

Cell–substrate interactions

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PREFACE

Cell–substrate interactions

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One of the most striking achievements of evolution is the ability to build cellular systems that are both robust and dynamic. Taken by themselves, both properties are obvious requirements: robustness reflects the fact that cells are there to survive, and dynamics is required to adapt to changing environments. However, it is by no means trivial to understand how these two requirements can be implemented simultaneously in a physical system. The long and difficult quest to build adaptive materials is testimony to the inherent difficulty of this goal. Here materials science can learn a lot from nature, because cellular systems show that robustness and dynamics can be achieved in a synergetic fashion. For example, the capabilities of tissues to repair and regenerate are still unsurpassed in the world of synthetic materials.

One of the most important aspects of the way biological cells adapt to their environment is their adhesive interaction with the substrate. Numerous aspects of the physiology of metazoan cells, including survival, proliferation, differentiation and migration, require the formation of adhesions to the cell substrate, typically an extracellular matrix protein. Adhesions guide these diverse processes both by mediating force transmission from the cell to the substrate and by controlling biochemical signaling pathways. While the study of cell–substrate adhesions is a mature field in cell biology, a quantitative biophysical understanding of how the interactions of the individual molecular components give rise to the rich dynamics and mechanical behaviors observed for cell–substrate adhesions has started to emerge only over the last decade or so.

The recent growth of research activities on cell–substrate interactions was strongly driven by the introduction of new physical techniques for surface engineering into traditional cell biological work with cell culture. For example, microcontact printing of adhesive patterns was used to show that cell fate depends not on the amount of ligand for adhesion receptors, but on its spatial distribution [1]. New protocols for the preparation of soft elastic substrates were essential to show that adhesion structures and cytoskeleton of adherent cells strongly adapt to substrate stiffness [2], with dramatic effects for cellular decision making. For example, it has been shown recently that differentiation of mesenchymal stem cells is strongly influenced by substrate stiffness [3]. Thus, physical factors appear to be equally important as biochemical ones in determining the cellular response to its substrate [4].

The introduction of novel physical techniques not only opened up completely new perspectives regarding biological function, it also introduced a new quantitative element into this field. For example, the availability of soft elastic substrates with controlled stiffness allows us to reconstruct cellular traction forces and to correlate them with other cellular features. This development enables modeling approaches to work in close contact with experimental data, thus opening up the perspective that the field of cell–substrate interactions will become a quantitative and predictive science in the future.

Because physical research into cell–substrate interactions has become one of the fastest growing research areas in cellular biophysics and materials science, we believe that it is very timely that this special issue gathers some of the on-going research effort in this field. In contrast to the non-living world, cellular systems usually interact with their environment through specific adhesion, mainly based

on adhesion receptors from the integrin family. During recent years, force spectroscopy has emerged as one of the main methods to study the physics of specific adhesion. In this special issue, single cell force spectroscopy is used by Boettiger and Wehrle-Haller to characterize the strength of cell-matrix adhesion and how it is modulated by the glycocalyx [5], while Chirasatitsin and Engler use force spectroscopy mapping to characterize the spatial distribution of adhesive sites on the substrate [6]. Scrimgeour *et al* describe a new method to adhesively pattern self-assembled monolayers for cell adhesion by a simple photobleaching setup [7] and Stricker *et al* demonstrate how elastic substrates can be combined with microcontact printing to improve the reconstruction of traction forces [8]. The work by Metzner *et al* shows that meaningful results on the cell-substrate interactions can be extracted also from experiments in which cells interact with biofunctionalized beads [9].

If cells start to adhere to a substrate, the main rate-limiting step is establishment of close contact between the plasma membrane and the substrate. This process can be followed with high spatial and temporal resolution with reflection interference microscopy, as demonstrated by Ryzhkov *et al* for mouse embryonic fibroblasts [10] and by Cretel *et al* for T lymphocytes [11]. Once mature adhesion has been achieved, the integrin-based focal adhesions providing anchorage to the substrate are strongly connected to the actin cytoskeleton, the main determinant of cell shape and structure. Heil and Spatz use microfabricated pillars to perturb the mechanical balance and quantitatively characterize the fast response of the focal adhesions [12]. A similar approach is used by Kirchenb uchler *et al*, who use deformation of an elastic substrate to demonstrate that the weak link in the mechanical system of substrate, adhesions and actin cytoskeleton is most likely located at the adhesion-cytoskeleton interface [13]. Rather than using external perturbations, Zemel *et al* quantify and model how cells spontaneously polarize their cytoskeleton in response to the physical properties of the substrate [14].

Quantitative analysis of cellular data has become standard in the field of cell-substrate interactions. Moreover, theoretical models for cell-substrate interactions help us to identify and understand the mechanisms underlying the observed phenomena in these complex systems. Recently, a large effort has been invested into understanding how force transmitted by the actin cytoskeleton changes the state of focal adhesions. In the contribution by Biton and Safran, this issue is addressed for the case that force arises from shear flow over an adhering cell [15]. Another important source for force on focal adhesions is actin retrograde flow, which has been demonstrated before to show variable coupling to the underlying layer of adhesion receptors. Two contributions discuss how stochastic bond dynamics at the cell-substrate interface is modulated by physical factors. The model by Sabass and Schwarz suggests that dissipation in the actin cytoskeleton stabilizes bond dynamics [16] and the model by Li *et al* suggests that catch bonding and multiple layers are important elements of the way focal adhesions function [17].

If interacting with an elastic environment, the combined system of focal adhesions and actin cytoskeleton can be used by cells to sense its rigidity and to make decisions on its response. Moshayedi *et al* show that great care has to be taken when preparing soft elastic substrates for cell culture studies and then use their protocols to quantitatively evaluate the mechanosensitive response of astrocytes from the brain [18]. The cellular system used by Lee *et al* is pericytes from the microvasculature, for which the authors show that they exert sufficient forces to stimulate vascular endothelial cells [19]. Buxboim *et al* use the technology of soft elastic substrates to measure how far mesenchymal stem cells can mechanically sense into their substrate [20].

The mechanical activity of cells observed in two-dimensional cell culture has significant consequences for both physiological and disease-related situations, including cell migration, tissue maintenance and tumor growth. Jannat *et al* show that chemotaxis of neutrophils, that is the first line of the immune system, is strongly modulated by mechanosensing on substrates of varying stiffness [21]. Mogilner and Rubinstein present a theoretical systems analysis for the shape of rapidly migrating keratocytes [22]. Saez *et al* show, with microfabricated pillar assays, how force is distributed within a layer of epithelial cells [23]. For three-dimensional tissue models, new techniques have to be developed to characterize the complex mechanics of hydrogels. Levental *et al* [24] and Kotlarchyk *et al* [25] approach this challenge with mechanical and optical methods, respectively. Narayanan *et al* combine experiments and continuum models to explore how chemo-mechanical interactions influence tumor growth [26].

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