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Collagen Fibril: A Friend or A Foe?

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Tissue fibrosis is characterized by excessive extracellular matrix (ECM) deposition and increased rigidity in interstitial tissues. TGF-b induced myofibroblast activation plays very important role in the development of tissue fibrosis. However, the mechanobiological mechanisms whereby TGF-b and/or other factors triggers myofibroblast activation has not been understood yet. Here we employed fibroblasts (derived from different tissues with physiological and pathological conditions) cultured on collagen gel and stimulated with TGF-b as the model of myofibroblast activation. To monitor the force generated within the cells as well as the force exerted by the cells during myofibroblast activation, we established an in vitro real-time monitoring system with fluorescent confocal microscope and atomic force microscope (AFM) to assess the elasticity of cells and FITC-conjugated collagen fibers. This platform enabled us to not only visualize, but also assess how fibroblasts or myofibroblasts remodel loose and soft collagen fibrils (good) into tight and stiff collagen fibrils (fibrosis). Our result showed that collagen fibers near fibroblast was stiffer than distant region. TGF-β stimulation increased the rigidity of renal fibroblast (NRK49F), as well as collagen fibers, but did not alter diameter of collagen fibers or the angle between collagen fibers and cultured cells. We observed that keloid fibroblast displayed markedly higher collagen fibril remodeling ability than normal fibroblast. Moreover, we discovered a new blood derived factor which exerted much higher collagen fibril remodeling capability than TGF-b in various type of fibroblasts. Collectively, we have demonstrated that co-axis fluorescent confocal microscope and AFM provides high resolution images for the studies of activation of myofibroblast and thereby to elucidate the mechanism of tissue fibrosis.