Cell Adhesion & Migration
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/kcam20

Foreword: Physics of Cell Migration

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Accepted author version posted online: 27 Aug 2015.

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Cell migration is an important phenomenon involved in several developmental, physiological and pathological processes, including embryonic development, tissue homeostasis, regeneration, or tumour metastasis, among others. Cell migration is a complex phenomenon which has attracted the attention of both biologists and physicists. The formers describe it mainly by the levels of expression of certain genes and signalling networks. On the other hand, physicists view migrating cells as dynamic and out-of-equilibrium systems where the internal cytoskeleton auto-organize in ordered polymerizing (and depolymerising) structures which can be described by means of soft matter physics laws. During the last decades both communities have started to work together in order to analyze and understand the working principle of migrating cells and significant advances have been obtained so far. Biologists have realized that some important events where cell migration is involved cannot be entirely described by means of genomics and proteomics approaches. Novel analytical and descriptive tools are needed in order to quantitatively describe this complex phenomenon. Physicists have made important contributions to biology by developing novel approaches for describing cell migration. This includes, among others, biophysical modelling and simulation tools, theoretical descriptions, mechanical studies or engineered biomaterials, which are paving the way for the development of a new framework for the understanding of cell migration. In collaboration with biologists, this new framework will contribute to reveal key mechanisms in cell motility and in the development of new therapies to combat diseases where cell migration is involved, such as in cancer.

In this special issue on the *Physics of Cell Migration* we have gathered eight reports reflecting the growing interest on the biophysical description of cell migration with a special emphasis to those topics with biological relevance. These contributions describe the state-of-the-art in this field and the challenges which need to be addressed in the future with exciting advancements continuously emerging.

Physical forces play a key role in the mechanism of cell migration. Contractile forces transmitted by the actomyosin cytoskeleton are fundamental to counteract matrix adhesion. Multiple studies have addressed the fundamental question between mechanical forces and adhesion and their influence on cell motility, both at the single and collective level. In this context, **Rubenstein and Mendes Pinto** nicely discuss about the spatiotemporal interplay between

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actomyosin contractility and adhesion. They describe how the force balance between actomyosin contractility and cell-cell and cell-extracellular matrix interaction regulate epithelia cell migration resulting in different modes of migration. A perturbation of this balance could lead to the formation of tumors and invasiveness caused by an increase on traction forces.

Mechanical forces also regulate the extravasation of tumor cells, which is the last and yet essential step of the metastasis cascade. **Goetz and colleagues** discuss this in a short review, where they elaborate on the importance of taking physical forces into account when studying this peculiar phenomenon. Tumor metastasis is a highly inefficient process that is successfully performed by only a small subset of cancer cells localized in the primary tumor. While the "seed and soil" hypothesis states that metastasis will occur at sites where the local microenvironment is favorable, the "mechanical" concept argues that metastasis occurs at sites of optimal blood flow patterns. Indeed, while growth of metastatic foci will depend on the compatibility and molecular interaction of tumor cells (the 'seed') with the local environment (the 'soil'), growing evidence suggests that the initial delivery and arrest of tumor cells is mainly driven by mechanical cues. This short review thus invites further studies aiming to dissect the contribution of mechanical forces to tumor cell extravasation during the metastasis cascade.

Coherence during collective cell migration is crucial for adequate tissue motion. Most studies have been mostly performed on tightly connected epithelial cells but less is known about how mesenchymal cells move collectively. **Szabó and Mayor** comment this on their review. They describe the mechanism through which placode and neural crest cells maintain their coherence during development. They discuss that their prolonged migration is a result of two opposing effects, paracrine chemotaxis and contact inhibition of locomotion, in a mechanism they call “chase and run”. This mechanism allows placode cells to run away from the chasing neural crest cells. Interestingly, they argue that this mechanism could be extrapolated to other morphogenetic and pathological processes involving collective cell migration.

Physical laws also govern tumor progression, a topic widely studied from a mechanical perspective. Metastasis can be considered as the end product of a multistep bio-mechano-chemical process where cancer cells disseminate to distant

organs and home in a new tissue microenvironment. Metastases are resistant to multiple therapies and are responsible for the large majority of cancer-related deaths. It is now clear that the invasion-angiogenesis-metastasis cascade is not only dependent on genetic and epigenetic alterations within cancer cells, but also involves non-neoplastic stromal cells that contribute to cancer progression. Importantly, the last decade has provided unprecedented insights demonstrating that mechanical forces shape each step of the metastasis cascade. Taking into account these key physical and mechanical processes may help to better understand the disease, and hopefully lead to the design of more efficient targeted therapies, as well as diagnostic and prognostic tools.

