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Editorial

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Alveolar Type I Epithelial Cells: The Forgotten Cells in Fetal Lung Development and Lung Injury

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The alveolar surface of the lung is covered by large flat type I epithelial cells. Even though type I cells represent only around 10% of the cells present in the alveolus; they cover much of the surface area in the developed lung.[1] Given their thinness and proximity to the capillary endothelium; it is well accepted that type I cells play an important role in gas exchange.[2] In addition, these cells are important to maintain adequate fluid balance in the alveolus[3] *via* the tight junctions,[4] ion transport channels[5] and aquaporin-5.[6] Recent studies also indicate that type I cells participate in innate immunity; they express toll-like receptor 4 and produce pro-inflammatory cytokines.[7,8] Studies from T1α knockout mice indicate that alveolar type I cells may be critical for normal lung development. T1α, a lung type I cell differentiation gene, is developmentally regulated and expressed only in type I cells. T1α knockout mice died at birth of respiratory failure. Histologic analysis show fewer alveolar type I cells and decreased alveoli.[9] All together, these investigations suggest a critical role for type I cells in gas exchange, alveolar fluid hemostasis, immunity and fetal lung development.

The typical flat morphology of type I cells begin to appear in the late canalicular period and increase in number during the saccular and alveolar stages of lung development.[10] It has been believed that type I cells are derived from type II cells.[11,12] However, recent studies[13] using specific markers for type I (T1alpha (T1α) and Receptor for Advanced Glycation Endproducts (RAGE))) and type II cells (SP-C, NKX2-1, and ABCA3) have demonstrated the presence in the distal lung of alveolar progenitor cells containing both phenotypes, before they became differentiated type I or type II cells. Therefore, these studies show that during fetal lung development, alveolar type I and type II epithelial cells are derived from a bipotent progenitor cell.[13] Hooper's group found that the numbers of "intermediate cells" expressing both phenotypes were strongly influenced by the degree of lung expansion,[14] supporting the role of mechanical signals in fetal lung development and differentiation of alveolar epithelial cells.

Many premature infants born with underdeveloped lungs develop Bronchopulmonary dysplasia (BPD), a chronic inflammatory lung disease with serious short- and long-term complications. Although the etiology of BPD is multifactorial, mechanical ventilation plays a central role.[15] Excessive stretch of the lung by mechanical ventilation can disrupt the integrity of the alveolar-capillary barrier, resulting in interstitial and alveolar edema. Neutrophils and macrophages recruited to the lung can then trigger and amplify an injury response by releasing cytokines and other inflammatory mediators.[16,17] Many of these pro-inflammatory cytokines are secreted by alveolar macrophages, fibroblasts, type II pneumocytes, and endothelial cells.[18] Distal lung parenchyma cells can be directly exposed to overstretch, and therefore to injury secondary to mechanical ventilation. It has been shown for example that type II epithelial cells release proinflammatory cytokines in response to mechanical injury.[19-22] Given that type I epithelial cells cover much of the distal epithelium of the lung, these cells are also at risk for injury mediated by mechanical ventilation. However, the contribution of type I cells to the pathogenesis of BPD is not clearly defined, in part because of the difficulty in isolating type I cells *in vitro*.[23] Nevertheless, recent studies have found these cells produce Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta or IL-1beta (IL-1β), and Interleukin 6 (IL-6) after exposure to Lipopolysaccharide (LPS).[24] In fact, some authors believe that alveolar type I epithelial cells

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are a more important source of pro-inflammatory cytokines than type II cells.[25] Moreover, the Receptor for advanced glycation end-products (RAGE) is found only on type I cells in the lung.[26] RAGE signaling is mediated *via* NF-κB pathway, stimulating production of pro-inflammatory cytokines and inducing apoptosis.[27]

The epithelial barrier is composed of tight junctions connected to the actin cytoskeleton *via* occludin or zonula occludens. It has been shown that mechanical strain of alveolar epithelial cells, mimicking mechanical ventilation with high tidal volumes, resulted in actin-mediated cell contraction with subsequent increased in paracellular permeability[28] and breakdown of intercellular junctions.[29,30] These junctions could be affected by mechanical injury, leading to pulmonary edema.[31,32] In addition to maintaining the integrity of the epithelial barrier by the tight junctions, epithelial cells need mechanisms to reabsorb the fluids present in the interstitium and alveolar spaces after lung injury mediated by mechanical ventilation.[33] This process is mediated by active transport of Na^+ through amiloride-sensitive cation channels Epithelial Na^+ Channels (ENaC) present in the apical cell membranes and the Na^+/K^+-ATPases localized mainly in the basolateral cell membrane.[34-37] Electron microscope studies provided clear evidence for the major abnormalities in the blood-gas barrier during lung injury. Damage of alveolar type I epithelial cells was observed in rabbits ventilated with a peak inspiratory pressure of 20 cm H_2O for 6 hours.[38] In these studies, some endothelial cells were detached from their basement membrane, resulting in the formation of intra-capillary blebs. There were also occasional breaks in endothelial cells. More prolonged exposure to injurious stress produced alveolar epithelial pathology ranging from inter- and intra-cellular gap formations with denuded basement membranes to extensive cell destruction.[39]

In summary, and as discussed in an excellent review by Dr. Rozycki,[23] alveolar development requires an orchestrated signaling cross-talk among different cells of the distal lung.[40] Given that type I epithelial cells are critical for normal lung development and to maintain the hemostasis of the distal lung, damage of these cells and/or their progenitors by mechanical ventilation and hyperoxia could not only disrupt normal pulmonary development but also have a significant contribution to the pulmonary edema and inflammation observed in patients with BPD. Future studies will provide more insights into the role of these forgotten cells in fetal lung development and lung injury of premature lungs.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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