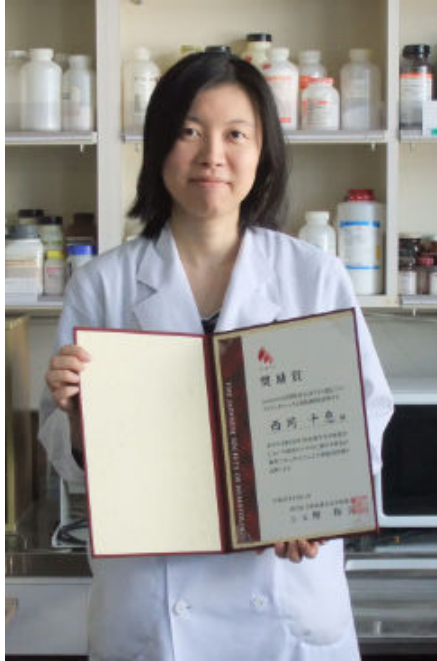


第 72 回日本血液学会・第 52 回日本臨床血液学会
2010 年 9 月 24-26 日、横浜、パシフィコ横浜

**Long-term exposure of leukemia cells to multitargeted tyrosine kinase inhibitor
induces epigenetic silencing of *PTEN* gene.**



西岡 千恵

(免疫学/日本学術振興会 特別研究員 PD)

Chie Nishioka,^{1,3} Takayuki Ikezoe,² Jing Yang,² Akihito Yokoyama,² Keiko Udaka¹

¹Department of immunology, ²Department of Hematology and Respiratory Medicine, Kochi Medical School, Kochi University, Nankoku, Kochi 783-8505, Japan., ²Research Fellow of the Japanese Society for the Promotion of Science (JSPS), Chiyodaku, Tokyo, Japan.

Abstract

Imatinib induces complete molecular response in patients with chronic myeloid leukemia (CML) and chronic eosinophilic leukemia (CEL). However, the development of resistance to imatinib has emerged as an important clinical problem for molecular targeted therapy in CML and CEL. In this study, we have established the imatinib-resistant CEL EOL-1 sublines (designated as EOL-1R) by culturing cells with increasing concentrations of imatinib for 6 months. Interestingly, EOL-1R cells showed the epigenetic silencing of the *phosphatase and tensin homolog deleted on chromosome ten (PTEN)* gene. Exposure of EOL-1R cells to imatinib failed to dephosphorylate AKT, ERK and STAT5, although PDGFR α was effectively inactivated. Forced-expression of PTEN negatively regulated these signal pathways and sensitized EOL-1R cells to imatinib. Notably, hypermethylation on the promoter region of the *PTEN* gene in association with down-regulation of this gene transcripts was identified in imatinib-resistant

leukemia cells isolated from individuals with CEL, CML and Philadelphia-positive acute lymphoblastic leukemia. In addition, anti-epigenetic agents restored *PETN* expression, resulting in sensitization of EOL-1R cells to imatinib.

Taken together, epigenetic silence of *PTEN* is one of the mechanisms which cause drug-resistance in individuals with leukemia after exposure to imatinib. Anti-epigenetic agents may be useful to overcome drug-resistance in such a case.

