# How silencing a gene-silencer could lead to new cancer drugs

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Deep inside our cells— each one complete with an identical set of genes— a molecular machine known as PRC2 plays a critical role in determining which cells become heart cells, vs. brain or muscle or skin cells.

When the machine is missing or broken, normal fetal development can't occur. If it's mutated, cells can grow uncontrollably, and cancer can

arise—a fact that has made PRC2 a source of keen interest for drug developers.

New research by scientists at University of Colorado Boulder and Harvard Medical School offers an unprecedented look at how PRC2, or polycomb repressive complex 2, does its job and, specifically, how ribonucleic acid (RNA) helps it switch genes on and off.

The findings, published Sept. 22 in the journal *Science*, shed new light on how development occurs and could pave the way for novel therapeutics for hard-to-treat cancers, including blood, pancreatic and colon cancer, leukemia and pediatric tumors.

"We know PRC2 is extremely important for development and for maintaining the identity of cells, and we know that RNA regulates it. But mechanistically, we didn't know how," said co-senior author Vignesh Kasinath, assistant professor of biochemistry at CU Boulder.

For the study, Kasinath's lab collaborated with Nobel Laureate Thomas Cech and colleagues at the BioFrontiers Institute to photograph PRC2 in action, using state-of-the-art "cryo-electron microscopy." The technique involves freezing samples ito extremely cold temperatures to preserve their native structure and then hitting them with an electron beam at speeds faster than the speed of light to create ultra-high-resolution 3D images.

Previous research has shown that this enzyme complex, made of multiple proteins, is a potent gene-silencer, effectively shutting off access to specific regions of the genome so a stem cell can differentiate into a particular cell type. In a budding heart cell, for instance, it plays a role in silencing genes that might guide it to become a kidney or liver cell.

How that happens remained a mystery.

"If you think of PRC2 as a car, we know a lot about what happens when it gets to its destination, but we don't know how to drive it there," said first author Jiarui Song, a Jane Coffin Childs postdoctoral fellow in the Cech Lab.

## Catching development in a freezeframe

To find out, the team synthesized PRC2 and RNA in the lab and used CU's cutting-edge Titan Krios Electron Microscopy Facility, which enables researchers to image molecules at the atomic level, to take the first-ever picture of PRC2 and RNA bound together.

They discovered that when one RNA molecule grabs on to two PRC2 proteins it clamps them down like a clamshell with RNA as the hinge, essentially gluing together their surfaces so they can't interact with DNA. In doing so, RNA effectively silences the silencer, enabling genes in certain regions of the genome to keep firing while others remain "off."

"RNA essentially acts as a checkpoint, making sure PRC2 only acts on certain regions of the genome," said Kasinath.

Using biochemistry and additional experiments in zebrafish, the research team was able to confirm what they saw under the microscope in living cells.

The study is the first to define, at the molecular level, how RNA regulates PRC2 activity and could pave the way for more effective, targeted treatments for diseases where PRC2 regulation is defective.

"Understanding this mechanism could enable the development of a new generation of RNA-based therapeutics. This work lays that foundation," said Kasinath.

**More information:** Jiarui Song et al, Structural basis for inactivation of PRC2 by G-quadruplex RNA, *Science* (2023). www.science.org/doi/10.1126/science.adh0059 , DOI: 10.1101/2023.02.06.527314