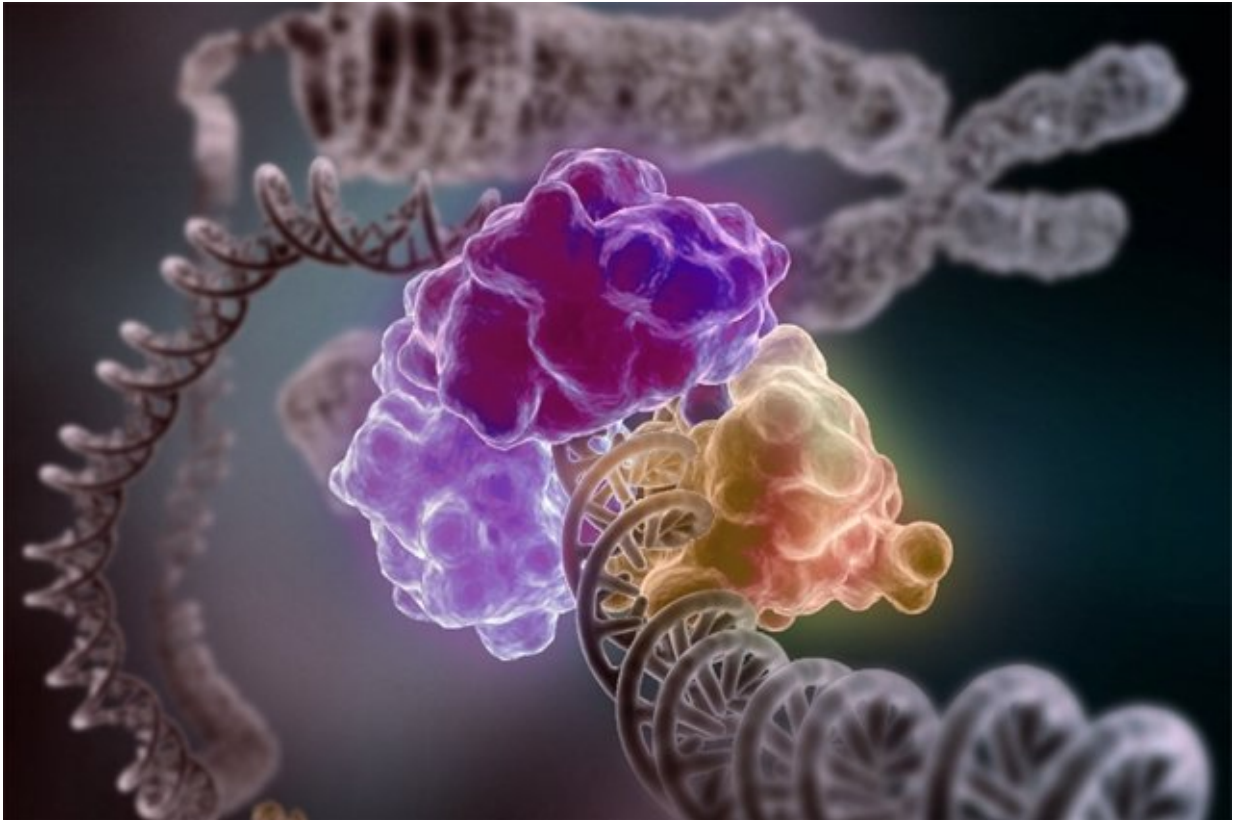


The long and short of CDK12

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An enzyme encircles the double helix to repair a broken strand of DNA. Credit: Tom Ellenberger/Washington University School of Medicine in St. Louis, Dave Gohara/Saint Louis University School of Medicine

Mutations in the BRCA1 and BRCA2 genes pose a serious risk for breast and ovarian cancer because they endanger the genomic stability of a cell by interfering with homologous recombination repair (HR), a key

mechanism for accurately repairing harmful double-stranded breaks in DNA. Without the ability to use HR to fix double-stranded breaks, the cell is forced to resort to more error-prone—and thus more cancer-prone—forms of DNA repair.

The BRCA1 and BRCA2 genes are not the only genes whose mutations foster tumorigenesis by causing an inability to repair DNA double strand breaks by HR. Mutations in twenty-two genes are known to disrupt HR, giving rise to tumors with what researchers call "BRCAness" characteristics. All but one of these BRCAness genes are known to be directly involved in the HR pathway.

The one exception, CDK12, is thought to facilitate a set of different processes altogether, involving how RNA transcripts are elongated, spliced and cleaved into their mature forms. While the connection between this RNA-modulating gene to DNA repair remained poorly understood, the identification of CDK12 as a BRCAness gene piqued significant clinical interest.

