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Researchers discover new mechanism of gene regulation

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In the cells of humans and other organisms, only a subset of genes are active at any given time, depending largely on the stage of life and the particular duties of the cell. Cells use different molecular mechanisms to orchestrate the activation and deactivation of genes as needed. One central mechanism is an intricate DNA packaging system that either shields genes from activation or exposes them for use.

In this system, the DNA strand, with its genes, is coiled around molecules known as histones, which themselves are assembled into larger entities called nucleosomes. Together, nucleosomes and DNA form chromatin, which is the primary substance of chromosomes. This DNA-packaging system is vital for managing development and maintaining health. When it goes awry, cancer can be the result.

In a study published in *Molecular Cell* this month, Alexei V. Tulin, PhD, Associate Professor at Fox Chase Cancer Center, and colleagues reported that chemical modification of one type of histone—called H2Av—leads to substantial changes in nucleosome shape. As a consequence, a previously hidden portion of the nucleosome becomes exposed. This newly exposed portion interacts with and activates an enzyme called PARP1. Upon activation, PARP1 assembles long branching molecules of Poly(ADP-ribose), which appear to open the DNA packaging around the site of the PARP1 activation, exposing specific genes for activation.

"Currently, the nucleosome is often portrayed as a stable, inert structure,

or a tiny ball," Tulin says. "We found that the nucleosome is actually a quite dynamic structure. When we modified one histone, we changed the whole nucleosome."

In addition to reevaluating how histones control gene activation, the study also reports a new mechanism of PARP1 regulation. Many standard cancer treatments, including chemotherapy drugs and radiation therapy, damage the DNA of rapidly dividing cancer cells. However, the effectiveness of these treatments is limited. Research has suggested that standard therapies combined with drugs that inhibit PARP1 can kill cancer cells, but clinical trials testing PARP1 inhibitors in cancer patients have produced disappointing outcomes. "I believe that to a large extent the previous setbacks were caused by a general misconception of the role of PARP1 in living cells and the mechanisms of PARP1 regulation," Tulin says. "Now that we know this mechanism of PARP1 regulation, we can design approaches to inhibit this protein in an effective way to better treat cancer."

The ability of PARP1 to control cellular processes is regulated by nucleosomes—the basic unit of DNA packaging, consisting of a segment of DNA wound in sequence around eight histone protein cores, similar to a thread wrapped around a spool. Histones undergo different chemical modifications that play an important role in regulating the activity of genes. Through this mechanism, histones control the ability of PARP1 to activate genes and repair DNA damage.

"This mechanism of PARP1 regulation by histones is still very new," Tulin says. "People believe that PARP1 is mainly activated through interactions with DNA, but we have found that the main pathway of PARP1 activation is through interactions with the nucleosome." In the new study, Tulin and his colleagues reevaluated how PARP1 is activated by changes in the nucleosome. They found that the addition of a phosphate group to a histone—called H2Av—triggered the entire

nucleosome to change shape, exposing previously hidden parts of the nucleosome that began to interact with and activate PARP1.

To follow up on these findings, Tulin and his team are now developing the next generation of PARP1 inhibitors. Designed to block the newly identified mechanism of PARP1 activation, these new inhibitors will specifically target PARP1, in contrast to the PARP1 inhibitors currently being tested in clinical trials.

"We expect that our targeted PARP1 inhibitors will be more effective at killing cancer cells while protecting important molecular pathways in normal cells," Tulin says. "For this reason, we believe that the specific inhibitors we are designing hold great promise for cancer treatment."

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