Scientists identify protein that keeps stem cells poised for action

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(PhysOrg.com) -- Like a child awaiting the arrival of Christmas, embryonic stem cells exist in a state of permanent anticipation. They must balance the ability to quickly become more specialized cell types with the cellular chaos that could occur should they act too early (stop shaking those presents, kids!). Researchers at the Stanford University School of Medicine have now identified a critical component, called Jarid2, of this delicate balancing act — one that both recruits other regulatory proteins to genes important in differentiation and also modulates their activity to keep them in a state of ongoing readiness.

"Understanding how only the relevant genes are targeted and remain poised for action is a hot topic in embryonic stem cell research," said Joanna Wysocka, PhD, assistant professor of developmental biology and of chemical and systems biology. "Our results shed light on both these questions." Wysocka is the lead author of the research, which will be published in the Dec. 24 issue of *Cell*.

Jarid2 works through a protein complex called PRC2, for Polycomb Repressive Complex 2. PRCs keep genes quiet by modifying DNA packaging proteins called histones. It's not quite tying a string around a brown paper package, but the concept is similar: Wrapping DNA up neatly around the histones helps it all fit in the tiny space and keeps it out of commission until the appropriate time. That's because, when wrapped, genes can't be converted into proteins to do the work of the cell. PRC2 adds a molecular "Do not open until Christmas" tag to ensure the DNA stays wrapped until it's needed.

PRC2 is necessary to regulate the expression of developmentally important genes in many types of cells. But Wysocka and her colleagues wanted to know specifically how it worked in embryonic stem cells. When they looked in mouse embryonic stem cells, they found that nearly all PRC2 is bound to a protein called Jarid2, which is more prevalent in embryonic stem cells than in non-stem cells.

Jarid2 had been previously identified as a protein important during development. But its role in embryonic stem cells hadn't yet been addressed. The Stanford researchers found that together PRC2 and Jarid2 occupied specific stretches of histone-bound DNA in both mouse and human embryonic stem cells. When they reduced the amount of Jarid2 in the cells, PRC2 was less able to bind the DNA and the cell began to churn out the proteins before they were needed — confirming Jarid2's importance in stem cell differentiation.

Surprisingly, though, the degree of modifications on the histones remained about the same, even though less PRC2 was bound to the DNA. This suggested that when PRC2 is bound to Jarid2, it puts fewer "don't open" tags on the histones.

"This was a crucial finding," said Wysocka, "because it shows that Jarid2 both recruits PRC2 to the DNA and modulates its ability to modify the histones." It also suggests that the Jarid2/PRC2 complex inhibits gene expression in other, as-yet-unidentified ways. Such fine-tuning of PRC2 activity, the researchers believe, allows the cell to carefully manage its degree of readiness for the subsequent unwrapping and expression of genes involved in differentiation of the embryonic stem cells into more specialized cells.

The researchers confirmed their findings in frog embryos, which are more easily studied at early stages of differentiation than are mouse embryos, by depleting Jarid2 expression. They found that embryos

missing Jarid2 were unable to complete a critically important developmental step called gastrulation.

"It was just as we would have predicted," said Wysocka. "Without Jarid2, which keeps the genes silent yet poised for activation, the embryos stop developing." The researchers now plan to further investigate the mechanism by which Jarid2 summons PRC2 to differentiation-specific genes in the stem cells, and how it affects gene expression. The interaction may be important in human cancers as well. "PRC2 is upregulated in some cancers," noted Wysocka, "which may help keep these cells in an undifferentiated, rapidly proliferating state. It will be interesting to see whether Jarid2 is also expressed at high levels in these diseases. There are all sorts of implications for stem cell biology, differentiation and human disease."

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