The researchers who pinpointed this connection, Sara Dubbury and Paul Boutz, both work in the laboratory of Phillip Sharp, Institute Professor, professor of biology, and member of the Koch Institute for Integrative Cancer Research. In a study appearing online in *Nature* on Nov. 28, they describe how they discovered a previously unknown mechanism by which CDK12 enables the production of full-length RNA transcripts and that this mechanism was especially critical to maintain functional expression of the other BRCAness genes.

When the researchers knocked out expression of CDK12, mouse stem cells showed many signs of accumulating DNA damage that prevented DNA replication from going forward, classic indications of a BRCAness phenotype. To identify what roles CDK12 may play in regulating gene expression, the researchers turned to RNA sequencing to determine

which genes had increased or decreased their overall expression.

To their surprise, only genes activated by p53 and early differentiation (side effects of accumulating unrepaired DNA damage and BRCAness in mouse stem cells) accounted for the lion's share of changes to RNA transcription. However, when the researchers instead focused on the types of RNAs transcribed, they found that many genes produced unusually short transcripts when CDK12 was absent.

Not every stretch of DNA in a gene makes it into the final RNA transcript. The initial RNA from a gene often includes sections, which researchers call "introns," that are cut out of transcript, the discovery that earned Sharp the 1993 Nobel Prize in Physiology or Medicine and the remaining sections. "Exons," are spliced together to form a mature transcript (mRNA). Alternately, an intronic polyadenylation (IPA) site may be activated to cleave away the RNA sequence that follows it preventing intron removal and generating a prematurely shortened transcript. These processes allow the same gene to produce alternate forms of messenger RNA (mRNA), and thus be translated into different protein sequences.

Surprisingly CDK12 knockout cells produced significantly more IPA-truncated transcripts genome-wide, while full-length transcripts for the same genes were reduced. These shortened mRNAs can vary greatly in their stability, their ability to be translated into protein, and their [protein function](#). Thus, even while a gene may be actively transcribed, its translation into functional proteins can be radically altered or depleted by IPA activation.

While this observation began to illuminate CDK12's role in regulating mRNA processing, what remained puzzling was why CDK12 loss affected the HR pathway so disproportionately. In investigating this question, Dubbury and Boutz found that BRCAness genes were

overrepresented as a group among those genes that have increased IPA activity upon CDK12 loss.

Additionally, while CDK12 suppresses IPA activity genome-wide, 13 of the other 21 BRCAness genes were found to be particularly vulnerable to CDK12 loss, in part, because they possess multiple high-sensitivity IPA sites, which have a compound effect in decreasing the total amount of full-length transcripts. Moreover, because multiple CDK12-sensitive BRCAness genes operate in the same HR pathway, the researchers believe that the disruption to HR repair of double-stranded DNA breaks is amplified.

CDK12 mutations are found recurrently in prostate and [ovarian cancer](#) patients, making them an attractive diagnostic and therapeutic target for cancer. However, not enough is known about CDK12 to distinguish between true loss-of-function mutations and so-called "passenger mutations" with no functional consequence.

"The ability to identify patients with true loss-of-function mutations in CDK12 would enable clinicians to label a new cohort of patients with bona fide BRCAness tumors that could benefit from certain highly effective and targeted chemotherapeutics against BRCAness, such as PARP1 inhibitors," says Dubbury, a former David H. Koch Fellow.

Dubbury and Boutz were able to confirm that IPA sites in key BRCAness [genes](#) were also used more frequently upon CDK12 loss in human tumor cells using RNA sequencing data from prostate and ovarian tumor patients with CDK12 mutations and by treating human prostate adenocarcinoma and ovarian carcinoma cells with a CDK12 inhibitor. This result suggests that the CDK12 mechanism observed in mouse cell lines is conserved in humans and that CDK12 mutations in human ovarian and prostate tumors may promote tumorigenesis by increasing IPA activity and thus functionally attenuating HR repair.

"These results not only give us a better understanding how CDK12 contributes to BRCAness, they also may have exciting potential impact in the clinic," Dubbury says. "Currently available diagnostic techniques could be used to probe the usage of IPA sites found in this study to rapidly screen for patients with true loss-of-function CDK12 mutations, who would respond to BRCAness-targeted treatments."

Paul Boutz, a research scientist in the Sharp Lab, is co-first author of the study, and has plans to follow-up many of these implications for ovarian and prostate cancer his lab at the University of Rochester School of Medicine and Dentistry.

"CDK12 provides a remarkable example of how factors that control the processing of RNA molecules can function as master regulators of gene networks, and thereby profoundly affect the physiology of both normal and cancerous cells," he says.

Phil Sharp, the senior author on the work, says "Sara's and Paul's surprising discovery that CDK12 suppresses intronic polyadenylation has implications for fundamental new insights into gene structure as well as for control of cancer."

More information: Sara J. Dubbury et al. CDK12 regulates DNA repair genes by suppressing intronic polyadenylation, *Nature* (2018). DOI: [10.1038/s41586-018-0758-y](https://doi.org/10.1038/s41586-018-0758-y)

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