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Special issue on “Mechanotransduction in cell fate determination” – from molecular switches to organ-level regulation

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Stereotypic formation of tissues requires coordination of cell fate with adhesive and cytoskeletal cues that control cell shape, positioning and motility. The importance of physical cues in shaping development has been demonstrated already a decade ago by observations that their removal arrests embryogenesis (Martin et al., 2009, Behrndt et al., 2012). Recent advances in technology and methods to quantify and experimentally manipulate adhesive and mechanical properties of cells and tissues has revolutionized the field. While many aspects of mechanical signaling have been covered by excellent reviews in the past, we invited experts in their respective fields of cell biology and biophysics review the most recent, exciting breakthroughs on the role of mechanotransduction in cell fate regulation. Amongst these breakthroughs are the advancement of imaging techniques that have allowed single molecule resolution analyses of adhesive structures and quantitative analyses of the mechanical properties of the extracellular matrix and cells, the identification of nucleo-cytoplasmic transport and ion channels as key players in mechanosensitive cell fate decisions, and the interdisciplinary studies combining physics and biology to understand the role of tension in coupling single cell behaviors to changes in tissue state.

Starting from the subcellular scale, several reviews in this issue deal with the fundamental structures that enable mechanotransduction. **Orré and coworkers** discuss in detail the role of perhaps the most widely known mechanosensitive structure, the integrin-mediated cell-matrix

adhesions (Orré et al., 2019). The authors address the processes of adhesion assembly, structure, distribution and dynamics, and how these properties enable force transmission from the extracellular matrix to cells, and subsequent mechanotransduction. In this review, the leaps in knowledge facilitated by super-resolution techniques become evident. **Isomursu and colleagues** (Isomursu et al., 2019) further discuss how integrin-mediated mechanotransduction affects stem cells. The authors dwell on the specificity of responses enabled by the elaborate complexity of integrin heterodimers and stem cell niche properties, a fascinating question that lies at the heart of specialization of tissue function.

Continuing on the central theme of cell-matrix adhesions, **Green and Brown** discuss what genetic studies in *Drosophila* have taught us about the molecular components of integrin adhesions and their specific functions during development (Green and Brown, 2019). Based on biochemical properties of integrin-associated proteins, their interactions with each other, and their mutant phenotypes, the authors propose an interesting, modular map of integrin linkages to various actin structures and downstream signaling: a core actin link of talin, kindlin and vinculin; a cell cortex link of ILK, PINCH, parvin, and RSU1; a signaling link containing GIT, PIX, PAK; and a regulator module containing tensin and FAK. This provides a useful framework for understanding the complex regulation of actin binding and dynamics at adhesion sites by the large variety of integrin interacting proteins.

Although significant focus in the mechanotransduction field has been on cell adhesion and the associated cytoskeleton, important roles for other means of sensing and transmitting mechanical signals are being uncovered. One important group of mechanosensitive signaling receptors are mechanosensitive ion channels. **He** and co-workers discuss recent studies where development of calcium imaging systems, pharmacological inhibitors and other manipulation tools have provided compelling evidence for mechanosensitive channels in regulating stem cell proliferation and differentiation in response to extrinsic mechanical forces such as tissue strain and crowding (He et al., 2019).

Besides the plasma membrane, another major hub of mechanosensitivity is the nucleus, with substantial evidence showing how it both experiences and responds to mechanical force. **Zijl and Lomakin** address this emerging topic, focusing on how force impacts on chromatin organization and thereby crucial cellular functions such as transcription (Zijl and Lomakin, 2019). Whereas force transmission to the nucleus via actin fibers is now well established, the authors discuss novel mechanisms of nuclear force generation, for instance by microtubules.

Another intriguing aspect is the role of actin and its polymerization states, which could trigger mechanical effects also within the nucleus.

Focusing further on the nucleus, another key mechanosensitive process is nucleo-cytoplasmic transport. Although a number of mechanosensitive transcription factors downstream of adhesion receptors and ion channels have been identified, among them the omnipotent YAP, the precise molecular mechanisms of their nuclear shuttling has only begun to emerge.

Kassianidou and coworkers discuss recent research on the multiple ways on how nucleocytoplasmic transport is sensitive to mechanical stimuli and how these mechanisms impact shuttling of transcription factors in particular to alter cell fate (Kassianidou et al., 2019). Such regulation includes exposure of cryptic or masked nuclear localization signals, phosphorylation or other biochemical modifications that activate transport, changes in nuclear pore properties, as well “piggyback” shuttling of transcription factors by binding to other proteins.

