Cell Adhesion & Migration

ISSN: 1933-6918 (Print) 1933-6926 (Online) Journal homepage: http://www.tandfonline.com/loi/kcam20

Application of synthetic biology approaches for understanding encounters between cells and their microenvironment

Benjamin Geiger & Joachim Spatz

To cite this article: Benjamin Geiger & Joachim Spatz (2016) Application of synthetic biology approaches for understanding encounters between cells and their microenvironment, Cell Adhesion & Migration, 10:5, 447-450, DOI: 10.1080/19336918.2016.1215184

To link to this article: http://dx.doi.org/10.1080/19336918.2016.1215184

Accepted author version posted online: 21 Jul 2016.
Published online: 21 Jul 2016.

CELL ADHESION & MIGRATION
2016, VOL. 10, NO. 5, 447–450

Taylor & Francis
Taylor & Francis Group

GUEST EDITORIAL

Application of synthetic biology approaches for understanding encounters between cells and their microenvironment

Throughout their life, all cells undergo vital interactions with their microenvironment. In unicellular organisms (e.g., bacteria, or nucleated "protozoa"), micro-ecosystems provide cells with local sources of nutrients, shelter, and relatively stable growth conditions. The evolution of multicellular forms of life (the so-called "metazoa"), commonly believed to have taken place between 1,300–1,600 million years ago,[2] brought new cellular survival strategies, manifested in the development of life forms arising out of cell colonies. Over time, these led to the development of independent, "individualized" metazoan organisms, most likely resembling today's sponges.[12] While in protozoan organisms, all life processes (e.g., reproduction, motility, protection, sustenance) were independently executed by each individual cell, in metazoans these tasks came to be performed by specialized subpopulations of cells.

With the advent of metazoan evolution, mainly during the "Cambrian explosion," an increasingly ordered body plan has evolved, leading to the development of specialized tissues and organs. The resulting metazoan life forms, with their increasing structural and functional complexity, introduced new challenges, such as the need for precise spatial and temporal coordination between the diverse cells in the developing organism. These challenges necessitated the development of new molecular mechanisms whereby cells continuously acquire positional environmental cues, integrate this information, and respond to it by altering their behavior or gene expression program.

As we can appreciate today, this "input-processing-output" mechanism is multi-parametric and extremely complex. The molecular input alone—namely, the number of extracellular molecules involved in meaningful interactions with cells, including components of the extracellular matrix (ECM), cell-cell adhesion molecules, and secreted or membrane-bound signaling molecules—is on the order of thousands, and if specific extracellular stimulation processes involve not just single extracellular cues but rather specific combinations of several ligand-receptor pairs, the level of complexity can further increase by several orders of magnitude. Furthermore, it was shown in recent years that environmental signaling is not limited to chemical recognition, and that physical properties of the environment, such as its degree of compliance, dimensionality, texture, inter-ligand spacing and strain, can be sensed by adhering cells, and can greatly modulate the environmental signaling process.[4]

These insights into the direct interplay between cells and their cellular and non-cellular microenvironments were derived from numerous analyses and perturbation experiments. Yet given the huge complexity, the poor multi-parametric and multi-scale definition, and the constant dynamic remodeling of cellular environments, it appears that current analytical and computational tools are insufficient for deciphering the molecular mechanisms underlying physiological adhesion-mediated signaling, at a systems-scale level.[1,6,7,9]

The historical roots of cell adhesion and migration research stretch back over the past century. During that time, recognition of the importance of cell adhesion and migration has steadily grown, especially since it became clear that these processes are critical for the normal development of multicellular organisms, and that their disruption can contribute to serious pathologies. Through the years, research efforts have yielded, among many other important findings, the identification of the cytoskeletal elements that provide cellular propulsion, and the discovery of the major families of adhesion molecules and their regulators. As a result, our overall knowledge of cell adhesion and motility has become vast and complex; yet at the same time, many details remain unclear.

