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Title: Tight junction proteins claudin 3 and 4 in bronchioles and bronchi of COPD and effect of cigarette smoke, slug and twist in vivo and in vitro

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Body: Tight junctions (TJ) form a barrier in airway epithelial cells against the exogenous compounds to prevent their access into lung tissue. Cigarette smoke exposure damages epithelial barrier function possibly by promoting TJ disassembly. It is not yet known how this phenomenon is involved in COPD pathogenesis. The aim of this study was to investigate changes in the expression of selected tight junction proteins (claudin 3 and 4) and transcription factors (slug and twist) in bronchiole and bronchi of non-smokers, smokers and COPD-patients in vivo by immunohistochemistry. The effects of cigarette-smoke extract exposure and twist or slug knockdown (KD) on levels of claudin 3 and 4 mRNA expression and transepithelial resistance (TER) were investigated by using BEAS-2B cells. Claudin 3 and 4 were increased in bronchioles of smokers and COPD with an association of pack-years. Claudin 3 was also enhanced in bronchi in COPD. Transcription factors were inversely associated with claudin expressions in bronchioles and bronchi. In vitro, the expression of mRNA of both studied claudins were upregulated in slug and twist KD cells. Cigarette smoke-extract up-regulated the expressions of claudin 4 in BEAS-2B cells and claudin 3 in slug KD cells, but did not have any major effect in twist KD cells. The TER was higher in twist KD cells than in BEAS-2B cells. In conclusion, claudin 3 and 4 were differently expressed in bronchioles and bronchus of smokers and COPD patients suggesting that the variable changes of TJ proteins may have a role in the pathogenesis of COPD. In vitro, cigarette smoke as well as slug and twist seemed to regulate expression of claudin mRNA.