Zooming out from single cells, **Khalil and de Rooij** address how cell-cell adhesions, and specifically their core components cadherins, mediate mechanotransduction (Khalil and de Rooij 2019). In multicellular systems, dissecting where and how mechanotransduction occurs is an important challenge. The authors discuss this in the specific context of collective cell migration, and the process by which the cells involved become leaders or followers in steering collective cell motion.

Das and colleagues (Das et al., 2019) bring the focus to an even larger scale, discussing the fascinating question of how organs and organisms sense their own shape and size.

Mechanosensitive ion channels such as those in the PIEZO family are essential in this, and their role is discussed. Intriguingly, the different review articles in this issue reveal that research on mechanotransduction mediated by ion channels or adhesions (either cell-cell or cell-matrix) remain largely disconnected, underlining the need for integrated understanding of mechanotransduction. This aspect is highlighted by another review analysing shape sensing, but this time at the cellular scale. In this case, **Luxenburg and Zaidel-Bar** (Luxenburg and Zaidel-Bar, 2019) discuss the role of the actin cytoskeleton and of transcription factors such as MAL and YAP, which are downstream of integrin- rather than ion channel-mediated mechanotransduction. This sensing of cell shape is addressed in the specific context of the epidermis, a complex stratified epithelium where coordinated cell fate specification and positioning is essential.

One of the first tissues where the relevance for mechanical signals in cell fate determination has been shown in vivo is the cardiovascular system, where fluid shear stress generated by blood flow plays critical roles in the development, physiology, and diseases of the vascular tissue. Importantly, shear stress varies greatly in terms of magnitude, pulsatility, and direction. **Min and Schwartz** discuss how endothelial cells interpret these various profiles and magnitudes of flow to regulate gene expression and specific cell behaviors (Min and Schwartz, 2019). A central conclusion on the current literature is that physiological shear stress conditions induces vessel stabilization. Deviations from this range this trigger vessel remodeling, whereas multidirectional or oscillatory flows induce inflammation and predispose to atherosclerosis. Interestingly, the signaling pathways and transcription factors utilized in these very different responses are partially overlapping, leaving important open questions for future mechanistic work on how these networks are tuned to generate specificity.

In addition to extrinsic forces regulating cell fate, cell fate changes impact the mechanical properties of cells, changing their ability to transduce forces back into their microenvironment, generating and interesting feedback loop. A prominent example of such bidirectional mechanical feedback is the myofibroblast activation cycle discussed by **Hinz and coworkers** (Hinz et al., 2019). Myofibroblasts are not only of clinical significance as cells of origin and therapeutic targets for fibrotic disease but also provide an interesting research paradigm to understand the molecular underpinnings of the collagen contraction machinery and the bidirectional relationships between extracellular matrix mechanics, the contractile cytoskeleton and cell fate regulation through mechanosensitive transcription factors. In this regard, a relevant and often overlooked aspect in cell mechanics is how cells and tissues regulate and maintain the level of mechanical tension they exert and withstand. **Boudou et al.** review our current understanding of this issue, and discuss potential mechanisms by which a state of “tensional homeostasis” could be maintained in environments where mechanical properties undergo constant spatiotemporal changes (Boudou et al., 2019).

French and Holmes take another perspective on matrix mechanics, from the point of view of cardiac infarction and post-injury regeneration (French and Holmes, 2019). The authors discuss the importance of the scar tissue in one hand scar tissue providing critical early mechanical stability to the infarcted heart, but on the other hand, through its extreme stiffness negatively impacting cardiac stem cell maturation, myocyte phenotype, and mechanical function of the heart. This dichotomy places matrix mechanics and mechanotransduction at

the core of cardiac post-infarction repair and poses stringent demands on therapies to balance the demands of generating contractile cardiomyocytes while managing the impact of post-infarction scarring.

Continuing on the theme of matrix mechanics, **Gilbert and Swift** discuss the role of mechanotransduction in aging and how changes in the mechanical properties of the extracellular matrix can compromise cellular functions through alterations in mechanosensitive signaling pathways and in particular nuclear mechanotransduction (Gilbert and Swift. 2019). Although this field is only beginning to emerge, models for physiological aging such as progeroid syndromes that impact the mechanical properties of the nuclear lamina, point to a critical role of nuclear mechanics in aging.

In all the physiological systems described above, dissecting the roles of mechanical and biochemical factors within a highly complex and inhomogeneous microenvironment is a major challenge. In this regard, **Cruz-Acuña and García** (Cruz-Acuña and García, 2019) discuss the promising use of organoids to recapitulate key functional features in simplified systems. Specifically, they address recent work in designing three-dimensional biomaterials for organoid culture. Advances in this field have led to biomaterials where key properties such as ligand density, stiffness, or pore size can be controlled independently, potentially enabling major advances in our mechanistic understanding of cell-matrix interactions.

