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Deficiency in milk fat globule-epidermal growth factor 8 delays thrombus resolution

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Background
Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by the obstruction of pulmonary vessels by organized thrombotic and fibrotic lesions. Efferocytosis refers to the engulfment of apoptotic cells (ACs) by phagocytes, a process that is facilitated by bridging proteins. Milk fat globule-epidermal growth factor 8 (MFG-E8) connects phosphatidylserine on ACs with integrin alpha-v beta-III on phagocytes. MFG-E8-deficient mice develop auto-immune disease closely resembling systemic lupus erythematosus. In humans, decreased MFG-E8 levels were observed in patients with coronary heart disease and chronic obstructive pulmonary disease. Whether defective efferocytosis is involved in failure to resolve thrombi in CTEPH remains unknown.

Purpose
We aimed to assess whether deficiency in MFG-E8 is responsible for of chronic non-resolving thrombosis in CTEPH.

Methods
We employed a murine model of chronic thrombosis by inferior vena cava ligation, in MFG-E8 knockout (KO) or wild-type (WT) mice to assess thrombus formation and resolution. Thrombus size at days 3, 7, 14 and 28 after ligation was assessed using either histologic trichrome stainings (n=4-13 per group and time point) or in vivo high-frequency ultrasound (n=10 per group and time point). We furthermore recruited CTEPH patients (n=60, 53% female, mean age 56±11 years) and sex- and age-matched healthy controls for measurement of MFG-E8 plasma levels using ELISA. In CTEPH patients, hemodynamic measurements were performed. Human lung specimens harvested during surgery for CTEPH or from healthy controls, and isolated monocytes from whole blood of CTEPH patients or controls were analyzed using RT-qPCR.

Results
We observed substantially increased thrombus volume in MFG-E8 KO mice compared to WT, which persisted until day 14 after ligation. In human CTEPH patients, MFG-E8 in plasma was increased compared to healthy controls. Similarly, CTEPH monocytes displayed higher concentrations of MFG-E8 mRNA. Conversely, MFG-E8 expression of CTEPH pulmonary artery specimens was downregulated. No correlations between MFG-E8 levels and hemodynamic parameters were observed.

Conclusion
MFG-E8 plays an important role in thrombus resolution. In CTEPH, dysregulation of efferocytosis via impaired MFG-E8 expression in the pulmonary arteries, might drive persistence of thrombus in pulmonary arteries. The absence of a correlation between MFG-E8 and hemodynamic measures argues against pressure...
as a confounder of the observation.