Mechanism of resistance to novel targeted therapy for ovarian cancer identified

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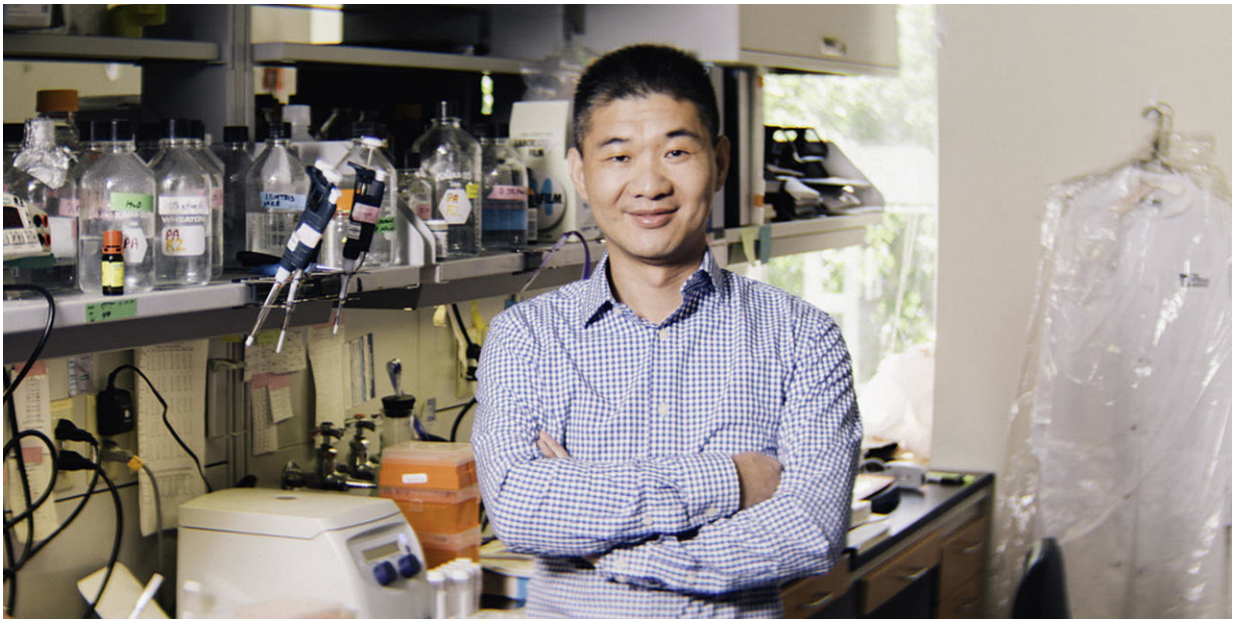

Credit: The Wistar Institute

Scientists at The Wistar Institute have unraveled a mechanism of resistance to EZH2 inhibitors in ovarian cancers with mutations in the ARID1A gene. The study, published in *Nature Communications*, suggests that inhibition of the cell death regulator BCL2 may be used to circumvent or prevent ovarian cancer treatment resistance.

Mutations in the ARID1A gene are frequent in clear cell ovarian cancer

and represent a known genetic driver in this type of malignancy. Previous Wistar research has shown that ARID1A-mutant ovarian cancers are sensitive to inhibition of EZH2, an enzyme that promotes compaction of the DNA, suggesting the use of EZH2 inhibitors, which are in clinical trials for the treatment of lymphoma, as a potential targeted therapy for ovarian clear cell carcinoma.

"Acquired resistance to targeted cancer therapies represents a substantial challenge and limits their utility. There is a pressing need to elucidate the molecular mechanisms underlying resistance so that we can design new strategies to circumvent it," said lead researcher Rugang Zhang, Ph.D., deputy director of The Wistar Institute Cancer Center, and professor and co-leader of the Gene Expression and Regulation Program. "We report the first mechanism of resistance to EZH2 inhibition in the context of ARID1A-mutant cancers and a potential approach to bypass the issue."

Zhang and colleagues discovered a molecular switch that happens in the SWI/SNF protein complex, of which ARID1A is a component, in ovarian cancer cells resistant to EZH2 pharmacologic inhibition. Because the SWI/SNF complex remodels chromatin and modulates gene transcription, this switch causes a shift in expression of a subset of genes and activation of factors that favor tumor cell survival.

The two proteins involved in the switch, namely SMARCA2 and SMARCA4, perform similar functions in the complex but do not work simultaneously, each being specific of certain conditions, like workers in different shifts. The researchers found that, while SMARCA4 is typically active in ovarian cancer cells, SMARCA2 takes on its job in EZH2 inhibitor-resistant cells. Consequently, several genes that are normally repressed by SMARCA4 are expressed at higher level and drive cell survival by inhibiting programmed cell death. The most relevant of these genes is BCL2, the Zhang Lab found.

Consistent with this finding, a small molecule inhibitor of BCL2 killed ovarian cancer cells resistant to EZH2 inhibition in vitro and caused shrinking of tumors established by injection of resistant cells in mice. This resulted in significant improvement in the survival of the tumor-bearing mice.

"We discovered a potential therapeutic strategy to revert resistance to EZH2 inhibition in ovarian clear cell carcinoma," said Shuai Wu, Ph.D., first author of the study and a postdoctoral researcher in the Zhang Lab. Our study also suggests that BCL2 inhibition may be used in combination with EZH2 inhibitors to prevent the onset of resistance."

The study identified a new therapeutic use for BCL2 inhibitors, which are approved for treatment of lymphoma.

More information: Shuai Wu et al, SWI/SNF catalytic subunits' switch drives resistance to EZH2 inhibitors in ARID1A-mutated cells, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06656-6

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