WHITEHEAD INSTITUTE

CUEING UP AT THE MEIOTIC STARTING LINE

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CAMBRIDGE, Mass. — Meiosis, the process of halving a germ cell's chromosomes in preparation for egg or sperm production, has been one of the most studied areas of cell biology. But in mammals, the field has been divided over the question of whether meiosis is triggered by a signal within a cell or by a signal coming from the cell's environment.

Now new research from the lab of Whitehead Director David Page reveals that both sets of signals are needed to initiate meiosis.

In 2006, the Page lab showed that an external signal of retinoic acid (RA), a derivative of vitamin A, starts the expression of the *Stra8* gene, which is seen at the very beginning of meiosis. While this research seemed to settle the controversy, researchers still had to deal with the reality that RA has signaling functions throughout the body at various points of development. How could such a nonspecific signal have such a specific effect on meiosis in embryonic germ cells? As it turns out, other researchers in Page's lab were grappling with that very issue.

Coincidentally, more than 10 years before the work on RA, Page's lab had been studying the effects of a few genes on human male fertility, noting at the time that one such gene, known as *Dazl*, codes for a germ cell-specific protein that binds to RNA. But at the time, no one knew that the *Dazl* gene is an integral part of the RA signaling pathway in embryonic germ cells.

"*Dazl* is in both the mouse and human genomes, but it has counterparts that are critical in germ cell biology throughout the entire animal kingdom," says Page.

To see how the *Dazl* gene affects germ cells' response to RA signaling, Page graduate students Yanfeng Lin and Mark Gill compared the embryonic ovaries of control mice to those of mice lacking the DAZL protein. They stained the ovaries for *Stra8* expression, a clear indicator of meiotic initiation. The ovaries without the DAZL protein failed to express *Stra8* and thus did not enter meiosis. Control mice, however, which had the DAZL protein, clearly expressed *Stra8* and became meiotic.

Gill explains that the *Dazl* gene and its protein prepare the cell to respond to RA. "We've uncovered a transition state in development in which the cells are primed for meiosis," says Gill. "This research further explains the specificity of the retinoic acid signaling pathway that had been previously described."

Although part of the meiosis initiation mystery has been elucidated, Page concedes this is only the beginning. "There's a lot of black box here, like what is going on in the cell during this transitional state. We're addressing that as well, which is why this is a very exciting time in this field."

Written by Nicole Giese Rura.

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David Page's primary affiliation is with Whitehead Institute for Biomedical Research, where his laboratory is located and all his research is conducted. He is also a Howard Hughes Medical Institute investigator and a professor of biology at Massachusetts Institute of Technology.

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"Germ-cell-intrinsic and extrinsic factors govern meiotic initiation in mouse embryos"

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