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Using Solid Mechanics to Reverse Fibrotic Disease

Mechanical forces govern cell fate. Cells sense their mechanical environment, respond by generating forces of their own, and remodel the extracellular matrix (ECM) that surrounds them. Recursive feedback between cells and ECM drives both healthy tissue homeostasis and pathological conditions such as fibrosis. The cellular signaling pathways mediating this feedback are so redundant that pharmaceutical interventions for fibrotic diseases, including pulmonary fibrosis, which carries a prognosis worse than most cancers, have shown limited efficacy. This talk will present our integrated experimental and computational work demonstrating that ECM mechanics itself can serve as a therapeutic target. Central to our approach is the recognition that cells respond to the full tensorial nature of stress, not simply its magnitude. Using techniques related to the traction microscopy approaches of Dr. Mollica, we show that stress anisotropy is the critical mechanical cue triggering the phenotypic transition that underlies fibrosis. This is driven by a self-reinforcing feedback loop in which cellular protrusions establish tension anisotropy through interactions with collagen fibers, which in turn stabilizes these protrusions and enhances contractile forces. Long-range mechanical communication through strain-stiffened ECM tension bands further coordinates this. We show that physiological dynamic stretching can interrupt this feedback loop by modulating the nonlinear mechanics of networked biological solids. Leveraging these insights, we developed a non-invasive ventilation protocol that reverses established pulmonary fibrosis in mice by physically disrupting pathological ECM crosslinks