Idiopathic pulmonary fibrosis (IPF) is a lethal fibrotic lung disease with no cure (1). Fibroblasts are key effector cells in the pathogenesis of lung fibrosis (2). In response to soluble (e.g., TGF-β [transforming growth factor β]) and insoluble (e.g., extracellular matrix) signals, fibroblasts transdifferentiate into myofibroblasts to drive the fibrotic process (3–5). Other investigators and we have shown that myofibroblast differentiation is dependent on extracellular calcium influx (6). The mechanosensitive cation channel TRPV4 (transient receptor potential vanilloid 4) and voltage-gated L-type calcium channels appear to play a secondary role in abrogating specific functions of the BK channel (big conductance potassium) channel studied in this work, was previously found to be a second messenger to mediate essential functions, such as myofibroblast transdifferentiation and contraction of pulmonary fibroblasts (6, 7). However, the effects of calcium-activated potassium channels on fibroblast function are poorly understood. This study provides new insights into the pleiotropic actions of the BK channel on induction of myofibroblast transdifferentiation and contraction of pulmonary fibroblasts. Although the action of BK channels in fibroblasts is the opposite of that observed in smooth muscle cells, it mirrors their effect in other mesenchymal cells, such as synoviocytes and dermal fibroblasts (12).

The DNA methylated gene KCNMB1, which encodes for the BK channel studied in this work, was previously found to be a highly expressed gene in a survey of lung tissue from patients with IPF compared with normal lung tissue (8). There are many KCNMB genes (β1–β4) that encode for multiple BK channels. The KCNMB β1 channel is highly expressed in lung fibroblasts as compared with its β2–β4 subunit expression. Furthermore, the authors show that expression of the β1 subunit is increased in IPF fibroblasts, and the β1 siRNA knockdown data demonstrate that β1 is necessary to induce myofibroblast transdifferentiation into lung fibroblasts. The cell-type specificity of the BK channel β1 subunit may allow for targeted actions through therapeutic manipulation. In addition, there is the possibility that BK channels couple with other ion channels in a tissue- or disease-specific manner. For example, calcium channel blockers, calcineurin inhibitors, and TRPV4 channel deletion have been shown to abrogate bleomycin-induced experimental PF in mice (6, 7, 15). Furthermore, given the heterogeneity of KCNMB1 expression in patients with IPF, this work may provide an avenue for personalized targeted therapy. Further studies of ion channels will likely provide better insight into the biology of myofibroblast transdifferentiation and fibrosis. Many unanswered questions remain to be addressed that can guide future research. For example, what is the mechanism of BK channel activation in response to TGF-β? If it is calcium, which calcium channels are involved and how are they activated? Precisely how
does activation of the BK channel alter the myofibroblast response to TGF-β—through ion flux or downstream signal mediators? Finally, what are the critical cell types and actions of BK channels that mediate PF in vivo? It is well known that calcium’s signaling specificity can be encoded in its spatiotemporal variation patterns (7). Thus, a detailed examination of calcium fluxes using real-time analysis at the subcellular level of resolution would be warranted to begin to address some of these key unresolved questions.

In summary, the identification of novel plasma membrane channels that regulate myofibroblast transdifferentiation makes a significant contribution to the fibrosis field, and may provide a therapeutic target in IPF. In the study by Scruggs and colleagues, the BK channel was shown to affect myofibroblast transdifferentiation in a calcium-dependent manner. The BK channel now joins other cation/calcium channels, such as TRPV4 and L-type channels, as potential therapeutic targets to treat pulmonary (and potentially other) fibrotic disorders.

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**Figure 1.** Proposed model for the cross-talk between cation channels, including the BK (big conductance potassium) channel and TGF-β (transforming growth factor β) signaling pathways in pulmonary fibrosis. This schematic is based on the findings of Scruggs and colleagues (11), which demonstrate that calcium-dependent potassium influx through BK channels cooperates with TGF-β to induce myofibroblast transdifferentiation via a calcium-dependent mechanism that remains to be determined. ER = endoplasmic reticulum; L-type= voltage activated calcium channel; TRPV4 = transient receptor potential vanilloid 4.