Eur J Cancer Clin Oncol. Vol. 24, No. 5, pp. 821–823, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00

Perspectives and Commentaries

The Role of Heterochromatin in the Origin of Isochromosome 1 in Neoplastic Cells

RAM S. VERMA, MICHAEL J. MACERA and ARVIND BABU*

*Division of Genetics, Long Island College Hospital and SUNY Health Science Center and *Division of Medical Genetics, Beth Israel Medical Center, New York, NY* 10003, *U.S.A.*

In 1939, Darlington [1] coined the term 'isochromosome' and explained that it originated through a transverse fracturing of the centromere, in which the two arms are of equal length and thus genetically homologous to each other. Isochromosomes are unstable in plants and insects owing to the irregular manner of centromeric division. However, in humans, their nature remains unknown because this type of genetic imbalance is quite lethal. Nevertheless, the presence of isochromosomes in bone marrow cells is frequently reported as an acquired anomaly in humans with neoplastic diseases [2, 3].

It is not known why there is preferential involvement of a particular homologue in the origin of isochromosomes. However, constitutive heterochromatin of the primary constriction (centromere) is quite variable, attributing to the uniqueness of the human genome [4]. In addition, the secondary constriction (h) in certain chromosomes provides constant and characteristic landmarks which vary (heteromorphic) from person to person but are consistent within an individual [5]. The h regions of chromosome 1 in humans contain constitutive heterochromatin of a highly diverse nature [6]. Using various selective staining techniques, it has been clearly demonstrated that chromatin of the centromere is highly heterogeneous and different in its composition when compared to the h region in chromosome 1 [7].

Accepted 14 September 1987.
Correspondence should be addressed to Professor Ram S. Verma, Chief, Division of Genetics, Long Island College Hospital, 340 Henry Street, Brooklyn, N.Y. 11238, U.S.A.

The heteromorphic nature of the h region of this chromosome is a well-documented fact [5]. However, the nature and clinical implication of this heteromorphism remains obscure. One area which has recently gained importance is the polymorphism of heterochromatin segments in neoplastic disease, because significantly larger sized h regions are frequently observed [8, 9]. Evidence suggesting that larger amounts of heterochromatin in the h region may promote neoplastic disease remains circumstantial; however, support of this concept is growing [10]. In view of the possible significance of the h region, it seem desirable that a detailed investigation be made of these heterochromatic variants in persons with cancer.

If the amount of heterochromatin plays any role in neoplastic transformation, it would be most appropriate to use only those techniques which reveal the maximum chromatin heterogeneity of the h regions [11]. One such example has been presented to demonstrate the importance of these selective staining techniques. Our patient was found to have acute myelocytic leukemia (AML) at which time his karyotype was a normal 46,XY. Upon his first relapse, 10 months after initial diagnosis, an abnormal karyotype was found, 48,XY,+i(1q),+8. The various staining techniques have clearly documented that the h region(s) are different sizes; for example, both normal chromosomes have different size h regions by DA/DAPI and *AluI*/Giemsa, while by C-banding alone this heteromorphism would have gone undetected.

After evaluation of the various staining techniques, it was determined that *AluI*/Giemsa

revealed slightly more heteromorphisms than DA/DAPI, however, both were superior to C-banding. Also, both *AluI*/Giemsa [12] and DA/DAPI-techniques [13] are far simpler procedures than routine C-banding. In addition, because of the heterogeneity of heterochromatin in the h regions, it is possible to document that the isochromosome originated from the normal homologue with the larger h region. In past investigations, the larger h region of chromosomes 1,9 and 16 were most frequently seen in neoplastic diseases as compared to controls. Therefore, it would be tempting to investigate the involvement of h regions in the origin of isochromosomes of this population, leading to a better understanding of the role of heterochromatin in hematopoetic diseases. Our present approach might provide some valuable information for the implication of heterochromatin in human cancer, which we believe at present is purely circumstantial [14]. Furthermore, the recent application of RFLP in molecular cytogenetics will enable us to understand the role of redundant DNA in the mechanism(s) of neoplastic transformation.

