

LETTER

Exit of leucocytes across the alveolar epithelium worsens lung injury

Persson and Uller are to be commended for their review highlighting the important role of leucocyte egression in the resolution of airway inflammation.¹ They go on to speculate that egression across the alveolar epithelium may be detrimental, because, unlike for the airways, there is no mucociliary escalator, and luminal cells that are not removed will interfere with gas exchange. They allay this concern citing work from Cory *et al*² using a mouse model of asthma. In this model a deficiency of matrix metalloproteinase (MMP)-2 and/or MMP-9 inhibits leukocyte egression across the airway epithelium and leukocytes accumulate in the interstitium around the bronchial wall. The MMP-2/MMP-9 knock-out (KO) mice died from asphyxia (presumably from bronchoconstriction). The wild type (WT) mice survive with less peribronchovascular inflammation, but more mild diffuse alveolar inflammation than the KOs.²

Persson and Uller present this as evidence that egression into the alveolar airspace, as for the airway lumen, may also be beneficial. But it would be dangerous to extrapolate

this to other inflammatory diseases for two reasons. First, the leucocytes may have reached the alveolar space not by crossing the alveolar epithelium, but from overspill of the exuberant egression into the airway lumen. Second, in the asthma model described death is by bronchoconstriction and modest alveolar inflammation may be tolerated. In addition, the hazards of egression have been convincingly demonstrated in a murine model in which bleomycin inhalation is used to induce alveolar (rather than airway) inflammation.³

Li and colleagues found that MMP-7 deficiency was protective against death following bleomycin lung injury. They went on to show, very elegantly, that MMP-7 is required to establish the chemoattractant gradient that drives leucocyte egression across the alveolar wall.³ The protective effect of the MMP-KO was reversed when n-formyl-nle-leu-phe (nFNLP) was instilled with bleomycin, and egression of leucocytes into the alveolar airspace was re-established.³

There is still much to be learnt about egression, and in particular the complex regulation and interplay of extravasation and egression in inflammation and resolution of disease. Our own research examines the molecular differences involved in egression across distinct epithelial barriers (alveolar vs bronchial), with a view to enhance the transepithelial exit of leucocytes across

the bronchial epithelium (beneficial) while limiting their exit across the alveolar epithelium (detrimental).⁴ The ability to differentially alter the exit of leucocytes across distinct epithelial barriers may be essential when designing drugs and biological compounds to enhance the resolution of inflammation.

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