Mechanobiology in Epithelial 3D Tissue Constructs

ME3T

GRK 2415

LECTURES

Martin Kiwanuka

Mechanobiology Institute, National University Singapore, Singapore

A MICROFLUIDIC STIFFNESS GRADIENT HYDROGEL PLATFORM FOR PROBING THE ROLE OF MATRIX STIFFNESS IN CANCER CELL INVASION

Avery Rui Sun

Mechanobiology Institute, National University Singapore, Singapore

HYBRID SCAFFOLDS ELUCIDATE DISTINCT ROLES OF EXTRACELLULAR MATRIX IN AGE-RELATED CARDIAC FIBROBLAST ACTIVATION

Thursday, December 7th, 2023
at 10:15 am

Seminarraum
Institute of Molecular and Cellular Anatomy (MOCA)
Wendlingweg 2, 52074 Aachen

Host: Jacopo Di Russo
Interdisciplinary Centre for Clinical Research (IZKF)

Contact : me3t@ukaachen.de

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Abstracts

A MICROFLUIDIC STIFFNESS GRADIENT HYDROGEL PLATFORM FOR PROBING THE ROLE OF MATRIX STIFFNESS IN CANCER CELL INVASION

Cancer cell behavior has been shown to depend on the stiffness of the microenvironment, which is elevated in tumors vs. healthy tissue. Most studies examining the role of tumor stiffness in cancer progression use materials of defined stiffness; however, the stiffness of the tumor microenvironment is heterogeneous. To address this, we developed a stiffness gradient hydrogel system ranging from E ~ 0.5-18 kPa in a microfluidic device mimicking healthy to breast tumor stiffness. The stiffness gradient was created by photo-crosslinking gelatin methacrylate (GelMA) with a gradient transparency photomask. The fabricated system was then used for screening metastatic (MDA-MB-231) and non-metastatic (MCF-7) breast cancer cell invasion in a 3D environment by separately seeding cells into the top channel of the device and culturing with or without chemoattractant (epidermal growth factor, EGF) added to the bottom channel of the device. After 5 days, samples were fixed and immunostained to analyze invasion, cellular morphology, mechanotransduction, and proliferation as a function of stiffness. Our results show that the invasion of the metastatic breast cancer cells increased with stiffness, and while EGF enhanced the rate of invasion, the invasion pattern was dictated by stiffness. Cell volume and shape were linearly correlated with stiffness, with larger, more spread cells observed in stiffer regimes. In contrast, non-metastatic breast cancer cells did not invade the hydrogels, likely due to a downregulation in MMPs and/or contractility. In the future, the developed stiffness gradient system can aid in the discovery of novel therapeutic strategies to combat cancer cell invasion.

HYBRID SCAFFOLDS ELUCIDATE DISTINCT ROLES OF EXTRACELLULAR MATRIX IN AGE-RELATED CARDIAC FIBROBLAST ACTIVATION

Extracellular matrix (ECM) remodeling of cardiac tissue is a key contributor to age-related cardiovascular disease and dysfunction. In aging, many ECM components have been shown to undergo aberrant secretion, structural alterations, and/or degradation. Importantly, heart tissue stiffens with age, which can directly lead to compromised organ physiology and cell behavior. However, these changes in ECM are a multifaceted phenomenon due to the fact that compositional alterations, which trigger biochemical signaling in cells, are often accompanied by stiffness changes, which alter mechanosensitive signaling. To identify the specific roles of these interconnected ECM cues in cellular function, we describe a decellularized ECM-synthetic hydrogel hybrid scaffold that maintains native matrix composition and organization of young or aged murine cardiac tissue with independently tunable scaffold mechanical properties that mimic young (~10 kPa) or aged (~40 kPa) cardiac stiffness. Using quantitative assays, immunohistochemistry, and nanoindentation, we confirmed the preservation of native ECM (collagen, fibronectin, laminin, GAG) and independently tunable stiffnesses. Re-seeding these scaffolds with primary cardiac fibroblasts (CFs) from young or aged murine hearts followed by immunofluorescence examining (a-smooth muscle actin, paxillin, yes-associated protein 1) and RNA-seq, we identify distinct age-dependent mechanisms of CF activation in which CFs integrate both biochemical cues and mechanical cues to determine their phenotypical transition toward myofibroblasts, while young ECM biochemistry can notably outweigh the profibrotic stiffness cues in maintaining CF quiescence. Ultimately, these tunable scaffolds allow for the precise investigation into the role of specific ECM properties in regulating aging dysfunction and rejuvenation.