**Haematology and Blood Transfusion** Vol. 31
Modern Trends in Human Leukemia VII
Edited by Neth, Gallo, Greaves, and Kabisch


# A Human Leukemic T-Cell Line Bears an Abnormal and Overexpressed *c-myc* Gene: Molecular and Functional Characterization of the Rearrangement *

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Activation of the *c-myc* oncogene has been implicated in the pathogenesis of T-cell malignancies in species other than man [1–3]. In order to establish a possible involvement of this oncogene in human T-cell neoplasias, we investigated the *c-myc* structure in several primary T-cell tumors as well as in several leukemic T-cell lines. The Hut 78 line, derived from a Sezary syndrome patient, was found to have a *c-myc* rearrangement beginning immediately 3′ to *c-myc* exon 3 [4]. The abnormal *c-myc* also appears to be duplicated compared to the normal allele. Chromosome analysis reveals that trisomy is the only cytogenetic anomaly involving chromosome 8, suggesting that the duplicated chromosome is the one carrying the abnormal *c-myc* and ruling out a Burkitt's type translocation event. This was also excluded by Southern blotting analysis, which showed a germ-line configuration of the heavy and light chain immunoglobulin genes. Similarly the involvement of the T-cell receptor $\alpha$ and $\beta$ chain genes has been excluded. Compared to other human leukemic T-cell lines, the Hut 78 cells express a high amount of *c-myc* transcript, suggesting that the 3′ *c-myc* abnormality may cause a deregulation of the expression of the gene. The transmission of this *c-myc* anomaly through multiple cell passages and its duplication imply a possible relationship either with the leukemic process involving the Hut 78 cells or the maintenance of the abnormal phenotype in culture. In order to better characterize this *c-myc* anomaly, we have cloned in the 788 phage arms a genomic 13.8 kb Hind III fragment derived from the Hut 78 DNA, containing the entire *c-myc* gene and 4.5 kb of the 3′ rearranged sequences. The latter are rich in human repetitive sequences, but a 1 kb *Eco*RI-Xba I fragment, useful as a probe, has been isolated.

By hybridization of this probe to a panel of human-hamster cell hybrids, the rearranged sequences may be located to either chromosome 2 or 8, while in situ hybridization confirms only the latter assignment. These data are compatible with the rearrangement in the Hut 78 cells being the product of either deletion of sequences 3′ to the *c-myc* or an inversion linking originally distant sequences to *c-myc*. By genomic mapping of normal DNA, a 19 kb *Sac*I fragment and a 16 kb *Bam*HI, segments have been identified as the most useful to explore the structure of large DNA regions extending at both sides of this probe and, on this basis, we have investigated the possibility of rearrangements of this area in other T-cell leukemias and hematologic malignancies. Preliminary results show that two T-cell leukemias present abnormal *Sac*I, but not *Bam*HI fragments. Therefore, these data suggest that both cases bear rearrangements

* This work was supported by CNR-Rome "P.F. Oncologia" and by AIRC; A.D. is recipient of an AIRC fellowship
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having breakpoint positions similar to that present in the Hut 78 cell line.

Other 3′ *c-myc* rearrangements in T-cell leukemias showing a t(8;14) translocation have been recently reported [5, 6]. In these cases a rearrangement with the genes coding for the TCR α chain has been demonstrated. Our study shows that a subset of T-cell leukemias may carry different *c-myc* abnormalities, arising from cytogenetically undetectable rearrangements within chromosome 8.

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