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Title: Diverse and altered distribution patterns of TLR5 and TLR7 in the distal lung of COPD patients

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Body: Activation of the innate immune system in the distal lung is a hallmark of COPD. Toll-like receptors (TLRs) trigger innate immune responses to pathogens. Although COPD patients are susceptible to infections, the distribution patterns of TLRs at different stages of disease have remained poorly studied. The present study characterizes TLR5 and TLR7 in the distal lung of COPD patients. Methods: GOLD I (n=6), GOLD II-III (n=13), GOLD IV patients (n=8), and controls (never smokers and smokers) (n=13) were enrolled in this study. Immunohistochemical staining was used to identify TLR5 and TLR7 positive cells. Results: TLR5 immunoreactivity was identified in sub-epithelial glands, airway smooth muscle, CD68+ macrophages, CD138+ plasma cells, CD208+ type II pneumocytes and the small airway epithelium. In control subjects and mild COPD epithelial TLR5 had a foremost apical distribution. In contrast, in advanced COPD the distribution of epithelial TLR5 shifted into a distinct basolateral expression that was higher in GOLD IV (p=0.002) compared to controls. TLR7 displayed a peri-nuclear expression in the small airway epithelium irrespective of the study group. However, the total epithelial TLR7-immunoreactivity was upregulated in GOLD IV-patients compared to never smokers (p=0.009). TLR7 expression was also detected in S100B+ nerve cells, CD68+ macrophages, B- and T-lymphocytes, and CD56+ NK cells. Conclusion: Both epithelial TLR5 and TLR7 are upregulated in advanced COPD. Whether the altered expression reflects a natural adaption to the increased pathogen burden in advanced COPD or is part of a dysfunctional immune-regulation in COPD remains to be determined.