

EDITORIAL

Leukocyte migration and activation in the lungs

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Leukocyte migration is critical for our survival. Patients with profound neutropenia or congenital disorders of neutrophil function are prone to life-threatening infections [1, 2]. Paradoxically, neutrophil migration and activation in the lungs is widely believed to be one of the fundamental contributing factors to the acute lung injury that occurs in patients with acute respiratory distress syndrome (ARDS) [3, 4]. This point of view is supported by observations that neutrophil depletion prevents lung injury in sheep [5]; that neutrophils and their oxidative products contribute to endothelial cell injury *in vitro* and lung injury *in vivo* [6]; and that neutrophils and their products accumulate in lung fluids of patients with ARDS [7]. On the other hand, more recent evidence that leukocyte migration does not injure the lungs of normal humans [8] or animals [9] has led to a more balanced perspective on the effects of neutrophil migration in the lungs. Nevertheless, important questions remain about the circumstances in which neutrophil activation and migration in the lungs causes injury to the lung endothelial and epithelial barriers, leading to increased protein permeability in the airspaces, and sustained abnormalities in gas exchange and lung function.

In this issue, JONES *et al.* [10] provide new information about the relationship between neutrophil migration and activation in the lungs of humans with bronchiectasis or bacterial pneumonia. Autologous ¹¹¹In-labelled neutrophils accumulated in the lungs (presumably airways) of four out of five patients with bronchiectasis, but not in the lungs of patients with acute bacterial pneumonia studied 3-4 days after the onset of symptoms. In contrast, neutrophil metabolic activity, measured by positron emission scanning using ¹⁸F-fluoro-2-D-glucose (¹⁸FDG), was greatest in the patients with pneumonia and undetectable in the lungs of patients with bronchiectasis. Studies with cells from lung lavage showed that the ¹⁸FDG signal was associated with neutrophils.

These observations show for the first time that there is a dissociation between neutrophil migration and neutrophil activation in the lungs of humans. Put another way, the data suggest that the degree of neutrophil activation that occurs during migration is minor (undetectable by positron emission tomography (PET)) as compared with the extent of neutrophil activation that occurs in the airspaces of patients with bacterial pneumonia. This is entirely consistent with an earlier observation that neutrophils can reach the airspaces with a full complement of primary granules, that contain myeloperoxi-

dase and proteolytic enzymes, and with normal oxidative and migratory responses to stimuli that might be present in the airspaces [8]. An important implication of the data from JONES *et al.* [10] is that in bacterial pneumonia, the lung injury that occurs is likely to be a consequence not of neutrophil migration through the microvasculature, but rather of the combination of bacterial products and leukocyte activation in the airspaces. This interpretation is consistent with data from sheep and rabbits, in which polymorphonuclear neutrophil (PMN) migration in response to bacterial lipopolysaccharide did not cause lung injury unless bacteria (*Pseudomonas aeruginosa*) were also present in the airspaces [9, 11]. This also provides a basis for understanding how epithelial injury might occur in the lungs, one of the important hallmarks of ARDS.

The study of JONES *et al.* [10] has limitations, as do most studies of pathophysiologic mechanisms in humans. The measurements of neutrophil accumulation and activation were not performed at the same time, and the patients with pneumonia were probably not studied at the time of maximal neutrophil migration, which this same group has shown occurs earlier in the course of bacterial pneumonia in animals [12]. In addition, the number of patients studied was quite small, owing to the complexity of the techniques involved. Nevertheless, these limitations do not weaken the interpretation of the results, as no activation signal was detected in patients in whom neutrophil migration was occurring (bronchiectasis) and neutrophil activation was easily detectable in patients with pneumonia in whom ¹¹¹In-labelled neutrophils did not accumulate in the lungs.

It would be premature, however, to conclude from this study that neutrophil migration is never associated with activation. The possibility that the activity of migrating neutrophils is governed in part by the activation state of the neutrophil and/or the endothelium was not tested by this study. Circulating neutrophils have been found to be activated in some patients with ARDS [13-15], in which the primary inflammatory or traumatic event may not be in the lungs. The approach used by JONES *et al.* [10] might be adaptable to the investigation of neutrophil migration and activation in humans with ARDS.

A great deal has been learned about the function and activation of the neutrophils *in vitro* and *in vivo*. The work of JONES *et al.* [10] takes us an important step further by showing that neutrophil migration and activation can be independent events *in vivo*, and by demonstrating that important questions remain about the relationship between neutrophil migration and activation in our lungs.

References

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