Alveolar Epithelial Cells Burn Fat to Survive Acute Lung Injury

Acute respiratory distress syndrome (ARDS) is a common and frequently lethal condition that affects 3 million patients annually worldwide (1). ARDS results from acute lung injury caused by a variety of insults, including infection, aspiration, and trauma. Histopathological findings in ARDS include alveolar epithelial damage, endothelial dysfunction, pulmonary edema, and inflammation (2, 3). Management of ARDS remains largely supportive, with mechanical ventilation being the mainstay of therapy (1). Mortality from ARDS remains high, and thus a greater understanding of the cellular pathways associated with disease pathogenesis is required before we can develop strategies that target ARDS directly to promote disease resolution.

Restoration of lung epithelial function after injury is critical to clear alveolar edema and reestablish gas exchange. The reepithelialization process is associated with the proliferation of type II alveolar epithelial cells and their differentiation into type I cells (4). This process is promoted by growth factors, including epidermal growth factor, keratinocyte growth factor, and hepatocyte growth factor (5); however, little is known about how other molecular pathways could be used to promote reepithelialization and recovery from acute lung injury. Cellular metabolism is increasingly recognized as an important regulator of proliferation and differentiation in many tissues as well as pluripotent stem cells (6, 7). It is unknown how cellular metabolism regulates epithelial homeostasis in the lung or how epithelial metabolism is altered during acute lung injury and contributes to the pathogenesis of ARDS.

In this issue of the *Journal*, Cui and colleagues (pp. 167–178) demonstrate that impaired oxidation of fatty acids by alveolar epithelial cells contributes to lung dysfunction after injury (8). Using RNA sequencing, the authors report that genes associated with mitochondrial biogenesis and fatty acid oxidation were among the most downregulated genes in alveolar epithelial cells after endotoxin-induced acute lung injury. These genes included the peroxisome proliferator-activated receptor γ (PPAR γ) coactivator 1 α (PGC-1 α , *Ppargc1a*), which is a master regulator of mitochondrial biogenesis, and carnitine palmitoyltransferase 1A (*Cpt1a*), which catalyzes the transfer of the acyl group of long-chain fatty acyl-CoAs onto carnitine, an essential step for the mitochondrial uptake of long-chain fatty acids before their oxidation. The authors demonstrated that alveolar epithelial cells, as well as MLE-12 cells (a murine alveolar epithelial cell line), readily oxidized exogenously applied palmitate. The response to palmitate was markedly decreased in alveolar epithelial cells isolated from mice after acute lung injury, and treatment with BAL fluid from injured mice was sufficient to reduce the expression of *Ppargc1a* and *Cpt1a*, and reduce cellular oxygen consumption in MLE-12 cells.

These findings suggest that impaired mitochondrial function in alveolar epithelial cells may contribute to the pathogenesis of acute lung injury. Indeed, the authors found that alveolar epithelial cell-specific knockout of *Ppargc1a* was

associated with significantly worse lung damage after endotoxin-induced injury, including increased inflammation, BAL fluid protein content, and epithelial cell apoptosis. Moreover, treatment of mice with fenofibrate, a PPAR α agonist, attenuated endotoxin-induced lung injury. While fenofibrate has previously been shown to be protective against acute lung injury in mice (9), Cui and colleagues provide evidence to suggest that restoration of fatty acid oxidation in alveolar epithelial cells may be partly responsible for this effect.

The authors' findings suggest that altered alveolar epithelial cell metabolism contributes to lung pathology after injury, and that lung epithelial cell metabolism may be targeted for treatment of ARDS. Indeed, work from other groups has demonstrated that hypoxia inducible factor-1 α , a key regulator of glycolytic metabolism, promotes reepithelialization after lung injury (10, 11). Although Cui and colleagues demonstrate that BAL fluid from injured mice, or treatment with TNF- α , is sufficient to reduce oxygen consumption in alveolar epithelial cells, the injured lung is characterized by regions of local hypoxia, and thus the environment is likely to play a major role in regulating epithelial cell metabolism in addition to cytokine signaling. It will be of interest to see whether the effects observed by Cui and colleagues are specific for endotoxin-induced lung injury, or whether clinically relevant models of acute lung injury produce similar effects on epithelial cell metabolism.

Another important question raised by this study revolves around the specific role that epithelial fatty acid oxidation may play in recovery from lung injury. Although the authors focused on epithelial cell apoptosis, the effects of modulating fatty acid oxidation on cell death were modest. A more interesting question may be how changes in cellular metabolism affect the reepithelialization process after lung injury. Which metabolic programs are required for proliferation of type II alveolar epithelial cells, or for their differentiation into type I cells? Delineation of the metabolic requirements for normal reepithelialization may shed light on aberrant metabolic programs seen in patients who exhibit impaired healing.

Metabolic enzymes are increasingly being targeted for therapeutic purposes, particularly in cancer (12). Although the metabolic changes associated with lung cancer are extensively studied, relatively little is known about how cellular metabolism contributes to noncancerous lung diseases. Recent studies have demonstrated metabolic reprogramming in lung fibroblasts associated with development of fibrosis (13–15); however, the report by Cui and colleagues is only one of several papers on metabolism in alveolar epithelial cells. It is likely that ARDS is associated with aberrant cellular metabolism not only in epithelial cells but also in the other cells of the lung, including endothelial cells, immune cells, and fibroblasts. Metabolic reprogramming has been shown to regulate the function of each of these cell types (16). A better understanding of such metabolic alterations will not only provide novel targets for ARDS therapy but may also help to answer some of the outstanding questions about ARDS.

pathogenesis. Why do some patients recover rather quickly while others have a protracted illness requiring long-term hospitalization? Why do some patients progress to develop fibroproliferative ARDS? Why do patients with obesity exhibit reduced mortality from ARDS? It is easy to speculate about ways in which altered cellular metabolism may contribute to ARDS pathogenesis. The study by Cui and colleagues represents a good starting point on which to build. ■

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Robert B. Hamanaka, Ph.D.
Gökhan M. Mutlu, M.D.
Section of Pulmonary and Critical Care Medicine
University of Chicago
Chicago, Illinois

ORCID IDs: 0000-0002-8909-356X (R.B.H.); 0000-0002-2056-612X (G.M.M.).

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