



## Review Article

## Introduction to the ECR special issue, “Mechanosensing via Cell-Matrix Adhesions”

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A cell's ability to sense its neighboring environment constitutes a key process that regulates the tightly coordinated functionality of cells in complex metazoans. Examination of developing multicellular organisms reveals the exquisite precision of morphogenesis, through which the dimensions of the organism and its constituent tissues and organs, tissue and whole body plasticity and, eventually, the fine cellular architecture are determined, maintained and continuously adapted to environmental changes. Upon such changes that occur, for example, during repair of damaged tissue or during disease processes such as inflammation or cancer, cells sense and then modulate or respond to the changes. The mechanism whereby cells within an organism receive “positional information” that guides their behavior and fate has been, and still remains, a major challenge to cell-, cancer- and developmental biologists, and involves such issues as the nature of the extracellular cues, the surface receptors that bind to components of the pericellular environment, and the process whereby the complex environmental information is integrated and consolidated into a specific cellular response such as stimulation or suppression of cell growth, modulation of differentiation, effects on cell survival, and changes in cell morphogenesis and migration.

Studies conducted in recent years point to the central roles of specific types of cell adhesions to the extracellular matrix (ECM) and to neighboring cells in this complex sensing endeavor, and shed light on the capacity of adhesion sites to serve as a macromolecular assembly that is responsive to both the chemical and physical properties of their immediate environment. The chemical cues are primarily mediated via the ECM receptors (mainly, though not exclusively, through integrins) and intercellular adhesion receptors (e.g., cadherins), both of which interact with multiple cytoplasmic proteins and cytoskeletal networks in executing their signaling functions. Particularly challenging is the more recent notion that adhesion-mediated signaling also involves mechanosensing; namely, the responsiveness to externally applied or internally generated mechanical forces.

This volume focuses on mechanosensing via cell-ECM adhesions, addressing a variety of complementary aspects of this process. One challenge considered in the article by Young et al. (3–6) is the complexity and heterogeneity of the ECM, and the ability of

cells to respond not only to the molecular composition of the ECM, but also to its mechanical properties – rigidity, micro-topography and ligand spacing – by means of employing specific synthetic scaffolds; they further discuss the relevance of these artificial scaffolds to physiological matrices. A systems-level view of the adhesion-associated sensory machinery (the so-called “integrin adhesome”) is presented by Humphries et al. (7–13), who describe our current understanding of how the physical properties of the matrix (e.g., rigidity) affect the molecular composition of the responding adhesome network. Burridge (14–20) takes this intriguing question one step further, addressing the role of the adhesion-associated and actin-rich stress fibers in maintaining the integrity of integrin adhesions and, possibly, their crosstalk with the nucleus. Zooming in on the role of specific adhesome components in mechanosensing, Atherton et al. (21–27) address the role of vinculin in the force-dependent assembly of nascent integrin adhesions, and the involvement of signaling via Rho family GTPases in this process. Rossier et al. (28–34) discuss a novel and powerful approach for studying the spatial molecular organization within focal adhesions, which is primarily based on super-resolution light microscopy data. In their article, the authors review both the nano-architecture and nano-dynamics that are clarified by this rapidly developing technique.

As indicated above, a conceptual dilemma underlying adhesion mechanosensing involves the conversion of a physical cue (e.g., tension) into a chemical process (e.g., protein-protein interactions or post-translational modifications). This topic is addressed by Wehrle-Haller et al. (35–41), who describe the transition of integrins and FA proteins from an auto-inhibited state, to a chemically activated state, to a mechano-activated state. Moving further into the post-adhesion intracellular signaling process, Dupont (42–53) describes the role of the Hippo signaling pathway in the mechanosensing process, and shows how extracellular and actomyosin-driven cues can, eventually, affect gene expression through the activities of the YAP/TAZ transcriptional activators. Pregararo et al. (54–59) take us to an additional level of complexity, viewing not just the interface between a single cell and the ECM, but rather considering a tripartite system, in which cells interact with the ECM as well as with neighboring cells, in a 2-dimensional culture system. This issue of dimensionality is further deliberated on by Doyle and Yamada, (60–66), who demonstrate some fundamental differences between the mechanical interplay of cells within a 2-dimensional substrate, compared to cells embedded in,

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and interacting with, a 3-dimensional matrix, either in culture or in vivo. Linder (67–72) addresses mechanosensing via another type of integrin adhesion; namely, podosomes, formed almost solely in cells of monocytic origin. He shows that these structures, which display an internal organization differing from that of focal adhesions are, nevertheless, involved in sensing the rigidity and micro-topography of the matrix.

The physiological and pathological implications of matrix mechanosensing are discussed in several articles in this volume. In her article, Robertson (73–81) reviews changes in the expression profiles of ECM components, and further modifications that affect matrix mechanics in breast cancer. Still on the topic of mechanosensing in cancers, two articles address an invasive ECM adhesion system;

namely, invadopodia. Revach et al. (82–88) discuss the role of GTPases in the regulation of invadopodia formation by comparing wild-type and a mutant Rac1 that is prominently expressed in melanoma. Finally, Parekh and Weaver (89–95) show that ECM rigidity and traction forces drive invadopodia formation and activation, and discuss the implications of these findings in the treatment of metastatic cancer.

Taken together, these articles provide a comprehensive and multifaceted view of adhesion-driven mechanosensing, ranging from cellular physics to synthetic biology, to structural cell biology, to functional analysis in living organisms. From these diverse studies, a novel concept has begun to emerge, suggesting that mechanical cues play a critical role in regulating cell behavior and fate, in both physiological and pathological states.