Fas and apoptosis in the alveolar epithelium: holes in the dike?

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ONE OF THE PERKS OF TEACHING respiratory physiology to graduate and medical students is the frequent opportunity to discuss the pathogenic mechanisms underlying acute lung injury and edema formation with a relatively unbiased audience. The available textbooks designed for these students do an excellent job of distilling and summarizing the current state of knowledge in a manner as unambiguous as possible without burdening the student with the unavoidable ambiguity and controversy associated with experimental data.

The distillate presented to students is hopefully an accurate reflection of the large body of literature, much of which has been published in the American Journal of Physiology-Lung Cellular and Molecular Physiology, describing cardiogenic and noncardiogenic mechanisms of pulmonary edema. Noticeably absent from most of these books, however, is a discussion of the important role of the alveolar epithelium in “backing up” the significantly more leaky capillary endothelium. As summarized very nicely by West (11), the interstitial edema resulting from a breach of the capillary wall will not proceed to alveolar flooding unless the epithelial barrier, normally an order of magnitude tighter than the endothelium (2), also becomes breached. Surprisingly, the body of literature describing the factors that are crucial to the collapse of the epithelial barrier seems tiny compared with that describing inflammation and its effects on endothelial barrier function. Understanding how the river initially overflows its banks is clearly important, but once the final levee has begun to fall, turning on the pumps and shoring up the remaining dike become equally if not more critical.

In recent years, the topic of apoptosis in the lung has received a burst of attention from some of us enamored with the cells of the vascular endothelium, epithelium, and immune system and interstitial cell populations (4). In vivo models have clearly indicated a physiological role for apoptosis in the resolution of lung inflammation, in the clearance of excess stem cells after hyperplastic repair of lung injury, and in the pathogenesis and resolution of pulmonary fibrosis (4). With regard to the epithelium, the initial demonstration by Fine et al. (3) that alveolar epithelial cells express functional Fas (CD95, APO1) was followed rapidly by the finding of Hagimoto et al. (5) that activation of Fas in vivo could induce epithelial apoptosis followed by fibrosis.

These observations might lead one to hypothesize that the induction of cell suicide in the epithelium would be likely to cause acute lung injury and concomitant collapse of epithelial barrier function. This expectation is dampened, however, by the realization that the type II epithelium has an extremely high capacity for repair; moreover, it also undergoes normal turnover and removal of damaged cells by apoptosis (10), all the while maintaining high integrity of barrier function through mechanisms yet to be elucidated. By analogy, the intestinal epithelium has been shown to be surprisingly resilient in terms of barrier function, even in the face of ongoing apoptosis (1).

For these reasons, the paper by Matute-Bello et al. (6) in this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology makes an important advance in our understanding of acute lung injury and edema formation. These investigators instilled recombinant human soluble Fas ligand (sFasL) into the lungs of rabbits and thereby produced acute lung injury as evidenced by apoptosis of alveolar epithelial cells, thickening of alveolar walls, and increased protein in bronchoalveolar lavage fluid. Their findings are the first to suggest a link between Fas-induced apoptosis and collapse of the alveolar epithelial barrier. Moreover, because the experimental instillate contained sFasL rather than Fas-activating antibodies, these results argue against previous suggestions (8, 9) that sFasL may not be physiologically important as a proapoptotic stimulus.

The results reported are also consistent with the recent findings by Matute-Bello et al. (7) that patients who die of acute respiratory distress syndrome have higher levels of sFasL in bronchoalveolar lavage fluid. Together, the available data are beginning to imply that a lung that is already “primed” by endothelial damage and the resulting interstitial edema might be...
“driven over the edge” by stimuli that are proapoptotic for the cells of the epithelial levee. Theoretically, these stimuli might include any proapoptotic signal sufficient to exceed the capacity of the epithelium for repair. Future efforts to define these stimuli, their interactions, and ways to block their action will be both interesting and informative indeed.

REFERENCES