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Special Issue: Wiring and Rewiring in Signal Transduction

Wired in

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Trends in Biochemical Sciences

In biochemical research, the wiring diagram is the ubiquitous symbol of a signal transduction pathway. These roadmaps of signaling circuitry reduce complicated protein–protein interaction cascades into simple(r), easy-to-follow summaries. The wiring of any signal transduction pathway ultimately boils down to a few key steps: the detection and transduction of the signal, amplification of that signal, and integration into a response. In this Special Issue, *TiBS* presents a selection of Reviews that focus on our emerging understanding of the molecular mechanisms involved in each of these key steps, and ultimately how they can be subverted and 'rewired' in different physiological contexts such as disease.

The first two Reviews examine mechanisms in the first step of signal transduction pathways: signal detection. The first Review, by **John Kuriyan and colleagues**, explores the structural consequences of ligand binding to receptor tyrosine kinases (RTKs). A key feature of RTKs is that they are single-pass transmembrane receptors; ligand binding causes dimerization or reorganization of constitutive dimers. Focusing on one of the most highly studied RTKs, epidermal growth factor receptor, their Review addresses several central questions: first, how binding of the ligand to the extracellular domain results in conformational changes that stimulate kinase activity; second, the mechanisms of ligand-independent receptor clustering, and what safeguards prevent inappropriate activation through this clustering; and finally, how disease-associated changes in the receptor sequence can affect each of these mechanisms.

The second Review, by **Joanne Chory, Jeffery Dangl, and colleagues**, is the only article in this issue to focus the diverse and complicated signaling of plants. This Review explores the mechanisms through which different members of one superfamily of kinases, the leucine-rich repeat receptor kinases (LRR-RKs), integrate competing growth and defense signals to make sophisticated trade-off decisions. They focus on the signaling mechanisms of two competing LRR-RK surface receptors: BRI, a steroid receptor that signals growth, and FLS2, an innate immune receptor that recognizes bacteria. Ultimately, the signaling pathways must cross-talk and integrate for the plant to make the best use of its limited resources.

One key caveat of wiring diagrams is that they often fail to account for the role of context. That is, although a wiring diagram may be accurate within a particular cell, subcellular location, or developmental lineage, the diagram may in fact be rewired at other times and locations. In the third Review of this Special Issue, **Norbert Perrimon and colleagues** explore the role that spatiotemporal organization plays in the wiring (and rewiring) of signaling pathways. Drawing from the extensive *Drosophila* literature, they provide didactic models for how the spatial and temporal context affects signaling through the regulation of each of the key steps in a signaling pathway.

Failing to account for the spatiotemporal context is not the only limit to wiring diagrams. Many wiring diagrams are often drawn as simple, linear flows of information. However, we now know that signaling pathways are anything but linear. It is becoming clear that virtually every pathway has redundancies, crosstalk with other pathways, and feedback mechanisms in place; these act as checks and balances that buffer against disturbances in cellular homeostasis. Although helpful in physiological conditions, these mechanisms are proving to be a significant hurdle in treating signaling-driven diseases such as cancer. In the fourth Review in this special issue, **Rene Bernards and colleagues** examine the mechanisms through which RTKs, a major driver for oncogenic signaling, circumvent therapies via crosstalk, feedback, and redundancies. In their Review they highlight combinatorial therapies that target multiple steps or branches of pathway as a potential solution.

Signal transduction and amplification is a key step in any signaling pathway. But at a molecular and structural level, how is this achieved? Two Reviews in this Special Issue explore structure-based mechanisms to transduce and amplify a signaling cascade: dimerization-induced allosteric regulation of kinases, and the formation of a dynamic nonmembranous signaling structure termed the signalosome. The Review by **Frank Sicheri and colleagues** takes a close look at the RAF and eIF2α kinase families as models for dimerization-driven regulation; however, their ideas and observations may be more generally applicable because dimerization is a common theme throughout the kinome. Interestingly, they note that although there is variability in the dimerization interface, the interface plays a crucial, consistent regulatory role because of its ability to allosterically activate the kinase site. The next Review, by **Mariann Bienz**, further explores the role of multimerization in activation of signaling pathways. Her Review focuses on three 'two-faced' protein–protein interaction domains that regulate the clustering of signaling proteins into a structure known as the signalosome. Signalosomes are particularly important for Wnt signaling, whose components include these domains. Switching which of the 'two faces' interact (resulting in side-to-side vs head-to-tail interactions)

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controls the activity of the pathway, reminiscent of the allosteric dimeric interactions described by Sicheri.

The seventh and final Review of this Special Issue approaches signal transduction wiring from the perspective of the systems biologist. This review by **James Ferrell** is the first of a short series by the author that will examine the concept of ultrasensitivity in the context of signal transduction. Ultrasensitivity describes the kinetics of a signaling system in which the magnitude of the change in output of the pathway is disproportionately large compared to the change in the signal. This results in a switch-like, sigmoidal response that will be familiar to anyone who works in signaling. Indeed, Ferrell will draw multiple examples from kinase/phosphatase systems. Understanding the logic of these systems will be important for successfully wiring synthetic signaling circuits – and rewiring pathological circuits – in the future.

In summary, I hope you enjoy this Special Issue on signal transduction. Although not all signaling pathways could be touched upon, I hope that this issue will offer useful reviews on some of the most exciting conceptual advances in how signaling pathways are wired – and rewired – using relevant examples from the literature. This collection of articles examines the themes, mechanisms, and logic behind each of the major elements of a wiring diagram, including detection and transduction, amplification, and integration of a response. However, they also touch on some of the regulatory features noticeably omitted from wiring diagrams, including the roles of time, space, and kinetics. Overall, I hope that they will inspire you to explore the unanswered questions facing the signal transduction field. I welcome your thoughts and comments on this Special Issue, which you can send to me at tibs@cell.com or *Twitter:* @TrendsBiochem.