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Detection of the Forces and Modulation of Cell-Substrate Interactions

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INTRODUCTION: The cell's organization and maintenance of tissues depend on the complex interplay between various cell types and the surrounding extracellular matrix and substrate. It is established by diffusible signalling molecules and direct mechanical interactions linking the intracellular cytoskeleton with the extracellular matrix or substrate hence creating a supra-cellular architectural framework. To detect and monitor changes in this framework, several methods have been developed ranging from the labelling of specific cytoskeletal components to the measurement of forces generated by individual cells. In this paper, we present the concept using nanomechanical cantilever sensors to quantify forces generated from the interplay of cells and cell layers with the supporting micrometer-thick substrate.

METHODS: Nanomechanical cantilever sensors are defined as tiny plate-like structures, which are fixed at the one end to the solid support. Machined from thin, and therefore flexible materials as silicon or polymeric materials they bend in reaction to contractile cell forces acting along their longitudinal axis (Fig. 1). With dimensions of 500 x 100 x 1 μm^3 forces as small as 0.01 mN/m have been detected via the deflection of a laser beam focused at the apex of the cantilever structure. Furthermore, measurements of mode changes in the resonance frequency of the loaded cantilevers have been monitored that allows determining the stiffness and mass changes on the sensor surface.[1] Such changes upon cellular transformation have recently been demonstrated.[2]

CONCEPTUAL RESULTS: The successful quantification of cellular forces generated by the cells onto their underlying flexible substrate date back to 1980.[3] However, the quantification was rather an rough estimate and the technical complexity prevented the widespread application for the investigation of the implications of cytoskeletal rearrangements on the supra-cellular organization of adherent cells. Nanomechanical cantilever sensors have been successfully applied for the determination of forces created by conformational changes of proteins and nucleic acids as well as the forces created by the expansion of lipid membranes upon the insertion of biomolecules. Varying size and especially thickness the sensitivity can be adopted. Therefore, micro-plates were used in preliminary experiments to quantify forces of fungi and different cell types including muscle cells. We are going to extend these studies to investigate the interactions of different cells of epithelial and fibroblastic origin with selected substrate materials. The study of contractile cell forces is helpful for the design of support materials and surfaces of medical implants, varying the substrate's morphology and its functionalization even by means of self-assembled nano- and micro-structures. The proposed method works label-free and can monitor architectural changes in real time thus allowing to also detect transient variations and to follow complex cytoskeletal rearrangements e.g. upon cell activation, apoptosis or malignant transformation.

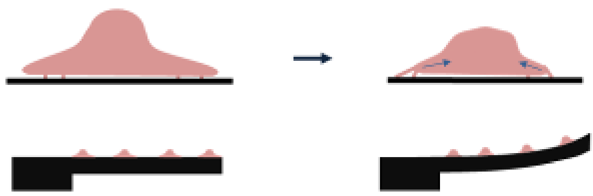

Fig. 1: Principle of real-time monitoring and quantification of contractile forces exerted by cells onto the substrate with cantilever sensors.

DISCUSSION & CONCLUSIONS: This communication presents an approach for the quantitative measurement of contractile cell forces on dedicated substrates with tailored morphology and function. It can be used to realize biological or chemical sensors or to improve the surface biocompatibility of medical implants. Consequently it is of fundamental interest and important for different kinds of applications.

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