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Potential New Way to Suppress Tumor Growth Discovered

Researchers at the University of California, San Diego School of Medicine, with colleagues at the University of Rochester Medical Center, have identified a new mechanism that appears to suppress tumor growth, opening the possibility of developing a new class of anti-cancer drugs.

Writing in this week's online Early Edition of the *Proceedings of the National Academy of Sciences* (*PNAS*), Willis X. Li, PhD, a professor in the Department of Medicine at UC San Diego, reports that a particular form of a signaling protein called STAT5A stabilizes the formation of heterochromatin (a form of chromosomal DNA), which in turn suppresses the ability of cancer cells to issue instructions to multiply and grow.

Specifically, Li and colleagues found that the unphosphorylated form of STAT promotes and stabilizes heterochromatin, which keeps DNA tightly packaged and inaccessible to transcription factors. "Therefore, genes 'buried' in heterochromatin are not expressed," explained Li.

Phosphorylation is a fundamental cellular function in which a phosphate group is added to a protein or molecule, causing it to turn it on or off or to alter its function. An unphosphorylated STAT lacks this phosphate group.

Li said that in previous studies with fruit flies, the unphosphorylated form of STAT caused chromatin to condense into heterochromatin, while the phosphorylated version prompted dispersal and loss of heterochromatin, furthering gene expression.

"Unphosphorylated STAT promotes and stabilizes heterochromatin formation, which in turn suppresses gene transcription," said Li. "When we expressed either HP1 (the central component of heterochromatin) or unphosphorylated STAT5A in human cancer cells, many genes important for cancer growth are suppressed. These cancer cells do not grow as fast or big as their control parental cancer cells in mouse xenograft models."

Most of the known tumor suppressors, such as p53 or Rb, function by inhibiting cell cycle progression or by spurring cell death, or apoptosis. Li said their findings reveal a potential new way to inhibit cancer gene expression, and may represent a new class of tumor suppressors.

“We are in the process of identifying small molecule drugs that may promote heterochromatin formation without stopping cell division or causing cell death,” he said. “These drugs, if found, may be effective in treating cancers with fewer side effects.”

Co-authors are Xiaoyu Hu, Amy Tsurumi and Hartmut Land, Department of Biomedical Genetics, University of Rochester Medical Center; Pranabananda Dutta, Jinghong Li and Jingtong Wang, Department of Medicine, UCSD.

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