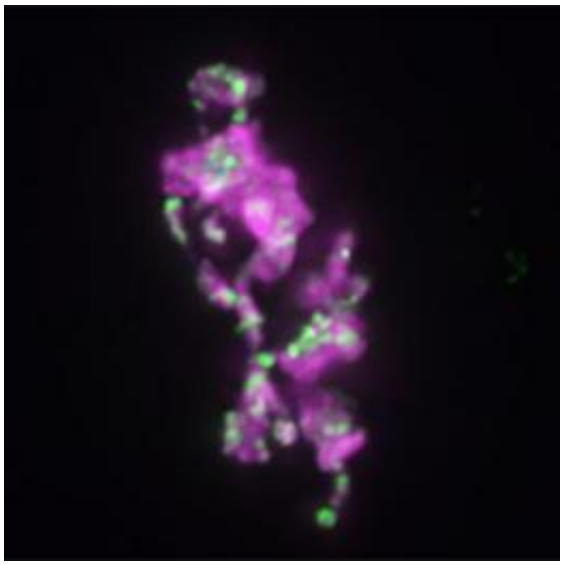
Experiments decipher key piece of the ‘histone code’ in cell division

16 August 2010



Credit: Rockefeller University

Reproduce or perish. That’s the bottom line for genes. Because nothing lives forever, reproduction is how life sustains itself, and it happens most fundamentally in the division and replication of the cell, known as mitosis. Now new research at Rockefeller University has detailed a key role in mitosis for a chemical modification to histone proteins that package lengthy strings of DNA into compact chromosomes.

The experiments, published Thursday in Science, add to an increasingly intricate picture of the precisely timed events that separate new copies of chromosomes to most fundamental processes involved in the reproduction of life.

“We’ve known that histones become decorated during mitosis for more than 30 years, but we haven’t really understood their function,” says Hironori Funabiki, head of the Laboratory of Chromosome and Cell Biology. “Now we’ve finally decoded exactly how one of these marks works.”

Funabiki says the findings provide hard evidence for the “histone code hypothesis,” advanced by Rockefeller’s C. David Allis and colleagues, which suggests that combinations of histone modifications attract or remove specific proteins, controlling the immediate environment of chromosomes in the cell. The orchestration of the exact timing and localization of the vast array of molecules and processes involved in reproducing the chromosomes is one of the basic wonders of biology and is at the core of both healthy living and diseases such as cancer, that arise when the process goes awry.

Funabiki, postdoctoral associate Alex Kelly, graduate student Cristina Ghenoiu and their colleagues focused on the addition of a phosphate group to histone H3 at the site theronine 3 (H3T3); it was first identified in 1980, but its function has remained a mystery. The researchers built on their previous work singling out the chromosomal passenger complex, a group of proteins in the cell that includes the enzyme Aurora B. This complex must be brought to chromosomes and activated to facilitate the assembly of cellular scaffolding called spindle microtubules, which are required to separate chromosomes in a dividing cell. In a series of new experiments, they showed that another member of the complex, Survivin (it’s highly similar to a class of proteins known to stem the process of programmed cell death, or apoptosis) recognizes the phosphate group at H3T3 and, in turn, activates Aurora B.

The researchers found that the phosphate group must be removed after the chromosomes are segregated so that the chromosomes can be properly repackaged to repeat the process over again, and they showed that the enzyme Haspin plays a role in adding the phosphate group that Survivin recognizes and is necessary for the chain of events to come off smoothly. Since both Survivin and Aurora B have been implicated in many cancers, molecules that disrupt the interaction

between histone H3 and Survivin could allow for a new avenue for targeted therapeutics.

The study also shows that how Survivin recognizes H3T3 phosphorylation is very similar to how “inhibitor of apoptosis” proteins (IAPs) bind to their own ligands, whose mimetics have been investigated as anti-cancer drugs. “It brings a lot of fields together. I think it will be exciting to a lot of people working on epigenetics, apoptosis and the cell cycle,” Kelly says. “We cracked one code,” Funabiki says, “but there are yet many to be decoded to understand how chromosomes orchestrate mitosis.”

Science online: August 12, 2010
Survivin Reads Phosphorylated Histone H3 Threonine 3 to Activate the Mitotic Kinase Aurora B
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More information: DOI: 10.1126/science.1189505

Provided by Rockefeller University