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Editorial

Focus on the Spatial Organization of Signalling

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A collection of eight reviews highlighting important insights into cellular processes provided by spatially resolved analysis of signal transduction pathways

Since the early days of light microscopy it has been apparent that cells are highly organized and compartmentalized. However, only in recent decades has the molecular basis of this spatial organization and its functional role in cellular signalling events emerged. Furthermore, modern molecular and imaging techniques, together with the intricate combination of cellular and developmental biological approaches, are extending our understanding of how individual cells respond to their environment and are organized within a tissue. Years of molecular and genetic analysis, coupled with recent advances in large-scale approaches, may have identified many of the core components of signalling pathways, although new layers of regulation, such as small RNAs and alternative splicing, continue to add complexity. Although the parts list may soon be completed, our understanding at the level of signal integration and cross-talk remains limited. The key to understanding cellular regulation is to complement biochemical assays *in vitro* with analysis on how spatial organization contributes to the properties of intra- and intercellular communication. This requires a real-time quantitative analysis of endogenous components in the cellular context, which has only recently became possible with advanced microscopy techniques and biosensors. These developments open a new era in the analysis of spatial organization on different biological scales from molecules to cells to tissues and organs.

The EMBO Journal covers a broad spectrum of subject areas and approaches, ranging from biochemical to cell biological, as well as those at the organism level. However, the journal has a longstanding tradition of hosting important papers on signalling, which is also mirrored by many EMBO-sponsored Conferences and Workshops on cellular signalling. Therefore, papers on the spatial organization of regulatory components and its importance for signal propagation in growth and development remain a focus of the journal. This Focus Issue highlights our commitment to the field: eight reviews describe the role of spatial organization of signalling from a variety of angles. Together, these authoritative articles provide an up-to-date overview on this exciting field.

Although it is clear that cellular membranes are not uniform in composition but are organized into microdomains, the direct role of these assemblies in influencing the outcome in signalling remains a controversial issue. Ivan Dikic, Amparo Acker-Palmer and colleagues review their role in signal integration and the physiological implications of higher-order receptor clustering in different cellular compartments. The spatial organization of signalling complexes does not stop at the plasma membrane, with various regulatory proteins being specifically targeted to endomembranes within the cell. This targeting to specific subcellular locations in a highly dynamic manner gives rise to asymmetry between different compartments and provides a means for rapid changes in their steady-state distribution upon initiation of signalling cascades. This concept of spatial cycling in cells is addressed by Philippe Bastiaens and colleagues, who use the small G-proteins as an example to describe how the reversible posttranslational modifications of regulatory factors alter their localization and, consequently, downstream signalling. Such targeting strategies can give rise to intracellular gradients depending on the localization of the modifying and demodifying enzymes. Gradients provide spatial information as a template for the organization of the cell, as described through the elegant example of the RanGTP gradient, which regulates directional transport and the re-establishment of the nuclear envelope after mitosis. The review also touches on how the modulation of the spatial organization of signalling components may be used as a therapeutic approach to pathophysiological situations.

One example of spatial cycling lies in the role of Rab G-proteins during vesicular trafficking and the maturation of transport vesicles. Selective recruitment of G-proteins is important for trafficking between organelles and the establishment of cellular polarity in eukaryotes. G-proteins also have an important role in establishment of the spatial distribution of the plant hormone auxin, which in turn has a key role in plant development. Jiri Friml and colleagues describe how auxin gradients are generated by directional intercellular transport mediated by the polar targeting of influx and efflux carriers. The spatial distribution of these transporters dynamically changes in response to environmental and developmental cues, with dramatic regulatory consequences.

While a significant amount of literature describes molecular crosstalk between signalling pathways, less is known about the crosstalk between organelles. Organelles are precisely organized and localized within the cell, and they appear to have a perhaps unexpectedly important role in the organization of signalling pathways, as illustrated by recent studies on signalling endosomes and primary cilia. However, the best-understood example remains the crosstalk between the endoplasmic reticulum and mitochondria, which

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is described by Luca Scorrano and colleagues. It has long been recognized that these organelles contribute to compartmentalization of secondary messengers such as calcium, and alteration of the magnitude and frequency of calcium signals encodes very different biological outcomes. The close spatial apposition between the ER and mitochondria, which are linked by the mitochondrial-associated membrane, is important for the transfer of phospholipids and calcium between these organelles, thus regulating mitochondrion-dependent apoptosis.

Although spatial organization clearly has an important role in eukaryotes, this is not an exclusive principle for this biological domain. As outlined by Victor Sourjik and Judith Armitage, spatial organization of the bacterial chemotaxis systems determines the signalling outcome in response to sensing different gradients of chemo-attractants. The *Escherichia coli* signal transduction can be recreated using several components *in vitro*; however, *in vivo* the receptors self-organize into large-scale clusters containing thousands of molecules. It is this higher-order spatial organization that is important for efficient signalling properties, such as defining the intracellular gradient of the signalling components, precision of adaptability and cooperative behaviour between receptors. The evolutionary organization of the chemotaxis pathway is discussed with an emphasis on the photosynthetic bacterium *Rhodobacter sphaeroides*, as it utilizes a particularly complex combination of pathways with both polar and cytoplasmic components.

Spatial organization of signalling also regulates chemotaxis in eukaryotic cells, as outlined in the review by Alan Hall and colleagues. Migration towards extracellular guidance cues leads to the activation of spatially restricted signalling pathways and the asymmetric distribution of signalling complexes, resulting in localized cytoskeletal rearrangements. The authors highlight similar principles at work in yeast bud formation, cell migration in individual cells and collective migration of border cells. Highly polarized neurons are the prime example of the exquisite spatial organization of cells, and they also describe the basis for polarized changes in neurons during axon formation and the establishment of neuronal polarity. In the subsequent review, Erin Schuman and colleagues describe the importance of local and spatially controlled mRNA translation and protein degradation in neurons, which enables fine-tuning of synaptic strength at individual synapses within individual cells.

Finally, Carl-Philipp Heisenberg and colleagues describe the role of spatial organization of signalling complexes at cell–matrix and cell–cell contact sites and their modulation by mechanical forces. These principles enable cells to coordinate extrinsic and intrinsic signals that influence cellular integrity, polarity and tissue morphogenesis. They also explain how spatiotemporal regulation of cell adhesion and mechanosensitivity govern cellular communication in tissues.

Although this review series touches only upon a few of the biological processes in which the spatial organization of signalling complexes is important, the selected examples illustrate universal concepts. Recent advances in the research tools available have enabled quantitative and spatially resolved insights opening truly a new era of molecular and cellular biology. We hope this set of reviews provides a general framework and a glimpse of what is to come.

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