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Title: The role of fibrocytes in bronchial remodelling during acute exacerbation of COPD

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Body: Background: Acute exacerbations of COPD are associated with increased bronchial inflammation and probably contribute to bronchial remodelling. Fibrocytes have emerged as key effector cells in diseases characterized by both chronic inflammation and remodelling, such as asthma or lung fibrosis. However, the recruitment of circulating fibrocytes to the lung and their involvement in bronchial remodelling during COPD exacerbations remain unknown. Methods: Circulating fibrocytes were quantified by flow cytometry in 33 COPD patients during an acute exacerbation and two months later in stable condition, and 26 age-matched control subjects. To address the mechanisms involved in fibrocyte migration to the lung during an acute exacerbation of COPD, COPD and control primary bronchial epithelial cells cultured under air-liquid condition were infected with rhinovirus RV16 to mimic in vitro such an exacerbation. The culture medium was then collected to induce fibrocyte migration. After 7 days of culture in serum free medium or serum free medium containing TNF-α, the cell morphology and α-smooth muscle actin expression as a marker of myofibroblast differentiation were both analyzed by immunocytochemistry. Results: The number of circulating fibrocytes is significantly increased during an acute exacerbation of COPD as compared to both controls and COPD in stable condition. RV16-infected COPD epithelium induces fibrocyte migration. Fibrocytes differentiate into myofibroblast-like cells expressing α-smooth muscle actin with an elongated shape in a TNF-α-dependent manner. Conclusion: These results strongly suggest that fibrocytes may play a crucial role in bronchial remodelling following COPD exacerbation.