nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06656-6 OPEN

SWI/SNF catalytic subunits' switch drives resistance to EZH2 inhibitors in *ARID1A*-mutated cells

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Inactivation of the subunits of SWI/SNF complex such as ARID1A is synthetically lethal with inhibition of EZH2 activity. However, mechanisms of de novo resistance to EZH2 inhibitors in cancers with inactivating SWI/SNF mutations are unknown. Here we show that the switch of the SWI/SNF catalytic subunits from SMARCA4 to SMARCA2 drives resistance to EZH2 inhibitors in *ARID1A*-mutated cells. SMARCA4 loss upregulates anti-apoptotic genes in the EZH2 inhibitor-resistant cells. EZH2 inhibitor-resistant *ARID1A*-mutated cells are hypersensitive to BCL2 inhibitors such as ABT263. ABT263 is sufficient to overcome resistance to an EZH2 inhibitor. In addition, ABT263 synergizes with an EZH2 inhibitor in vivo in ARID1A-inactivated ovarian tumor mouse models. Together, these data establish that the switch of the SWI/SNF catalytic subunits from SMARCA4 to SMARCA2 underlies the acquired resistance to EZH2 inhibitors. They suggest BCL2 inhibition alone or in combination with EZH2 inhibition represents urgently needed therapeutic strategy for *ARID1A*-mutated cancers.

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