DOCK-t(w)o Pleural Fibrosis

Pleural fibrosis is a serious pulmonary morbidity characterized by thickening and stiffening of the pleura, together with progressive fibrosis in the subpleural compartment, which leads to impaired lung function, reduced life quality, and increased mortality (1, 2). Pleural fibrosis often ensues from a variety of inflammatory events that result from thoracic irradiation, parapneumonic effusion (empyema), asbestos injury, hemothorax, and tuberculosis and other microbial infections. The disease pathogenesis involves multiple cell populations, including pleural mesothelial cells (PMCs), fibroblasts and myofibroblasts, and different types of immune cells. In addition, it involves many abnormal processes, including aberrant chemoattraction, unbalanced coagulation, and fibrinolysis (1–3). There is currently no effective therapy to reverse established pleural fibrosis.

PMC is the major cell type in the pleura where it forms a cell monolayer. This cell population is of mesodermal origin during the lung development, although it exhibits unique epithelial characteristics (4, 5). It has been recognized that the PMC plays a pivotal role in the initiation and progression of pleural fibrosis. On pleural injury, PMCs are first-line cells that initiate an immune response by releasing proinflammatory cytokines and chemokines. These cells also produce profibrotic mediators, including TGF-β (transforming growth factor-β), PDGF (platelet-derived growth factor), and bFGF (basic fibroblast growth factor), as well as mediators regulating fibrin turnover (4–6). PMCs have been found to undergo a phenotypic change in response to profibrotic stimuli, termed mesothelial–mesenchymal transition (MesoMT), a process defined by the acquisition of mesenchymal features and production of excess extracellular matrix components. There is an increasing appreciation of the important role of MesoMT in pleural fibrosis (4, 7–9). However, the underlying molecular mechanism remains poorly understood.

In this issue of the *Journal*, Qian and colleagues (pp. 171–182) describe a novel role of DOCK2 (dedicator of cytokinesis 2) in the MesoMT and pleural fibrosis processes (10). DOCK2 is an atypical Rac activator predominantly expressed in hematopoietic cells. Its role in hematopoietic cells is widely studied and investigations of its functions in nonhematopoietic cell types have also started to emerge (11–14). This study found that DOCK2 is significantly upregulated and its expression is colocalized with both the MesoMT marker α-SMA (α-smooth muscle actin) and the mesothelial marker calretinin in the thickened pleura of patients with nonspecific pleuritic fibrosis and mice with TGF-β, CBB (carbon black/bleomycin), and streptococcal empyema–induced pleural fibrosis. The authors determined the role of DOCK2 in this disease by comparing the streptococcal empyema–induced pleural fibrosis in wild-type mice and DOCK2 global knockout mice and found that DOCK2 deficiency protected the mice from this pathology, suggesting that DOCK2 is a critical mediator of the disease pathogenesis. In mechanistic studies, they show that TGF-β, a potent MesoMT inducer, transcriptionally increases DOCK2 expression in the primary PMCs and demonstrates that DOCK2 is an important mediator of TGF-β–induced MesoMT in PMCs *in vitro*. Their data also suggest that Snail, one of the major transcription factors responsible for epithelial–mesenchymal transition, may mediate the DOCK2 promotion of MesoMT in PMCs. Overall, their findings provide clear evidence that DOCK2 is involved in MesoMT and thereby contributes to the pleural fibrogenesis (Figure 1).

There are several limitations to this study. As mentioned above, DOCK2 is primarily expressed in immune cells and plays a pivotal role in immune cell activation, chemoattraction, and lymphocyte migration and proliferation (11, 12). These events are known to greatly contribute to the initiation and progression of pleural injury, repair, and fibrosis (1–3). The lessened pleural fibrosis demonstrated in the DOCK2 knockout mice after intrapleural *Streptococcus pneumoniae* infection may be attributed not only to a negated MesoMT but also to a dampened inflammatory cell activation and infiltration as a result of DOCK2 ablation. Thus, the precise role and contribution of PMC DOCK2 and DOCK2-mediated MesoMT in pleural fibrosis requires further investigation. These questions can be partially addressed by using conditional mesothelial-specific DOCK2 knockout mice and/or wild-type mice with DOCK2$^{-/-}$ bone marrow composition in the pleural fibrosis model.

