Embryonic patterning system reveals cell coordination to create astonishingly precise patterns

May 14 2018, by Lori Dajose

A cell turns blue as it emits chemical signals that diffuse throughout its environment. When nearby cells receive the signal, they turn yellow. This movie illustrates the process by which cells talk to each other and make decisions about how to develop. Credit: P. Li / Elowitz laboratory

As an embryo develops from a little glob of primitive cells, it patterns itself into precise, spatially organized regions and tissues. This requires that individual cells coordinate with one another over long distances by releasing and detecting specialized signaling molecules. How can cells, communicating only in this indirect manner, create such precise patterns?

Caltech researchers have developed a way to recreate in a Petri dish the kind of cell-to-cell communication process that underlies tissue patterning in an embryo. By doing this, they have established a simpler and more accessible way to observe and manipulate this fundamental process. Using this method, the researchers focused on a communication system called the Hedgehog signaling pathway, which establishes spatially organized structures in diverse tissues and organs. They discovered that the pathway possesses a sophisticated molecular circuit architecture that helps ensure precise patterning.

The work was done in the laboratory of Michael Elowitz, professor of biology and bioengineering, Howard Hughes Medical Institute Investigator, and executive officer for biological engineering. The research is described in a paper appearing in the May 4 issue of the journal *Science*.

The Hedgehog pathway is vital for proper development of the central nervous system, limbs, and many other organs and tissues. Defects in Hedgehog-related genes lead to developmental diseases. Understanding how the Hedgehog pathway precisely organizes cells in space would enable researchers to predict the pathway's behavior and thus its response to drugs. Additionally, the new technique of engineering self-patterning cells in the lab could help open up novel ways to engineer spatially complex tissues for use in regenerative medicine.

Within an embryo, certain cells ("senders") broadcast information by releasing molecules, called morphogens, that diffuse through the intercellular environment and reach surrounding cells ("receivers"). Receivers closer to the senders pick up more morphogens than cells further away. Cells use these quantitative differences to figure out where they are and what cell types they should become. How such a seemingly precarious mechanism produces perfectly patterned embryos over and over again has been a long-standing puzzle.

Instead of dealing with a complex embryo—in which many processes occur simultaneously and it is difficult to observe and perturb specific genes—the researchers created a tissue-like layer of cells in a Petri dish. They started with mouse fibroblast cells; fibroblasts are responsible for forming the framework of animal tissue structures. These cells are "blank slates" in the sense that they do not form tissue patterns on their own. The team then synthetically engineered the fibroblasts to produce and respond to the morphogen Sonic Hedgehog, which cells use to estimate their position in a developing tissue.

Upon sensing Sonic Hedgehog, each cell initiates a set of signal relays that modifies its own gene expression. The team had genetically altered the cells to glow blue when sending a Sonic Hedgehog signal, or to glow yellow when receiving a signal. In this way, they could watch messages flow in real time from cell to cell.

Importantly, this new system allowed the researchers to effectively rewire the pathway, playing with its architecture to help them understand what features enabled the system to generate highly precise spatial patterns. By tinkering genetically with the pathway and then using microscope movies to observe how the cells behaved, the researchers discovered that the Hedgehog pathway has an unusual molecular architecture that ensures the accuracy of cell-to-cell communication.

"In biology, we're much better at ripping systems apart than putting them together," says the study's first author, postdoctoral scholar Pulin Li. "So, reconstructing a multicellular patterning system outside of an embryo can reveal principles that would be very hard to discover in conventional ways."

"Here we learned that certain features of the Hedgehog system—once thought to be inscrutable and even counterintuitive—actually work together in a beautiful way to ensure precise patterning," says Elowitz. "This is really just the beginning. With this system in place, we can now imagine programming cells to generate even more complex patterning behaviors to enable the design of tissues, which is a major goal of synthetic biology."

The paper is titled "Morphogen gradient reconstitution reveals Hedgehog pathway design principles."

More information: Pulin Li et al. Morphogen gradient reconstitution reveals Hedgehog pathway design principles, *Science* (2018). DOI: 10.1126/science.aao0645

Provided by California Institute of Technology