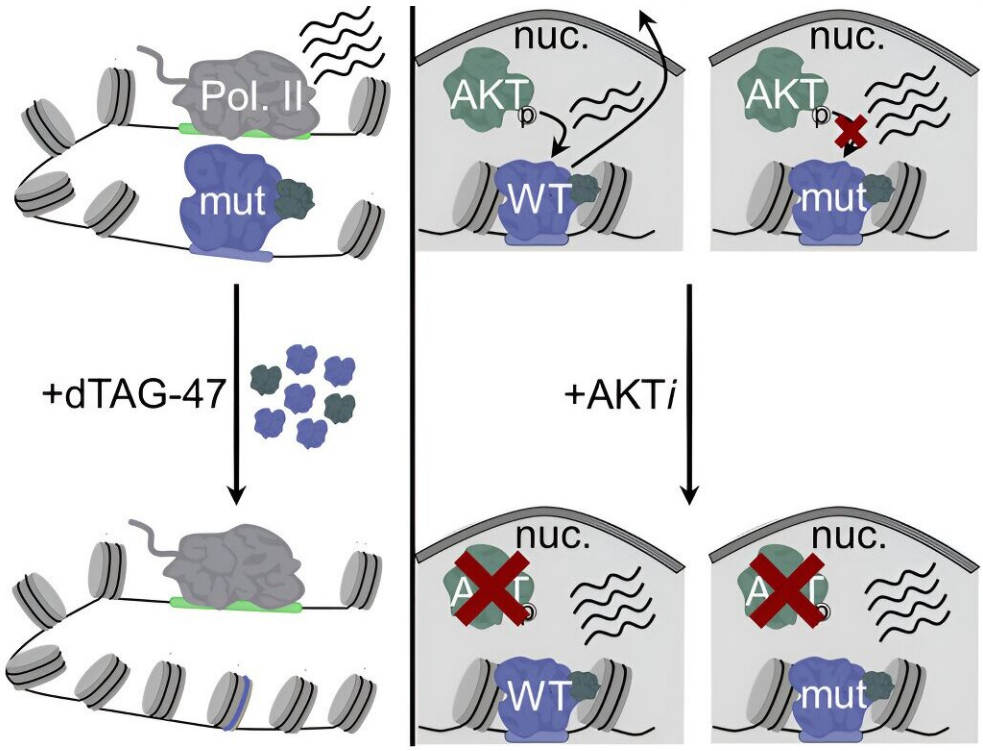
Q&A: Understanding protein mutations that affect gene expression to promote cancer progression

May 30 2024, by Marissa Shapiro



Graphical abstract. Credit: *Cell Genomics* (2024). DOI: 10.1016/j.xgen.2024.100537

Graduate student Hillary Layden studies transcriptional control of cancer

in the lab of Scott Hiebert, Hortense B. Ingram Chair in Cancer Research and professor of biochemistry.

Below, Layden shares the results from her research in which she used a deep genomic analysis to determine how protein mutations influence gene expression to promote cancer progression.

The study is published in the journal *Cell Genomics*.

What issue does your research address?

Mutations in proteins that control gene expression are common across human cancers, but we don't understand how these mutations affect gene expression, contribute to disease, or impact response to treatments. In this study, we focused on identifying the direct gene targets of the transcription factor FOXO1 and how mutations in FOXO1 found in B-cell lymphoma patients affect the expression of these genes.

Our approach took advantage of several recently developed technologies, including degron tags and nascent transcript analysis, to analyze transcription immediately after the loss of FOXO1.

What were your findings?

We found that wild-type FOXO1 activates the transcription of genes that are key regulators of B-cell identity and are known oncogenes, maintaining chromatin accessibility at enhancer elements. Mutant FOXO1 controls transcription in the same way but is insensitive to signaling events that inactivate wild-type FOXO1. This allows mutant FOXO1 to maintain the expression of genes that contribute to lymphoma cell growth in cellular conditions that wild-type FOXO1 cannot.

In other words, mutations in FOXO1 affect an on/off switch, locking FOXO1 in the "on" position. When FOXO1 is "on," it increases the expression of target genes, which are critical for cell growth and survival.

What do you hope will be the outcomes of this study?

Patients with mutations in FOXO1 are more likely to relapse on the current standard of care therapy. We hope that a better understanding of how these mutations affect the function of FOXO1 can be translated into new treatments that better serve this patient population in the long term.

In the short term, this work provides several target genes that can be used as proxies for FOXO1 transcriptional function in B-cells. These targets can be used to identify drugs that affect FOXO1 transcriptional activity or other proteins required for FOXO1 transcriptional function. This work also provides much-needed clarity on how lymphoma-associated mutations in FOXO1 affect the transcription of target genes.

More information: Hillary M. Layden et al, Mutant FOXO1 controls an oncogenic network via enhancer accessibility, *Cell Genomics* (2024). DOI: 10.1016/j.xgen.2024.100537

Provided by Vanderbilt University