In more recent years, scientists from various backgrounds—including biochemistry, biophysics, materials science and engineering—have also become interested and involved in adhesion and migration research. Their important contributions have shifted the focus of attention to novel regulators of cell behavior and fate: the forces produced by cells in order to move, the involvement of physico-chemical signals in triggering adhesion and motility, or the nanomolecular differences between adhesion-supporting and adhesion-suppressing substrates, to name but a few. This interdisciplinary slant has not only produced new perspectives, but has also supported the

development of novel methods and technologies, and has brought a different 'method of questioning' into play.

How can a particular biological function be recreated with less complexity, utilizing only a specific subsystem of known units and modules? What does it take to manipulate or engineer this function in artificial environments? These questions constitute the core idea of synthetic biology, which aims to simplify the complexity of biological systems to a level that can still be relevant and reliably modeled.[3,8] Synthetic biology, with its unique perspective, has already played an important role in elucidating biological processes, paving the way toward a deeper understanding of the workings of cells. To illustrate its impact on the study of cell adhesion and migration, the following are examples of tools and models designed to address fundamental questions in the field:

'Tunable' synthetic biomaterial substrates have become common devices for studying cell biology and tissue engineering, for two main reasons: their structural and physico-chemical similarities to natural cell environments, and their use in controlling matrix stiffness and ligand density over a broad range with high precision, alongside the option of coupling a large variety of ligands to which cells can attach.

To elucidate cellular mechanics, the simplest models are based on a "bottom-up biology" approach: systems reconstituted *in vitro*, and comprised of the minimal number of proteins required to model, for example, cytoskeletal motor systems.[10,11] On a more complex scale, efforts have been made to create cell-mimetic minimal functional systems with self-assembling, self-propelling and environmental sensing properties, using large lipid vesicles functionalized with specific proteins. In this context, microfluidic technology can be employed to load vesicles with transmembrane integrins, integrin-binding proteins, and specific sets of scaffolding and signaling proteins found at the adhesion sites, to model cell adhesion and migration.[5] The long-term goal of such experimental approaches (most of which are still in their infancy or early childhood) is to utilize the biological insights gained from the synthetic models to reverse-engineer living cells with tailored adhesive and mechano-chemical sensory properties.

The focus of this issue, "Synthetic Biology Approaches and Studies in Cell Adhesion and Migration," provides a synopsis of the latest research in the field, addressing some of the basic questions that are still in search of a mechanistic solution.

In his commentary, Eli Zamir discusses fundamental questions in systems biology that concern cell-matrix adhesion, and how synthetic biology approaches applied to molecular dynamics can help resolve these issues (pg. 451).

Clearly, successful research in synthetic biology depends on a solid foundation of robust and well-characterized tools. Orit Siton-Mendelson and Anne Bernheim-Groswasser have authored an overview of the various reconstituted model systems developed during the past decades, most of which focus on very specific steps in the process of cell motility. In doing so, they discuss the main challenges toward the realization of a synthetic motile cell (pg. 461). A commentary authored by Mathijs Vleugel, Maurits Kok, and Marileen Dogterom examines the microtubule-intrinsic process of dynamic instability, the effects of external factors on this process, and how the resulting forces influence various biological systems. They further show how individual components involved in regulating or transmitting microtubule-driven forces have been utilized for a reductionist, *in vitro* reconstitution approach (pg. 475).

Improving the bioactive and cell-responsive character of synthetic hydrogels is the aim of Stéphanie M. C. Bruekers and colleagues in the Wilhelm Huck lab. They describe two different approaches that may be utilized to tune the fibrillar structure and mechanical properties of fibrin hydrogels, in order to more closely mimic the complex fibrin-fiber architecture of the ECM (pg. 495). The article by E. Ada Cavalcanti-Adam and her group examines the effects of integrin-specific crosstalk, instances in which elements of a signaling pathway, activated by the binding of a specific integrin to its ligand, affect other signaling pathways and, thereby, the cell's interaction with the extracellular matrix. They employ nanoarrays of gold particles presenting immobilized, integrin-selective peptidomimetic ligands to elucidate the roles of $\alpha 5\beta 1$ and $\alpha v\beta 3$ integrins in the precise regulation of cell adhesion, spreading and migration (pg. 505).

