Genetics and Molecular Biology, 23, 4, 1115-1116 (2000)

Short Communication

Centromeric, pericentromeric and heterochromatin abnormalities in chromosomal rearrangements of human leukemia*

Roland Berger

INSERM U434 and CNRS SD 401 No. 434, Institut de Génétique Moléculaire, 27 rue Juliette Dodu 75O10 Paris, France. E-mail: roland.berger@cephb.fr

*Presented at the International Graduate School Course and Workshop on "New Approaches in the Study of Radiation-Induced and Cancer-Associated Chromosomal Aberrations"

PRESENT STATUS

Centromeric and pericentromeric chromosome abnormalities have been reported to occur in malignant cells many years ago. Their incidence seems to be different in different types of malignancy. In human leukemia, recurrent and clonal dicentric chromosomes have been found to be associated with some subtypes of leukemia, such as dic(5;17), dic(17;18) in myeloid cell proliferations, and dic(7;9), dic(9;12), dic(9;20) in acute lymphoblastic leukemias. As shown by using C-banding technique and more recently fluorescent *in situ* hybridization (FISH), some so-called Robertsonian translocations were indeed dicentric chromosomes. Isodicentric chromosomes may also be present as clonal abnormalities, like idic(8)(p11) and idic (14)(p11) in lymphoid cell proliferations, and idic(21) (p11), idic(Ph), idic(X)(q13) in myeloid cell proliferations. The existence of dicentric and isodicentric chromosomes, classically known to be instable, addresses the question of nonfunctional ("inactive") centromeres to explain how dicentric-like structures can pass through successive cell divisions without being broken at anaphase. This is why the term pseudo-dicentric seems to be more appropriate when some DNA sequences usually present in centromeres and centromere-binding proteins (CENPC, CENPE for instance), that are necessary components of an active centromere, are not detected.

In a study of chromosomal abnormalities of leukemia, we detected several unexpected dicentric and pseudodicentric chromosomes occurring as clonal abnormalities in various subtypes of hematopoietic malignancies. These abnormalities were undetected or only suspected with banding techniques and were ascertained by using FISH techniques, particularly those using chromosome-specific probes for centromeric DNA sequences, such as alpha satellite DNA. In a short series of 10 patients with acute leukemia and pericentric rearrangements, the presence of dicentric chromosomes was ascertained in seven cases. Only two of them were detected and one suspected with banding techniques (Berger and Busson-Le Coniat, 1999). Although the incidence of dicentric and pericentric chromosomes could not be deduced from this very short series of patients, we question now whether this incidence has been underestimated until now.

In a systematic study of cytogenetic abnormalities of acute lymphoblastic leukemia, an acquired translocation t(1;19)(q12;p13) with an apparent breakpoint in the heterochromatin area of chromosomes 1 was observed in a child with leukemia. A collaborative study of 36 patients with various types of hematopoietic malignancies and various rearrangements involving the proximal part of the long arm of chromosome 1 (1q) was undertaken in order to determine the precise location of chromosomal breakpoints (Busson-Le Coniat *et al.*, 1999). Starting from the conventional banded chromosome studies, FISH techniques were applied using heterochromatin and centromeric chromosome 1-specific probes (alpha satellite, DNA satellite 2 and 3) mapping to 1cen to 1q12, and more telomeric probes covering the BCL9, and ARNT genes mapping to 1q21. A breakpoint within satellite 2-3 DNA area of chromosome 1 or between alpha satellite and satellite 2-3 DNA was detected in 14 patients, whereas the breakpoint was located between the satellite 2 and 3 area in eight patients, and between the centromeric area and ARNT locus in two further cases.

In the present study, as in the previous one, the incidence of rearrangements within heterochromatin was high, athough it was biased by the recruitment of the patients based on banded metaphase chromosome analysis. However, because of the difficulty to precisely localize the breakpoint in the proximal part of 1q by cytogenetic techniques alone, the FISH technique was very useful for the localization of the chromosomal breakpoints in heterochromatin in 14 patients. The rearranged chromosomes may consequently be qualified as pseudodicentrics.

FINAL COMMENTS

The results summarized above justify further investigation of these kinds of abnormalities for several reasons. The first series of questions concerns the mechanisms of production of the abnormalities. Several factors may favor rearrangements of heterochromatin and illegitimate recombination resulting in acquired translocation. They are somatic pairing, DNA sequence homologies between centromeric DNA, methylation status that can stretch DNA and favor chromosomal breakage in the corresponding area, presence of transposons within heterochromatin DNA, and even herochromatin polymorphism that has been suspected to favor an abnormal recombination rate. The second series of questions concerns the possible consequences of heterochromatin rearrangements. They are quantitative disequilibrium (partial trisomies and monosomies), silencing of genes located in the vicinity of the chromosomal breakpoints due to the translocation of heterochromatin to ectopic location and functional alterations of genes and proteins associated with heterochromatin. Many of these directions of research can now be tested because of the dramatic advances recently made in molecular biology and functional studies. The present task of cytogeneticists is to increase the number of cases studied to determine the types of abnormalities involving heterochromatin in malignancy.

REFERENCES

Berger, R. and **Busson-Le Coniat, M.** (1999). Centric and pericentric chromosome rearrangements in hematopoietic malignancies. *Leukemia 13*: 671-678.

Busson-Le Coniat, M., Salomon-Nguyen, F., Dastugue, N., Maarek, O., Lafage-Pochitaloff, M., Mozziconacci, M.-J., Baranger, L., Brizard, F., Radford, I., Jeanpierre, M., Bernard, O.A. and **Berger, R.** (1999). Fluorescence *in situ* hybridization analysis of chromosome 1 abnormalities in hematopoietic disorders: rearrangements of DNA satellite II and new recurrent translocations. *Leukemia 13*: 1975-1981.

(Received November 23, 2000)