Pharmacological inhibition of c-Abl compromises genetic stability and DNA repair in Bcr-Abl-negative cells.

Abstract:
Imatinib inhibits the kinase activity of Bcr-Abl and is currently the most effective drug for treatment of chronic myeloid leukemia (CML). Imatinib also blocks c-Abl, a physiological tyrosine kinase activated by a variety of stress signals including damaged DNA. We investigated the effect of pharmacological inhibition of c-Abl on the processing of irradiation-induced DNA damage in Bcr-Abl-negative cells. Cell lines and peripheral blood mononuclear cells (PBMCs) from healthy volunteers were treated with imatinib or dasatinib before gamma-irradiation. Inhibition of c-Abl caused an enhanced irradiation-induced mutation frequency and slowdown of DNA repair, whereas imatinib was ineffective in cells expressing a T315I variant of c-Abl. Mutation frequency and repair kinetics were also studied in c-Abl-/- murine embryonic fibroblasts (MEFs) retransfected with wild-type c-Abl (wt-Abl) or a kinase-defect variant of Abl (KD-Abl). Enhanced mutation frequency as well as delayed DNA repair was observed in cells expressing KD-Abl. These data indicate that pharmacological inhibition of c-Abl compromises DNA-damage response.

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