IN VolVEMENT OF THE p53 TUMOR SUPPRESSOR GENE IN Ph'-POSITIVE AND Ph'-NEGATIVE MYELOID LEUKEMIA

To the Editor:

R. Becher et al. recently published an interesting study on isochromosome 17q [i(17q)] found as the sole structural chromosomal anomaly in Philadelphia chromosome (Ph')-negative leukemia. Their data suggest that this anomaly seems to identify a distinct subgroup of mostly myelodysplastic and, less frequently, myeloproliferative disorders that progress rapidly to acute nonlymphoblastic leukemia, respond poorly to chemotherapy, and are associated with short survival after transformation. Similar correlation has already been proposed previously. At least some of the patients with Ph'-negative leukemia and with i(17q) had no bcr/abl rearrangement. Discussing the functional significance of an i(17q), Becher et al. suggest that the resulting monosomy of 17p could well be the more significant event because it leads to the loss of one allele of the p53 gene located at 17p13, and because disregulation of this oncogene was reportedly involved in the process of transformation or disease progression. I would like to point out that (1) to avoid any confusion, the p53 gene should now be included in the class of tumor suppressor genes, also sometimes designated anti-oncogenes or recessive oncogenes, and not in the class of (dominant) oncogenes; and (2) a role of p53 in the pathogenesis of these Ph'-negative leukemia can also be suspected by the frequent presence of the same chromosomal anomaly [i(17q)] and of p53 gene rearrangements in Ph'-positive leukemia.

While oncogenes are identified by their positive role in transformation of appropriate host cells (dominant genetic abnormalities), tumor suppressor genes have an essentially negative effect, blocking transformation and driving cells toward normality (recessive abnormalities). The p53 gene was originally but erroneously identified as an oncogene because inadvertently used mutant gene derivatives, and not the wild-type gene, could immortalize primary rodent cells on their own and could cooperate with ras for transformation. These mutants, when overexpressed, may indeed function in transformation by acting in a trans-dominant fashion, as inhibitory proteins that block the activity of wild-type endogenous p53, probably through the formation of inactive heterodimers (dominant negative phenotype).

Similarly to the association of i(17q) with the rapid development of acute nonlymphoblastic observed in patients with Ph'-negative leukemia, i(17q) and p53 gene rearrangements have been found to be associated with the blast crisis of patients with Ph'-positive chronic myelogenous leukemia (CML). The i(17q) is one of the three major changes [+8, +Ph', i(17q)] occurring, as chromosome clonal evolution, alone or in combination in over 70% of these patients in blast crisis. As an isolated change additional to Ph', i(17q) has been found in 27% (107 of 550) of the patients. In the search for clinical and chromosome correlations, the emerging data was the association of i(17q) with signs of myeloid differentiation of blasts and a marked basophilia. Molecular structural study of the p53 gene indicated that 30% of the patients with Ph'-positive CML at either accelerated or blast crisis exhibited rearrangements of this gene.

These data suggest a role of the p53 gene in the development of acute nonlymphoblastic leukemia in patients with myelodysplastic disorder or with Ph'-positive or Ph'-negative CML. The involvement of this tumor suppressor gene in cell transformation results from its inactivation. Two mechanisms can be envisioned; they may occur successively, which would be consistent with suggested mechanisms of tumor progression. At one step, mutations of the p53 gene may induce cell transformation by competing with the normal p53 protein. These mutations, which are sometimes associated with very high p53 expression, have been found in a highly conserved region of the gene. At another step, loss of the normal remaining p53 allele would result in a more pronounced effect in cell transformation. Such genetic abnormalities of the p53 gene are found in osteosarcomas, as well as in lung and colon cancers. In leukemic cells with i(17q), an allele of the p53 gene has been lost. To document the role of this tumor suppressor gene in pathogenesis, it would be informative to study the expression and perform further structural analysis of the remaining allele.

THIERRY VELU
Erasme Hospital
Free University of Brussels
Belgium

REFERENCES

RESPONSE

We agree with Dr Velu that the p53 gene probably plays the most significant role in the origin of Ph-negative myeloid leukemia with an isochromosome 17. We are presently collecting cases with or without the Ph-chromosome and an isochromosome 17 for further molecular studies; however, we have no results so far. I appreciate the comment by Dr Velu and think it should stay without further comment from our side.

R. BECHER
Universitätsklinikum Essen
FRG
Involvement of the p53 tumor suppressor gene in Ph1-positive and Ph1-negative myeloid leukemia [letter; comment]

T Velu