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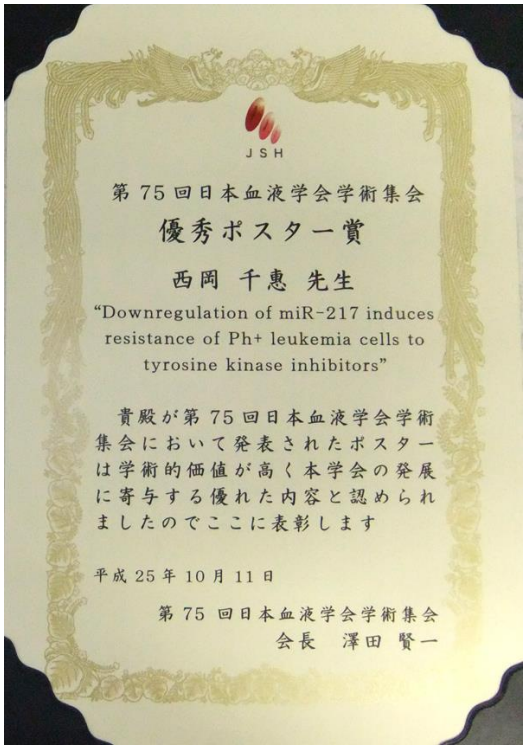
Downregulation of miR-217 induces resistance of Ph+ leukemia cells to tyrosine kinase inhibitors



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Abstract

This study found that long-term exposure of chronic myelogenous leukemia (CML) K562 cells to BCR/ABL thyrosine kinase inhibirors (TKIs) induced drug-resistance in association with an increase in levels of DNA methyltransferases (DNMTs) and polycomb group (PcG) protein embryonic ectoderm development (EED) and a decrease in levels of microRNAs (miRNAs) including miR-217. The levels of DNMTs and EED were elevated in leukemia cells isolated from individuals with TKI-resistant Ph+ ALL and CML in parallel with downregulation of miR-217 as compared with those at initial diagnosis. Notably, lentiviral transduction of miR-217 sensitized dasatinib-resistant K562 cells to dasatinib in parallel with downregulation of DNMT3A. In addition, combination of dasatinib (10 nM, 1 month) and DNMTs inhibitor 5-Aza-2'-deoxycytidine

(5-AzadC) (0.1 &muM, 1 month) potently inhibited proliferation of K562 cells in vitro and in vivo in parallel with upregulation of miR-217 and downregulation of DNMT3A. Taken together, long term exposure of ph+ leukemia cells causes drug-resistance via downregulation of miR-217 and upregulation of DNMT3A. DNMT3A may be a promising therapeutic target for preventing TKIs resistance.