Reader of epigenetic marks could be 'game changer' for certain cancers

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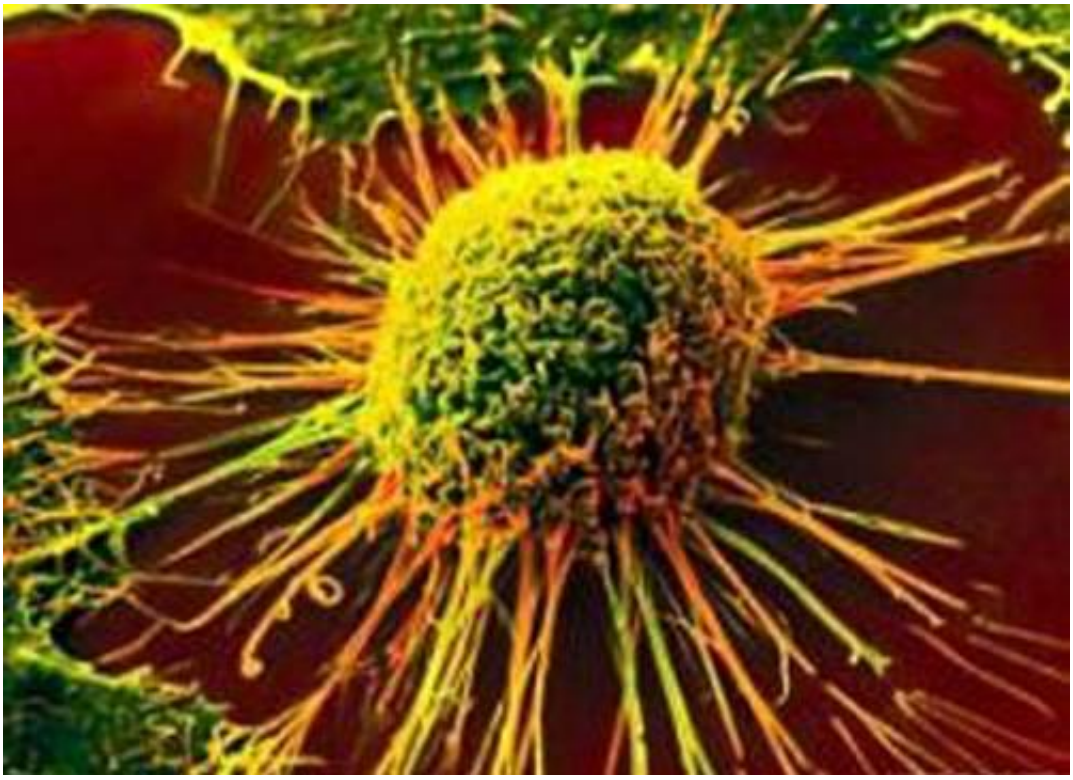

If genes form the body's blueprint, then the layer of epigenetics decides which parts of the plan get built. Unfortunately, many cancers hijack epigenetics to modulate the expression of genes, thus promoting cancer growth and survival. A team of researchers led by Tatiana Kutateladze, PhD, University of Colorado Cancer Center investigator and professor in

the Department of Pharmacology at the University of Colorado School of Medicine, and Brian Strahl, PhD, professor in the Department of Biochemistry & Biophysics at the University of North Carolina School of Medicine, published a breakthrough report in the journal *Nature Chemical Biology* describing the essential role of YEATS domain proteins in reading epigenetic marks that regulate gene expression, DNA damage response, and other vital DNA-dependent cellular processes. This newly discovered player in epigenetic regulation is closely related to known cancer promoters, including the bromodomain proteins, a handful of which are targeted in current human clinical trials.

"Every cell in an organism has the same DNA. So how does a heart cell become a heart cell and a skin cell become a skin cell? There's a language called epigenetics that helps determine which genes are turned on and turned off at any given moment," says Forest Andrews, PhD, a postdoctoral fellow in Kutateladze's laboratory and, together with Stephen Shinsky, PhD, a postdoctoral fellow in Strahl's laboratory, a co-first author on the paper.

Epigenetic mechanisms control how often a gene's blueprint ultimately yields a protein, modulating the structure and dynamics of chromatin, a complex consisting of DNA and histone proteins. The addition or removal of epigenetic marks on histone proteins is one of such mechanisms that helps expose some regions of DNA to promote gene expression, while keeping other regions of DNA hidden inside the chromatin fiber.

The study by Andrews et al. has uncovered the YEATS domain as the first reader of histone lysine crotonylation, a critical epigenetic mark, which was discovered only recently and is strongly linked to the initiation of protein production. The authors found that the yeast YEATS protein recognizes this epigenetic mark through a unique mechanism that has not been previously reported for any protein-protein interaction.

This fundamental basic science discovery also has compelling implications for human disease and could be a potential game-changer for some cancers as two human YEATS proteins have been implicated in leukemia and another is dysregulated in glioblastoma.

Furthermore, the YEATS proteins are closely related to bromodomain proteins, which Andrews calls "a hot target for cancer drugs". In fact, Andrews and Kutateladze teamed up with the group of Donald Durden, MD, PhD, professor in the Department of Pediatrics at the University of California San Diego (UCSD) and associate director of Pediatric Oncology at the Moores UCSD Cancer Center, to develop novel dual activity bromodomain/kinase inhibitors that target epigenetic and PI3K signaling pathways. This work is presented at the American Association for Cancer Research 2016 Annual Meeting.

Mechanisms of the epigenetic regulation are at the focus of research in Kutateladze's laboratory. "We hope these discoveries open up new opportunities and strategies to diagnose, prevent or treat cancer," says Kutateladze.

More information: The Taf14 YEATS domain is a reader of histone crotonylation, *Nature Chemical Biology*, DOI: 10.1038/nchembio.2065

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