CELL'S SENSE OF SLOPE

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Cells have developed multiple mechanisms to apprehend and adapt finely to their environment. Signals from the extracellular matrix are known to influence spatio-temporal organization of cells and tissues, guiding many processes such as morphogenesis, pathology, and repair. A physical cue that is gaining importance in the comprehension of cell mechanics is the role of local geometry. Here, the effects of surface curvature on the focal adhesions dynamics and cytoskeletal rearrangement will be investigated through the development of a microfluidic device. The cell-material interactions, which determine cellular functions and influence their responses to stimuli, are highly dynamic and not easily replicable in traditional cell culture systems. The advent of microfluidics allows to present mechanical/morphological signals to the cell that are controlled both in space and in time. In this work, a device will be designed and fabricated to vary in a cyclic and controlled way the curvature of the substrate on which the cell adheres. To fulfil this purpose, it will be implemented as schematically shown in figure 1. In detail, the pressure inside the air chamber (in Fig. 1) will be controlled through a vacuum generator. The pressure drop inside the chamber will be associated with a consequent deformation of the polydimethylsiloxane membrane (PDMS) on which the cells have been previously seeded. By appropriately choosing the value to be imposed, higher or lower than the atmospheric pressure (pressure value associated with the undeformed configuration of the membrane), it will be possible to obtain convex or concave surfaces respectively.

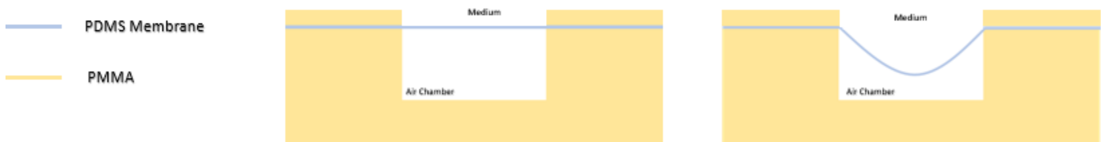

Figure 1 - Trasversal section of the microfluidic device

To understand how surface curvature affects cellular plasticity, it is necessary to study the molecular pathway induced by the mechanical stimulation. Cells are able to sense the substrate properties through the focal adhesions. These structures, in fact, anchor the cell to the extracellular matrix, triggering the cascade of events that lead to the formation of cytoskeletal filaments and regulate their tension. Then, we will focus the attention on a network of actin filaments in the peri-nuclear space, called "actin-cap", which directly connects the cytoskeletal filaments to the nuclear membrane through the KASH proteins. These filaments can transmit forces to the nuclear membrane to rearrange chromatin architecture and, consequently, control the positioning of genetic loci to coordinate transcription processes. The degree of accessibility of the genetic material depends on histones, proteins that compact chromatin and whose state depends on the post-translational modifications to which they are subjected. The research project presented aims to identify, through a dynamic analysis, the series of events that lead to the reorganization of focal adhesions and cell morphology as the substrate curvature varies. Moreover, it will be interesting to establish how tuning the slope of the substrate is possible to modify cellular perception of the substrate. Particularly, modifying the curvature of the substrate is possible to impose a specific mechanical state to the cell without changing substrate stiffness that is the widely accepted mechano-regulator parameter. This will improve the understanding of mechanosensing and mechanotransduction phenomena with possible implications also from a clinical point of view, there are in fact different pathologies, such as tumours and neurodegenerative diseases, associated with malfunctions of these biological processes. In conclusion, the surface curvature seems to be a promising factor for the realization of instructive-devices capable of guiding cell organization and controlling its differentiation

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