Work with fungus uncovering keys to DNA methylation

December 15 2008

Researchers in a University of Oregon lab have shed more light on the mechanism that regulates DNA methylation, a fundamental biological process in which a methyl group is attached to DNA, the genetic material in cells of living organisms.

DNA methylation is essential for normal growth and development in plants and animals. It has been implicated in long-term memory, and irregularities in its process are associated with diseases such as cancer.

In the UO's Institute of Molecular Biology, Eric U. Selker and members of his laboratory use a quickly reproducing and easy-to-manipulate fungus, Neurospora crassa, to explore the control of DNA methylation. Neurospora is considered the simplest model organism for such research.

Reporting in the Dec. 15 issue of the journal *Genes & Development*, Selker and Keyur K. Adhvaryu, a postdoctoral researcher in the Selker lab, document that the enzyme protein phosphatase PP1 is necessary for normal methylation of DNA.

In the nucleus of eukaryotic cells, DNA is wrapped around histone proteins to form chromatin, and one histone, H3, turns out to be critical for DNA methylation. "It was long thought that histones were simply structural proteins, but we are learning that these proteins are also informational," Selker said.

This was demonstrated in the journal *Nature* in 2001 by Selker and his

former postdoctoral research associate Hisashi Tamaru. They found that a protein required for DNA methylation, DIM-5, is an enzyme that adds a methyl group onto lysine 9 of histone H3. "This was the first solid indication that chromatin is important for DNA methylation," Selker said.

The new paper by Adhvaryu and Selker shows that PP1 is important to remove phosphates attached to serine 10 of H3, the site immediately adjacent to the site that DIM-5 needs to methylate, leading to DNA methylation.

In an accompanying article in the same issue of Genes & Development, Wolfgang Fischle, a biochemist at the Max-Planck Institute for Biophysical Chemistry, praises the findings of Selker and Adhvaryu. He writes that there appears to be extensive "crosstalk" involved in the chemical modifications that occur on histones to influence other enzymes that interact with chromatin "Adhvaryu and Selker provide novel insights into an intricate regulatory network involving histone phosphorylation, histone methylation and DNA methylation," he noted.

"DNA methylation seems to be a luxury item in Neurospora, which means we can manipulate it as we wish, making mutants that don't do it and thereby identify important players," Selker said. "We are identifying how DNA methylation is controlled and what it does in this organism. Our assumption is that a lot of what we find in Neurospora will be applicable to other systems."

In this case, Selker said, Keyur demonstrated very nicely, in a couple different ways, that protein phosphatase PP1 is required for normal DNA methylation. "DNA methylation is involved in a silencing of invasive DNA as well as a variety of normal genes, including those on the inactive X chromosome, those subjected to imprinting, and well as tumor suppressor genes," he said, adding that methylation of the latter

class of genes can lead to cancer.

Source: University of Oregon