Altogether, these reviews provide a comprehensive update on the multifaceted roles of mechanical signals in cell fate regulation both in health and disease. They also highlight the gaps in knowledge that the community is currently trying to fill. Mainly, current challenges lie in rigorously and unambiguously linking molecular mechanotransduction mechanisms at the nanoscale to organism scale behavior, and finding systematic approaches to accurately map the mechanical and biochemical pathways regulating cell fate in complex, three dimensional environments. As these challenges are progressively addressed in the near future, we can expect to see exciting new paradigms revealed, with increasing avenues to turn knowledge into therapeutic and diagnostic opportunities for a wide range of diseases.

About the editors

Sara A. Wickström is an Associate Professor of Tissue Architecture at the University of Helsinki. Her group studies how complex but stereotyped tissues are formed, maintained, and

regenerated through local growth, differentiation and remodeling, using mammalian epidermis as a model. Her research aims to establish quantitative principles of how multicellular stem cell niches self-organize, and how mechanical forces and cellular interactions allow coordination of single stem cell behaviors on the population level and further couple this behavior to surrounding tissue architecture.

Pere Roca-Cusachs is Associate Professor at the University of Barcelona, and senior group leader at the Institute for Bioengineering of Catalonia. The research of his group aims to unravel the physical and molecular mechanisms by which cells detect and respond to mechanical signals. By combining biophysical tools, computational modelling, and molecular biology, his work aims to find common principles of mechanosensing across different biological systems, all the way from the initial steps in force transmission to the downstream effects in transcriptional activation.

References:

Behrndt, M., Salbreux, G., Campinho, P., Hauschild, R., Oswald, F., Roensch, J., Grill, S. W. and Heisenberg, C.-P. (2012). Forces driving epithelial spreading in zebrafish gastrulation. *Science* 338, 257-260.

Boudou T, Andersen T, Balland M. (2019). On the spatiotemporal regulation of cell tensional state. *Exp Cell Res.* 378(1):113-117.

Cruz-Acuña R and García AJ. (2019). Engineered materials to model human intestinal development and cancer using organoids. *Exp Cell Res.* 377(1-2):109-114.

Das R, Wieser S, Krieg M. (2019). Neuronal stretch reception - Making sense of the mechanosense. *Exp Cell Res.* 378(1):104-112.

French BA and Holmes JW. (2019). Implications of scar structure and mechanics for post-infarction cardiac repair and regeneration. *Exp Cell Res.* 376(1):98-103.

Gilbert HTJ and Swift J. (2019). The consequences of ageing, progeroid syndromes and cellular senescence on mechanotransduction and the nucleus. *Exp Cell Res.* 378(1):98-103.

Green HJ and Brown NH. (2019). Integrin intracellular machinery in action. *Exp Cell Res.* 378(2):226-231.

He L, Ahmad M, Perrimon N. (2019). Mechanosensitive channels and their functions in stem cell differentiation. *Exp Cell Res.* 374(2):259-265.

Hinz B, McCulloch CA, Coelho NM. (2019) Mechanical regulation of myofibroblast phenoconversion and collagen contraction. *Exp Cell Res.* 379(1):119-128.

Isomursu A, Lerche M, Taskinen ME, Ivaska J, Peuhu E. (2019). Integrin signaling and mechanotransduction in regulation of somatic stem cells. *Exp Cell Res.* 378(2):217-225.

Kassianidou E, Kalita J, Lim RYH. (2019). The role of nucleocytoplasmic transport in mechanotransduction. *Exp Cell Res.* 377(1-2):86-93.

Khalil AA and de Rooij J. (2019). Cadherin mechanotransduction in leader-follower cell specification during collective migration. *Exp Cell Res.* 376(1):86-91.

Luxenburg C, Zaidel-Bar R. (2019). From cell shape to cell fate via the cytoskeleton - Insights from the epidermis. *Exp Cell Res.* 378(2):232-237.

Martin, A. C., Kaschube, M. and Wieschaus, E. F. (2009). Pulsed contractions of an actin-myosin network drive apical constriction. *Nature* 457, 495-499.

Min E, Schwartz MA. (2019). Translocating transcription factors in fluid shear stress-mediated vascular remodeling and disease. *Exp Cell Res.* 376(1):92-97.

Orré T, Rossier O, Giannone G. (2019). The inner life of integrin adhesion sites: From single molecules to functional macromolecular complexes. *Exp Cell Res.* 379(2):235-244.

Zijl S and Lomakin AJ. (2019). The "nuclear physics" behind epigenetic control of cell fate. *Exp Cell Res.* 376(2):236-239.