The developmental genetics of space and time: Developmental genes often take inputs from two independent sources

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(Phys.org) —Albert Erives, associate professor in the University of Iowa Department of Biology, and his graduate student, Justin Crocker, currently a postdoctoral researcher at the Howard Hughes Medical Institute (HHMI) Janelia Farm Research Campus, have conducted a study that reveals important and useful insights into how and why developmental genes often take inputs from two independent "morphogen concentration gradients."

The study appears in the Genomes & Developmental Control section of the online June 1 issue of the journal *Developmental Biology*.

Understanding the concept of morphogen gradients—the mechanism by which a signal from one part of a developing embryo can influence the location and other variables of surrounding cells—is important to developmental biology, gene regulation, evolution, and human health.

Morphogen gradients subdivide a field of cells into territories characterized by distinct cell fate potentials and allow cells to "know" their position within a developing embryonic tissue and to differentiate appropriately. In order to function, such systems require a genetic mechanism to encode a spectrum of responses at different target genes.

This genetic mechanism takes the form of transcriptional enhancers, which are DNA sequences that display a cryptic code of transcription

factor (TF) binding sites. During development and/or environmental perturbation, these enhancers serve as assembly scaffolds for TF protein complexes that orchestrate differential gene expression.

However, enhancers targeted by morphogen signaling may drive temporally inappropriate expression because morphogen gradients also provide temporal cues. That is, the morphogenic gradient builds up and decays over a specific window of developmental time.

Using the powerful *Drosophila* (fruit fly) genetic system, which includes diverse species with fully sequenced genomes, the Erives Lab identified a case of spatial and temporal conflict in the regulation of the ventral neurons defective (vnd) gene, which must be precisely regulated in order for the fly's nervous system to be properly specified. The vnd gene is induced by a concentration gradient of a key embryonic factor (dorsal/NFkB) that patterns the dorsal/ventral (D/V) axis of the embryo. In particular, the vnd gene plays a critical role in specifying distinct D/V neural columnar fates of the ectodermal compartments by encoding a repressor of additional regulators.

The role of vnd in this regulatory hierarchy requires early temporal expression, which is characteristic of low-threshold responses, but its specification of ventral neurogenic ectoderm demands a relatively high-threshold response to the morphogen.

The study shows that the vnd gene's Neurogenic Ectoderm Enhancer (NEE) takes additional input from a complementary gradient of the Dpp morphogen via a highly-conserved Schnurri/Mad/Medea silencer element (SSE), which is integral to its NEE module. In this regard, the NEE at vnd is unlike NEEs at other genetic loci, which are not involved in the neural specification circuit and have no resident SSE. They also show that an SSE could be added to a single-input NEE and cause spatial restriction of its activity. These results show how requirements for

conflicting temporal and spatial responses to one morphogen gradient can be solved by additional inputs from complementary morphogen gradients.

The Erives Lab at the UI's Department of Biology studies the structure, function, and evolution of enhancers within the context of gene regulatory circuits underlying the evolution and development of animals by using molecular, genetic, and evolutionary genomic approaches. Within these areas, the Erives Lab has published several landmark papers notable for demonstrating how whole genome sequences can be used to accelerate biological research on outstanding questions in biology.

More information: The complete paper can be found at: http://www.sciencedirect.com/science/article/pii/S0012160613001310.

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