

Fundamental aspects of myofibroblast contraction

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The high contractile force generated by myofibroblasts is beneficial for physiological repair but detrimental for organ function when it becomes excessive such as in the dramatic contractures characterizing Dupuytren's diseases. I will present a new model of how myofibroblast contraction leads to irreversible tissue contractures. We support this model with recent findings combining Ca^{2+} fluorescence imaging with atomic force microscopy, culture on compliant substrates, and microbead tracking using myofibroblasts in cell culture. We show that Rho/ROCK signaling promotes strong isometric cell contraction that can locally relax fibrils within a stressed matrix. This is analogous to creating slack by binding off regions of tension in a stretched rubber band. Unrestrained matrix is then free to be remodeled by weak and short-ranged microcontractions. Microcontractions occur periodically and are regulated by spontaneous cytoplasmic Ca^{2+} oscillations. This is the first time that two functionally and regulatory independent modes of contraction are shown to collaborate in the same cell to promote overall matrix contracture. We want to exploit our knowledge to therapeutically interfering with myofibroblast contraction to suppress connective tissue contractures.