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Introduction to alveolar liquid clearance during lung injury: a crucial function – long ignored

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Two reviews in this issue of *Intensive Care Medicine* present an updated vision of the role of alveolar liquid clearance during acute lung injury [1, 2]. It is now well established that the epithelium that lines airways and alveoli is responsible for most if not all of the removal of excess liquid from the airspaces. The importance of the alveolar epithelium has long been ignored. Its very existence as a continuous layer was even denied for a long time because of the limitations of light microscopy, which did not allow the visualisation of thin type I cells. It is amazing to read that Flint [3] wrote in 1907: "... following the use of the lungs or respiration, there is ... a flattening of the connective tissue between the alveoli, yielding practically a single membrane containing the blood vessels between the two layers of respiratory epithelium. This ... consists of the two basement membranes and the interalveolar framework of the adjacent alveoli." However, some doubt remained whether alveolar spaces were indeed covered by a continuous epithelial layer until the development of electron microscopy and the work of Low [4]. The epithelium is so attenuated in most of the surface it covers, with such sparsely disseminated cells that looked metabolically active (the type II cells that secrete surfactant), that the opinion prevailed that the alveolar epithelium was simply part of a passive barrier separating alveolar gas from blood or lung interstitium. Guyton et al. developed a sophisticated model aiming at demonstrating that alveolar oedema liquid was pumped

from the airspaces across the alveolar epithelium by the conjunction of alveolar surface forces, a subatmospheric interstitial pressure and the oncotic pressure of plasma proteins [5]. New means to study the properties of alveolar epithelium appeared when alveolar type II cells were isolated and cultured. A symposium held at the 1982 American Thoracic Society meeting [6] launched two decades of research that have shown the importance of the epithelium for the resolution of alveolar oedema. The first evidence that alveolar epithelial cells were able to perform ion transport was obtained, showing that monolayers of cultured alveolar epithelial cells indeed transported Na^+ and water [7, 8]. Whether similar transport occurred in vivo remained unclear, however, and the ultimate questions were, as Crandall [6] wrote: "... does adult mammalian alveolar epithelium actively transport solutes (and therefore fluid) from alveolar space to interstitium? ... What are the relative roles of active and passive alveolar epithelium transport properties in normal lung fluid balance and in alveolar pulmonary oedema?" An amazingly simple experiment brought the answer. When autologous serum was instilled in the airspaces of a sheep, water was removed much faster than proteins, and this water removal persisted despite the fact that alveolar protein concentration rose to levels such that no known mechanical or osmotic force could explain this fluid movement [9, 10]. The only possible explanation was active (i.e. energy-consuming) ion transport by alveolar/airway

epithelial cells. Additional works on whole animals or isolated lungs helped delineate the basic mechanisms of this alveolar liquid clearance and its modulation. Liquid absorption from alveoli occurs chiefly as a result of active transepithelial Na^+ transport: Na^+ enters alveolar cells through apical Na^+ channels and Na^+ -coupled solute transporters and is pumped out at the basolateral membrane by the Na^+ pump (Na^+ - K^+ -ATPase) [11]. A transepithelial transport of a small solute like Na^+ that would result in only 1 mmol concentration difference would lead to an osmotic pressure difference of 25 cmH₂O across the alveolar epithelial layer, because the reflection coefficient for Na^+ is very close to unity due to the tightness of this epithelium. This represents a strong driving force for water absorption. Epithelial tightness is thus an essential component of liquid clearance. Failure to clear liquid from alveolar spaces during acute lung injury may thus be due to persistence of the mechanisms that lead to oedema formation (i.e. increased microvascular permeability, increased microvascular transmural pressure or both) or reduced alveolar liquid clearance, either because epithelial cells have a reduced rate of Na^+ transport or because epithelial barrier continuity is destroyed, making this transport unable to develop an efficient Na^+ concentration difference. Preservation of liquid clearance is essential for

the patient's recovery during acute lung injury and acute respiratory distress syndrome [12]. Animal models have been important for the understanding of how and why alveolar liquid clearance may be abnormally low during lung injury. The review by Morty et al. [1] presents the various experimental models of acute lung injury that have been developed for that purpose together with the few clinical studies addressing this matter. Some of these models have been used to test which therapy may help in restoring a higher level of liquid clearance. Among these therapies, beta-adrenergic treatment appears promising. It has been known for a long time that beta-adrenergic agonists increase alveolar epithelium Na^+ transport and alveolar liquid clearance in intact lungs, via the cAMP second-messenger pathway [11]. A recent clinical trial suggests that this treatment may be effective during acute lung injury [13]. Upregulation of Na^+ , K^+ -ATPase activity is one of the possible mechanisms for the effect of beta-adrenergic agonists on Na^+ transport. The importance of the Na^+ pump for alveolar liquid clearance and its modulation is the subject of the second review, by Vasdasz et al. [2]. These two reviews emphasise the importance of the alveolar epithelium and of restoring its anatomical and physiological integrity for the resolution of acute lung injury and the acute respiratory distress syndrome.

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