From pre-gut cells to glory

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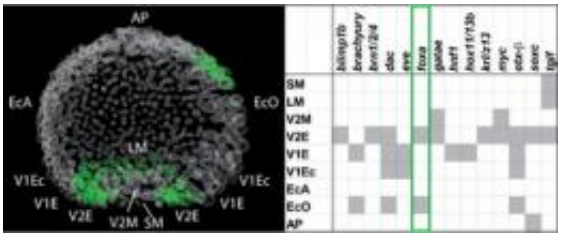

Left: A gut-specific gene (foxa) is expressed long before a gut is present in cells (V2E) destined to form parts of the gut. Right: A diagram describing where the regulators of gut formation are expressed (grey) or not expressed (white) in different domains of the sea-urchin embryo. Credit: Emmanuel Faure/Caltech

For all animals, development begins with the embryo. It is here that uniform cells divide and diversify, and blueprints are laid for future structures, like skeletal and digestive systems. Although biologists have known for some time that signaling processes—messages that tell a cell to express certain genes so as to become certain parts of these structures—exist at this stage, there has not been a clear framework explanation of how it all comes together.

Now, a research team at the California Institute of Technology (Caltech) has outlined exactly how specific sets of cells in sea-urchin embryos differentiate to become the endoderm, the early domain of the embryo that eventually forms the gut. Their findings were reported in a paper entitled "A gene regulatory network controlling the embryonic specification of endoderm," published by the journal *Nature* online on

May 29, in advance of the print version.

"If you only look at the genetic information of cells in an embryo, they all have the same genome and they all start from the single-cell zygote," says Isabelle S. Peter, a senior postdoctoral scholar at Caltech and coauthor of the study. "But then cells start to divide and, at some point, these cells are no longer identical in the genes that they express. We wanted to know how this process is achieved—how differences are established in cells in the right place and at the right time."

In order for undifferentiated cells to change their state and become a specific part of the body, the right genes need to be expressed, and the wrong ones repressed. The most important genes are regulatory genes, which control the expression of other genes, and form a gene regulatory network (GRN) that doles out differentiation instructions by turning genes on or off at specific times during embryonic development.

In the work described in the Nature paper, Peter and Eric H. Davidson, the Norman Chandler Professor of Cell Biology at Caltech and the other coauthor on the study, were able to analyze systematically the specification process controlled by the GRN and map out a master plan that, for the first time, shows the relationships between all the regulatory genes in specific parts of the embryo.

They studied sea-urchin embryos over a 24-hour period, beginning at hour eight of the embryo's existence. During this period, different physical domains exist in the embryo, each of which represents a future structure in the body, like the gut. All the regulatory genes known to exist in the sea-urchin genome and to be expressed in the embryo have been studied, and it was found that certain regulatory genes are expressed in the cells of each domain. Some of the domains will express certain regulatory genes in common, but the combination of genes found in each domain is unique. In addition, they found that this process is

dynamic—where the genes are expressed changes over time. For example, two genes that are coexpressed in one domain at an early stage of the process may then be expressed in different domains at a later stage.

"It's like you are building a complicated edifice," explains Davidson. "And before anything is actually there, the building instructions have already been handed to all the workers. They all know what they are going to have to do once the bulldozer comes in and starts moving earth around."

The team focused on pinning down the precise regulatory genes in the progression of pre-gut cells (which eventually form the gut), following them from their initial stage as undifferentiated cells, to the point of gastrulation. During gastrulation the endoderm cells reorganize from a single layer into an internal tube with three regions that serve as the foundation for the future foregut, midgut, and hindgut structures. The researchers were able to pinpoint which regulatory genes were expressed at which specific times in the 24-hour period, and how those genes interacted over time to turn each other on and off.

"The instructions for development have to be in the genome somewhere, but you would be surprised how fragmentary the information about how that works was until we did this system-level analysis," says Davidson. "You can never understand it by looking at one gene. You can never understand it by looking at a third of the genes. You really have to get the whole system mapped out—and that's what we did."

In 2008, Davidson—who has been studying the biological processes of sea urchins for many years—led a research team that sketched a rough outline, for the first time, of how the GRN works to produce the sea urchin's skeletal system. "We are light-years beyond that with this new study," he says. "That was about solving network subcircuits, but now we

have a framework that causally explains the far more complex process of development required for gut formation in terms of the genome's regulatory instruction code." This advance opens a much larger range of developmental scenarios to causal network analysis.

Sea urchins' gene regulatory systems, Davidson points out, are the closest—among the thoroughly studied invertebrate systems—to those of mammals, in terms of evolutionary relationships. This means the mechanisms the team uncovered in their work are likely to illuminate our own developmental regulatory systems. This could have implications for human health.

"If you believe that medicine consists of putting Band-Aids on things, then we have no relevance to that," says Davidson. "But if you believe that we should understand how life works before trying to find a cure when something goes wrong, then understanding biological processes from their initial stages comes first."

The team would next like to take their framework analysis and apply it to later stages in development—to when the gut is actually present. "We would like to understand how the different compartments in the gut are established, which would also make the work more directly informative to the development of the human gut," says Peter.

They would also like to extend the analysis to as much of the sea-urchin embryo as they can, says Davidson, as well as to formalize their findings to make an abstract computer model of how the gene regulatory system works. This will allow them to validate this particular network and to eventually do experiments that involve manipulating the cells to produce different results.

"Basically everything that happens in us, or in any animal during development, is encoded in genomic regulatory instructions," says

Davidson. "Now we have an explanation as to how that works, which is very exciting. We can only move forward from here."

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