Genetic traffic signal orchestrates early embryonic development

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You are the product of metamorphosis. During the third week of your embryonic existence, fateful genetic choices were made that began to transform a tiny ball of identical stem cells into a complex organism of flesh and blood, bone and sinew, brain and heart and gut and lung. But what directed this remarkable developmental choreography?

New research by UC San Francisco stem cell biologists has revealed that a DNA-binding protein called Foxd3 acts like a genetic traffic signal, holding that ball of undifferentiated cells in a state of readiness for its great transformation in the third week of development.

"This protein's ability to get complex gene programs poised and ready to go at a moment's notice adds an important new layer to our fundamental understanding of how development works," said study senior author Robert Blelloch, MD, PhD, professor and vice chair for basic research in UCSF's Department of Urology and a member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF.

In addition, defects in Foxd3 and related proteins are very likely to play key roles in developmental and adult diseases, Blelloch said: "Too little activity could cause tissues not to develop properly, while too much could be associated with tissue overgrowth, as seen in cancer."

The new discovery, published online Jan. 7, 2016, in the journal *Cell Stem Cell*, is part of an ongoing revolution in geneticists' understanding of the importance of gene enhancers. These tiny pieces of DNA play a key role in coordinating the genetic programs that determine a cell's role within the body, such as what makes a neuron different from a kidney cell or muscle cell.

"We all start as a single fertilized egg and become these unbelievably complex creatures with trillions of cells that all play different roles in the body, despite the fact that each cell has the same DNA," Blelloch said. "One of the big questions is: How does it happen so fast? It takes us years to build a building, and that's not nearly as complex as the human body."

Only in the past few years have researchers realized that more than a million of these tiny regulatory elements make up nearly 10 percent of the human genome - in contrast to our 25,000 or so genes, which only comprise about 2 percent of our DNA. Researchers such as Blelloch suspect that our enhancers are what truly make us human: Although we share most of our genes with other mammals, our enhancers provide a unique blueprint for how to use these common genes to construct a human and not some other creature.

"You switch our enhancers around and you could convert you or me to a mouse pretty easily," Blelloch said.

Transcription factor Foxd3 poises stem cells for crucial transformation

In the new study, Blelloch's team studied embryonic stem cells in a dish to model a crucial early stage of development. They employed recently-developed genetic tools that use fluorescent markers to track the cells' transformation from undifferentiated stem cells into more specialized epiblast cells. Using these tools, they sought to identify which enhancers and transcription factors - proteins that bind to DNA and coordinate how it gets transcribed and translated - were involved in orchestrating this crucial transition.

They found that the Foxd3 transcription factor regulates the timing of this transition by pulling gene transcription in two opposing directions. On the one hand, Foxd3 primes DNA enhancers by rolling back the chromatin scaffolding that had kept them dormant. But at the same time the transcription factor holds the genetic programs in stasis, preventing them from becoming fully activated until just the right moment. This is the first time anyone has seen a transcription factor play these two roles at once, Blelloch says, simultaneously priming and repressing enhancer activity through epigenetic tagging of the histone molecules that package DNA.

This push-pull mechanism for priming enhancers' gene programs could prove to be a fundamental trick employed by cells at many stages of development to coordinate the precisely timed sequence of gene activation that is crucial to the awesome task of building a human body.

"These are cells that have to make everything and have to make it fast," Blelloch said. "In just a few days they go from this undifferentiated mass to an organized embryo with different germ layers and the beginnings of a neural tube. Every cell has to transform in a coordinated way or it all becomes a confused mess. The only way to do that is to have everything poised. Everything has to be set up and organized and ready to go."

Blelloch and his team are currently searching for additional transcription factors that perform this role at other stages of development, and exploring potential clinical connections to human development and disease.