Fatty acid metabolism and drug resistance to EZH2 inhibition

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Numerous studies in the past decade have demonstrated that human cancers are not only genetic diseases, but also frequently associated with epigenetic alterations. Among these epigenetic alterations, aberrant accumulation of trimethylation at histone H3 lysine residue 27 (H3K27Me3), a chromatin mark that results in nucleosome condensation and gene silencing, is correlated with disease progression in many cancers. Deposition of H3K27Me3 to chromatin requires the polycomb repressive complex 2 (PRC2), an evolutionarily conserved protein complex whose core is composed of EZH2, SUZ12, EED and RbAp46/48. Multiple pharmacologic inhibitors have been developed to diminish the activity of PRC2 for suppressing cancer growth. Most of these inhibitors compete with EZH2, the catalytic component of PRC2, for S-adenosyl-l-methionine (SAM), a universal methyl donor for methyltransferases. Among them, Tazverik (tazemetostat), developed by Epizyme Inc., was approved by US FDA in 2020 to treat advanced epithelioid sarcoma with SMARCB1 loss (SAM), a universal methyl donor for methyltransferases.

In this issue of eBioMedicine, Zhang et al. analyzed the transcriptomic and metabolic responses to GSK126, an EZH2 inhibitor under clinical investigation, in B16F10, a murine melanoma cell line that is intrinsically resistant to EZH2 inhibitor treatment. They uncovered that GSK126 induced the expression of multiple genes involved in fatty acid metabolism, such as SCD1, a rate limiting enzyme responsible for the conversion of saturated fatty acids to monounsaturated fatty acids that promotes cancer cell growth by enhancing membrane turnover and energy production. Zhang et al. validated these regulations in multiple human solid tumor cell lines and demonstrated that they are direct effects from the loss of H3K27me3 upon EZH2 inhibition by ChIP analyses. The subsequent metabolic profiling further confirmed the effect of GSK126 on cellular metabolism in B16F10 cells. In agreement with the upregulation of fatty acid metabolic genes, Zhang et al. discovered that GSK126 increased the abundance of a number of fatty acids, mostly polyunsaturated fatty acid (PUFA), in GSK126-treated B16F10 cancer cells. In contrast, while GSK126 treatment also affected the cellular metabolism of Daudi, a lymphoma cell line sensitive to EZH2 inhibition, neither the expression of fatty acid metabolism genes nor the abundance of PUFA was altered by GSK126. Notably, addition of fatty acids (palmitic acid and stearic acid) rescued the growth suppression in Daudi cells treated by GSK126, suggesting that increased fatty acid synthesis may provide a growth advantage for cells to survive the treatment of EZH2 inhibitors.

Next, Zhang et al. evaluated the potency of targeting SCD1 through either genetic suppression or pharmacologic inhibition in cancer cells resistant to EZH2 inhibition. As expected, suppressing SCD1 increased cellular response to EZH2 inhibition in vitro and in vivo. Lastly, as SCD1 inhibitors are at preclinical stages, Zhang et al. investigated the tumor-suppressive effect of combining the clinical lipid-lowering drug fenofibrate with GSK126. Their results revealed that the drug combination had a significant stronger reduction on cell growth

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than each treatment alone in vitro, suggesting a possible rapid translation of their finding into clinical trials.

This study from Zhang et al. suggests a great potential of targeting fatty acid metabolism to improve the clinical utility of EZH2 inhibitors. However, there are several unsolved questions: (1) What is the mechanism underlying the selective induction of fatty acid metabolism genes in cancer cells intrinsically resistant to EZH2 inhibition? Is it related to MLL1 expression? (2) Can the expression of certain fatty acid metabolism genes serve as biomarkers to predict patient’s response to EZH2 inhibitors? (3) Will deregulation of fatty acid metabolism, particularly PUFA, be one key mechanism for acquired resistance to EZH2 inhibitors in epithelioid sarcoma and EZH2-mutant follicular lymphoma cancer cells? (4) Will the availability of fatty acid in tumor microenvironment and its uptake into cancer cells impact cellular response to EZH2 inhibitors? (5) As both tazemetostat and fenofibrate treatments are accompanied by side effects such as headache, nausea and uncomfortableness in stomach, is the combined treatment of an EZH2 inhibitor and fenofibrate tolerable in patients?

Nevertheless, this discovery by Zhang et al. is existing. Future development of clinically useful SCD1 inhibitors will be warranted to advance this finding to clinical testing.

Author’s contributions
Y.W.: conceptualization, literature search, writing.

Declaration of interests
I have no conflict of interest to declare.

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