A ROLE FOR THE BONE MORPHOGENETIC PROTEIN TYPE 2 RECEPTOR (BMPR2) IN DIFFERENTIATION OF THE COMMON MYELOID PROGENITOR LINEAGE IN MICE AND HUMANS

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Rationale There is increasing evidence of a link between abnormalities in the myeloid cell lineage and pulmonary arterial hypertension (PAH). Heterozygous mutations in the gene encoding the bone morphogenetic protein type 2 receptor (BMPR2) are the most common genetic cause of PAH. We sought to characterise the impact of the genetic loss/reduction of BMPR2 function in the myeloid lineage in mice and humans, and whether this altered susceptibility to PAH.

Methods Mx1-cre mice were crossed with bmpr2<sup>lox/lox</sup> mice. At approximately 8 weeks of age cre-recombinase was induced with polyinosinic-polycytidylic acid (Poly I:C). Control mice (bmpr2<sup>lox/lox</sup> mice with no cre) were also induced with Poly I:C. At approximately 16 weeks post-induction mice underwent right-heart catheterisation, exsanguination and tissue was removed for analysis. The spleens were weighed and histology was performed on the femurs. Mouse data are presented as mean ± SEM. In a large cohort of PAH patients with (n=160) and without (n=831) BMPR2 mutations blood count indices were analysed. Data presented as median [IQR].

Results 16 weeks after induction of cre-recombinase in Mx1-cre/bmpr2<sup>lox/lox</sup> mice we observed significant increases (p<0.05) in red blood cells (x10<sup>6</sup>/mm<sup>3</sup>) (12.7±0.9 compared with 12.1±0.2), haematocrit (%) (64.8±0.7 compared with 62.6±1) and haemoglobin (g/dl) (16±0.9 compared with 15.4±0.2) compared with bmpr2<sup>lox/lox</sup> mice alone. A significant increase in circulating monocytes (x10<sup>3</sup>/mm<sup>3</sup>) was also observed (p<0.05) (0.4±0.05 compared with 0.3±0.05). In addition, we identified a significant increase (p<0.05) in megakaryocytes in the femurs (80±10 compared with 17±5) and a significant increase (p<0.01) in the ratio of spleen weight/ body weight (0.003±0.0001 compared with 0.002±0.0001) in Mx1-cre/bmpr2<sup>lox/lox</sup> mice. During right heart catheterisation right ventricular systolic pressures were similar in both groups. In PAH patients significant differences (p<0.05) were seen in haemoglobin (BMPR2 mutation: 162 g/L [151.75–173] vs. no mutation: 150 g/L [135 – 163]), haematocrit (0.48 [0.35–0.52] vs. 0.44 [0.41–0.48]) and white blood cells (8.8 [7.3–10.4] vs. 8.11 [6.77–9.61]).

Conclusions We have identified a role for bmpr2 in the differentiation of the mouse myeloid lineage, which was also confirmed in PAH patients with BMPR2 mutations. BMPR2 appears particularly important in the differentiation of megakaryocyte-erythrocyte lineage.