CANCER DISCOVERY 10

Research Articles

The Folate Cycle Enzyme MTHFR Is a Critical Regulator of Cell Response to MYC-Targeting Therapies

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Abstract

Deciphering the impact of metabolic intervention on response to anticancer therapy may elucidate a path toward improved clinical responses. Here, we identify amino acid–related pathways connected to the folate cycle whose activation predicts sensitivity to MYC-targeting therapies in acute myeloid leukemia (AML). We establish that folate restriction and deficiency of the rate-limiting folate cycle enzyme MTHFR, which exhibits reduced-function polymorphisms in about 10% of Caucasians, induce resistance to MYC targeting by BET and CDK7 inhibitors in cell lines, primary patient samples, and syngeneic mouse models of AML. Furthermore, this effect is abrogated by supplementation with the MTHFR enzymatic product CH_3-THF. Mechanistically, folate cycle disturbance reduces H3K27/K9 histone methylation and activates a SPI1 transcriptional program counteracting the effect of BET inhibition. Our data provide a rationale for screening *MTHFR* polymorphisms and folate cycle status to nominate patients most likely to benefit from MYC-targeting therapies.

Significance: Although MYC-targeting therapies represent a promising strategy for cancer treatment, evidence of predictors of sensitivity to these agents is limited. We pinpoint that folate cycle disturbance and frequent polymorphisms associated with reduced MTHFR activity promote resistance to BET inhibitors. CH_3-THF supplementation thus represents a low-risk intervention to enhance their effects.

See related commentary by Marando and Huntly, p. 1791.

This article is highlighted in the In This Issue feature, p. 1775

Footnotes

- **Note:** Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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