Core tenets of the 'histone code' are universal

September 6 2007

In one of biology's most impressive engineering feats, specialized proteins called histones package some six-and-a-half feet of human DNA into a nucleus that averages just five microns in diameter.

DNA wraps around histone proteins, which are then chemically modified at their histone tails — long chains of amino acids that protrude from the coiled DNA. A decade ago, scientists observed that the chemical modifications of very particular amino acids control gene expression. Now new research, published in Molecular Cell, shows that the biochemical principles governing this "histone code" is not unique to these specialized proteins. They extend to nonhistone proteins as well.

When DNA coils around a single histone, it forms a complex called a nucleosome, and multiple nucleosomes are then strung together like beads to form chromatin. Histone tails jut out from these tightly coiled beads, making themselves available for chemical modification. One modification, the methylation of lysine 9, the ninth amino acid on the tail on histone H3 (each histone consists of four distinct proteins: H2A, H2B, H3 and H4), involves the transfer of a group of atoms to that amino acid. The protein responsible for the transfer of these methyl groups to lysine 9 is aptly called G9a methyltransferase.

The lysine 9 methylation is a mark that silences gene transcription without altering the underlying DNA. Instead, methyl groups create a binding platform for and direct the docking of the protein HP1, which configures chromatin in a way that represses gene transcription. Then another chemical modification, the phosphorylation of serine 10, the

amino acid immediately adjacent to lysine 9, counteracts the effect of methylation by preventing the recruitment of HP1.

In a crucial experiment, Alexander Tarakhovsky, Irene Diamond Professor of Immunology and head of the Laboratory of Lymphocyte Signaling, and his colleagues found that the sequence of amino acids — and modifications that occur at specific amino acids to regulate gene transcription — are preserved in the very protein responsible for inducing these changes in the first place: G9a methyltransferase. Nonhistone proteins have been identified as targets for lysine methylation before, but Tarakhovsky and his colleagues show that proteins directly involved in carrying out the principles of the "histone code" are no exception.

"Why this is so is a mystery," says first author Srihari Sampath, a biomedical fellow in the Tarakhovsky lab. "But it probably means that by studying proteins containing 'histone mimics' such as those in G9a, we will learn a lot about the functions of histone and nonhistone methylation."

When Tarakhovsky noticed that a sequence of amino acids on this nonhistone protein strongly resemble the sequence of amino acids at the site of lysine methylation on H3, he and his colleagues wondered whether G9a methyltransferase could undergo the same series of chemical modifications governing the histone code.

G9a methyltransferase, although responsible for modifying lysine 9 on H3, is also responsible for recognizing and chemically modifying its own lysine residue. When G9a methyltranferase modified itself, the methyl groups created a binding platform for HP1 — mimicking the very process that occurs on H3. Moreover — and this came as the biggest surprise to the researchers — the phosphorylation of an amino acid adjacent to lysine selectively blocked the binding of HP1 to G9a

methyltransferase, just as the phosphorylation of serine 10 prevented the recruitment of HP1 onto methylated lysine 9 on H3.

“The way that lysine is targeted for recognition and modification has been conserved in nonhistone proteins,” says Tarakhovsky. “The methylation of lysine and its consequences does not represent a peculiarity in histone biology. It's likely that this mark represents a particular instance of a more universal ‘protein code.’”

Citation: Molecular Cell 27(4): 596-608 (August 17, 2007)

Source: Rockefeller University