Biochemists take a bead on gene-controlling code

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(PhysOrg.com) -- DNA may provide the blueprint for life, but scientists are learning more about the role of a chemical code that governs the way that blueprint is read.

University of Wisconsin-Madison researchers have developed a new technique for observing the proteins that operate by that controlling code — called the epigenome — and assembled a library of interactions between the proteins and key positions on packets of DNA.

“There are all sorts of genes that do not play an active role in the life of a cell, but they are still there in the DNA,” said John Denu, UW-Madison biomolecular chemistry professor. “There are instructions signaling which genes will be active and which will not, and we have developed a method that matches the code readers to the epigenetic code.”

In order to fit meters-long strands of human DNA into a miniscule cell nucleus, the DNA is spooled around proteins called histones to form a string of beads called nucleosomes. When the wound DNA must be read to guide cellular function, subtle differences in the chemical makeup of the histones guide the proteins that do the reading.

“They’re scanning the DNA-protein complex for information, and they’re seeing on one nucleosome you’ve got one kind of chemical modification — say, phosphorylation — and this one you’ve got another — methylation,” Denu said. “Based on what they see, they bind in a certain way to the DNA. They’re taking those instructions and saying

‘OK, this is a gene we should express,’ or, ‘This is a gene that has been turned off.’”

With UW-Madison graduate students Adam Garske, Samuel Oliver and Elise Wagner, Denu recreated a section of a histone called H3 that sticks out among the DNA beads. The H3 tail is a handy starting point for the protein readers, and has been singled out as particularly active in expressing or silencing genes.

Strings of molecules that make up H3 were attached to tiny resin beads, each bead carrying one of 5,000 variations on the different chemical modifications that could possibly occur on the histone’s tail. The beads were doused with five different reader proteins active in human cells, with the full array of protein-binding preferences showing up as a range of blue coloring on the beads.

The library of compatible epigenetic interactions included the revelation of a new chemical mark that draws the attention of reader proteins, and showed protein readers simultaneously interpreting multiple chemical marks.

“They’re paying attention to what else is going on in that histone, and that’s how you can get the complexity of regulating gene expression,” Denu said. “The code on the histone can work like a switch, turning a gene on or off. It can also work like a rheostat, and decide whether that gene will be expressed a little bit or a lot.”

The code-exposing method, published Feb. 28 in the journal *Nature Chemical Biology,* improves on tests that were able to examine just one or two protein-marker interactions at a time. Command of the epigenetic code could yield a new understanding of tumors and developmental diseases and provide a precise tool for counteracting or correcting the damage done by gene mutations.

“If we know the code that is recognized by a particular code reader, we can design particular drugs that target that interaction,” said Denu, who worked with collaborators at the University of Colorado-Denver and Princeton University on the research, which was funded by the National Institutes of Health.

The chemical markers at work in epigenetics can be altered even by diet or physical activity, making them far more malleable than DNA.

“You can’t change somebody’s DNA,” Denu said. “If there’s a mutation that we find is over-expressed in certain types of cancer, there’s not a whole lot you can do to reverse that mutation. But if you could just turn down that over-expression, perhaps you could disrupt that disease specifically.”

Provided by University of Wisconsin-Madison