

# Upregulated pneumococcal adhesion molecule (platelet-activating factor receptor) may predispose COPD patients to community-acquired pneumonia

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## Dear editor

We read with great interest the recent paper by Braeken et al which analyzed the associations between COPD and community-acquired pneumonia (CAP), published in your journal.<sup>1</sup> In this large population-based study, the authors have concluded that the risk of CAP increases fourfold in patients with COPD, independent of smoking status. The authors briefly discuss potential smoking-induced mechanisms leading to increased risk of CAP in COPD, such as host physiological and structural changes, increased bacterial virulence and impaired host immunity. The authors also stress the need for further mechanistic studies on the cause of this increased risk of CAP in COPD patients.<sup>1</sup>

We believe that some of our recent work is relevant to these findings. We have published several studies that have found increased respiratory tract epithelial expression of specific bacterial adhesion factors in COPD, in particular platelet-activating factor receptor (PAFr) which is the major pneumococcal and *Haemophilus influenzae* adhesion molecule.<sup>2,3</sup> This could well be one important mechanism that the authors did not mention that could significantly increase the risk of *Streptococcus pneumoniae* respiratory infection in COPD. Pack-years of smoking were strongly related to epithelial PAFr protein levels in COPD patients.<sup>2</sup> Notably, *S. pneumoniae* expresses phosphorylcholine in its cell wall that specifically binds to PAFr, leading to initial attachment and subsequent translocation of bacteria into deeper tissue.

In addition, cultured respiratory epithelial cells exposed to cigarette smoke extract exhibited significantly increased PAFr protein expression and greater *S. pneumoniae* adhesion. Notably, blocking PAFr by specific PAFr-antagonist (WEB-2086) reduced adherence of *S. pneumoniae* to the levels seen in control cells.<sup>4</sup> This opens the possibility that PAFr could be targeted therapeutically in COPD patients to limit chronic bacterial adhesion and potentially acute exacerbations, but also CAP in this vulnerable population.

Translational research in this area of bacterial–epithelial interactions is still in its infancy but has huge potential to provide novel insights into COPD pathogenesis and its natural history, as well as new therapeutic targets. Blocking the initial stages of bacterial adhesion and colonization in already activated epithelium in COPD patients could emerge as a promising target for the development of alternate, non-antibiotic pharmacotherapies for the management of the disease and its infective complication.<sup>5</sup> Preliminary data in both in vitro and in vivo models is so promising that further clinical

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research on anti-PAFr therapies is now warranted to ascertain their efficacy in preventing and treating bacterial infections in COPD. There may be broader application to other chronic respiratory diseases, such as cystic fibrosis, given that *Pseudomonas aeruginosa* is the third “common respiratory pathogen” that also adheres to PAFr. Indeed, there seems to be no other obvious mechanism that links these three quite disparate organisms, making them so dangerous to the respiratory tract in very particular circumstances.

## Disclosure

The authors report no conflicts of interest in this communication.

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## Authors' reply

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## Dear editor

We would like to thank Shukla et al for their interesting and valuable addition to our study, which showed that the risk of community-acquired pneumonia (CAP) was fourfold increased among patients with COPD, regardless of their smoking status.<sup>1</sup> They first speculate that their observation of expression of adhesion molecules (PAFr) in several bacteria that can cause CAP among COPD patients may explain our findings. Although they observed a significantly increased expression of PAFr among smokers with COPD versus smokers with a normal lung function, PAFr expression was not elevated among COPD patients who were ex-smokers.<sup>2</sup>

Thus, these observations are not supportive of the fourfold increased risk of CAP among patients with COPD regardless of their smoking status.<sup>2</sup> Also, they are not in line with another study by the same group<sup>4</sup> in which there was no difference in in vivo expression of PAFr between current- and ex-smoking COPD patients. It should also be noted that there is limited comparability between both study populations: while non-small-cell lung cancer was an inclusion criterion in the study by Shukla et al,<sup>2</sup> we evaluated COPD and non-COPD patients from the general population, and only 13%–14% had a history of any malignancy, excluding non-melanoma skin cancer.<sup>2</sup> The hypothesis by Shukla et al is also not supported by their observation that a 6-month intervention with inhaled corticosteroids (ICS) did not affect PAFr expression, while ICS use is a well-established risk factor of CAP in patients with COPD.<sup>3,4</sup> Thus, while the hypothesis is interesting, it certainly requires more and larger clinical studies.

## Disclosure

The authors report no conflicts of interest in this communication.

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