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PII: S1568-7864(17)30023-X
DOI: http://dx.doi.org/doi:10.1016/j.dnarep.2017.08.002
Reference: DNAREP 2411

To appear in: *DNA Repair*

Received date: 13-1-2017
Revised date: 28-6-2017
Accepted date: 7-8-2017

Please cite this article as: Youjia Tian, Guochao Liu, Hui Wang, Zhujun Tian, Zuchao Cai, Fengmei Zhang, Yue Luo, Shue Wang, Gongshe Guo, Xiaowei Wang, Simon Powell, Zhihui Feng, Valproic Acid Sensitizes Breast Cancer Cells to Hydroxyurea through Inhibiting RPA2 Hyperphosphorylation-Mediated DNA Repair Pathway, DNA Repairhttp://dx.doi.org/10.1016/j.dnarep.2017.08.002

Valproic Acid Sensitizes Breast Cancer Cells to Hydroxyurea through Inhibiting RPA2 Hyperphosphorylation-Mediated DNA Repair Pathway

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Running title: VPA disrupts DNA repair pathway induced by replication arrest

Highlights :

- The combination of VPA and HU can sensitize breast cancer cells for the chemotherapy.
- VPA can resulte in the accumulation of more DNA DSBs in response to HU-induced replication arrest.
- The mechanism of combinatorial drug effects is that VPA can block HU-stimulated RPA2-p-mediated HR.

Abstract

Abbreviations: VPA (valproic acid); HU (hydroxyurea); IR (ionizing radiation); DSBs (double-strand breaks); HR (homologous recombination); RPA (replication protein A); RPA2-p (hyperphosphorylation of RPA2); wtRPA2 (wild-type RPA2); muRPA2 (hyperphosphorylation mutant RPA2); HDACis (histone deacetylase inhibitors); DMBA (dimethylbenzanthracene); SSBs (single-strand breaks)

It was reported that valproic acid (VPA, a histone deacetylase inhibitor) can sensitize cancer cells to hydroxyurea (HU, a ribonucleotide reductase inhibitor) for chemotherapy, although the mechanism of VPA-induced HU sensitization is unclear. In this study, we systematically characterized VPA-induced HU sensitization of breast cancer cells. Multiple breast cancer cell models were employed to investigate whether the safe concentration of 0.5 mM VPA and 2 mM HU can result in DNA double-strand breaks