Mechanical signaling cascade central to fibrotic scar tissue development defined

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In a new study published in *Science Signaling*, Cleveland Clinic researchers have identified a novel target for new therapies that may help to treat or prevent a host of fibrotic conditions, which contribute to

nearly half of overall mortality in the United States.

Fibrotic diseases are characterized by the overproduction of extracellular matrix (ECM), with resultant formation of scar tissue. Cells called myofibroblasts are thought to be the major producers of the scar tissue. Two key signals are needed to generate these myofibroblasts—active TGF-β (transforming growth factor-β) and a mechanical signal.

Previous research (published in the *Journal of Clinical Investigation*, 2014), led by Mitchell Olman, MD, a researcher in Cleveland Clinic Lerner Research Institute's Department of Inflammation & Immunity and practicing pulmonologist, identified an ion channel called TRPV4 (transient receptor potential vanilloid), as the key transducer of the mechanical signal that leads to myofibroblast generation.

The team knew that blocking these ECM-producing pathways is an important step in identifying potential targets for anti-fibrotic therapies and kept them hard at work.

In the current study, research teams led by Dr. Olman and S.V. Naga Prasad, Ph.D., also of Lerner Research Institute, discovered that TRPV4 selectively binds to a kinase called PI3Kγ (phosphoinositide 3-kinase γ) to form an intracellular protein complex. This TRPV4-PI3Kγ complex—which is recruited by TGF-β—migrates from inside the cell to the plasma membrane and subsequently amplifies the actions of each individual protein, ultimately resulting in the differentiation of fibroblasts to myofibroblasts. Myofibroblasts produce and expel ECM outside of the cell, and contract the ECM to generate scar tissue—the hallmark of fibrotic diseases.

Taken together, these findings suggest that blocking TRPV4 and PI3Kγ binding may be an unexplored avenue for treating or preventing fibrotic conditions of many major organs. While additional research is necessary,

this study provides promising support and rationale for a new treatment approach.

More information: Lisa M. Grove et al, Translocation of TRPV4-PI3Kγ complexes to the plasma membrane drives myofibroblast transdifferentiation, *Science Signaling* (2019). DOI: 10.1126/scisignal.aau1533