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Targeting RRM2 and mutant BRAF is a novel combinatorial strategy for melanoma

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Abstract

© 2016 American Association for Cancer Research.The majority of patients with melanoma harbor mutations in the BRAF oncogene, thus making it a clinically relevant target. However, response to mutant BRAF inhibitors (BRAFi) is relatively short-lived with progression-free survival of only 6 to 7 months. Previously, we reported high expression of ribonucleotide reductase M2 (RRM2), which is rate-limiting for de novo dNTP synthesis, as a poor prognostic factor in patients with mutant BRAF melanoma. In this study, the notion that targeting de novo dNTP synthesis through knockdown of RRM2 could prolong the response of melanoma cells to BRAFi was investigated. Knockdown of RRM2 in combination with the mutant BRAFi PLX4720 (an analog of the FDA-approved drug vemurafenib) inhibited melanoma cell proliferation to a greater extent than either treatment alone. This occurred in vitro in multiple mutant BRAF cell lines and in a novel patient-derived xenograft (PDX) model system. Mechanistically, the combination increased DNA damage accumulation, which correlated with a global decrease in DNA damage repair (DDR) gene expression and increased apoptotic markers. After discontinuing PLX4720 treatment, cells showed marked recurrence. However, knockdown of RRM2 attenuated this rebound growth both in vitro and in vivo, which correlated with maintenance of the senescence-associated cell-cycle arrest. Implications: Inhibition of RRM2 converts the transient response of melanoma cells to BRAFi to a stable response and may be a novel combinatorial strategy to prolong therapeutic response of patients with melanoma.

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