To depict biological systems more precisely than do current, qualitative descriptions, a "versatile tool box"—as Philipp J. Albert and Ulrich S. Schwarz would say—of mathematical models has been developed. Homing in on cell behavior on micropatterns, they review recent advances in predicting and explaining cell shape, traction forces and dynamics, by means of mathematical models (pg. 516). In their article, Jinglei Hu and others from Thomas R. Weikl's group review recent results from theory and simulations of cell adhesion that lead to novel insights into how membranes and the molecular properties of anchoring proteins affect the binding equilibrium and kinetics of membrane-anchored receptors and ligands during the adhesive process (pg. 576).

Forces propelling the movement of cells in a straight line (1D migration) are the emphasis of an article by Sangyoon J. Han and other researchers in the Nathan Sniadecki lab. They focus on how fibroblasts coordinate formation of adhesions, traction forces, and release of their trailing edge, when moving along a collagen fiber. Using a bio-chemo-mechanical model to analyze traction forces and adhesion dynamics, they conclude that the relationship observed between traction forces at the front and back of a cell traveling in one dimension is possible, only when cellular elasticity is lower than the elasticity of the cellular environment (pg. 529).

Cells can sense a variety of physico-chemical signals, which, turn, can induce, direct, or disrupt cell adhesion and migration. Such signals usually stem from the network of extracellular molecules in which the cells are embedded, or neighboring cells in their vicinity. Denise Denning and Wouter H. Roos discuss recent advances in our understanding of the molecular mechanisms underlying the cellular response to biophysical cues (pg. 540). Mukund Gupta and others from the Benoît Ladoux lab author a review focusing on biophysical methods used for measuring cell-traction forces, and the mechanosensitive processes that drive cellular responses as a reaction to matrix rigidity, to determine how cells sense matrix stiffness (pg. 554).

On a more medically relevant note, Simona Sorrentino and others from Ohad Medalia's research group investigate platelet stiffness, working to understand how structural changes modulate the stiffness of platelets during activation and adhesion. Platelet adhesion, activation and aggregation on the extracellular matrix are essential for hemostasis, but can also lead to occlusion of diseased vessels. In their article, they present high-resolution 3D structural information on the platelet cytoskeleton, using cryo-electron tomography to provide *in situ* structural analysis, and atomic force microscopy to map platelet stiffness (pg. 568).

Cell adhesion and migration regulate many physiological and pathological events, among them proliferation, differentiation and apoptosis. Despite decades of research, many issues concerning the underlying molecular mechanisms of these cellular processes remain unsolved. Synthetic biology, an interdisciplinary branch coupling biology and engineering, provides a unique perspective from which to consider, analyze, and ultimately comprehend the molecular mechanisms underlying adhesion and migration. Through the application of such novel technologies, we believe that this field will continue to advance in the future.

Benjamin Geiger
Department of Molecular Cell Biology
Weizmann Institute of Science, Rehovot, Israel
benny.geiger@weizmann.ac.il.

Joachim Spatz
Department of Biointerphase Science & Technology
Max Planck Institute for Medical Research
Jahnstraße, Heidelberg, Germany

Laboratory of Biophysical Chemistry
Institute of Physical Chemistry, University of Heidelberg
Im Neuenheimer Feld, Heidelberg, Germany
Spatz@is.mpg.de

http://dx.doi.org/10.1080/19336918.2016.1215184

References

[1] Adutler-Lieber S, Zaretsky I, Platzman I, Deeg J, Friedman N, Spatz JP, Geiger B. Engineering of synthetic cellular microenvironments: Implications for immunity. J Autoimmun 2014; 54:100-111; PMID:24951031; http://dx.doi.org/10.1016/j.jaut.2014.05.003