In addition, the mechanism by which DOCK2 regulates TGF-β activity needs further exploration. It is well established that DOCK2 is a key regulator of activation of the small GTPase Rac-1 (11, 15). Furthermore, Rac-1 is known to be an important modulator of the TGF-β signaling cascade and it participates in the pathogenesis of fibrosis in multiple organs (16, 17). Thus, it is important to determine the role of Rac-1 activation in DOCK2 regulation of the TGF-β signaling in PMC and MesoMT. An improved knowledge of the regulatory interactions among DOCK2, Rac-1, and TGF-β signaling in PMC may provide new mechanistic insight into their respective contributions to pleural fibrosis.

It is also worth noting that PMC DOCK2 expression may be subject to distinct regulatory mechanisms in the three different pleural fibrosis models used in this study. Although the authors focused on how TGF-β induces DOCK2 expression, the potentially different mechanisms associated with PMC DOCK2 upregulation in the CBB and bacterial infection models and in human patients with pleural fibrosis should not be overlooked. Indeed, previous studies have shown that activation of pathogen- or danger-associated molecular pattern receptors, such as Toll-like receptors, leads to DOCK2 upregulation (18, 19). Thus, DOCK2 induction in PMCs

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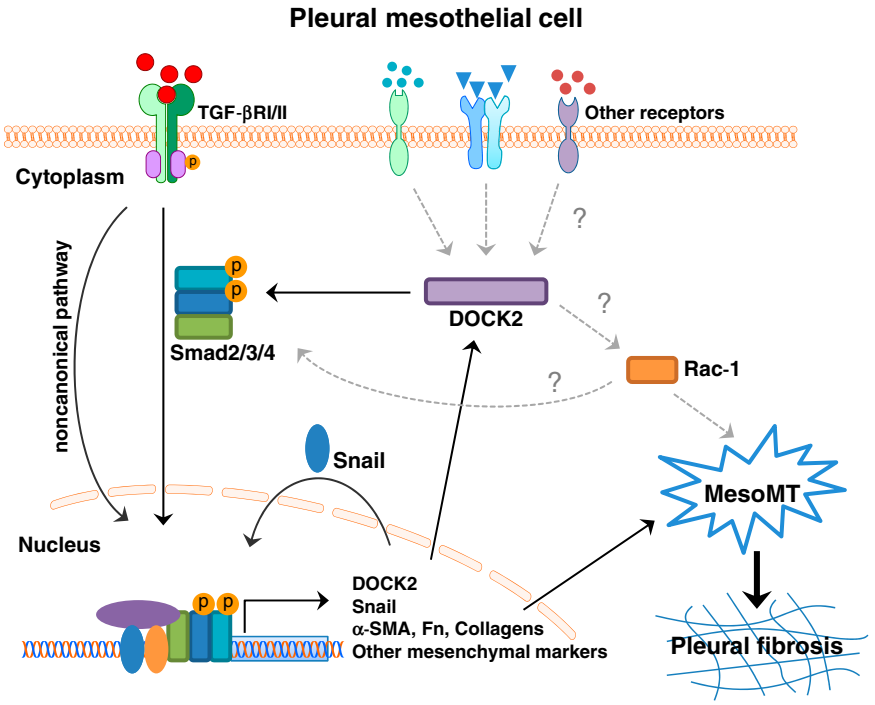

Figure 1. DOCK2 promotes pleural fibrosis by mediating MesoMT in pleural mesothelial cells. α-SMA = α-smooth muscle actin; DOCK2 = dedicator of cytokinesis 2; Fn = fibronectin; MesoMT = mesothelial–mesenchymal transition; Rac-1 = Ras-related C3 botulinum toxin substrate 1; TGF-βR I/II = transforming growth factor-β receptor I/II.

involved in pleural fibrosis is likely a collective effect of diverse stimulations.

Nevertheless, the study of Qian and colleagues identifies a previously unrecognized role of DOCK2 in MesoMT and pleural fibrosis. Continued elucidation of the DOCK2 regulation and its downstream signaling pathway controlling PMC activation will shed new light on the pathogenesis of pleural fibrosis and may lead to the identification of novel therapeutics for this disease. ■

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