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Title: Angiogenesis in chronic thromboembolic pulmonary hypertension (CTEPH)

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Body: Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by organized thrombi in the pulmonary arteries leading to right heart failure and death. In a murine venous thrombosis model we were able to demonstrate that endothelial cell-specific deletion of vascular endothelial growth factor receptor 2 (VEGF-R2)/ fetal liver kinase-1 leads to misguided thrombus resolution. Following the hypothesis that CTEPH is based on inadequate thrombus resolution, we studied the role of angiogenesis in CTEPH. Methods: Fibrotic CTEPH thrombi, their red fresh portions, and unthrombosed pulmonary arteries were collected from patients undergoing pulmonary endarterectomy. Real Time PCR, immunohistochemistry, in vitro 3D angiogenesis and proliferation assays were performed. Results: Biochemical analyses revealed that angiogenic molecules such as angiopoietin-2, VEGF, basic fibroblast growth factor and markers for endothelial cells (ECs) such as VEGF-R2, von Willebrand factor and VE cadherin were decreased in CTEPH thrombi compared with pulmonary arteries and fresh pulmonary clots. However, homogenized CTEPH thrombi promoted angiogenesis in an in vitro 3D angiogenesis assay, and stimulated the proliferation of human umbilical vein ECs. Conclusion: Angiogenic molecules are downregulated in fibrotic CTEPH thrombi compared with parent pulmonary arteries and fresh clots. However CTEPH thrombi appear to promote angiogenesis using ECs from healthy donors. Downregulation of genes involved in angiogenesis and lack of functional ECs in CTEPH thrombi may drive thrombus persistence, while the angiostimulatory effect of devascularized thrombi may attract bronchial artery collateralization in the direction of the thrombus.