[2] Conway Morris S. The question of metazoan monophyly and the fossil record. Prog Mol Subcell Biol 1998; 21:1-19; PMID:9928534; http://dx.doi.org/10.1007/978-3-642-72236-3_1

[3] Frohnmayer JP, Brüggemann D, Eberhard C, Neubauer S, Mollenhauer C, Boehm H, Kessler H, Geiger B, Spatz JP. Minimal Synthetic Cells to Study Integrin-Mediated Adhesion. Angewandte Chem Int Ed Engl 2015; 54:12472-8; PMID:26257266; http://dx.doi.org/10.1002/anie.201503184

[4] Geiger B, Spatz JP, Bershadsky AD. Environmental sensing through focal adhesions. Nat Rev Mol Cell Biol 2009; 10:21-33; PMID:19197329; http://dx.doi.org/10.1038/nrm2593

[5] Janiesch JW, Weiss M, Kannenberg G, Hannabuss J, Surrey T, Platzman I, Spatz JP. Key Factors for Stable Retention of Fluorophores and Labeled Biomolecules in Droplet-Based Microfluidics. Anal Chem 2015; 87:2063-7; PMID:25607822; http://dx.doi.org/10.1021/ac504736e

[6] Kruss S, Erpenbeck L, Amschler K, Mundinger TA, Boehm H, Helms HJ, Friede T, Andrews RK, Schon MP, Spatz JP. Adhesion maturation of neutrophils on nanoscopically presented platelet glycoprotein Ibalpha. ACS Nano 2013; 7:9984-96; PMID:24093566; http://dx.doi.org/10.1021/nn403923h

[7] Liu Y, Medda R, Liu Z, Galior K, Yehl K, Spatz JP, Cavalcanti-Adam EA, Salaita K. Nanoparticle tension probes patterned at the nanoscale: Impact of integrin clustering on force transmission. Nano Lett 2014; 14:5539-46; PMID:25238229; http://dx.doi.org/10.1021/nl501912g

[8] Platzman I, Janiesch JW, Spatz JP. Synthesis of nanostructured and biofunctionalized water-in-oil droplets as tools for homing T cells. J Am Chem Soc 2013; 135:3339-42; PMID:23419177; http://dx.doi.org/10.1021/ja311588c

[9] Rahmouni S, Lindner A, Rechenmacher F, Neubauer S, Sobahi TRA, Kessler H, Cavalcanti-Adam EA, Spatz JP. Hydrogel Micropillars with Integrin Selective Peptidomimetic Functionalized Nanopatterned Tops: A New Tool for the Measurement of Cell Traction Forces Transmitted through $\alpha(v)\beta(3)$- or $\alpha(5)\beta(1)$-Integrins. Adv Mater 2013; 25:5869-74; PMID:23913640; http://dx.doi.org/10.1002/adma.201301338

[10] Roos WH, Roth A, Konle J, Presting H, Sackmann E, Spatz JP. Freely suspended actin cortex models on arrays of microfabricated pillars. Chemphyschem 2003; 4:872-7; PMID:12961988; http://dx.doi.org/10.1002/cphc.200300712

[11] Streichfuss M, Erbs F, Uhrig K, Kurre R, Clemen AE, Bohm CH, Haraszti T, Spatz JP. Measuring forces between two single actin filaments during bundle formation. Nano Lett 2011; 11:3676-80; PMID:21838252; http://dx.doi.org/10.1021/nl201630y

[12] Wiens M, Mangoni A, D'Esposito M, Fattorusso E, Korchagina N, Schröder HC, Grebenjuk VA, Krasko A, Batel R, Müller IM, et al. The molecular basis for the evolution of the metazoan bodyplan: Extracellular matrix-mediated morphogenesis in marine demosponges. J Mol Evol 2003; 57:S60-75; PMID:15008404; http://dx.doi.org/10.1007/s00239-003-0008-1