Researchers Discover Key to Human Embryonic Stem-Cell Potential

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What exactly makes a stem cell a stem cell? The question may seem simplistic, but while we know a great deal of what stem cells can do, we don't yet understand the molecular processes that afford them such unique attributes.

Now, researchers at Whitehead Institute for Biomedical Research working with human embryonic stem cells have uncovered the process responsible for the single-most tantalizing characteristic of these cells: their ability to become just about any type of cell in the body, a trait known as pluripotency.

"This is precisely what makes these stem cells so interesting from a therapeutic perspective," says Whitehead Member Richard Young, senior author on the paper which will be published September 8 in the early online edition of the journal Cell.

"They are wired so they can become almost any part of the body. We've uncovered a key part of the wiring diagram for these cells and can now see how this is accomplished."

Once an embryo is a few days old, the stem cells start to differentiate into particular tissue types, and pluripotency is forever lost. But if stem cells are extracted, researches can keep them in this pluripotent state indefinitely, preserving them as a kind of cellular blank slate.

The therapeutic goal then is to take these blank slates and coax them

into, say, liver or brain tissue. But in order to guide them out of pluripotency with efficiency, we need to know what keeps them there to begin with.

Researchers in the Whitehead laboratories of Young, Rudolf Jaenisch, MIT-computer scientist David Gifford, and the Harvard lab of Douglas Melton focused on three proteins known to be essential for stem cells.

These proteins, Oct4, Sox2, and Nanog, are called "transcription factors," proteins whose job is to regulate gene expression. (Transcription factors are really the genome's primary movers, overseeing, coordinating, and controlling all gene activity.)

These proteins were known to play essential roles in maintaining stem cell identity—if they are disabled, the stem cell immediately begins to differentiate and is thus no longer a stem cell.

"But we did not know how these proteins instructed stem cells to be pluripotent," says Laurie Boyer, first author on the paper and a postdoctoral scientist who divides her time between the Jaenisch and Young labs.

Using a microarray technology invented in the Young lab, Boyer and her colleagues analyzed the entire genome of a human embryonic stem cell and identified the genes regulated by these three transcription factors. The research team discovered that while these transcription factors activate certain genes essential for cell growth, they also repress a key set of genes needed for an embryo to develop.

This key set of repressed genes produce additional transcription factors that are responsible for activating entire networks of genes necessary for generating many different specialized cells and tissues. Thus, Oct4, Sox2, and Nanog are master regulators, silencing genes that are waiting

to create the next generation of cells.

When Oct4, Sox2, and Nanog are inactivated as the embryo begins to develop, these networks then come to life, and the stem cell ceases to be a stem cell.

The new work provides the first wiring diagram of human embryonic stem-cell regulatory circuitry. "This gives us a framework to further understand how human development is regulated," says Boyer.

"These findings provide the foundation for learning how to modify the circuitry of embryonic stem cells to repair damaged or diseased cells or to make cells for regenerative medicine," says Young. "They also establish the foundation for solving circuitry for all human cells."

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