Cell biology: Centrosomes in inner space

Ulrich S. Schwarz
Institute for Theoretical Physics and BioQuant, Heidelberg University, Heidelberg, Germany
Correspondence: schwarzz@thphys.uni-heidelberg.de
https://doi.org/10.1016/j.cub.2021.01.085

Centrosome positioning is essential for many processes in animal cells, in particular during development and migration. A new study using quantitative analysis of enucleated cells plated on adhesive micropatterns reveals that microtubules position the centrosome in the geometric center of the intracellular space defined by the actin cytoskeleton.

As one observes animal cells under the microscope, it becomes apparent that their shapes are highly variable and dynamic, especially during development and migration. Today we understand that animal cell shape is mainly determined by the cytoskeleton, which is composed of three main biopolymers: filamentous actin, microtubules and intermediate filaments like vimentin. The organization of the actin cytoskeleton, in particular, strongly depends on extracellular cues, including the spatial distribution of binding sites for cellular adhesion receptors. The resulting cell shape then impacts the way the cell is organized internally, and this in turn modifies cell behavior and fate. About 20 years ago, a direct relationship between cell shape and fate was demonstrated using adhesive micropatterns generated with microcontact printing. Later, similar approaches have been used to identify that activation of the transcriptional regulators YAP and TAZ provides an important molecular link between cell organization in response to extracellular cues and cell fate. Today, control of cell shape, behavior and fate using adhesive micropatterns has become a standard approach in cell biology and cellular biophysics, fueled also by new technical advances like photopatterning. For example, adhesive micropatterns have been used to study how cells spread in structured environments, revealing an important role for contractile actin bundles that can pull cells forward.

How exactly does cell shape affect the internal organization of cells? To answer this important question, we first have to recall how an animal cell is typically organized. The periphery is usually characterized by an actomyosin cortex underlying the plasma membrane. In regions of strong adhesion, the cortex is partially replaced by more specialized actin structures, like lamellipodia or contractile actin networks and bundles. Although the central region of the cell is usually occupied by the nucleus, its main organizer seems to be a juxtanuclear organelle — the centrosome. The centrosome is present in most animal cells and acts as a microtubule-organizing center by nucleating an aster of microtubules that grow towards the periphery and thus can detect cell shape. Traditionally it is thought that this leads to centrosome positioning at the geometric center of the cell, as suggested by the situation in round eggs and in embryos, and by in vitro experiments with microtubule asters. A new study from the lab of Manuel Théry, published in this issue of Current Biology, now challenges this view for adherent cells and suggests that it is not so much the outer cell shape, but rather the inner region of the cell defined by the actin cytoskeleton that determines centrosome positioning.

The conclusions of Théry and colleagues are based on cell shape control through adhesive micropatterns and a quantitative analysis of the resulting cell organization. Centrosome positioning can easily be detected, for example using a fluorescent label for the centriolar protein centrin, and compared with the geometric center of the cell, as determined from the cell shape. The authors found that centrosome positioning and the geometric center of the cell only coincide when cells are plated on very symmetrical patterns like discs or equilateral triangles. The more asymmetric the patterns, the more the centrosome is located towards the periphery, for example as seen with L-shapes or isosceles triangles. However, the same effect occurs with the positioning of the nucleus. To disentangle positioning mechanisms for the centrosome and the nucleus, the authors analyzed cytoplasts, i.e. cells from which the nucleus has been removed by centrifugation. To avoid a vimentin cage forming around the ghost of the removed nucleus, they generated cytoplasts from cells lacking vimentin. In these cytoplasts, the same movement of the centrosome away from the geometric center is observed as pattern asymmetry increases.

