Histone-modifying proteins, not histones, remain associated with DNA through replication

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It's widely accepted that molecular mechanisms mediating epigenetics include DNA methylation and histone modifications, but a team from Thomas Jefferson University has evidence to the contrary regarding the role of histone modifications.

A study of Drosophila embryos from Jefferson's Department of Biochemistry and Molecular Biology published ahead of print in Cell August 23 found that parental methylated histones are not transferred to daughter DNA. Rather, after DNA replication, new nucleosomes are assembled from newly synthesized unmodified histones.

"Essentially, all histones are going away during DNA replication and new histones, which are not modified, are coming in," said Alexander M. Mazo, Ph.D., professor of Biochemistry and Molecular Biology at Jefferson, and a member of Jefferson's Kimmel Cancer Center. "In other words, what we found is that histone modifying proteins are hiding on the way over replicating DNA, instead of histones 'jumping' over as currently thought."

"What this paper tells us," he continues, "is that these histone modifying proteins somehow are able to withstand the passage of the DNA replication machinery. They remained seated on their responsive binding sites, and in all likelihood they will re-establish histone modification and finalize the chromatin structure that allows either activation or

repression of the target gene."

The team suggests that since it appears these histone modifying proteins—the Trithorax-group (TrxG), which maintain gene expression, and the Polycomb-group (PcG), which plays a role in epigenetic silencing of genes—re-establish the histone code on newly assembled unmethylated histones, they may act as epigenetic marks.

Epigenetics is the study of heritable changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence. Epigenetic marks have become an important focus in recent years because they are thought to have the potential to explain mechanisms of aging, human development, and the origins of diseases, like cancer, heart disease, and mental illness.

According to widely-accepted models applied today, the tails of methylated histones turn genes in DNA "on" or "off" by loosening or tightening nucleosome structure, thus changing the accessibility of transcription factors and other proteins to DNA.

"People believe that everything gets worked off of DNA during the replication process and that these methylated histones act as epigenetic marks, since they are believed to rapidly jump from parental to daughter DNA" said Dr. Mazo. "But there is no experimental evidence to back this up."

The researchers used chromatin immunoprecipitation (ChIP) assay, and developed several new approaches to analyze protein interactions with newly synthesized DNA, tracking both modified and unmodified histones, and non-histone proteins to determine their presence and role from the initial split of DNA through the various embryonic stages.

This new evidence that TrxG and PcG proteins but not methylated

histones remain associated with DNA through replication could have significant impacts on how scientists study epigenetic marks.

Instead of focusing on numerous types of modified histones, it is probably more practical to assess which non-histone proteins remain stably associated with their sites on DNA following DNA replication, as they may potentially carry essential epigenetic information by restoring the state of histone modifications in the daughter cell, according to Dr. Mazo.

"It is also important to understand whether the way nucleosomes are assembled in mammalian cells is similar to that detected in *Drosophila* embryos and whether these mechanisms remain unchanged during cell differentiation in development and disease," he added.

Provided by Thomas Jefferson University