Putting microRNAs on the stem cell map

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Embryonic stem cells are always facing a choice—either to self-renew or begin morphing into another type of cell altogether. It's a tricky choice, governed by complex gene regulatory circuitry driven by a handful of key regulators known as "master transcription factors," proteins that switch gene expression on or off.

In the past few years, scientists in the lab of Whitehead Member Richard Young and their colleagues have mapped out key parts of this regulatory circuitry, but the genes that produce the tiny snippets of RNA known as microRNAs have until now been a missing piece of the map. Since microRNAs are a second set of regulators that help to instruct stem cells whether to stay in that state, they play key roles in development.

Young and colleagues have now discovered how microRNAs fit into the map of embryonic stem cell circuitry. With this map, the scientists have moved one step closer to understanding how adult cells can be reprogrammed to an embryonic state and then to other types of cells, and to understanding the role of microRNAs in cancer and other diseases.

"By understanding how master transcription factors turn microRNAs on and off, we now see how these two groups of gene regulators work together to control the state of the cell," says Young, senior author on the study reported in the August 8 issue of *Cell*. "MicroRNAs are a special class of molecules because they not only contribute to cellular control but they play important roles in disease states such as cancer."

Previous studies had shown that the microRNA machinery is important

in maintaining embryonic stem cells in their embryonic state, but offered only partial views of how microRNA genes fit in with the overall gene regulation circuitry. To do so required mapping the sites in the genome from which microRNA genes start, explains Stuart Levine, co-lead author on the paper and postdoctoral scientist in Young's lab.

"Knowing where genes start is essential to understanding their control," says Levine. "Based on our knowledge of microRNA gene start sites we were able to discover how these genes are controlled by the master transcription factors."

The researchers first created genome-wide maps of human and mouse embryonic stem cells that pinpoint where transcription factors bind to DNA and launch gene expression. This pinpointed where four master transcription factors (known as Oct4, Sox2, Nanog and Tcf3) were occupying sites where microRNA genes start to be transcribed. They found that the four core transcription factors are interacting with two key sets of microRNA genes. One set of microRNA genes is actively expressed in embryonic stem cells. The other set is silenced in those cells by other gene regulatory proteins known as Polycomb proteins. These proteins repress genes that are key for later development, a role previously described by Young lab researchers and their colleagues.

"We now have a list of what microRNAs are important in embryonic stem cells," says Alex Marson, co-lead author on the paper and an MD/PhD student in the Young lab. "This gives us clues of which microRNAs you might want to target to direct an embryonic stem cell into another type of cell. For example, you might be able to harness a microRNA to help drive an embryonic stem cell to become a neuron, aiding with neurodegenerative disease or spinal cord injury."

Moreover, the results give scientists a better platform for analyzing microRNA gene expression in cancer and other diseases. "We and others

are finding that the overall gene circuitry for embryonic stem cells and cancer cells is very similar," notes Marson. "Now that we have connected the circuitry to microRNAs, we can begin to compare microRNAs that are regulated in embryonic stem cells to those in cancer cells."

Source: Whitehead Institute for Biomedical Research