WASP functions. The lymphocytes with the dual mutations apparently had an advantage over the cells with the single mutation in terms of cell growth in vivo. These findings encourage future attempts of gene therapy for WAS. Introduction and expression of the normal WASP gene even in small numbers of hematological stem cells could be enough to obtain clinical benefit in gene therapy for WAS patients.

ACKNOWLEDGMENT

We thank Prof K. Kobayashi (Department of Pediatrics, Hokkaido University School of Medicine, Sapporo, Japan) for his critical reading of this manuscript. Supported by a grant from the Ministry of Health and Welfare, Japan.

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REFERENCES


c-kit Activating Mutations and Mast Cell Proliferation in Human Leukemia

To the Editor:

Activating mutations of c-kit proto-oncogene have been causally related to neoplastic transformation of mast cell lineage. The first evidence in humans was found in mast cell leukemia cell line HMC-1 with the detection of two mutations in codons 560 (V560G) in the juxtamembrane domain and 816 (D816V) in the cytoplasmic domain of c-kit, resulting in ligand-independent activation of the c-kit product. The predominant effect of D816V could be established by functional studies that demonstrated its pathogenetic role in mast cell transformation.

The cytofluorimetric finding of a subset of CD117

+4 karyotype in all the metaphases analysed. The concomitance of two AML-specific chromosomal changes and D816Y kit mutation raises the question of their timing and role in the onset and evolution of leukemia in the patient under study. Translocation t(8;21) corresponds to the D814Y mutation identified and characterized in the murine P815 mastocytoma cell line. Stem cell factor (SCF) transcripts were not detected by reverse transcription-polymerase chain reaction in leukemic blasts from bone marrow and peripheral blood from the patient. This finding indicates that the massive mast cell growth and differentiation observed in the patient’s bone marrow is not dependent on SCF stimulation. Thus, the c-kit activating D816Y mutation leads to independent SCF growth like its murine D814Y counterpart also in humans.

Cytogenetic analysis on the patient’s blasts showed a 47, XY t(8;21) +4 karyotype in all the metaphases analysed. The concomitance of two AML-specific chromosomal changes and D816Y kit mutation raises the question of their timing and role in the onset and evolution of leukemia in the patient under study. Translocation t(8;21) has proved to play a primary role in M2 acute myeloid leukemia and the blast immunophenotype clearly pointed to this event being a primary one in our case. Based on the cytofluorimetric finding of a subset of CD117 blasts (23%) in our patient, we argue that the D816Y mutation was a
secondary event occurring in a proliferating CD117+ myeloid subclone responsible for the spontaneous mast cell differentiation. The effect of D816Y on Kit signaling may be further enhanced by trisomy of chromosome 4 (carrying the c-kit gene). We favor the hypothesis that the c-kit activating mutation preceded trisomy formation, which then provided further grounds for this hypothesis to be considered. Evidence accumulated so far on c-kit activating mutations in man points to c-kit being involved in oncogenic conversion of mast cells. In any case, the cooperation of c-kit with other cancer genes to support proliferation of leukemic blasts is exemplified by the unusual case described here and also by data on c-kit expression in most cases of AML. The pattern of expression of c-kit activating mutations probably depends on their timing compared with other leukemogenic events and the target cell type in which the mutant gene product accumulates.

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REFERENCES

Fig. 1. Exon 17 of human c-kit. Hot spot for activating mutations in mast cell disease.
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