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Research explains mechanism at work in tumor

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These new details on a tumor suppressor, called UTX, show that it acts on histones—the protein clothespins that keep DNA strands coiled neatly and quietly within the nucleus of cells. The Stanford team, led by Howard Chang, MD, PhD, associate professor of dermatology, found that UTX rubs off chemical marks on certain histones that allow genes to activate and tell cells not to divide.

Unfortunately, cell proliferation is unwanted in cancers, and many instances are associated with mutations in UTX.

“UTX influences hundreds of genes, and some of these are the best-known tumor suppressors,” said Chang, a member of Stanford’s Cancer Center and an early career scientist for the Howard Hughes Medical Institute. In many instances, he said, “it’s what controls the decision of a cell to divide.”

UTX plucks off methyl groups at key control points for genes; that molecular action slams the brakes on cell division. A gene that prevents cancers from growing is called a tumor suppressor, by definition. And

UTX is one that controls other tumor suppressors. Its importance is hinted at by the fact that it is present in the most primitive worm, through the mammalian line, to people.

Chang, the senior author of the research published online Feb. 1 in Genes and Development, had collaborated with Harvard researchers to discover UTX in 2007. Developmental biologists have since gathered clues about UTX, and the new study by Chang's team shows an expanded role for the protein.

The findings show that UTX governs a set of tumor suppressor molecules, called RB binding proteins, that force a cell to stop dividing and then specialize to take on a particular role. Cancer cells do not specialize, but just keep on dividing.

"UTX bound directly to multiple genes that encode proteins that … function in the RB pathway," the scientists noted in the study. "It makes the connection between several important players," Chang said.

Some human leukemias and lymphomas result in decreased levels of UTX. In breast cancer, low UTX activity was predictive of patient death, the researchers found. Although UTX would not be a strong enough biomarker to predict cancer response in a particular patient, Chang cautioned, he believes that it is a root cause in many individual cancers. Already, other cancer researchers have identified mutations of UTX in certain human tumors. Chang's study provides the first explanation of why UTX mutations can lead to cancer.

"People search for mutations in patient samples," Chang said, "If they see mutant UTX over and over, that implies it's important. This is definitely one of the drivers."

Graduate student Jordon Wang is the lead author of the study. Other

collaborators include Stanford postdoctoral scholar Miao-Chih Tsai, and researchers at Children's Hospital Boston, Harvard Medical School and University of Manchester, U.K. The research was funded by the California Institute for Regenerative Medicine, the National Cancer Institute and the American Cancer Society.

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