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# 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 result 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

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