New role in spatial chromosome organization identified for often mutated cancer protein

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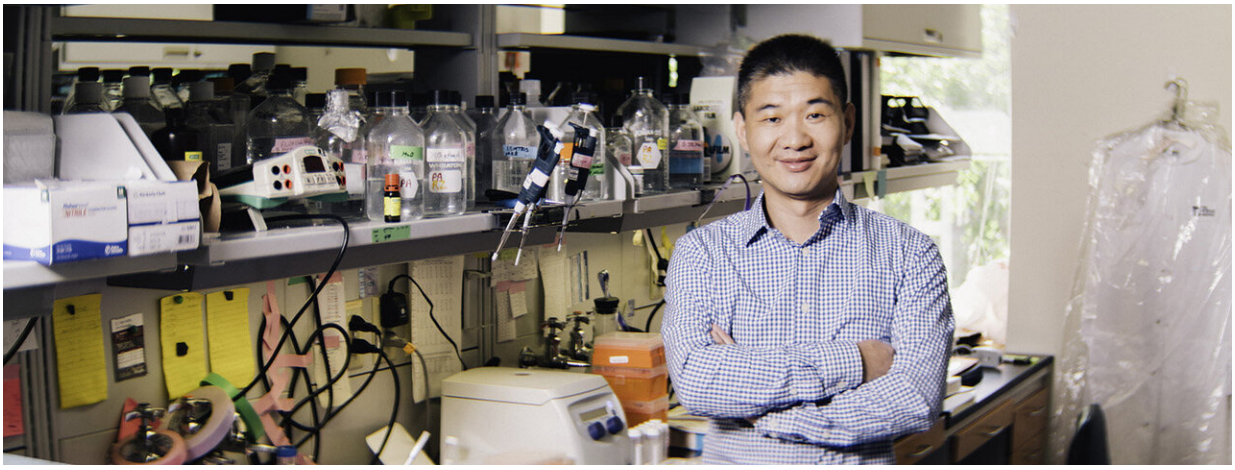

Rugang Zhang, Ph.D. Credit: The Wistar Institute

New research from The Wistar Institute sheds light on the function of the ARID1A protein, encoded by a gene that is among the most frequently mutated across human cancers. According to the study, published online in *Science Advances*, ARID1A plays a role in the spatial organization of the genome; therefore, its loss has broad effects on global gene expression. This finding adds critical information towards deciphering the molecular alterations associated with several cancer types and especially with ovarian cancer.

"My lab has been studying the role of ARID1A in gene expression

regulation as part of a complex known as SWI/SNF," said principal investigator Rugang Zhang, Ph.D., deputy director of The Wistar Institute Cancer Center, and professor and co-program leader of the Gene Expression and Regulation Program. "In our search for new interacting proteins of this complex, we discovered one that offers new perspectives on the function of ARID1A as a genome-wide regulator of spatial chromosome organization."

The three-dimensional organization of the genome dictates how several feet worth of DNA molecules are packed in a microscopic space while also allowing each gene to be accessible for transcription and expression at the appropriate time. The team found that ARID1A interacts with a component of the condensin II complex, which regulates gene expression through organizing chromosome structure.

"This is a finely regulated process and we revealed that ARID1A has a critical role in it," added Zhang.

Results showed that ARID1A dictates the genome-wide positioning of condensin II on certain DNA regulatory elements called enhancers. Therefore, when ARID1A function is lost as a consequence of gene mutation, condensin II distribution is altered and so is expression of a large set of genes.

Zhang and colleagues also revealed that, through its interaction with condensin II, ARID1A controls how different parts of chromosomes are spatially organized together in regions known as chromosomal territories that facilitate the coordinated expression of certain sets of genes.

"Our findings add an important piece to the field of chromatin regulation in cancer," said Shuai Wu, Ph.D., co-first author of the study and a postdoctoral researcher in the Zhang Lab. "By altering the special organization of chromosomes, ARID1A loss is expected to have much

broader consequences on gene expression than we originally thought."

More information: "ARID1A spatially partitions interphase chromosomes" *Science Advances* (2019). advances.sciencemag.org/content/5/5/eaaw5294

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