Orchestrating development in the fly embryo

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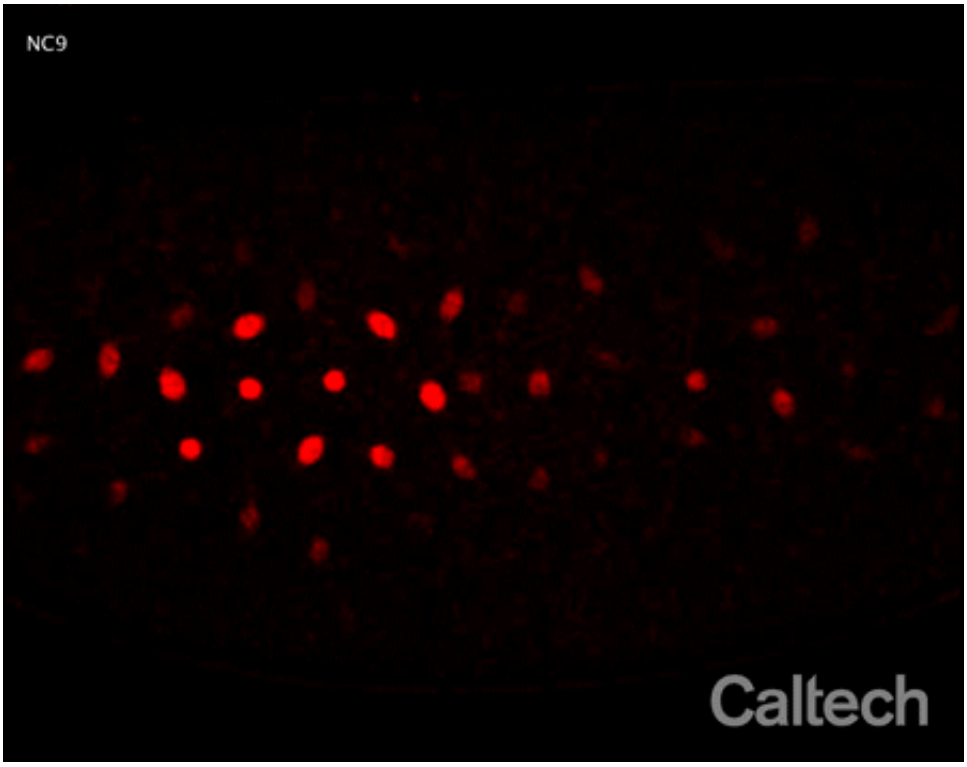

A movie of gene expression dynamics live in the developing Drosophila embryo. Individual nuclei are shown in red, while certain gene transcripts are shown in blue. Credit: Caltech

Most multicellular organisms on Earth—including you—begin as a single fertilized egg and then undergo a complex choreography of cellular growth to become a functioning adult composed of countless cells. Understanding this process is a major goal in the field of developmental biology. Now, using the fruit fly Drosophila melanogaster

as a model system, a new study illustrates how two proteins act like conductors, giving cues during the very earliest stages of a fruit fly's development.

The work was done in the laboratory of Angelike Stathopoulos, professor of biology, and appeared in a paper in the journal *Cell Reports* on July 23.

Though they may seem very different from humans, fruit flies are often used as a model organism to understand the basic biology that underlies our development. A large part of the Stathopoulos lab's research focuses on answering the question: How does an embryonic fruit fly's cells make decisions about which genes to express at the right times in order to develop into the right body parts?

The key to the processes of cellular differentiation—the ability of cells to develop specialized functions at specific locations—involves the regulation of gene expression. Though every cell in a fly has the same copy of the fly's genome, individual cells express genes differently over time. As an analogy, one can think of a symphony: all of the musicians in an orchestra receive the same, complete score, but each musician only plays their own part.

At the earliest stages of Drosophila development, the embryo is shaped like an American football. Some of the 5,000 cells that make up the embryo, localized together within a stripe aligned lengthwise down the middle of the football shape (where the stitches would be on the ball), are destined to make specific types of cells, such as neurons. To support this differentiation, the cells in the stripe make decisions to express particular genes that are not made by the cells localized outside this domain. This spatial difference in gene expression is a key part of maintaining the stripe pattern.

The differences in cellular gene expression are made possible by proteins called activators (which increase expression of genes) and repressors (which decrease expression of genes). The most commonly studied repressors are spatially localized, meaning they are confined to cells in specific locations. However, Stathopoulos and postdoctoral scholar Theodora Koromila aimed to study two repressors, called Runt and Suppressor of Hairless [Su(H)], that are broadly expressed, meaning that they are found in cells throughout the whole embryo.

"Initially, we had assumed that broadly expressed repressors would have consistent activities throughout development, but it was a surprise to find that they play temporally distinct roles in regulating gene expression. They even switch behavior in time, from repressor to activator, which tells us that these proteins have complex functions," says Koromila.

The team found that Runt actually orchestrates the timing of gene expression in the embryo. Like an orchestral conductor might hold up a hand to ensure that an instrumental section does not come in too early, the Runt repressors suppress certain gene expression until the time is right in embryonic development. Su(H), on the other hand, controls the levels of gene expression, similar to a conductor gesturing for a section to play louder or softer.

For this research, Koromila used a live imaging technique in which she made movies of the Drosophila embryo as it developed in real time to study where and when the repressors were acting. Then, in further experiments, Koromila genetically mutated DNA sequences to eliminate input by the Runt and Hairless proteins to examine live how the embryo's development was consequently affected. Previous work in this field had focused only on small sections of the fly embryo, but Koromila's imaging approach allowed her to examine the entire embryo at once.

"Embryos develop quickly, and gene expression is dynamic. Therefore, it is important to understand how development proceeds over time. In the past, we've taken a static view, focusing on fixed embryos, but now we have the exciting capability to look at development live by taking movies. This allows us to uncover new insights, including how transcription factors work over time," says Stathopoulos. "More than half of the genes in a fruit fly also work in humans, so understanding how a simple fruit fly develops is very relevant to us."

The paper is titled, "Distinct roles of broadly-expressed repressors support dynamic enhancer action and change in time."

More information: Theodora Koromila et al. Distinct Roles of Broadly Expressed Repressors Support Dynamic Enhancer Action and Change in Time, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.06.063

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