Chromosome 16 Inversion in Acute Myelogenous Leukemias with Bone Marrow Eosinophilia

Recent progress in molecular analysis has shown that abnormal chromosome constructs cause aberrant gene expression, leading to cancer. The chromosome rearrangements so far described include deletions, insertions, translocations and inversions. Analysis of chromosomal translocations and inversions has attracted a great deal of attention, especially in hematological malignancies. There are two principal mechanisms of oncogene activation by translocations and inversions; proto-oncogene activation by juxtaposing genes having potent enhancer effects, like immunoglobulin genes, and formation of fusion genes encoding for oncogenic chimeric proteins (1). Representatives of the former include $c$-$myc$ of t(8;14), and $c$-$abl$ of t(9;22) is a good example of the latter. Interestingly, such chromosomal aberrations have been found to be specific to particular subtypes of leukemias, implying cytogenetic-clinico-pathological correlations, which might allow understanding of the pathogenesis of these important malignancies.

One of the most frequent chromosomal rearrangements detected in the de novo acute myelogenous leukemia (AML) in the chromosome 16 inversion [inv(16)(p13;q22)], which has been reported to account for up to 12% of the karyotypic abnormalities found with this neoplasm (2). This abnormality is highly correlated with, but not uniformly restricted to, acute myelomonocytic leukemias with bone marrow eosinophilia (5% or more of the nonerythroid cells), the French-American-British (FAB) type M4Eo (3). Of this subgroup, almost all have inv(16), del(16)(q22), or t(16;16)(p13;q22), and in the majority of such patients this is the only apparent rearrangement. Identification of inv(16) or the two related rearrangement [del(16), t(16;16)] is important because they have been found to be associated with a relatively good prognosis in terms of long-term disease-free survival (4, 5).

The breakpoints in the inv(16) have recently been cloned and have been shown to involve the $CBFB$ gene on 16q22 and the $MYH11$ gene on 16p13 (6, 7). $CBFB$ codes for the $\beta$ subunit of the core binding factor (CBF), a heterodymeric transcription factor known to bind to the enhancers of various murine leukemia viruses and to similar motifs in the enhancers of T-cell receptor (TCR) genes. $MYH11$ encodes the smooth muscle form of myosin heavy chain protein. The fusion creates an inframe fusion messenger RNA consisting of upstream $CBFB$ fused to downstream $MYH11$ coding sequences, and the resultant chimeric protein has the potential for transforming activity in vitro. The mechanism of action of the inv16 protein is unknown, but the inv16 protein complex with the $\alpha$ subunit of CBF, which binds to the DNA, may alter the assembly of sequence specific transcription factors on adjacent sites in the enhancers of certain target genes (7).

Since the cloning of inv(16), several groups have tested and verified that the $CBFB$-$MYH11$ fusion is the primary molecular event associated with this inversion. Claxton et al (8) studied a series of 37 leukemia patients with either inv(16) or t(16;16) using the reverse transcriptase-polymerase chain reaction (RT-PCR) and showed all patients except one to exhibit $CBFB$-$MYH11$ fusion mRNA. Another group (9) revealed $CBFB$-$MYH11$ fusion messages in 33 of 37 cases with inv(16) and in all of four t(16;16)-containing cases. These data also indicated that the genetic consequences of rearrangements in inv(16) and t(16;16) are identical. In addition, Marlton et al (10) reported six patients with 5'-$CBFB$-$MYH11$-3' chimeric transcripts to have a deletion of the chromosome 16p arm containing the exon of the 5' portion of the MYH11 gene, using fluorescence in situ hybridization (FISH), confirming that the 5'-$CBFB$-$MYH11$-3' transcript, rather than the reciprocal 5'-MYH11/CBFB-3', is the critical product for inv(16) leukemogenesis.

Of the three related chromosome 16 rearrangements observed cytogenetically in leukemia patients, the only one that has not been analyzed at the molecular level is the del(16)(q22). Usuki et al in this issue (11) describe an AML case with this rearrangement, providing RT-PCR evidence of the expression of the CBFB-MYH11 fusion transcript. Sequence analysis of the fusion transcript demonstrated inframe fusion of 5' $CBFB$ at position 495 to 3' $MYH11$ at 1201, which corresponds to one of the typical chimeric cDNAs detected in inv(16) or t(16;16). The described data indicated that leukemia cells diagnosed as del(16)(q22) from cytogenetical analysis, contain inv(16) or t(16;16). This is the first report featuring detailed studies of del(16)(q22) at the molecular level. The findings, in line with the literature, suggest that RT-PCR and FISH molecular analyses of more patients with del(16)(q22) or variant translocations such as the t(5;16)(q33;q22) (12) may shed important light on the mechanisms of leukemogenesis caused by the inversion 16 fusion gene.

Ryuizo Ueda, MD
The Second Department of Internal Medicine, Nagoya City University Medical School, 1, Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467

See also p 327.
References