Experimental Cell Research 358 (2017) 1–2

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Introduction

Introduction to the ECR special issue on "Cell sensing and signaling via cell-cell adhesions"

Cell structure, behavior and fate, within all metazoan organisms, are regulated by a tightly coordinated cross-talk between the endogenous transcriptional and signaling networks that function within each cell, and "environmental cues" that include both biochemical and mechanical signals, such as the proteins present on neighboring cells and the force with which they pull or push. In recent years, considerable effort was directed towards understanding this complex process whereby individual cells, each with its genomic, epigenetic and transcriptomic background, integrate multiple environmental signals and respond to them with a remarkable temporal and spatial precision, eventually leading to the formation of a well-structured and functioning organism (e.g. [1]).

This "instructive pericellular environment" comprises three major components: diffusible molecules, extracellular matrix (ECM), and neighboring cells. Diffusible molecules include growth factors, cytokines and chemokines, which form morphogenetic gradients (see e.g. [2,3]) with considerable robustness and positional precision. More localized signals are provided by ECM networks that directly affect associated cells via specialized cell-ECM receptors (e.g. integrins) and adhesion sites (e.g. focal adhesion, hemidesmosomes). Close-range signals are mediated via specific types of cell-cell junctions, such as adherens junctions, tight junctions, desmosomes and gap junctions.

In a previous ECR special Issue [4], edited by Geiger and Fässler, the special sensory capacity of cell-ECM adhesions was reviewed, directing special attention to "mechanosensing" processes, whereby internal and matrix-mediated mechanical forces, applied to specific (mostly integrin-mediated) adhesion sites, locally regulate the assembly and turnover of the adhesions, and trigger "global" cellular processes as cell spreading and migration, division, gene expression, and survival.

In this ECR special issue, we focus on recent advances in our understanding of the mechanisms underlying the communication between cells, which is mediated via cell-cell junctions, and primarily – via cadherin-mediated adherens type junctions. The fact that cells, in metazoan organisms, from sponges to man, establish stable adhesions that are essential to their structure and function, was appreciated for a long time [5]. Early ultrastructural studies, carried out nearly 60 years ago, indicated that inter-cellular adhesions are mediated via specialized junctions, with distinct morphology [6]. This was followed by many studies, in vivo and in cell culture models, in which the functional roles of specific junctions (e.g. tissue integrity and polarity, separation of body compartments, mechanical stability) were investigated [7]. In parallel, multiple molecular studies, demonstrated the rich diversity of adhesion molecules, and their differential association with particular junctional complexes (e.g. [8]). Furthermore, the development of powerful approaches for modulating protein expression in live organisms and in culture models, enabled the detailed characterization of the physiological roles of specific molecules, as well as their involvement in disease (e.g. [9]).

This volume focuses on cell sensing and signaling via cell-cell adhesions, addressing a variety of complementary aspects of this process. An evolutionary perspective is provided by Sahin Gul, Hulpiau et al. (ECR-17-59R1) who describe the functions, phylogenetic classifications and co-evolution of the cadherin and catenin protein families. While focusing on metazoan cadherins, protocadherins, cadherin-related proteins and catenins, they also discuss cadherin-like and catenin-like molecules outside the animal kingdom. Diving into the biophysical aspects of classical cadherin molecular interactions, Sivasankar et al. (ECR-17-182) summarize studies of the structure and cis and trans interaction kinetics of E-cadherin; they also discuss how mechanical stimuli alter the structure, interaction kinetics and organization of cadherins and thus tune adhesion. How the biophysical properties of cadherin receptors come into play within cells is addressed by Biswas and Zaidel-Bar (ECR-17-22), who integrate recent results from studies using hybrid systems of cells interacting with cadherin-functionalized supported lipid bilayers; they provide an updated view of the process of E-cadherin junction formation with an emphasis on the role of molecular mobility, receptor clustering, and active cellular processes.

A hallmark of cell-cell junctions is their connection with the cytoskeleton. Arnold et al. (ECR-17-94) focus on the linkage between the apical junctional complex and the actomyosin cytoskeleton and the role of Rho GTPases in regulating both actomyosin and cell adhesion dynamics; they describe relevant upstream regulators and downstream effectors of Rho GTPases and also highlight junctional actin-binding proteins that play a role maintaining proper cell-cell adhesion. Another aspect of the regulation of junction barrier function by the cell signaling machinery, particularly small GTPases, is addressed by Ridley and Cerutti. In their article, (ECR-17-460), they describe the roles of Rho and Rap in the differential regulation of endothelial tight junction permeability to fluids and small molecules, and the transendothelial migration of Leukocytes to neighboring tissue, during inflammatory conditions. Campbell et al. (ECR-17-41) zoom out of the apical junctional complex, showing the molecular integration of tight junctions and adherens junctions; they highlight both physical and signaling linkages between the two junctions and the role of actomyosin in their coupling. Goodwin and Nelson (ECR-17-42R1) examine the interplay between cadherin-mediated cell adhesion and the consequent generation of contractile actomyosin forces and their crucial role in tissue 3D morphogenesis, including the folding of epithelial sheets, tube formation and the generation of branching or fusing epithelial networks. They also discuss how this knowledge can be applied toward tissue engineering.

