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Developmental Erk Signaling Illuminated

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How a small number of signaling pathways can be re-used in distinct embryonic contexts to control different fates remains unclear. In this issue of *Developmental Cell*, Johnson and Toettcher (2019) use optogenetic approaches to explore how different dynamic ERK signaling states control specific developmental fates in the *Drosophila* embryo.

Developmental processes make usage of a surprisingly limited number of morphogens and signaling components to control a plethora of tissue specification and morphogenetic events. A prime example is the Ras/Erk MAPK cascade in which a complex atlas of spatially defined Erk signaling patterns has been documented over the last decades during development of flies and other organisms (Patel and Shvartsman, 2018). Classic genetic approaches have mapped the different molecular networks that control these co-existing Erk activity pools, but precise mechanistic insight into how a single pathway can control different developmental fates at different *Drosophila* embryo locations is still lacking. This is in part limited because long-term genetic perturbations lead to feedback inhibition, precluding the analysis of spatiotemporally regulated processes at adequate time/length scales.

Recent progress in signaling optogenetics now solve some of these problems by allowing acute manipulation of cellular processes with unprecedented spatial and temporal resolution. In a previous paper, Toettcher and colleagues constructed and validated opto-SOS, an optogenetic actuator that allows precise spatiotemporal control of Erk signaling by blue light (Johnson et al., 2017). They found that such optogenetic control can induce higher levels of Erk activity than a panel of gain-of-function mutations, suggesting that this acute perturbation modality bypasses feedback inhibition due to long-term perturbation. Also, they found that only early embryogenesis (e.g., until 4 h post-fertilization) is sensitive to optogenetic Erk perturbations. After this interval, embryogenesis is robust against ectopic Erk activation.

In the present study, Johnson and Toettcher (2019) more precisely dissect the logic of Erk-mediated spatiotemporal control of three distinct cell fates in the early embryo. At the anterior pole, Erk activation combined with Bicoid expression triggers head structures. On the lateral side, Erk controls neural ectoderm fates characterized by *ind* expression. At the posterior pole, Erk controls tissue contraction leading to gut endoderm fate characterized by *mist* expression. Intriguingly, a light-triggered, 30-min Erk pulse potentiates *ind* expression and the neural ectoderm fate, while a 120-min Erk pulse leads to loss of this fate. Posterior endoderm fate requires at least 1 h of light-triggered Erk signaling. This strongly suggests that these two different fates are controlled by distinct dynamic Erk signaling states of different durations. The authors take advantage of the power of optogenetics to explore additional aspects of Erk-mediated fate specification. First, they test how dynamic Erk signaling states are interpreted during fate specification. By optogenetic modulation of the width, the frequency, and the amplitude of Erk signaling, they infer that embryonic fates are determined by the cumulative load rather than the persistence of the dynamic Erk signaling state. Second, they observe that different Erk-dependent transcriptional outputs react differently to temporal Erk inputs. Some transcriptional outputs vary linearly, while others react non-linearly, and display switch-like behavior with increasing Erk input. Together, these results strengthen the concept that dynamic Erk signaling states specify fate decisions, a concept that has been widely documented in cultured cells (Albeck et al., 2013; Santos et al., 2007). Further, the precision level of optogenetic perturbations provides new hints about the spatiotemporal scale at which transcriptional outputs fluctuate, providing fresh insights about the potential transcriptional network architecture that decode dynamic Erk signaling states. The arena is open to systematically interrogate the dynamics of transcriptional outputs in response to dynamic optogenetic inputs at higher spatiotemporal resolution to characterize in detail how different transcriptional networks that operate in space and time specify different fates during embryogenesis.

Which other approaches can complement signaling optogenetics to paint a more complete picture of developmental Erk signaling? For now, the authors have dynamically manipulated Erk signaling but measured the Erk output at steady-state using classic immunofluorescence techniques (Johnson and Toettcher, 2019). Recent studies using live cell biosensors indicate that Erk can display a wide variety of dynamic signaling patterns that fluctuate on minute timescales. Depending on the cellular context, Erk activation can be transient or sustained (Santos et al., 2007), pulsatile (Albeck et al., 2013), oscillating (Shankaran et al., 2009), and even display propagating waves across cell collectives (Aoki et al., 2017). As one example that is relevant to developmental biology, pulsatile Erk activity regulates *C. elegans* vulval precursor cell fate specification (de la Cova et al., 2017). In this model, cells that will adopt different fates exhibit different frequencies of Erk activity pulses of fixed amplitude. The Erk pulse frequency is in part regulated by the cell's location with respect to a point source of EGF, suggesting a mechanism by which a morphogen gradient is interpreted. Using Erk biosensors, it will

be therefore important to systematically explore whether distinct, more subtle, dynamic Erk activity patterns occur at different locations within the embryo. With the help of a growing list of biosensors that can be adapted to be spectrally compatible with optogenetic actuators (Regot et al., 2014), one can envision how the production of dynamic Erk signaling output maps in response to precisely timed optogenetic inputs. Previous studies have shown that this is a powerful approach to map the signaling network structure that encodes dynamic Erk signaling states (Ryu et al., 2015). Together, signaling biosensors and optogenetic approaches have the potential to map how dynamic Erk signaling states are encoded by signaling networks and then subsequently decoded into transcriptional states that control different fates at specific embryo locations.

To summarize, this study highlights how signaling optogenetics, by allowing acute perturbation of cellular processes with unprecedented spatiotemporal resolution and by bypassing feedback inhibition due to long-term genetic perturbations, can provide novel insights that will complement traditional genetic approaches. The quantitative nature of such methodologies, combined with mathematical modeling, will provide new insights to precisely decipher the whole information flow from receptor to transcriptional program during developmental fate specification.

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Vitamin E Function in Stress Sensing and Signaling in Plants

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Vitamin E is involved in heat stress acclimation. In this issue of *Developmental Cell*, Fang et al. (2018) uncover a new link between Vitamin E and plant retrograde signaling and show that vitamin E is required for the accumulation of 3′-phosphoadenosine 5′-phosphate, an inhibitor of exoribonucleases, to protect microRNAs from degradation.

The advent of oxygenic photosynthesis by cyanobacteria ca. 2.4 billion years ago was one of the major evolutionary triggers for the establishment of the complex life forms now existing on Earth (Harel et al., 2015). A great diversification of multicellular complex life forms occurred with aerobic life, and all eukaryotes took advantage of aerobic metabolism to evolve sophisticated cellular signaling mechanisms, including retrograde signaling in plants. Retrograde signals from chloroplasts to the nucleus can be divided into two classes: those related to chloroplast biogenesis and the formation of the photosynthetic apparatus (biogenic control) and those related to the operation of the chloroplast in the plant response to environmental stimuli (operational control). Vitamin E, and most particularly α-tocopherol, evolved alongside oxygenic photosynthesis as a potent antioxidant exclusively synthesized in cyanobacteria and consequently present in chloroplasts of all other photosynthetic organisms. α-Tocopherol, which is produced from homogentisate and phytyl diphosphate (Figure 1A), can eliminate reactive oxygen species (ROS), as well as inhibit the propagation of lipid