Mechanical forces have been suspected to play a critical role in wound healing and fibrosis but the precise mechanisms have remained poorly understood. Recent studies have demonstrated that mechanical forces can significantly impact the biologic response to injury and fibrosis. Our laboratory has identified a critical role for fibroblast specific focal adhesion kinase (FAK) in the development of scar and fibrotic tissue. Transcriptomic analysis has demonstrated that mechanical signaling activates hundreds of different pathways leading to increased inflammation and fibrosis. Conversely, blocking mechanical signaling by transgenic or pharmacologic approaches prevents fibrosis in preclinical models and human clinical trials. Manipulating biomechanical signaling networks using either device or pharmacologic approaches holds the promise to reduce fibrosis and promote tissue regeneration.