECs also increases endothelial cell responses to hypoxia in vitro. These findings suggest increased CLIC-4 expression in PAECs in PAH may play a role in pathogenesis of PAH and provide novel insights in to disease pathogenesis and treatment strategies.

Occupational asthma

S157 PREVALENCE OF ASTHMA RELATED TO EMPLOYMENT IN THE UK

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It is widely held that 10–15% of adult asthma is causally related to occupation. It is likely that this fraction varies importantly depending on historical and international variations in employment. Further uncertainties arise from misclassification in the diagnosis of asthma and in exposure assessment, particularly if based on self-report. We carried out a postal survey of adults listed as asthmatic through general practices across the UK. Cases, who were defined as those who had experienced onset of asthma or worsening of pre-existing childhood asthma within 2 years of starting a new job, were compared to controls who declared an equivalent onset or deterioration more than 2 years from the start of a job. Of 8535 individuals targeted, 3115 (37%) returned a completed questionnaire. Almost 40% of these (n=1198) experienced a deterioration of pre-existing childhood asthma or onset of adult asthma whilst working; 441 were cases and 757 controls. A priori analysis of risk was performed using an asthma-specific JEM, the ECRHS asthma 'high risk occupations' and data from the UK SWORD surveillance scheme. Odds ratios (adjusted for sex, smoking and era of onset and stratified by onset type)—displayed in Abstract S157 Table 1—did not suggest an increased risk of asthma within 2 years of starting a high-risk job. A posteriori analysis of all occupations demonstrated an increased risk of asthma within 2 years of starting a new job in sales and elementary occupations. The calculated population attributable risk (PAR) for these occupations was 15.9% and was higher in women than men. The results from this study suggest that a priori assessment of risk does not identify occupation as a significant cause of asthma in this contemporary adult workforce in the UK. Jobs which do appear to increase risk of new asthma are not those typically associated with an excess risk of the disease. These findings highlight the disparity between epidemiological and clinical assessments of asthma related to occupation, and the need to consider novel occupations as a cause of asthma.