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Potential therapeutic targets in ARID1A -mutated cancers

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Abstract

© 2015 © 2015 Taylor & Francis. ARID1A is a subunit of the Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin-remodeling complex that regulates gene expression by controlling gene accessibility. ARID1A shows one of the highest mutation rates across different human cancer types. For example, ARID1A is mutated in ~ 50% of ovarian clear cell carcinoma (OCCC). There is considerable interest in developing cancer therapeutics that correlate with ARID1A mutational status. A recent study demonstrated a synthetic lethality by targeting EZH2 histone methyltransferase activity in ARID1A-mutated OCCC using a clinically applicable small-molecule inhibitor. The observed synthetic lethality correlated with inhibition of PI3K/AKT signaling. In addition, there is evidence indicating that ARID1A-mutated cancer may also be subjected to therapeutic intervention by targeting residual SWI/SNF activity, the PI3K/AKT pathway, the DNA damage response, the tumor immunological microenvironment and stabilizing wild-type p53. In summary, we propose EZH2 inhibitor-based combinatorial strategies for targeting ARID1A-mutated cancers.

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Keywords

ARID1A, EZH2, ovarian cancer, synthetic lethality