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Lipid Metabolism: A New Player in the Conundrum of Lung Fibrosis

Fibrotic lung diseases are a diverse mixture of conditions that scar the lung and induce varying degrees of respiratory insufficiency. Although these conditions are caused by many different types of pulmonary insults, wound-healing responses are almost always triggered by damage to the lung's epithelial surfaces. As with other wounded surfaces, the initiation of fibrotic responses is believed to serve an important physiological purpose, namely, to restore barrier protection while the lung's epithelial lining recovers. However, in cases in which epithelial recovery is incomplete or does not occur at all, chronic remodeling ensues, resulting in a buildup of scar tissue along with structural and functional impairments in the lung.

In the distal airspaces of the lung, the primary cell responsible for regenerating most of the damaged epithelium is the alveolar epithelial type II cell. Numerous studies have shown that these cells undergo enormous expansion in response to pulmonary insults, not only repopulating dying and dead cells but also replenishing the progenitor cell pool. In idiopathic pulmonary fibrosis (IPF) and several other chronic fibrotic lung conditions, death and/or dysfunction of these cells is now believed to play a causal role in the development of disease (1).

A characteristic feature of dysfunctional alveolar epithelial type II cells in pulmonary fibrosis is that the cells become more vulnerable to apoptosis and accumulate large quantities of aggregated and misfolded proteins in their endoplasmic reticulum (ER), a condition known as ER stress. To date, the mechanisms leading to the development of ER stress remain poorly understood, although mutations causing the misfolding of surfactant proteins have been described in some cases of IPF, and other factors, such as elevated levels of reactive oxygen species, mitochondrial dysfunction, and reduced expression of specific chaperone proteins, have been implicated in various experimental models (2–4). Furthermore, recent studies have suggested that ER stress might also relate to defects in the unfolded protein response, an evolutionarily conserved mechanism that was designed to reduce ER stress but can also trigger cell death when it is ineffective (5).

In this issue of the *Journal*, Chu and colleagues (pp. 737–746) add another layer of complexity to our understanding of the factors that contribute to ER stress in the lung epithelium (6). Specifically, these investigators propose that elevated concentrations of saturated fatty acids, perhaps from the diet, disrupt ER protein homeostasis. Chu and colleagues initially found support for this hypothesis by observing elevated levels of the saturated fatty acid palmitate in the lungs of patients with IPF compared with control subjects. Based on this finding, they went on to examine whether a palmitate-rich, Western diet (only for 2 weeks, to avoid obesity) impacted pulmonary responses to bleomycin in mouse lungs. Of note, they found that not only were ER stress markers increased, but also lung fibrosis and mortality after bleomycin were markedly increased. Furthermore, they showed that palmitate was directly toxic to lung epithelial cells, causing a dose-dependent increase in ER stress and apoptotic markers, and that these effects could be abrogated by genetic deletion of the CD36 lipid receptor gene.

Like all interesting studies, this work raises many additional questions. For instance, why do saturated fatty acids accumulate in the lungs of patients with IPF, and at what levels are these lipids actually toxic? Also, if saturated fatty acids are toxic, why are obese individuals and individuals with different types of lipid disorders not more prone to develop pulmonary fibrosis? That said, support for the concept that dysregulated mitochondria and metabolic pathways contribute to the development of pulmonary fibrosis extends far beyond this study (7). For example, Sunaga and colleagues showed that levels of Elovl6 (elongation of long-chain fatty acids family member 6), a rate-limiting enzyme in catalyzing the elongation of fatty acids, is reduced in IPF lung tissues and that deficiency of this enzyme in mice leads to spontaneous thickening of alveolar walls and increased susceptibility to bleomycin-induced pulmonary fibrosis (8). Similarly, Romero and colleagues recently reported that levels of SCD1 (stearoyl CoA desaturase 1), an enzyme involved in the desaturation of fatty acids, was reduced in IPF lung tissues, and that pharmacological inhibition of this enzyme caused ER stress and induced fibrotic remodeling in the mouse lung (5). Finally, Huang and colleagues previously reported that levels of lysocardiolipin acyltransferase, a mitochondrial lipid-remodeling enzyme, were reduced in IPF lung tissues and that overexpression of this enzyme ameliorated several indices of lung fibrosis in mice (9).

Although Chu and colleagues did not elucidate the mechanisms by which saturated fatty acids induce ER stress in the lung epithelium, we wonder if answers might lie in discoveries from other fields. For example, in diabetes, altered lipid metabolism favors the synthesis and accumulation of triglycerides and cholesterol, which have been linked to elevated levels of transforming growth factor-β and the development of tubulointerstitial fibrosis (10). Moreover, in the obesity field, it has long been believed that organ dysfunction results, at least in part, from the accumulation of saturated fatty acids outside of adipose tissue, particularly in the cell membranes of cardiovascular tissues (11). In turn, this is believed to cause other downstream consequences, such as the induction of ER stress by inactivating membrane receptors and disrupting the flow of protein trafficking in cells.

Finally, even though Chu and colleagues performed their study mostly in mouse tissues, we believe their findings may have immediate clinical implications. For example, patients with end-stage lung disease are often prescribed a high-fat diet to combat the

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weight loss associated with advanced disease. At the very least, this study suggests that physicians should be cautious with this recommendation. Moreover, this study also suggests that a closer look should be given to other therapeutic modalities currently being used to target lipid metabolism. Along these lines, Rangarajan and colleagues recently showed that metformin, an activator of AMPK (5′ adenosine monophosphate-activated protein kinase) and an inhibitor of lipid synthesis, reversed established fibrosis in mice (12). Moreover, others have shown that fenofibrate and ciprofibrate, which have been approved by the U.S. Food and Drug Administration for lowering circulating lipids, can effectively reduce lung fibrosis in mice and decrease collagen production and myofibroblast differentiation in IPF fibroblasts (13, 14).

Altogether, research in the field of pulmonary fibrosis continues to suggest that metabolic dysregulation acts as a key contributor to the pathogenesis of the disease, and that drugs targeting different aspects of cellular metabolism, including glycolysis, mitochondrial oxygen consumption, and lipid metabolism, should be strongly considered for treatment of this disease. ■

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