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Molecular Cancer Therapeutics

Expression of leukemia associated fusion proteins increases sensitivity to histone deacetylase inhibitor induced DNA damage and apoptosis.

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Histone deacetylase inhibitors (HDI) show activity in a broad range of hematological and solid malignancies, yet the percentage of patients in any given malignancy who experience a meaningful clinical response remains small. In this study, we sought to investigate HDI efficacy in acute myeloid leukemia (AML) cells expressing leukemia associated fusion proteins (LAFPs). HDI have been shown to induce apoptosis in part through accumulation of DNA damage and inhibition of DNA repair. LAFPs have been correlated with a DNA repair deficient phenotype, which may make them more sensitive to HDI-induced DNA damage. We found expression of the LAFPs PLZF-RARα, PML-RARα and RUNX1-ETO (AML1-ETO) increased sensitivity to DNA damage and apoptosis induced by the HDI vorinostat. The increase in apoptosis correlated with an enhanced down-regulation of the pro-survival protein BCL2. Vorinostat also induced expression of the cell cycle regulators p19INK4D and p21WAF1, and triggered a G2-M cell cycle arrest to a greater extent in LAFP expressing cells. The combination of LAFP and vorinostat further led to a greater down-regulation of several base excision repair (BER) enzymes. These BER genes represent biomarker candidates for response to HDI-induced DNA damage. Notably, repair of vorinostat-induced DNA double strand breaks was found to be impaired in PLZF-RARα expressing cells, suggesting a mechanism by which LAFP expression and HDI treatment cooperate to cause an accumulation of damaged DNA. These data support the continued study of HDI based treatment regimens in LAFP-positive AMLs.

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