

Correspondence

Reduced granulocyte counts in sputum may reflect aggravated disease

To the Editor:

We read with interest the work by Hernandez et al¹ demonstrating that IL-1-receptor antagonist (anakinra) reduces endotoxin-induced sputum neutrophilia. This careful study builds on the authors' experience with human inhalational endotoxin, and a previous article showing that IL-1-receptor antagonism inhibits sputum neutrophilia in endotoxin-challenged rats (cited in Hernandez et al¹). The authors have carried out a "proof-of-concept" study of potential treatment interest in severe asthma in which corticosteroids are insufficient.¹ They discuss "airway inflammation." However, there may be distinctions between lumen/sputum, which they analyze, and airway tissue, which is not studied. Here, we highlight the possibility that granulocytes in the bronchial lumen and wall, respectively, may differ dramatically. For example, inhibition of lumen/sputum granulocytes may reflect the accumulation of these cells in the wall.

Various interventions in animal asthma models (anti-FAS mAb, inhibition of intercellular adhesion molecule 2, matrix metalloproteinase-7, matrix metalloproteinase-9, and viral infection followed by allergen challenge) have been demonstrated to reduce the number of granulocytes in bronchial lumen yet increase their numbers in bronchial walls. The result has been severe, even lethal, aggravation of lung inflammation (reviewed in Sheppard² and Persson and Uller³). Such findings make it of interest to learn what effects anakinra has on bronchial wall neutrophils.

Several studies involving human asthma have demonstrated that after allergen challenge the inflammation resolution phase exhibits decreasing bronchial wall eosinophilia along with increasing (!) numbers of these cells in the lumen. Similarly, a singular study demonstrated the occurrence of increasing neutrophil counts in tracheal aspirates in severe asthma along with clinical improvement until extubation (reviewed in Persson and Uller³). Attenuation of asthma exacerbation in mice has also been associated with drug-induced increase in lumen neutrophil counts.⁴ Recently, a CCR1 antagonist, known to reduce lumen neutrophilia, caused aggravation of chronic obstructive pulmonary disease in a phase II clinical trial; tissue neutrophils were not studied (reviewed in Persson and Uller³).

Taken together, the above observations on actual and potential tissue-lumen distinctions underscore the possibility that transepithelial exit is an important route of elimination of disease-driving bronchial wall granulocytes.³ Hence, relying solely on sputum cell data¹ in drug characterization studies appears insufficient.

The notion entertained by Hernandez et al¹ that neutrophils are pathogenic in severe asthma is supported by indirect evidence and awaits validation by selective treatments. Although defense roles of neutrophils are not discussed, Hernandez et al¹ commendably emphasize the increased risk of infection in patients treated with anakinra. Yet, a role of neutrophils in host defense is undisputed, and it is possible that an antineutrophil action of anakinra contributes to the increased risk of infection.

Zhang et al⁵ demonstrated that corticosteroids spare or enhance several mechanisms of innate immunity likely involved in host defense. It is also possible that increased expression of neutrophil attractants, produced *in vivo* in human bronchi by corticosteroids (reviewed in Persson and Uller³), is a component of innate immunity-enhancing effects of these drugs. In conclusion, to discover treatments that are improvements over antiasthma corticosteroids, novel molecular targets are of interest.^{1,6,7} With ensuing drug candidates, effects on both bronchial wall and lumen indices of inflammation would need attention as would the little understood balance between inhibition of disease-driving inflammation and effects on protective innate immunity.

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