Phenotype Control through a Defined Microenvironment: Mechanotransduction and the Clustering of Integrins

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For adherent cells the binding of integrins to the extracellular matrix is crucial for survival, regulating many cellular processes, such as motility and proliferation, and influencing the establishment of a specific phenotype. The importance of the chemical aspects of such binding events, the binding of a recognition sequence, and the associated conformational and chemical changes in the receptor as well as the signaling cascades following the binding event have been established for some time. Similarly, the importance of soluble signaling factors is long recognized. In contrast, topographic and mechanical parameters, such as texture and porosity as well as the elastic modulus of the adhesive matrix, spreading restrictions, and the dimensionality of the matrix have only recently been recognized to be of equal importance for determining the phenotype. Mechanical interactions with the extracellular matrix are also fundamental for cell motility, which is crucial for tissue formation and wound healing, but also in cancer neoplasia, angiogenesis, and metastasis. Our approach is to modulate cell adhesions so that the forces transmitted through these adhesions allow for the control of the cell phenotype. In particular, we aim to create adhesions of controlled transmitted force through lithographically defined nanoareas, measure the forces exerted by the cell, determine the elements in the cellular signaling cascade that are responsible for this type of mechanotransduction, and develop techniques to integrate the tools into the most commonly used biomaterials. Our goal is to integrate these materials features with spatio-temporally controlled delivery of soluble factors and local measurements of their concentrations.

In order to investigate the mechanotransduction through adhesions of controlled size, we have developed techniques to create nanopatterned surfaces with well-defined biochemical functionality over cm^2 areas, allowing us to direct cellular adhesion sites (focal adhesions) to controlled nanoareas, and thereby vary the number of integrins within individual focal adhesion sites. These binding restrictions change the cell phenotype to a more proliferative and highly motile form, which is reflected in the distribution of adhesions and the organization of the cytoskeleton, as well as in the generation of fibronectin fibrils. We present results of the influence of integrin clustering and outline a strategy to measure the force exerted on single nanometer-sized adhesion sites.