Myofibroblast–Macrophage Interactions Turn Sour in Fibrotic Lungs

A quiet revolution has been occurring in biology in recent years. Traditionally, scientists in this field appeared to distinguish between "active" responses to cellular or tissue injury, such as activation of signaling pathways or cell-to-cell interactions, and processes that were believed to be "housekeeping" or homeostatic, such as extracellular matrix deposition and cellular metabolism. Only recently has the recognition sunk in that the extracellular matrix and the cellular metabolism may not be neutral bystanders but may both be affected by and contribute to the disease process and resolution of injury. This recognition has provided significant insights into the biology and pathogenesis of many lung diseases, such as asthma and chronic obstructive pulmonary disease; however, the interaction of the metabolism with extracellular matrix remodeling is especially clear in the pathogenesis of the disease commonly known as idiopathic pulmonary fibrosis (IPF).

Despite recent advances in treatment, IPF, a progressive intractable deposition of scar tissue in the distal airways that eventually leads to respiratory failure and death, remains a devastating and incurable disease. A better understanding of IPF pathogenesis has been an ongoing goal and will drive novel treatments that will improve patient survival. Metabolic derangements in lung fibrosis, such as lipid metabolism, mitochondrial dysfunction in injured epithelia, and the metabolic reprogramming of the activated myofibroblast, have been the focus of intensive research. This research has revealed that metabolic alterations in the fibrotic lung are closely linked to the unfolded or misfolded protein response, oxidative stress, senescence, apoptosis, and collagen deposition (1–5).

Given that myofibroblasts are the main driving cell for extracellular matrix deposition, their metabolism has been studied extensively (3, 6). A hallmark of the metabolic changes in activated fibroblasts is the upregulation of "noncanonical" pathways such as glutaminolysis (the conversion of the amino acid glutamine to glutamate and α-ketoglutarate) and aerobic glycolysis (the conversion of glucose to pyruvate under normoxic conditions) (2). There is already evidence that endogenously produced lactate activates myofibroblasts in an autocrine manner (6–8). In this issue of the *Journal*, Cui and colleagues (pp. 115–125) now take the concept of metabolic effects in fibrosis a step further by looking into the cross-talk of myofibroblasts and macrophages in fibrotic lung disease (9). Their work suggests that lactate of myofibroblast origin promotes a profibrotic phenotype in macrophages, which thus contributes to a fibrotic milieu in the lung. The authors demonstrate the increased lactate in fibrotic lungs in the mouse model and then show that exogenous lactate can be taken up by macrophages and lead to an epigenetic modification (histone lactylation), which is evident in the macrophages of fibrotic human and mouse lungs. Lactate exposure independently leads to the upregulation of a panel of fibrotic genes, which is associated with lactylation of their promoters, whereas knockdown of p300, a histone acetyltransferase that can lactylate histones, reduces the expression of fibrotic genes in macrophages as well as overall histone lactylation levels.

The recognition of a role for lactate as an intracellular mediator and as an epigenetic regulator across cells is highly exciting. Recent work has demonstrated that macrophages can sense and receive lactate from their environment, and that this lactate may lead to increased lactylation in macrophage DNA, leading to epigenetically driven gene expression changes (10). Cui and colleagues demonstrate a biologically relevant application of this concept in fibroblast–macrophage cross-talk in fibrotic lungs and uncover yet another metabolism-based pathway of cell–cell cross-talk in lung injury.

Like every good research endeavor, this work opens new unanswered questions. Although it is assumed that the myofibroblasts are the main source of lactic acid in an IPF lung, this is not yet settled; other cells such as neutrophils, epithelia, or hypoxemic tissue may contribute (11). Furthermore, because lactate activates myofibroblasts in an autocrine manner (6, 8), the contribution of an indirect "myofibroblast-to-macrophage-to-myofibroblast" effect remains to be elucidated. Nevertheless, the concept is intriguing. Macrophages are now recognized as central mediators of the injury resolution response, or, conversely, as important mediators in the march toward fibrosis (12), and may be attractive targets for antifibrotic therapies. More generally, we could also wonder if there is something about fibrotic macrophages or their microenvironment that makes them particularly susceptible to profibrotic epigenetic reprogramming. Lactate production is not unique to pulmonary fibrosis and can be found in inflammatory milieus, such as cystic fibrosis airways (11). Given that lactate production in the lungs is elevated even at baseline (13), is there a "good" level of lactate that should be maintained for homeostasis? And is the observed effect in lung fibrosis a result of extremely high lactate concentrations locally in the fibrotic microenvironment or a two-hit mechanism whereby the macrophages are biased toward a profibrotic response because of other activating factors, or perhaps both?

The work by Cui and colleagues also further underscores potential implications and applications of metabolic interventions as treatment modalities in IPF. Kottmann and colleagues previously demonstrated the salutary effect of gossypol, a polyphenolic inhibitor of lactate production, in preventing lactate-induced myofibroblast proliferation (7), and an *in vivo* effect was demonstrated in liver fibrosis (14). This suggests that pharmacological

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(or perhaps even dietary) interventions may modulate the profibrotic milieu in several key cell populations and thus impact the development of lung fibrosis. Fibrotic lungs may turn sour, but recent research insights, such as the paper by Cui and colleagues, promise a more palatable future. ■

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