Chaos in the cell's command center

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A defective operating system is never a good thing. Like computers, our cells depend on operating systems to drive normal functions. Gene expression programs comprise the software code our cells rely on, with each cell type controlled by its own program. Corrupted programs can trigger disease.

Cellular operating systems can be corrupted by viruses, mutations, or malfunctions that occur as cells change from one type to another. Unlike computers that can use one operating system for their entire existence, differentiating cells need to switch operating systems as they mature -- from stem cell to, for example, nerve or muscle cell. In simple terms, differentiation requires two key steps: the genes active in the initial operating system must be deactivated; and the genes of the new cellular operating system must be turned on. If the switch is not flawless, a transitioning cell may die or be driven by a disease-causing program.

New research from Whitehead Institute scientists reveals the critical role one enzyme, lysine-specific demethylase 1 (LSD1), plays as embryonic stem cells differentiate into other cell types. Their research is published online this week in the journal *Nature*.

LSD1 was known to be critical to development, but little was known about the key role it plays during differentiation, when operating systems are switched.

"We knew that cells express a new set of genes when the operating switch occurs," says Steve Bilodeau, one of the *Nature* paper's authors

and a postdoctoral researcher in the lab of Whitehead Member Richard Young. "But this study shows it is also essential to shut off genes that were active in the prior cell state. If you don't, the new cell is corrupted."

By investigating gene silencing during cell state transitions, Bilodeau and Warren Whyte, a Young lab graduate student and co-author of the *Nature* paper, redefined LSD1's role and described a previously unknown mechanism for silencing genes.

When they looked at the embryonic stem cell operating system genes that must be turned off during differentiation, Whyte and Bilodeau found LSD1 poised on the stem cell genes' enhancers, short bits of DNA that act as a landing pad for the proteins that enhance a gene's transcription and ultimately its protein production. When LSD1 receives the signal that the stem cell is transitioning into a more differentiated state, the enzyme pops into action and silences the ESC genes' enhancers. With their enhancers no longer operational, transcription of the stem cell genes is silenced, shutting down the stem cell operating system. As this occurs, other mechanisms switch on the cell's new operating system.

"This reveals the critical function of LSD1 in cell differentiation," says Whyte. "The enzyme decommissions the stem cell enhancers, thus allowing the new cell to function entirely within the parameters of the new operating system."

Although the work focuses on one enzyme's job in normal cells, Young sees broader implications. LSD1 is a member of a class of molecules that regulate both gene activity and chromosome structure, so the findings about LSD1 could give insight into how related regulators function. Also, knowing how a mechanism operates in normal cells provides a solid foundation for teasing apart what is going wrong in abnormal cells.

"This new knowledge brings us one important step closer to understanding defective operating systems in diseases such as cancer," says Young. "And this may give us a new angle on drug development for these diseases."

More information: "Enhancer Decommissioning by LSD1 During Differentiation of Embryonic Stem Cells" *Nature*, published online February 1, 2012

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