Title

Epigenetic modification of the VWF promotor drives platelet aggregation on the pulmonary endothelium in chronic thromboembolic pulmonary hypertension

Authors

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Introduction: Von Willebrand Factor (VWF) mediates platelet adhesion during thrombosis. While chronic thromboembolic pulmonary hypertension (CTEPH) is associated with increased plasma levels of VWF, the role of this protein in CTEPH has remained enigmatic. In this study we aimed to identify the role of VWF in CTEPH.

Methods: CTEPH-specific patient plasma and pulmonary endarterectomy material from CTEPH patients were used to study the relationship between inflammation, VWF expression and pulmonary thrombosis. Cell culture findings were validated in human tissue and proteomics and chromatin immunoprecipitation were used to investigate the underlying mechanism of CTEPH.

Measurements and main results: VWF is increased in plasma and in the pulmonary endothelium of CTEPH patients. In vitro, the increase in VWF gene expression and the higher release of VWF protein upon endothelial activation resulted in elevated platelet adhesion to CTEPH endothelium. Proteomic analysis revealed that Nuclear Factor κB 2 (NFκB2) was significantly increased in CTEPH compared to control. We demonstrate reduced histone tri-methylation and increased histone acetylation of the VWF promotor in CTEPH endothelium, facilitating binding of NFκB2 to the VWF promotor and driving VWF transcription. Genetic interference of NFκB2 normalized the high VWF RNA expression levels and reversed the pro-thrombotic phenotype observed in CTEPH-PAEC.

Conclusion: Epigenetic regulation of the VWF promotor contributes to the creation of a local environment that favors in situ thrombosis in the pulmonary arteries. It reveals a direct molecular link between inflammatory pathways and platelet adhesion in the pulmonary vascular wall, emphasizing a possible role of in situ thrombosis in the development or progression of CTEPH.

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