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Nucleolytic Cleavage of the Mixed Lineage Leukemia Breakpoint Cluster Region during Apoptosis*

Sai-Peng Sim‡ and Leroy F. Liu‡§¶

Author Affiliations

Abstract

VP-16 (etoposide) has recently been shown to induce topoisomerase II (TOP2)-mediated DNA cleavage within the mixed lineage leukemia (MLL) breakpoint cluster region (bcr), suggesting a role of TOP2 in MLL gene rearrangement. In our current studies, we have compared the induction of DNA cleavage within the MLL bcr in different cell lines after treatment with various anticancer drugs. All anticancer drugs tested including VP-16 (a TOP2-directed drug), camptothecin (a topoisomerase I-directed drug), 5-fluorouracil and methotrexate (antimetabolites), and vinblastine (a microtubule inhibitor) induced the same site-specific cleavage within the MLL bcr. This cleavage was shown to be nuclease-mediated but not TOP2-mediated by the following observations: 1) drug-induced cleavage within the MLL bcr was not protein-linked; 2) unlike TOP2-mediated cleavage, drug-induced DNA cleavage within the MLL bcr was kinetically slow and coincided with the formation of the apoptotic nucleosomal DNA ladder; 3) drug-induced cleavage within the MLL bcr was unaffected in cells with reduced nuclear TOP2; and 4) drug-induced cleavage within the MLL bcr was abolished by the caspase inhibitor, Z-Asp(OCH_3)-Glu(OCH_3)-Val-Asp(OCH_3)-FMK. The possibility that an apoptotic nuclease may be involved in cleavage of the MLL bcr and MLL gene translocation is discussed.

- Abbreviations:

  t-AML
  : therapy-related acute myeloid leukemia
  TOP2
  : topoisomerase II
  CPT
  : camptothecin
  VP-16 (etoposide)
  : 4′-demethylepipodophyllotoxin 9-[4,6-O-ethylidene-β-D-glucopyranoside]
  MLL
  : mixed lineage leukemia
  bcr
  : breakpoint cluster region
  CAD
  : caspase-activated DNase
  ICAD
  : inhibitor of caspase-activated DNase
  Z-DEVD-FMK
  : Z-Asp(OCH_3)-Glu(OCH_3)-Val-Asp(OCH_3)-FMK
  PCR
  : polymerase chain reaction
  kb
  : kilobase(s)

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