Scientists discover secret life of chromatin

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Chromatin - the intertwined histone proteins and DNA that make up chromosomes – constantly receives messages that pour in from a cell's intricate signaling networks: Turn that gene on. Stifle that one.

But chromatin also talks back, scientists at The University of Texas MD Anderson Cancer Center report today in the journal *Cell*, issuing orders affecting a protein that has nothing to do with chromatin's central role in gene transcription - the first step in protein formation.

"Our findings indicate chromatin might have another life as a direct signaling molecule, that it can signal back to other proteins irrespective of gene transcription," senior author Sharon Dent, Ph.D., professor and chair of MD Anderson's Department of Molecular Carcinogenesis and director of the Center for Cancer Epigenetics.

In a series of yeast experiments, Dent and colleagues show that a signal through a histone protein regulates another protein called Dam1 that is involved in the separation of chromosomes during cell division.

Signaling cascades don't dead-end at DNA

"It's a basic change in our way of thinking about cell signaling – that all signals go into the nucleus and dead-end at DNA, that they point to chromatin and stop," Dent said. "Our data show that's not the case. We have a new fundamental aspect of cellular regulation that we need to now explore." DNA is tightly intertwined with histones and assembled in histone/DNA units called nucleosomes along the connecting length of a

string of DNA. This structure is often described as being like beads on a string.

Genes are turned on by transcription factors, proteins that attach to the gene's promoter region and order the gene to make an RNA copy of its DNA that can be translated into a protein. Histone proteins regulate access to genes, blocking or facilitating transcription.

Histones and other proteins are modified by the attachment of chemical groups to specific spots on the protein. Attachment of a methyl group (a carbon atom joined to three hydrogen atoms) to a histone can help or hinder gene transcription depending on where the methylation occurs on the histone, Dent said.

Crucial cross-talk between proteins

In a 2005 Cell paper, Dent and colleagues reported that a methyl group-transferring protein called Set1 methylates the protein Dam1, which is part of a structure that assists in the orderly separation of chromosomes during cell division.

Set1 is part of a protein complex that works along with multiple regulatory factors to facilitate transcription by attaching methyl groups to a specific histone, H3, which was the only previously known target of Set1.

Dent's team set out to discover the exact mechanism by which Set1 methylates Dam1. To their surprise, they found that Dam1 methylation does not depend on gene transcription, revealing news roles for proteins formerly thought to be involved only in that process.

Rather, the crucial step is the attachment of a single signaling molecule called ubiquitin to a histone protein called H2B. This event was known

to direct addition of methyl groups to histone H3, but Dent's work indicates it is also required for methylation of Dam1.

Communication between H2B and Dam1 is the first such instance of cross-talk between histone and non-histone proteins, the authors report. The signaling connection between a chromatin change and a non-DNA-templated process such as chromosome separation is also new.

Connections between histone ubquitination and histone methylation also occur in human cells, and mutations in a protein highly related to Set1, called MLL, are involved in leukemia. Dent's work raises the possibility that histones can signal to non-histone proteins in human cells and that mismanagement of these events caused by MLL mutations might contribute to leukemia development.

Dent's group is looking for other proteins that might be affected by histone modifications in both yeast and human cells. And they are studying the details of Dam1 methylation and its function in chromosome separation.

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