Department of Biochemistry and Molecular Biophysics Seminar

Monday, August 10 at 4:00 p.m. in Ackert 120

Coffee and cookies at 3:45 p.m. in Chalmers 168

Dr. Peleg Hasson, Associate Professor

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Mechanics or enzymatics? Regulation of fibroblast identity and extracellular matrix assembly

Fibroblasts are the principal extracellular matrix (ECM)-producing cells of connective tissues and are essential for development, tissue homeostasis, regeneration, and repair. Single-cell studies have revealed extensive fibroblast heterogeneity, yet the mechanisms governing the emergence of distinct fibroblast populations and their functional specialization remain poorly understood. We combine developmental and translational approaches to define how mechanical and extracellular matrix cues regulate fibroblast identity and function. During skeletal muscle development, we show that fibroblasts diversify during the transition from embryonic to fetal myogenesis into two major subpopulations corresponding to adult interstitial and delineating fibroblasts, which occupy distinct anatomical niches, display unique transcriptional programs, differentially regulate myogenesis, and respond differently to mechanical stimuli. We identify muscle contraction as the key driver of this diversification: fibroblast heterogeneity fails to emerge in paralyzed embryos, whereas premature or externally applied mechanical forces induce precocious diversification. These findings establish that fibroblast heterogeneity is developmentally programmed through a spatiotemporally regulated, force-dependent mechanism.

Building on the central role of ECM remodeling in fibroblast function, we further demonstrate that disrupting lysyl oxidase (LOX)-dependent fibronectin (FN) fibrillogenesis using novel FN-derived peptidomimetic inhibitors suppresses fibroblast-to-myofibroblast differentiation in vitro and in vivo and markedly improves wound healing in vivo. Topical treatment reduces scar size and dermal fibrosis. We find these inhibitors directly target fibronectin and inhibit the cells' ability to exert significant mechanical forces thus inhibiting their transition into becoming myofibroblasts. Our findings demonstrate that direct targeting of the ECM, rather than the immune system, could be a novel route for treating fibrosis. Together, our findings reveal how mechanical forces and ECM organization cooperate to regulate fibroblast identity and activity across development and tissue repair.