CONCISE REPORT

C-sis and C-abl Expression in Chronic Myelogenous Leukemia and Other Hematologic Malignancies

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Cellular oncogenes have been localized at the breakpoints of characteristic chromosomal rearrangements occurring in certain hematologic malignancies. This has been reported to result in aberrant expression of the involved oncogenes. Over 90% of chronic myelogenous leukemia (CML) is characterized by a reciprocal translocation that brings c-abl from chromosome 9 to chromosome 22, and c-sis from chromosome 22 to chromosome 9. To investigate the possible role of these two oncogenes in the leukemic process, we studied their expression in a number of fresh samples obtained from patients with various forms of leukemia, by Northern blot analysis using c-onc probes. Seven of 24 samples obtained from patients with either CML or chronic myelomonocytic leukemia expressed a normal 4.0-kilobase (kb) c-sis transcript. C-sis expression was found only in the accelerated/blast phases but not in the chronic phase of CML. All of the CML Philadelphia chromosome-positive (Ph') samples expressed an aberrant 8-kb c-abl transcript. The expression of c-sis in hematopoietic malignancies constitutes a novel finding.

RESULTS

As shown in Fig 1 and Table 1, we detected a 4-kb c-sis transcript in three samples obtained from patients in the accelerated phase (AP) of CML (CML-AP), in two samples obtained from patients in the lymphoid CML blast crisis (BC) phase (CML-BC), and in the K562 cell line, derived from a patient with CML-BC. C-sis expression was of low intensity and comparable with the level detected in the Hut 102 cell line, derived from a patient with cutaneous T cell lymphoma and known to express c-sis. We also found c-sis expressed in two samples from patients with CMMI, a disorder frequently confused with CML, and often called Ph'-negative (Ph') CML. With the exception of one patient with CML-BC, all the samples that expressed the 4-kb c-sis transcript also expressed a less intense 3-kb species as reported by others (Fig 1). An analysis of the DNA using the restriction enzymes EcoRI and BglII and probes from both ends of the c-sis gene disclosed no DNA amplifications or rearrangements in those samples that expressed c-sis (data not shown).

Fig 2 and Table 1 show our results using the c-abl probe. An aberrant 8-kb transcript was expressed in all Ph' CML samples.
samples. This 8-kb c-abl transcript was not detected in fresh samples obtained from patients with Ph' diseases: CMML, chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), and the Hut 102 cell line. The two normal c-abl transcripts of 7- and 6-kb were present in both Ph' and Ph+ samples with the exception of two samples obtained from patients with CML in blast crisis. The 8-kb transcript was the predominant c-abl-related mRNA species in those samples expressing it. In four of six samples obtained from patients with CML-BC, the expression of this abnormal 8-kb transcript was increased to levels comparable with those in the K562 cell line, known to have an amplified c-abl gene. Analysis of the DNA from these fresh samples, using the restriction enzymes EcoRI and BglII and probes from both the 5' and 3' ends of the c-abl gene disclosed no c-abl amplifications or rearrangements (data not shown).

DISCUSSION

C-sis, the cellular homologue of the simian sarcoma virus oncogene, is the structural gene for the B chain of platelet-derived growth factor (PDGF), the major mitogen of human serum. C-sis expression has been found in osteosarcomas, fibrosarcomas, and gliomas, but not in hematologic malignancies with the exception of the cell line Hut 102. The mitogenic properties of PDGF may be involved in tumor development, according to an autocrine model in which the neoplastic cells proliferation is driven by growth factors produced by the tumor itself. Since PDGF is reported to have mitogenetic effects on hematopoietic cells as well as hematopoietic microenvironment cells when exogenously administered, perhaps the product of c-sis in CML is secreted and does have a direct dysregulatory effect on hematopoiesis. Alternatively, the product of c-sis in CML is not secreted and the neoplastic cells are rendered mitogenically competent by PDGF's effects on internal cellular structures as suggested by others studying an osteosarcoma cell line. In any event, the role of c-sis in CML and CMML remains speculative at present, and its expression may be a consequence of the neoplastic state, rather than being a causal factor. The fact that c-sis is expressed in Ph1+ disease suggests that its expression is not a consequence of the 9:22 translocation. It is also of note that c-sis expression was found only in the accelerated or blast phases, but not in the chronic phase of CML (Table 1), raising the possibility that it may have a role in the progression of the disease.
The finding of an aberrant 8-kb c-abl transcript in Ph+ CML has been reported previously. We have extended these observations to include more patient samples and report that the 8-kb aberrant transcript is present in all patients and in all phases of the disease. Other investigators have recently demonstrated in the K562 cell line and fresh CML samples the presence of an abnormal c-abl protein with tyrosine kinase activity that is not present in normal cells. It is conceivable that this protein is encoded by the 8-kb c-abl transcript. The nature of the 8-kb mRNA has been recently clarified by cDNA cloning. It appears to be a fused transcript of the bcr gene of chromosome 22 and of the translocated c-abl gene. Our study confirms the uniform size of the aberrant transcript in spite of variable breakpoints on both chromosomes. This suggests that the splicing of the large primary transcript must occur at common donor–acceptor sites.

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REFERENCES

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