The main difference between the cells on the different patterns is the organization of their adhesion and actin systems. The authors therefore reasoned that the microtubules emanating from the centrosome do not detect the shape of the cell, but instead that of the inner region of the cytoplasm that is devoid of prominent actin networks and bundles, called the actin inner zone (AIZ). Using image analysis, they indeed found that the central microtubules are straight and radially oriented only in the AIZ. Once these microtubules entered the actin-rich regions, they started to bend, in agreement with earlier results on the mechanical effects of a dense actin network on microtubules and the increased frequency of microtubule dynamic instabilities at mechanical boundaries.
asymmetric the pattern on which the cytoplasts are plated, the more asymmetric the actin cytoskeleton and the centrosome positions itself. The work by Théry and colleagues sheds new light on an important question in cell biology, namely how cells organize themselves in response to extracellular cues and, in particular, how they establish polarity, e.g. during development and migration. It also strengthens the emerging view that the different cytoskeletal networks are much more closely connected to each other than formerly appreciated. In general, it demonstrates the strength of using new technologies and quantification, without which their conclusions would not have been possible. Finally, this work also nicely shows how model systems can be used to dissect a complex system in a stepwise manner. In reconstituted centrosome, actin system is absent and the geometric center is selected by the centrosome. With cytoplasts, the role of the actin system becomes apparent and the centrosome positions itself in the center of the AIZ, yet the nucleus is absent. In nucleated cells, the centrosome and nucleus strongly interact with each other, both mechanically (e.g. through their connection by the linker of nucleoskeleton and cytoskeleton (LINC) complex) and sterically by using the same tight space. On flat substrates, this often results in the centrosome being positioned at the side of the nucleus, but the exact position can still depend on context, in particular on the geometric and mechanical properties of the extracellular matrix. It remains to be seen how much the microtubule–actin interactions now revealed in the new work by Théry and colleagues contribute to the interplay between the nucleus and centrosome in such more complex situations. Understanding the organization of the actin and adhesion systems is a formidable challenge by itself and there certainly will be chemical and mechanical feedback between the different parts of the cell. These important open questions notwithstanding, however, it is now clear that the actin cytoskeleton surrounding the cell center should be considered to be an essential factor in all processes involving the centrosome, at least in strongly adhering cells, and that adhesive micropatterns offer a rewarding route to further investigate where and how it is positioned.

REFERENCES

Decision making: How the past guides the future in frontal cortex

Bharath Chandra Talluri, Anke Braun, and T.H. Donner
Section Computational Cognitive Neuroscience, Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Correspondence: bharathchandra.talluri@gmail.com (B.C.T.), a.braun@uke.de (A.B.), t.donner@uke.de (T.H.D.)
https://doi.org/10.1016/j.cub.2021.01.020

Our judgments of our environment are often shaped by heuristics and prior experience. New research shows that the resulting biases are encoded, and combined with new sensory input, by groups of neurons in the frontal cortex during decisions under uncertainty.

We often need to choose actions on the basis of uncertain interpretations of the state of our environment, for example when deciding whether or not to cross the street in busy traffic. Such decisions depend not only on the momentary sensory input, but also on our prior expectations. These expectations may result from similar decisions made in the past or their outcomes — for example, almost being hit by a car when crossing at the same spot the day before — and are often generated through idiosyncratic heuristics. An important goal for neuroscience is to understand how such expectations are formed, and to pinpoint their representation in the neural circuits involved in the control of goal-directed behavior. A new study reported in this issue of Current Biology by Mochol et al. shows that, when new decisions are made, populations of neurons in prefrontal cortex encode a bias inherited from previous decisions, and combine this bias with current sensory input.

Mochol et al. recorded the activity of many neurons from a region in the macaque monkey prefrontal cortex known as the pre-arcuate gyrus (PAG). Two monkeys had to choose one of two targets (T1 and T2) by making a saccadic eye movement. On each trial of the task, the targets were presented first, followed by a cloud of dots, some of which moved jointly in the direction of the correct target (Figure 1A). It was already known that neural population activity in PAG reliably tracks the evolution of the decision while monkeys are processing this motion stimulus. Mochol et al. moved beyond this by showing that patterns of PAG activity, measured before the motion stimulus onset, encode a bias inherited from previous trials and predict the upcoming choice (Figure 1B). Using a clever analysis, the authors further showed that the neural representations of history bias and upcoming choice were ‘aligned’ in the high-dimensional space of neural population activity in PAG (Figure 1C). This indicates that the history bias is the major factor contributing to the choice-predictive PAG-activity before stimulus onset.