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CU Boulder Today

A key ‘kill switch’ in a gene-regulating protein group

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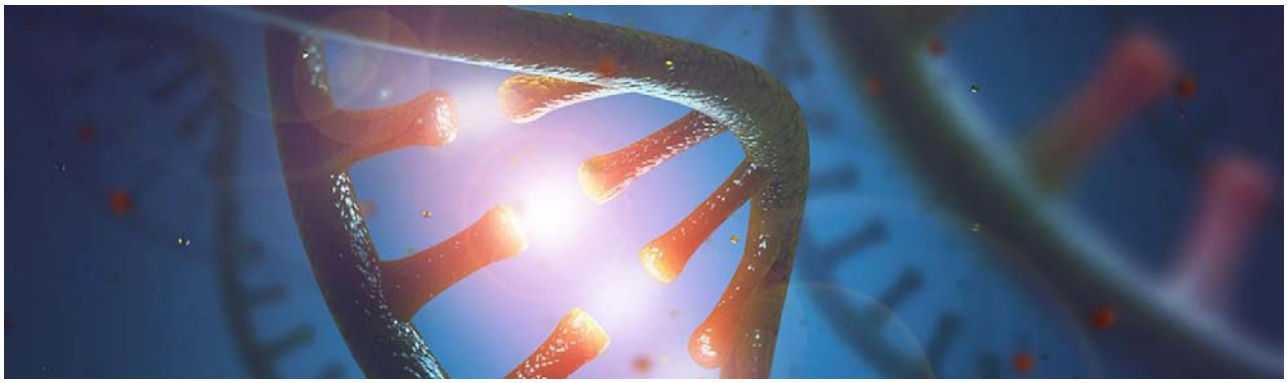

Illustration: National Institutes of Health

CU Boulder and Howard Hughes Medical Institute (HHMI) biochemists have revealed a key regulatory process in a gene-suppressing protein group that could hold future applications for drug discovery and clinical treatment of diseases, including cancer.

The new research, recently published in the journal *Genes & Development*, centered on a protein group known as Polycomb Repressive Complex 2 (PRC2), which acts as a gatekeeper for gene expression as cells differentiate and tissues develop.

“PRC2 plays a critical role in stem cell differentiation to make sure that irrelevant genes are switched off,” said Yicheng Long, an HHMI post-doctoral fellow and a co-author of the study. “If you have a muscle cell, for example, PRC2 shuts off genes that are specific to the brain.”

When that regulation goes awry, however, abnormal PRC2 activation is suspected to play a role in the development of diseases such as cardiac hypertrophy, Huntington’s Disease and multiple types of cancer.

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Researchers from HHMI and CU Boulder's Department of Biochemistry began by re-examining exactly how PRC2 achieves methylation, a complex epigenetic process by which proteins modify the structure of regions of chromosomes.

While examining the activity of human PRC2, the scientists began to notice a "mystery band" appearing in the data. As PRC2 was previously known to modify an important histone protein that is a fundamental unit of human chromosome, the scientists indeed observed this modification in vitro. Surprisingly, the scientists noticed another modification event indicated by this "mystery band." Although other scientists had seen this band before, nobody could understand how and why it was happening.

"This unexpected band caught our attention and we suspect that this could represent a novel activity and function of PRC2," said Xueyin Wang, one of the two co-first authors of the study and a then-CU Boulder graduate student now with A2 Biotherapeutics Inc. in California.

Further investigation revealed that this "mystery band" is a self-modification event (named "automethylation") which have important physiological functions. Using mass spectrometry, it became apparent that PRC2 automethylates three lysines of a flexible, evolutionarily conserved loop. The loop essentially holds the key to its own lock within its own structure and remains poised in an inhibited state. Automethylation of the three lysines unlocks this loop from PRC2's catalytic center and thus relieves PRC2 from the poised state.

"The interesting question is why nature would devise such a mechanism," Long said.

The researchers hypothesize that with abundant level of PRC2 in stem cell, the flexible loop ensures that most of it stays inactive until needed, like a fire sprinkler that stays closed during normal operations, only opening when a fire needs to be extinguished. If that sprinkler ever malfunctions and remains open (as in a cancerous mutation), biochemists can now foresee a means of re-closing it to prevent unwanted flooding.

"Others have found the way to activate PRC2," Long said. "We found a key to turning it off."

"I expect that many other examples of automethylation will be found," said Nobel Laureate and Distinguished Professor Thomas Cech, the senior author of the study and an HHMI Investigator. "Many enzymes that regulate our genes do so by adding methyl groups to their target proteins. So they're also primed to add methyl groups to themselves, allowing them to self-regulate their own activity."

With greater knowledge of PRC2's form and function, the research could one day lead to more specific clinical focus on inhibiting activations associated with tumor formation and other known disease pathways.

- Science & Technology