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MIGRATION AND TRACTION FORCE CHARACTERIZATION OF PANCREATIC DUCTAL ADENOCARCINOMA CELLS ON STIFFNESS-TUNABLE SUBSTRATES

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies [1]. In PDAC, the activation of stellate cells causes excessive production of extracellular matrix (ECM) with subsequent increase of tissue stiffness (Young's modulus E~1-4 kPa in healthy pancreas, E~4-43 kPa in neoplastic tissue [2]), highly impacting tissue vascularization and limiting the effect of chemotherapy [3]. Solid stress and cancer-related stiffness are also associated with increased invasive potential. Understanding how PDAC cells respond to tissue stiffness and detecting the key players in the mechanotransduction processes could provide potential candidates for PDAC targeting. Here, we developed and used stiffness-tunable hydrogels and micropillar arrays to investigate *in vitro* the influence of substrate stiffness on PDAC collective and single cell behavior.

Methods

To mimic the stiffness of healthy pancreas and PDAC, two polyacrylamide (PAM) substrates (PAM low and PAM high, respectively) were fabricated as thin films bound to coverslips, following a published protocol [4]. The effective modulus E^* of the PAM substrates, without and with a collagen coating, was characterized by nanoindentation tests (PIUMA, Optics11) performed in wet conditions (PBS) at 37°C. Human pancreatic cancer cell line (PANC-1) cells were then seeded on the collagen-coated PAM substrates (n=3 for each type), kept at 37 °C and 5% CO_2, and imaged every 10 min for 6 h for random migration assays. MtrackJ plugin of ImageJ (NIH) was used to calculate the migration rate v (µm/min) between two consecutive time points. Finally, for characterizing the traction forces exerted by the PANC-1 cells, two polydimethylsiloxane (PDMS) micropillar arrays with different bending stiffness (k_L = 72.3 nN/µm and k_H = 217.2 nN/µm) were designed (Solidworks) and fabricated by soft litography. PANC-1 cells were then seeded on the fibronectin-coated micropillars, stained with rhodamine phalloidin after 24h, and after additional 24h fluorescence images were acquired and analysed (ImageJ, Matlab), measuring pillar deflections, and evaluating traction forces (F) as:

$$F = k \cdot x \qquad (1)$$

where k is the pillar bending stiffness (nN/µm) and x is the measured pillar deflection (µm).

Results

The PAM low and PAM high substrates, without and with a collagen coating, exhibited effective modulus values in the range of pancreatic healthy and tumor tissue, respectively (Fig. 1A; PAM low: E^*=0.56±0.36 kPa and E^*=1.05 ± 0.76 kPa w/ collagen; PAM high: E^*=18.79±5.29 and E^*=15.98 ± 5.08 w/ collagen). PANC-1 cells seeded on PAM high substrates showed a higher migration rate (v=0.34±0.004 µm/min for PAM high; v=0.18±0.003 µm/min for PAM low, Fig. 1B). When seeded on micropillar arrays, PANC-1 cells exerted significantly higher mean traction forces on stiffer micropillars (F=14.2±3.9 nN for k_L, F=32.5±9.7 nN for k_H, Fig. 1C).

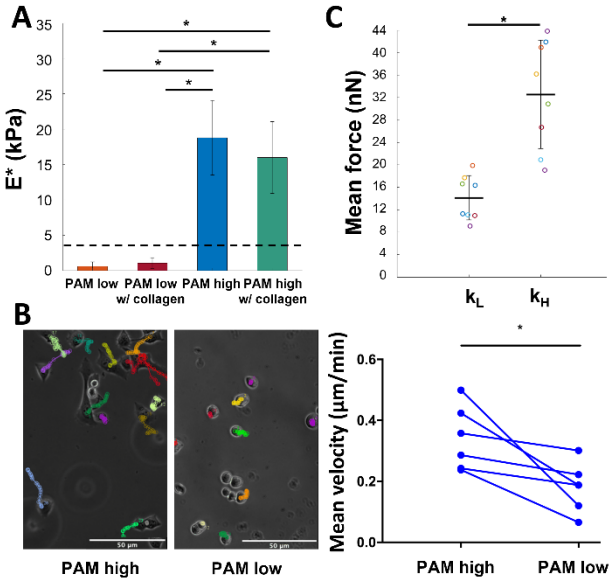

*Figure 1: A) Effective modulus of PAM substrates; B) Random migration assay; C) Mean cell traction forces. (*p<0.01).*

Discussion

Nanoindentation tests confirmed the suitability of PAM substrates in mimicking the stiffness of pancreatic healthy and tumor tissue. Biological tests showed that PANC-1 cells migrate faster on PAM high substrates and exert significantly higher mean traction forces on stiffer micropillars, confirming that the physical environment plays a critical role in cell behavior. Thus, the proposed approach could provide further insights into PDAC mechanotransduction processes. Tests on PANC-1 and fibroblasts co-cultures on PAM hydrogels and further micropillar array optimization are ongoing.

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