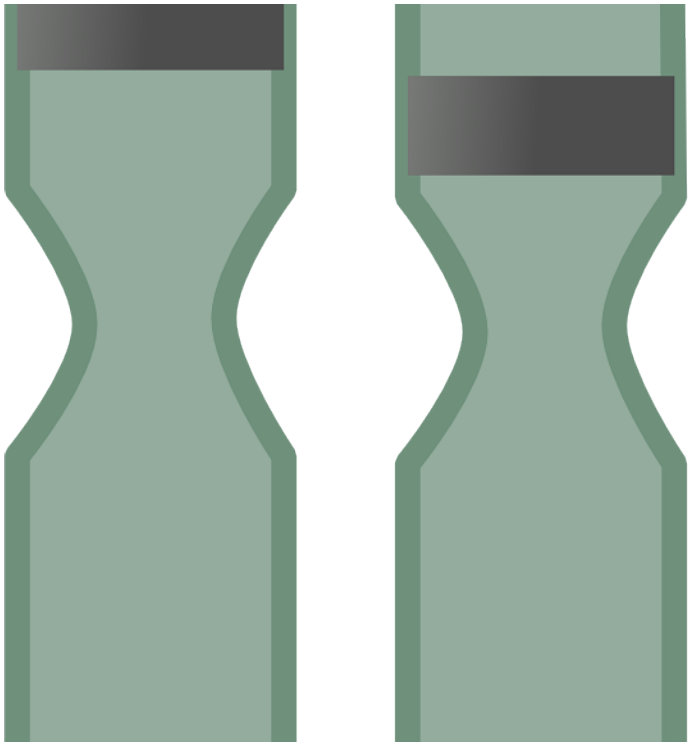
Unraveling role of tumor suppressor in gene expression and ovarian tumorigenesis

June 26 2018



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The tumor suppressor protein ARID1A controls global transcription in ovarian epithelial cells, according to new research conducted at The Wistar Institute, which provided mechanistic insight into tumorigenesis mediated by ARID1A loss in ovarian cancer. Study results were published online in *Cell Reports*.

ARID1A is the most frequently mutated epigenetic regulator across human cancers, with highest prevalence of mutations in ovarian clear cell carcinoma—nearly 60 percent of patients diagnosed with this cancer carry mutations that result in loss of ARID1A protein function.

The study led by Alessandro Gardini, Ph.D., assistant professor in the Gene Expression & Regulation Program at Wistar, was the first systematic, genome-wide profiling of ARID1A activity in ovarian epithelial cells.

"Despite a large body of evidence implicating ARID1A in ovarian tumorigenesis, the mechanism remained elusive," said Gardini. "Our work shed light onto the physiological role of the protein in global gene transcription, elucidating the oncogenic consequences of its mutation."

Gardini and his team manipulated ARID1A expression in epithelial ovarian cells and performed in-depth genomics analysis to study the role of ARID1A in genome-wide chromatin remodeling and regulation of transcription. ARID1A ablation caused dramatic and widespread transcriptional repression with a mechanism independent of chromatin remodeling.

The researchers found that ARID1A controls a fundamental regulatory step in transcription—the pausing of RNA polymerase II enzyme that is designated to the transcription of protein-coding genes—thus dictating the physiological rate of transcription for a large fraction of genes in epithelial ovarian cells.

As a consequence of ARID1A ablation, increased expression of a similar protein called ARID1B was observed as a compensatory mechanism to restore transcription and allow ovarian cancer cells to cope with the loss of ARID1A.

"ARID1B covers for ARID1A, but not entirely," said Gardini. "We identified a set of genes whose expression is strictly dependent on ARID1A and is not rescued by its colleague. The resulting dysregulation paves the way to malignant transformation."

In fact, the identified ARID1A-specific targets include genes involved in DNA repair, cell proliferation and survival.

"Because ARID1A is commonly mutated in several other cancer types, our observation might be extended to other models," said Marco Trizzino, Ph.D., a postdoctoral researcher in the Gardini Lab and first author of the study. "Further studies will determine if impaired RNA polymerase pausing is a universal mechanism that mediates the role of ARID1A as a tumor suppressor."

More information: *Cell Reports* (2018). DOI: 10.1016/j.celrep.2018.05.097

Provided by The Wistar Institute