Proteins in histone group might influence cancer development, study shows

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Spool-like proteins called histones play a crucial role in packaging the nearly seven feet of DNA found in most human cells. A new study shows that a group of histones that are thought to behave the same way actually are functionally distinct proteins.

The findings by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) indicate that replication-dependent histone isoforms can have distinct cellular functions, and that changes in expression of the various isoforms might play a role in cancer development.

The study is published in the journal *Nucleic Acids Research* as a Breakthrough Article, placing it among the top 2-3 percent of papers presented by the journal in terms of significance and excellence.

"Replication-dependent histone isoforms have always been thought to be functionally identical, but we show that they have distinct functions, and that altering the levels of these isoforms can influence cell proliferation and tumor development ," says principal investigator Mark Parthun, PhD, professor of Molecular and Cellular Biochemistry and a member of the OSUCCC – James Experimental Therapeutics Program.

"These highly novel results provide a new mechanism for the regulation of chromatin structure, Parthun says."

Replication-dependent histones are highly expressed just before the onset of DNA replication during the cell cycle, and they are repressed when DNA replication is completed.

The genes that encode these histones are located in large clusters that can contain dozens of histone genes. "This localization in gene clusters led to the belief that these histones are regulated as a group, and that the multiple genes encoding each histone are functionally equivalent," Parthun says.

However, the proteins encoded by replication-dependent histone genes are not identical. For example, 16 genes encode the replication-dependent histone called H2A. Strikingly, these genes encode 11 distinct protein variations, he notes.

Parthun and his colleagues conducted the study using three bladder-cancer cell lines. Key findings include:

- The abundance of replication-dependent histone H2A isoforms showed dramatic differences in bladder cancer cells vs. normal bladder cells;
- Replication-dependent H2A isoforms were expressed at different levels in cancer cells; expression of one isoform was 10-fold higher than the others;
- Knocking down the messenger RNA of a specific replication-dependent H2A isoform increased cell proliferation and tumorigenicity;
- Replication-dependent H2A isoforms show evidence of individualized regulation.

Provided by Ohio State University Medical Center