Nature Reviews Molecular Cell Biology | AOP, published online 11 June 2008; doi:10.1038/nrm2433

DOI:
10.1038/nrm2433

CELL MORPHOLOGY

Breaking the spatial code

Cells come in different shapes and sizes. But how is cell shape determined? And does shape have a role in the regulation of signalling?

Julie Theriot and colleagues used motile epithelial keratocytes derived from fish skin to address the first question. Keratocyte shapes were described by four primary shape modes: cell area, 'D' versus 'canoe' shape, cell-body position and left–right asymmetry. Measurements of cell motility, surface area and other morphological features in a large number of cells, and examination of the distribution of actin filaments along the leading edge to relate the cell-shape measures with cellular actin dynamics, revealed that cell shape is dynamically determined. Cell morphology perturbation studies indicated that cell shape and motility depend on a cellular history-independent, self-organizing mechanism that is characterized by a small number of cellular parameters that stay constant over time (such as the available quantities of membrane or cytoskeletal components).

The authors next developed a quantitative physical model of cell shape and movement that could explain the main features of keratocyte shapes. Based on the findings that the surface area is constant and that the density of filamentous actin along the leading edge is graded, and based on previous observations that showed that the lamellipodial actin network undergoes treadmilling with net assembly at the leading edge and net disassembly towards the rear, Theriot and colleagues propose a model in which actin-network treadmilling drives from within the forward protrusion of an inextensible membrane bag (characterized in two dimensions by its total surface area). This model can quantitatively recapitulate the range of keratocyte shapes and predict both cell shape and motility.

The second question concerns the relevance of cell shape for cellular functions. An emerging concept proposes that cell signalling is nonhomogeneous in space and that spatiotemporal dynamics of signalling molecule activities create a code that confers signalling specificity. Iyengar and colleagues used computational and experimental approaches to model the flow of spatial information from β-adrenergic receptors (β-ARs) to mitogen-activated protein kinase (MAPK) in neurons *in vivo*.

In hippocampal neurons, the cell body and dendrites have the same surface density of β-ARs, generating similar adenyl cyclase activities and cyclic AMP (cAMP) levels near the cell surface. cAMP gradients arise from the spatial segregation of adenylyl cyclase activities and phosphodiesterase in the cytosol. Numerical simulations indicate a gradient decay length of ~4 μm that can decrease to ~2.5 μm when phosphodiesterase is activated. In the neuronal soma (20–30 μm diameter), cAMP becomes progressively hydrolysed as distance from the cell membrane increases. By contrast, in the dendrite, cAMP can remain high because of its small diameter (1–4 μm). Interestingly, similar phenomena occur in migrating cells, in which protrusions such as filopodia and lamellipodia at the leading edge are much thinner than the cell body and trailing edge. Signalling molecules, such as the GTPase CDC42, become preferentially activated in the leading edge, where the surface-to-volume ratio is increased.

Ravi Iyengar and colleagues also addressed how spatial heterogeneity affects the propagation of the input signal to downstream effectors and how network design is linked to the spatial code implemented by signalling microdomains. Their results indicate that cell shape controls the dynamics of local biochemical activity of negative regulators to determine the size of signalling microdomains, and that negative regulators control the flow of spatial information to downstream components within the cell.

Ekat Kritikou

ORIGINAL RESEARCH PAPERS Keren, K. *et al.* Mechanism of shape determination in motile cells. *Nature* **453**, 475–480 (2008) | Neves, S. *et al.* Cell shape and negative links in regulatory motifs together control spatial information flow in signaling networks. *Cell* **133**, 666–680 (2008)
FURTHER READING Lecuit, T. & Lenn, P.-F. Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis. *Nature Rev. Mol. Cell Biol.* **8**, 633–644 (2007) | Kholodenko, B. N. Cell-signalling dynamics in time and space. *Nature Rev. Mol. Cell Biol.* **7**, 165–176 (2006)