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# 'Misreading' of histone code linked to human cancer

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(PhysOrg.com) -- The development of blood from stem cell to fully formed blood cell follows a genetically determined program. When it works properly, blood formation stops when it reaches maturity. But when it doesn't, genetic mutations can prevent the stop signal and cause the developing cells to turn cancerous. In research published in *Nature*, Rockefeller University scientists show for the first time that a misreading of the blood cells' histone code is responsible for acute myeloid leukemia, a rare form of the deadly blood cancer.

"We've shown that deregulation of a PHD finger, which normally acts as a reader of histone modifications, is linked to cancer in humans," says C. David Allis, senior author and head of Rockefeller's Laboratory of Chromatin Biology and Epigenetics. "We believe that further research will show the involvement of PHD fingers in other diseases."

Research by Allis and other scientists on specialized DNA-packaging proteins called histones has revealed that patterns of chemical modifications on histones alter the balance of on and off states in chromosomes, and cause genes to be switched on or off. The work has led Allis and colleagues to propose a "histone code" for gene regulation. One specific chemical change, methylation of the amino acid lysine 4 (K4) on the tail of histone H3, has been shown to activate genes.

The process of producing blood cells is regulated by the Hox-A gene cluster. When operating normally, Hox genes expand the pool of blood stem cells until the developmental program shuts them down. In

leukemia, two different chromosomes break apart and fuse together. This translocation produces an altered protein that prevents the progenitor or blood stem cells from differentiating into specialized, mature cells. Instead, they continue to divide and proliferate. Exactly how many of these fusion proteins work has remained a mystery.

To answer this question, Gang (Greg) Wang, a postdoctoral researcher in Allis's lab and a fellow of the Leukemia and Lymphoma Society, focused on the fusion protein NUP98-PHD. Comprised of bits of a nuclear pore protein (NUP98) and a PHD finger motif, NUP98-PHD has been shown clinically to be involved in the development of acute myeloid leukemia in humans. PHD fingers "read" the methylation state of histone lysines, and previous research from Allis's lab showed that some PHD finger-containing factors regulate expression of genes in the Hox cluster.

Wang cloned NUP98-PHD from human leukemia cells and inserted the fusion protein into blood-forming progenitor cells derived from the bone marrow of mice. The cultured mouse bone marrow cells divided indefinitely, as would be expected in leukemia. The researchers then transplanted these cells into normal mice and found that the mice developed acute myeloid leukemia. A control group of mice, transplanted with cells cultured with a similar protein that lacked the PHD finger, did not get sick.

The Rockefeller researchers collaborated with a structural biology group led by Dinshaw Patel at Memorial Sloan-Kettering Cancer Center to identify specifically how the PHD finger recognizes the methylated lysine 4 of histone H3.

According to Wang and Allis, the fusion protein interferes with the Hox genes' ability to regulate blood formation.

“The fusion protein perturbs the histone modification state and blocks the appropriate silencing of the HoxA9 gene cluster, preventing differentiation and maintaining the stem cell properties of the bone marrow progenitor cells,” says Wang.

There are more than 200 PHD fingers in human cells, and now that a link between a PHD finger and histone modifications has been established, Allis thinks this could lead researchers to identify misregulation of PHD fingers in other diseases. With respect to acute myeloid leukemia, this finding could lead to new ways to treat the blood disorder.

“Greg’s finding may open up therapeutic strategies where you could reverse the PHD finger’s effect by targeting the reader with a drug,” says Allis.

More information: *Nature* online: May 10, 2009, Haematopoietic malignancies caused by dysregulation of a chromatin-binding PHD finger; Gang G. Wang, Jikui Song, Zhanxin Wang, Holger L. Dormann, Fabio Casadio, Haitao Li, Jun-Li Luo, Dinshaw J. Patel and C. David Allis

Provided by Rockefeller University (news : web)