Non-homologous DNA End Joining Repair in Normal and Leukemic Cells Depends on the Substrate Ends

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Double-strand breaks (DSBs) are the most serious DNA damage which, if unrepaired or misrepaired, may lead to cell death, genomic instability or cancer transformation. In human cells they can be repaired mainly by non-homologous DNA end joining (NHEJ). The efficacy of NHEJ pathway was examined in normal human lymphocytes and K562 myeloid leukemic cells expressing the BCR/ABL oncogenic tyrosine kinase activity and lacking p53 tumor suppressor protein. In our studies we employed a simple and rapid *in vitro* DSB end joining assay based on fluorescent detection of repair products. Normal and cancer cells were able to repair DNA damage caused by restriction endonucleases, but the efficiency of the end joining was dependent on the type of cells and the structure of DNA ends. K562 cells displayed decreased NHEJ activity in comparison to normal cells for 5′ complementary DNA overhang. For blunt-ended DNA there was no significant difference in end joining activity. Both kinds of cells were found about 10-fold more efficient for joining DNA substrates with compatible 5′ overhangs than those with blunt ends. Our recent findings have shown that stimulation of DNA repair could be involved in the drug resistance of BCR/ABL-positive cells in anticancer therapy. For the first time the role of STI571 was investigated, a specific inhibitor of BCR/ABL oncogenic protein approved for leukemia treatment in the NHEJ pathway. Surprisingly, STI571 did not change the response of BCR/ABL-positive K562 cells in terms of NHEJ for both complementary and blunt ends. Our results suggest that the various responses of the cells to DNA damage *via* NHEJ can be correlated with the differences in the genetic constitution of human normal and cancer cells. However, the role of NHEJ in anticancer drug resistance in BCR/ABL-positive cells is questionable.

Key words: Non-homologous DNA End Joining (NHEJ), BCR/ABL Oncogenic Tyrosine Kinase, Imatinib (STI571)