http://dx.doi.org/10.1016/j.yexcr.2017.07.016

Moving in vivo, Togashi and Katsunuma (ECR-17-44) address the role of cadherin and nectin adhesion in cell sorting and patterning of sensory epithelial layers, namely the auditory and olfactory epithelium; they show how hemophilic and heterophilic interactions within and between both adhesion systems provide cells with the differential adhesive affinities required for complex cellular pattern formations during development. Ventrella et al. (ECR-17-195) also examine mechanisms underlying tissue compartmentalization and boundary formation, based on differential expression of distinct cadherins, or different concentrations of the same cadherins, in adjacent tissue regions. They further address the roles of two signaling networks, namely, Eph/ephrins and NOTCH in cellular patterning, and their importance for maintaining normal tissue compartmentalization. Tackling the complex process of organ morphogenesis, McFaul and Fernandez-Gonzalez (ECR-17-254) call attention to the roles of cadherin-mediated adhesions in the formation of the heart in *Drosophila melanogaster*; they discuss the roles of cellular mechanics in cell alignment and in regulating coordinated cell migration and fate. The authors also address how cell-cell adhesion and the cytoskeletal are remodeled to form the heart lumen.

The physiological importance of epithelial cell-cell adhesion is highlighted by Choi et al. (ECR-17-201), who focus on mechanisms by which epithelial barriers are assembled, maintained, and regulated in the context of the gastrointestinal tract. They explain how transcellular and paracellular transport are coordinated, and the importance of tight junction architecture and dynamics in health and gastrointestinal diseases. Another human disease strongly associated with perturbed cell-cell junctions is cancer. Kourtidis et al. (ECR-17-133) address the role of down regulation of E-cadherin, in the framework of epithelial-mesenchymal transition (EMT), in supporting a “malignant phenotype” that includes activation of beta-catenin and p120 signaling, and activation of receptor tyrosine kinases, PI3K/AKT, Rho-GTPases and HIPPO signaling.

Taken together, these articles provide a comprehensive and multifaceted view of cell-cell adhesion and signaling, ranging from biophysical studies of single molecules to 3D engineered tissues, and from developmental models to human disease.

References

[1] T. Aegerter-Wilmsen, M.B. Heimlicher, A.C. Smith, P.B. de Reuille, R.S. Smith, C.M. Aegerter, K. Basler, Integrating force-sensing and signaling pathways in a model for the regulation of wing imaginal disc size, Development 139 (17) (2012).
[2] D. Ben-Zvi, B.-Z. Shilo, N. Barkai, Scaling of morphogen gradients, Curr. Opin. Genet. Dev. 21 (6) (2011) 704–710.
[3] B.-Z. Shilo, N. Barkai, Buffering global variability of morphogen gradients, Dev. Cell 40 (5) (2017) 429–438.
[4] B. Geiger, R. Fässler, Introduction to the ECR special issue, “mechanosensing via cell-matrix adhesions, Exp. Cell Res. 343 (1) (2016) 1–2.
[5] R.O. Hynes, Q. Zhao, The evolution of cell adhesion, J. Cell Biol. 150 (2) (2000) F89–F96.
[6] M.G. Farquhar, G.E. Palade, Junctional complexes in various epithelia, J. Cell Biol. 17 (1963) 375–412.
[7] Q. Wei, H. Huang, Chapter five – insights into the role of cell–cell junctions in physiology and disease, Int. Rev. Cell Mol. Biol. 306 (2013) 187–221.
[8] R. Zaidel-Bar, Cadherin adhesome at a glance, J. Cell Sci. 126 (Pt2) (2013) 373–378.
[9] T. Pieters, J. van Hengel, F. van Roy, Functions of p120ctn in development and disease, Front. Biosci. (Landmark Ed.) 17 (2012) 760–783.

Ronen Zaidel-Bar Guest Editor
The Mechanobiology Institute, National University of Singapore, Singapore
Benjamin Geiger Guest Editor
The Weizmann Institute of Science, Rehovot, Israel

[1] Current address: Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.