Wolf and Krause beautifully discuss the efficiency of tumor invasion, one of the main hallmarks of cancer. They elaborate on the need for tumor cells to optimally negotiate existing and natural pores within the desmoplastic stroma and describe how tumor cells can adapt to those physical barriers imposed by neighboring cells and extracellular matrix. Their review, largely based on their own work, nicely shows that invading tumor cells can rapidly deform their largest and stiffest organelle, the nucleus, to allow its passage through limiting physical barriers. Nuclear deformability is mostly governed by chromatin organization and nuclear lamina expression. Additionally, they further show how tumor cells can also locally degrade resistant extracellular matrix fibers to ensure their successful navigation through these natural physical barriers.

Discussion arround that timely topic is provided through a second review by **Claudia Mierke**. The author again strongly insists on the ability that cells have to switch before different migration modes for performing active migration and invasion through tissues, which is natural and essential to many biological phenomena such as embryonic development, wound healing processes, tissue assembly and regeneration, immune cell trafficking and cancer. This review accurately discusses the mechanical prerequisites that cells, and in particular tumor cells, need to adopt for performing efficient invasion through constrained three-dimensional microenvironments by switching their migration mode. The review provides an interesting angle by further dissecting the plasticity of tumor cell invasion and how cellular and environmental biomechanics drive the transition to blebbing and protrusive motility modes. This exciting discussion allows the reader to better understand how cell migration and invasion through complex environments is

kept efficient, and how external and internal mechanical forces work in concert with cellular signaling machineries for constantly reacting and adapting to new obstacles.

Cells sense their surrounding environment by transducing mechanical forces into biochemical signals, regulating certain cellular responses and processes. Defects in mechanotransduction could lead to abnormal cell function and diseases, such as atherosclerosis, which is caused by a perturbed flow pattern with low shear stress. The identification of the key sensory cellular actors are therefore of crucial importance for proper vascular morphogenesis and physiology. In this context, **Conway and Schwartz** comment on their recent study where they dissected the blood flow mechanosensory complex consisting on VE-Cadherin and PECAM-1. Using a developed FRET tension sensor, they show that VE-Cadherin and PECAM-1 act as mechanosensors of fluid flow shear stress in endothelial cells. Strikingly, they show that flow triggers opposite forces changes on two important adhesion molecules. Indeed, while flow decreases tension of VE-cadherin, it increases tension of PECAM-1, suggesting that flow sensing abilities of endothelial cells are actively controlled They further discuss how PECAM-1 flow sensing potential strongly depends on its close interaction with the cytoskeleton, in particular vimentin, an intermediate filament protein. This elegant study provides important insights in order to understand how blood flow forces are transduced to the endothelium, and how this signal regulates both vascular morphogenesis and disease.

Statistical physics provides also a framework to describe complex biological phenomena with inherently stochastic nature. As an example, the random – Brownian – motion of molecules within the cell, or the fluctuations in gene expression in living cells, can be understood using this framework. The concepts and laws of statistical physics can also be applied in describing cell motion. Cell migration is not only a consequence of chemoattractants, but other gradient-free cues can also contribute to cell motility, which in general, prevents the quantitative prediction of the motion. In this context, **Riveline and co-authors** comment on a recent work of their group about the key role of protrusion fluctuations and adhesion in the physicochemical mechanism of cell migration. Similar to a Feynman ratchet mechanism, they use the stochastic nature of protrusions to direct NIH3T3 cell motion on asymmetric adhesive patches. Their analysis of protrusion statistics allows the prediction of cell motility in a wide variety of conditions.

Finally, the authors define novel protrusion-based biophysical concepts and parameters and use them to develop a theoretical model capable to predict migration efficiency and persistence. Altogether, this work nicely highlights the importance of stochasticity in protrusions activity in cell motility and directionality, providing new and exciting insights in the description of cell motion.

Overall, this special issue demonstrates the importance of using physics laws for the description of cell migration, and paves the way towards a new paradigm in understanding cell motility. Finally, we hope that the contributions will provide the readers with interesting new insights and help them to reveal key mechanisms involved in cell migration.