Caveolin-1 stops profibrogenic signaling?

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CAVEOLAE ARE SMALL, invaginated surface structures in the plasma membrane of fully differentiated cells such as endothelial cells, epithelial cells, adipocytes, and fibroblasts. The principal components of caveolae are proteins called caveolins, of which caveolin-1 (cav-1) is best characterized. The expression of cav-1 decrease in transformed cells, implying that cav-1 is an important molecule for inhibiting signaling pathways that regulate cell proliferation and migration (3, 7, 8). Additionally, cav-1 is also involved in cholesterol transport, transcytosis, and microorganism entry into hosts (7). In the absence of cav-1, mice appear normal, but they are physically weak, and their lungs display severe abnormalities with hyperplasia and lymphocytes infiltration (3).

Reduction of cav-1 levels in type I pneumocytes has been reported during lung fibrogenesis (6) in irradiated rats. In the bleomycin-induced lung fibrosis model, we have demonstrated that cav-1 levels were downregulated with increased production of ECM proteins (18). Given that cav-1 negatively modulates a plethora of signaling molecules at the ligand receptor level (7, 8), it would be reasonable that cav-1 inhibits or attenuates profibrogenic signaling pathways.

The response to various noxious stimuli in the lung can lead to lung fibrosis. It is now believed that lung fibrosis is mainly an epithelial/fibroblasts-linked disease in which stimuli first disrupt the homeostasis of parenchymal epithelial cells, resulting in epithelial cell activation (12, 17) and recruitment of immune cells (15). Activated epithelial and immune cells are thought to release potent profibrogenic molecules and cytokines, such as TGF-β1, which, in turn, trigger the transdifferentiation of fibroblasts into myofibroblasts and augment their production of ECM (collagen type I and fibronectin) in mesenchymal cells (12, 15, 17). A perpetuated cycle of injury and repair eventually results in progressive fibrosis, accumulation of ECM, and loss of the lung parenchyma. Recently, Tager et al. (15) provided evidence that lung fibrosis is also mediated by lysophosphatic acid (LPA), a lipid metabolite synthesized by different cell types including immune cells (4). LPA seems to be the main chemotractant for resident lung fibroblasts but not for circulating fibrocytes, another source of myofibroblasts (10, 15). In addition, various chemokines and their receptors have been shown to function as chemoattractants and regulators of angiogenesis and vascular remodeling in lung fibrosis (14). Since the receptors for growth factors, chemokines, and lipid mediators take advantage of caveolae or clathrin-coated pits for their proper signaling and internalization (2, 4, 5, 11), it is not surprising that cav-1 may participate in lung fibrogenesis. For instance, clathrin-dependent internalization into the endosome promotes TGF-β signaling. In contrast, the caveolae internalization pathway is required for rapid receptor turnover, thus braking TGF-β-mediated signaling (2). Therefore, trafficking of the receptor to distinct internalization routes might regulate signaling and receptor turnover, fine tuning the amplitude of signals from extracellular milieu (Fig. 1).

In this issue of *AJP-Lung*, Tourkina et al. (16) demonstrate that cav-1 acts as a protective regulator of pulmonary fibrosis. They utilized a cell-permeable peptide equivalent of cav-1 scaffolding motif fused with internalization sequences (1). By measuring the end products of ECM proteins, such as tenascin-C and collagen and lineage marker, α-smooth muscle actin, they showed antifibrotic potential of cav-1 fragments peptide. Cav-1 scaffolding domain (amino acids 82–101) has been shown to regulate signal transduction through binding of its scaffolding domain to key signaling molecules (1, 7). They also conducted mechanistic studies for MAPKs, and again the cav-1 scaffolding peptide successfully inhibited the hyperactivation of these kinases in fibroblasts from scleroderma patients. Previously, we demonstrated that cav-1 expression was markedly reduced in lung tissue from patients with idiopathic pulmonary fibrosis and that this reduction was predominant in alveolar epithelial cells. In parallel, we found that fibroblasts, the key players in fibrosis, had low levels of cav-1 expression from patients with idiopathic pulmonary fibrosis. Intratracheal administration of cav-1 conferred resistance against bleomycin-induced fibrosis in mice and restored lung structural integrity (18).

The observations of Wang et al. (16) and Tourkina et al. (18) show that cav-1 is an essential regulator of fibroblast proliferative activity. Reduction of cav-1 levels in type I pneumocytes has been reported during lung fibrogenesis (6) in irradiated rats. In the bleomycin-induced lung fibrosis model, we have demonstrated that cav-1 levels were downregulated with increased production of ECM proteins (18). Given that cav-1 negatively modulates a plethora of signaling molecules at the ligand receptor level (7, 8), it would be reasonable that cav-1 inhibits or attenuates profibrogenic signaling pathways.

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ation and ECM production. These data also imply that cav-1 is a logical target for therapeutic intervention to reduce the development and progression of pulmonary fibrosis. Moreover, treatment approaches that augment cav-1 bioavailability as shown in the experiments of Tourkina et al. (18) may help restore normal alveolar epithelial repair and regeneration. Particularly, by employing small peptide with cell-permeable sequences, Tourkina and colleagues (18) seem to increase the bioavailability of cav-1 protein in their model systems.

Albeit that the antifibrotic activity of cav-1 in vivo fibrosis models is well-documented, we may need caution to deliver the protein into circulation. Investigators have found that cav-1 expression increased in endothelial cells of fibrotic lung and liver (6, 13). The increased expression of cav-1 and its interaction with endothelial nitric oxide synthase impaired vascular reactivity in those tissues. If cav-1 expression is differentially regulated in a cell type-specific manner, we need to consider targeting strategy to maximize the beneficial effects of cav-1 while suppressing unwanted effects.

REFERENCES