CELL'S SENSE OF SLOPE

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Introduction

Cells have evolved a remarkable ability to sense and respond to their environment. They can detect a wide range of physical and chemical cues, including signals from the extracellular matrix (ECM) that influence their spatio-temporal organization and behavior. These signals play a critical role in guiding essential cellular processes such as morphogenesis, tissue repair, and disease progression. In recent years, the local geometry of the ECM has emerged as an important factor that can affect cell mechanics and signaling [1]. Here, the effects of surface curvature on cellular behavior, including the dynamics of focal adhesions and cytoskeletal rearrangement, have been investigated using a molecular-mechanical model. Then, to validate model formulation, experiments have been carried out to test its predictions. Understanding how cells respond to surface curvature has implications for tissue engineering, regenerative medicine, and the development of new therapeutic strategies.

Methods

Cells are capable of probing tissue properties via their adhesive molecular machinery, which is commonly referred to as the "molecular clutch". In this work, to better understand the behavior of cells in response to concave and convex substrates, we developed a modified version of the molecular clutch model [2]. This updated model incorporates master equations governing the dynamic evolution of the system, taking into consideration the spatial organization of actin stress fibers in relation to the slope of the substrate. Monte Carlo simulations have been employed to describe the binding and unbinding events of the clutch. In order to investigate the model predictions, single cell analyses on curved PDMS substrate have been carried out coupling immunofluorescence technique and atomic force microscopy. These substrates consisted of microarrays of concavities and convexities with controlled radii of curvature. By characterizing the mechanical identity of NIH/3T3 cells grown on these substrates, we were able to gain a deeper understanding of the role of surface curvature in cell mechanics and mechanotransduction.

Results

This study investigates the impact of substrate curvature on cytoskeletal activity and cell adhesion using a computational model implemented in MATLAB. Our results reveal that on concave surfaces, the equilibrium condition of the cell, that is associated to the minimum of the actin retrograde flow rate, is characterized by a lower number of clutches compared to planar surfaces. Conversely, convex substrates show a reversed trend with a higher number of clutches involved in the adhesion process compared to planar surfaces. The model predicts that these slope-dependent changes in clutch dynamics lead to substantial differences in the mean traction forces exerted on curved versus flat substrates. Moreover, our experimental results confirm the model predictions, showing an increase in focal adhesion size and cell Young's modulus on convex substrates compared to concave ones.

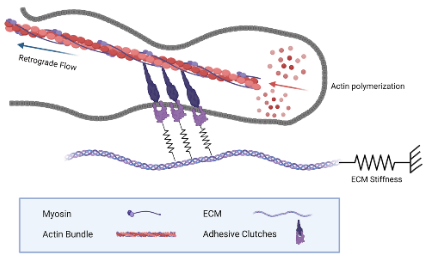

Figure 1: Physical schematization of the molecular clutch model on non-flat substrate.

Discussion

The concavity induces a softening effect in the cellular perception of substrates with cells adopting a spider-like configuration characterized by a lower number of involved clutches than in the planar case. On the other hand, the convexity induces a stiffening effect that results in cells adopting a snail-like configuration with a higher number of clutches involved in the adhesion and exerting a greater force on the substrate [3]. Cell mechanosensing is not mediated only by substrate stiffness but also the curvature plays a key role in the mechanical response of the cell. Overall, our findings highlight the importance of surface curvature in the way that cells respond to mechanical stimuli and underscore the critical role of the molecular clutch in mechanotransduction. We believe that our molecular clutch model provides a valuable tool for investigating the complex relationship between cell mechanics and ECM architecture and can be applied in a wide range of biological and biomedical studies.

References

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