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Title: Molecular mechanisms of plasminogen activator inhibitor-1 elevation in COPD sputum

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Body: [Backgrounds] Plasminogen activator inhibitor-1 (PAI-1) is an important regulator of fibrinolysis at sites of vascular injury and thrombus formation. Oxidative stress is known to involve in PAI-1 expression. We previously reported that mean PAI-1 levels in sputum of COPD was significantly higher than that of age-matched controls and significantly correlated both with sputum malondialdehyde (a oxidative stress marker) and NF-kB DNA binding activity in sputum macrophages. However, the precise mechanisms of PAI-1 elevation in COPD were not clarified. We hypothesised that HDAC2 reduction in COPD involves in PAI-1 elevation. The aim of this study was to investigate the association between HDAC2 reduction and elevated PAI-1 expression. [Methods and Results] A549 cells were transfected with SiRNA of HDAC2 to knockdown HDAC2 and followed by treatment with TGF-β. HDAC2 knockdown (KD) significantly upregulated PAI-1 release (Wild type (WT) vs. HDAC2 KD: 2.9±0.2 vs. 4.1±0.3 ng/ml with 0.01ng/ml TGF-β, 7.4±0.4 vs. 8.4±0.5 ng/ml with 0.1ng/ml TGF-β). To investigate the association between NF-kB DNA binding activity and HDAC2, HDAC2 KD cells were stimulated by 10 ng/ml TNF-α for 2hrs, and NF-kB DNA binding activity and p65 acetylation were evaluated with TransAM NF-kB p65 Activation Assay kit and Western blot, respectively. NF-kB DNA binding activity was significantly increased in HDAC2 KD cells (activity(OD) / protein: WT vs. HDAC2 KD; 76±4 vs. 98±4). Acetylation of p65 also significantly upregulated in HDAC2 KD cells (acetyl-p65/p65: WT vs. HDAC2 KD; 2.3±0.1 vs. 3.1±0.1). [Conclusion] HDAC2 reduction in COPD seems to cause PAI-1 elevation in COPD via activation of NF-kB DNA binding by p65 acetylation.