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Editorial: Signaling pathways instruct the blueprint of life

How do cells communicate to coordinate building an organism from a single cell? Clearly this subject is broad enough to consistently fill several journals worth, with new discoveries modifying our understanding regularly. From discoveries as early as the Spemann-Mangold organizer, first described in 1924, the study of cell signaling has been inextricably linked to elucidating the concepts of developmental biology. For this special issue, we aimed to cherry-pick cell signaling mechanisms with broad implications across species and organ systems, to show how nature has solved specific challenges during development. Thanks to intensive studies of signaling mechanisms in a wide variety of contexts, fundamental aspects of cell signaling regulation of development are beginning to reveal a blueprint for organism development.

Cellular signaling mediates communication, but how is this communication conveyed? How does a secreted ligand traffic from its site of production to its receptor-expressing cellular target? The concept of morphogens, as in the “French flag” model, describes a gradient of diffusible ligand from a source to a sink that specifies distinct cell types based on threshold morphogen concentrations that the cells encounter. This elegant simplification however, has been subject to extensive revision and reimagining over the nearly sixty years since it was proposed. The dispersal of TGF-β ligands, for which several mechanisms have been proposed, provides a case study for Rogers and Müller, in which they discuss the experimental evidence for various modes of Nodal and BMP dispersal in zebrafish development. It has been debated whether morphogens are freely diffusible, or are disseminated by other mechanisms including cellular processes termed cytonemes that synapse between signal-producing and -receiving cells. Tom Kornberg discusses this non-diffusion mechanism in a perspective piece and further explores how similar mechanisms might be employed in syncytial embryos such as the *Drosophila* blastoderm and *Stentor coeruleus*. The mechanisms of signal reception during development continue to be refined as well. A prime example of this is the increasing appreciation of the importance of primary cilia in the reception and transduction of various signaling pathways. Elliott and Brugmann provide an overview of the mechanisms of ciliary signaling during development and the consequences of loss of cilia in human development in a class of diseases termed ciliopathies.

Once the embryo consists of a critical number of cells, symmetry and homogeneity must repeatedly be broken, in different developing organ systems, to achieve specialization of cells and compartmentalization. Whereas morphogen signaling is critical for determining cell fate specification, these signals are not sufficiently sharp for the cellular resolution required in many developmental contexts. Cell sorting or cell segregation sharpens developmental compartment boundaries that are initially established by morphogen signaling. Eph/ephrin signaling is a critical regulator of cell position in the embryo, often acting to help to refine boundaries by driving cell sorting. The roles and signaling mechanisms of Eph/ephrin signaling are discussed in a review from Niethamer and Bush, providing an overview of our current understanding of Eph/ephrin signaling in some of these contexts. Another mechanism inducing sharp boundaries during development is lateral inhibition, in which one cell instructs a neighboring cell to adopt an alternative cell fate. This signaling mechanism, often driven by Notch signaling, is discussed by Sjöqvist and Andersson, as well as examples in which Notch instead drives lateral induction – a process in which one cell induces neighboring cells to adopt the same fate as the signaling cell and to further propagate the inductive signal. The net output of signaling pathways depends on whether positive or negative feedback amplifies signaling, silences it, or induces oscillatory signaling. Neben et al., discuss positive and negative feedback of receptor tyrosine kinase (RTK) signaling, highlighting how these mechanisms dictate the amplitude and duration of signaling.

Finally, three reviews focus on processes highly regulated by signaling, rather than specific signaling pathways per se, with an enormous impact on development, using models from C elegans to human embryo development. The authors discuss how these processes regulate signaling pathways (autophagy), behave like signaling pathways (metabolism), or may unexpectedly be regulated by signaling pathways (chromosomal (in)stability). Entire signaling pathways are fine-tuned by microRNAs (miRNAs) which are fine-tuned by autophagy, as discussed by Palmisano and Meléndez, who also highlight a number of other developmental contexts in which autophagy plays a key role. Teuwen et al., discuss how metabolism, regulated by availability of glucose, glutamine and fatty acids, controls development of blood and lymph vessels. Finally, despite our appreciation of the importance of widely used signaling pathways in a variety of contexts, there remains areas of development where their importance is less well understood. A review from Tsuiko et al., speculates on whether, and how, well-studied developmental pathways play a role in maintaining genomic stability during early stages of human embryo development.

It would be impossible to thoroughly review the importance of cell signaling in development in a single issue. It is instead our hope that the topics covered here, which include commonly used developmental organisms and span topics related to biochemical mechanisms, morphogenesis, cell fate specification and human disease, will spark new contemplation in these areas, which will in turn add new details to the blueprint of development.

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Jeffrey O. Bush
Department of Cell and Tissue Biology and Program in Craniofacial Biology, Institute for Human Genetics, University of California at San Francisco, San Francisco, CA 94143, USA
E-mail address: Jeffrey.Bush@ucsf.edu
Emma R. Andersson
Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden
Department of Cell and Molecular biology, Karolinska Institutet, Stockholm, Sweden
E-mail address: emma.andersson@ki.se