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Title: Administration of fibrin Bβ15-42 (FX06) delays venous thrombus resolution

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Body: BACKGROUND: Chronic thromboembolic pulmonary hypertension (CTEPH) is a late sequel of venous thromboembolism affecting up to 4% of patients surviving symptomatic pulmonary embolism. CTEPH is characterized by organized thrombi in the pulmonary arteries leading to right heart failure and death. Previous studies have demonstrated that in vitro fibrin clots from CTEPH patients were resistant to plasmin-mediated lysis, causing persistence of the N-terminus of the β-chain of fibrin. We employed FX06, a natural occurring fibrin derived peptide that represents the sequence Fibrin Bβ15-42, in a mouse model of stagnant flow venous thrombosis to investigate the biological impact of these residues on thrombus resolution. METHODS: Thrombosis was induced in the infrarenal vena cava of BALB/c mice by creating a venous stenosis with a silk suture. After ligation, mice were injected i.p. daily twice with 100µL FX06 (n=20; 2.4 mg/kg) or saline (control; n=20) until sacrifice. Thrombi were harvested on days 3, 7, 14 and 28 after surgery for analysis. RESULTS: Thrombus cross-sectional area analysis demonstrated a significant increase in thrombus area by day 14 and 28 after surgery in animals treated with FX06 compared with controls. Immunohistochemical staining revealed a delayed appearance of thrombus macrophages and microvessels in FX06 treated mice. CONCLUSION: Administration of FX06 leads to impaired venous thrombus resolution. The data suggest that FX06 may inhibit leukocyte transmigration into experimental thrombi. The presence of the N-terminal fragments entailing an inhibition of leukocyte recruitment may be a mechanism for thrombus non-resolution in CTEPH.