New study supports a stem cell origin of cancer

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Researchers at the University of Southern California (USC) recently made significant strides toward settling a decades-old debate centering on the role played by stem cells in cancer development.

According to the study's findings, which appear in an upcoming issue of *Nature Genetics* and now available online, genes that are reversibly repressed in embryonic stem cells are over-represented among genes that are permanently silenced in cancers; this link lends support to the increasingly discussed theory that cancer is rooted in small populations of stem cells.

USC researchers uncovered this link after observing that of 177 genes repressed by Polycomb group (PcG) proteins, fully 77 showed evidence of cancer-associated enzymatic modification of DNA (known as methylation). "Finding that a Polycomb target in an embryonic stem cell is 12 times more likely to become abnormally methylated in cancer is highly significant," says Peter Laird, Ph.D., one of the lead researchers and associate professor of surgery, biochemistry and molecular biology, and director of basic research for surgery at the Keck School of Medicine of USC.

Laird and his colleagues discovered that some genes repressed by Polycomb in embryonic stem cells are essentially pre-marked to become permanently silenced by DNA methylation. "This permanent silencing," Laird explains, "prevents embryonic stem cells from differentiating, and they thus become the seeds of cancer development later in life." USC

researchers made these observations in relation to breast, colorectal, lung, and ovarian cancer.

Not only does the USC study provide empirical evidence for a stem cell origin of cancer, but, according to Laird, "It also supports a very early involvement of epigenetics in cancer. We found that cancer arises in cells that have already undergone epigenetic alterations," he adds, "which points to epigenetic events preceding genetic events in cancer development." Laird notes that this theory, while relatively new, is gaining support among scientists.

Findings from the USC study also can be applied to stem cell research funded by the California Institute for Regenerative Medicine (CIRM), which was created through passage of California Proposition 71 in 2004. "One of CIRM's aims," says Laird, "is to culture and differentiate embryonic stems cells – cells that would then be placed into patients. Since our research shows that cancer is rooted in stem cells, it would be very important to screen for the epigenetic abnormalities that we uncovered, so as to prevent people from receiving potentially cancer-prone cells."

Looking ahead, Laird and his USC colleagues would next like to focus on what causes some genes to transition from temporary repression to permanent silencing. "Once we determine that," Laird explains, "we can turn to the fundamental question: How can we prevent this transition?"

Citation: Martin Widschwendter, Heidi Fiegl, Daniel Egle, Elisabeth Mueller-Holzner, Gilbert Spizzo, Christian Marth, Daniel J. Weisenberger, Mihaela Campan, Joanne Young, Ian Jacobs, Peter W. Laird, "Epigenetic Stem Cell Signature in Cancer," *Nature Genetics*, February 2007, Volume 39, Number 2.

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