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Title: IL-8 and TSLP production as markers of bronchial epithelial cell activation in IL-17A mediated airway inflammation in COPD: Role of tiotropium

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Body: We measured IL-17A levels in sputum supernatants (ISSs) from healthy controls (HC) (n=10), healthy smokers (HS) (n=10), and COPD patients (n=10). Furthermore, human bronchial epithelial cells (16HBE) were stimulated (4 hrs and 24 hrs, 37°C) with ISSs from HC (n=6), HS (n=6), or COPD (n=6), and with recombinant human (rh) IL-17A. 16HBE were pretreated with antiIL-17 receptor MoAb before incubation with ISSs from COPD (n=3). IL-8 and TSLP were evaluated in 16HBE supernatants and in cell lysates by ELISA and WB, respectively. HDAC2 activity was evaluated in nuclear cell lysates by a commercial colorimetric assay kit. Finally, the effect of Tiotropium (Spiriva®) (100 nM) was tested in this model. IL-17A was increased in ISSs from COPD and HS when compared with HC. IL-8 and TSLP were higher in cell lysates and supernatants of 16HBE stimulated with ISSs from COPD and HS than in16HBE stimulated with ISSs from HC, and in the cells stimulated with rhIL-17 when compared with untreated cells. HDAC2 activity was reduced in nuclear cell lysates of 16HBE stimulated with hrIL-17 when compared with untreated cells. The preincubation with antiIL-17R reduced IL-8 and TSLP levels while increased HDAC2 in the cells stimulated with ISSs from COPD. Finally, Tiotropium counteracted the above mentioned effects. We suggest that IL-17 present in the airway of COPD patients might increase the IL-8 and TSLP production due to a markedly reduction of the HDAC2 activity. Tiotropium controls the IL-17 activity in COPD.