REFERENCES

1. Darlington CD. Misdivision and the genetics of the centromere. *J Genet* 1939, **37**, 341–364.
2. LeBeau MM, Rowley JD. Chromosomal abnormalities in leukemia and lymphoma: clinical and biological significance. *Adv Human Genet* 1986, **15**, 1–54.
3. Verma RS. Chromosomal abnormalities in neoplastic diseases. In: C.J. Rosenthal ed. *Manual of Clinical Oncology*. New York, Elsevier 1988.
4. Babu A, Verma, RS. Cytochemical heterogeneity of the C-band in human chromosome 1. *Histochem J* 1986, **18**, 329–333.
5. Verma RS, Dosik H. Human chromosomal heteromorphism: nature and clinical significance. *Int Rev Cytol* 1980, **62**, 361–383.
6. Verma RS. *Heterochromatin: Molecular and Structural Aspects*. New York, Cambridge University Press, 1988.
7. Babu A, Verma RA. Characterization of human chromosomal constitutive heterochromatin. *Can J Genet Cytol* 1986, **28**, 631–644.
8. Atkin NB. Chromosome 1 aberrations in cancer. *Cancer Genet Cytogenet* 1986, **21**, 279–285.
9. Atkin NB, Brito-Babapulle V. Heterochromatin polymorphism and human cancer. *Cancer Genet Cytogenet* 1981, **3**, 261–272.
10. Mamaeva SE, Mamaeva NN, Jartseva NM, Belyaeva LV, Scherbakova EG. Complete or partial trisomy for the long arm of chromosome 1 in patients with various hematologic malignancies. *Human Genet* 1983, **63**, 107–112.
11. Babu A, Verma RS. Identification of marker chromosomes by restriction endonuclease/Giemsa/technique in neoplastic cells. *Cancer Genet Cytogenet* 1987, **24**, 367–369.
12. Babu KA, Verma RS. The application of restriction endonucleases *AluI* and *HaeIII* in evaluation of heteromorphic regions in human chromosomes. *Karyogram* 1985, **11**, 23–27.
13. Schweizer D, Ambrose P, Andrle M. Modification of DAPI banding on human chromosomes with a DNA binding oligo-peptide antibiotic: distamycin A. *Exp Cell Res* 1978, **111**, 327–332.
14. Verma RS. Heteromorphisms of constitutive heterochromatin in patients with neoplastic diseases. *Am J Human Genet* 1985, **37**, A41.

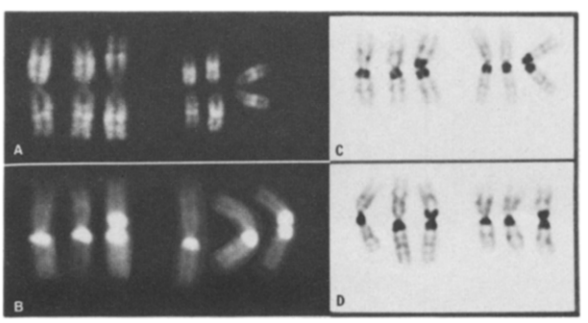

Fig. 1. *Partial karyotype of an individual with isochromosome* 1, *i.e.* *i*(1*q*). *A, Metaphase stained by QFQ-technique. B, Metaphase stained by DA/DAPI-technique. C, Metaphase stained by CBG-technique. D, Metaphase treated by restriction endonuclease AluI and stained by Giemsa, i.e.* AluI/*Giemsa-technique. The involvement of chromosome* 1 *with the larger h-region in the origin of isochromosome could be clearly demonstrated by DA/DAPI and* AluI/*Giemsa-techniques. CBG-technique, routinely used in previous investigations, was not informative in the present study (see text).*