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Role of bone morphogenetic protein receptor type II in vascular remodeling during thrombosis

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Background

Several lines of evidence have implicated the role of inheritance and genetics in pathogenesis of pulmonary arterial hypertension (PAH). Mutations in the bone morphogenetic protein type II receptor (BMPR2), a member of the TGF-β superfamily, have been identified as a risk factor for pulmonary arterial hypertension. Fibrotic vascular occlusion is a feature of PAH and chronic thromboembolic pulmonary hypertension (CTEPH), therefore we intended to study the role of BMPR2 in murine model of venous thrombosis.

Aim

In the present study we investigated the role of BMPR2 deficiency in thrombosis. In patients, we studied the cellular composition of material excised during pulmonary endarterectomy (PEA) surgery.

Methods

We utilized a mouse model of stagnant flow venous thrombosis to study the effect of BMPR2 deficiency on thrombus formation/resolution. Wild type mice and transgenic mice, bearing a heterozygous knock-in allele of human BMPR2 mutation, R899X, were subjected to subtotal ligation of the inferior vena cava. Thrombus was harvested at different time points (days 1, 3, 7 and 14 after IVC ligation) and histological and molecular analysis were performed. Trichrome stain was performed to assess the accumulation of matrix components. Immunohistochemistry was performed on thrombotic material obtained during PEA to determine its cellular composition.

Results

We observed a significant increase of thrombus cross-sectional areas and volumes on days 1, 3 and 7 in transgenic mice. During early time points (days 1, 3 and 7) mice with BMPR2 deficiency showed more fibrin within their thrombi than wild type controls. By day 14, transgenic mouse thrombi seem to have more accumulation of extracellular matrix components like collagen. In the patients, thrombotic material was found to be enriched in differentiated cells expressing smooth muscle actin and vimentin.

Conclusions

These results indicate a role of BMPR2 during early thrombosis, impacting fibrotic remodeling thereafter. Pulmonary endarterectomy specimens were found to be enriched in differentiated cells carrying fibroblast/myofibroblast markers.
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