LEADING ARTICLE

CHROMOSOMAL CHANGES IN CHRONIC MYELOID LEUKAEMIA

Y Y Leong

SING MED J. 1988; 29:98–99

INTRODUCTION

The association of chromosomal abnormalities with tumour cells began to be recognised during the late 19th and 20th century. As early as 1914, Theodore Boveri put forward a hypothesis that tumour development may have its basis in mitotic errors that produce abnormal chromosomal complements.

The study of chromosome pattern in tumour cells has been an area of exciting research over the last 20 years and in the last 10 years with the application of new chromosome banding techniques, specific cytogenetic abnormalities have been described in many malignancies eg leukaemias, Burkitt lymphoma, neuroblastoma and Wilm's tumour. Chromosomal abnormalities in tumours of the lymphohematopoietic system have been the most extensively studied and its application in diagnosis and prognosis is now widely used. This application is best seen in chronic myeloid leukaemia.

Chromosomal Changes in Chronic Myeloid Leukaemia

Nowell & Hungerford in 1960 reported the first consistent chromosome change associated with chronic myeloid leukaemia. They described the Philadelphia Chromosome which in later years was shown to be a result of a translocation between chromosome 9 and chromosome 22. Studies have shown that the Philadelphia chromosome (Ph^1) is present in 85% to 90% of patients with chronic myeloid leukaemia and these patients have a better prognosis than those who are Ph^1-negative (absence of Philadelphia chromosome). The mean survival of Ph^1 + patients is about 30 to 40 months compared to only 12 to 15 months for Ph^1 negative patients.

Other karyotypic changes may be associated with Ph^1 translocation. These include an additional chromosome 8, a second Ph^1 chromosome, loss of Y chromosome and various structural abnormalities. Presence of these additional abnormalities together with Ph^1 chromosome at the time of diagnosis has not been shown to have a poorer prognosis than those who have Ph^1 chromosome alone. In the other 10% of cases about half of the cases had a translocation involving chromosome 22 and some other chromosomes while the others had a complex re-arrangement involving chromosome 22 and 2 or more other chromosomes. The significance of these variant translocations is controversial.

Chronic myeloid leukaemia frequently terminates by going into an acute phase or blastic crises. In 80% of the patients this is preceded or associated by additional chromosomal abnormalities. In 65% of the cases the leukaemic cells become hyperdiploid with modal chromosome numbers of 47 to 50 due to additional chromosomes 8, 19 or second Ph^1 chromosome

Hypodiploid clones were observed in 6% of cases in blastic crises and there is some evidence that patients whose marrow cells are hypodiploid may respond better to therapy.

There are conflicting data regarding the prognostic significance of karyotypic evolution in acute phase of CML. Prignogina and Fleischman observed a higher remission rate and a longer survival in patients who retained the 46 Ph^1 + cell line unchanged compared with those whose marrow cells acquired additional changes. However other investigations have reported that survival time of patients who developed additional chromosomal abnormalities was similar to that of patients whose karyotype did not change.

If the lymphoblastic crisis responds to therapy, the additional structural abnormalities disappear but the Ph^1 chromosome remains even in remission. This is in contrast to Acute lymphoblastic leukaemia where the Ph^1 chromosome disappear if remission is obtained.

Role of Oncogenes

During the last few years there has been remarkable discoveries about the molecular basis for malignant transformation of cells with the discovery of oncogenes located in chromosomes. Cellular oncogenes (C-oncgenes) or protooncogenes are located on various chromosomes and these oncogenes normally regulate the ordered growth of cells in the body. The Oncogenes may be activated to produce tumours in a variety of ways eg as a result of viral infection, chromosomal

Dept of Paediatrics
Singapore General Hospital

Leong Yuet Yow MBBS, M. Med. (Paediatrics)
Consultant Paediatrician

translocations, deletions and gene mutation.

An example of chromosomal translocation activating an oncogene is seen in chronic myeloid leukaemia.

The Ph' chromosome results from a translocation between chromosomes 9 and 22 with breakpoints at 9q34 and 22q11. It was discovered that the breakpoint 9q34 is where an oncogen C-abl is situated and 22q11 is the site of the λ light chain immunoglobulin gene. As a result of the translocation these 2 genes are brought together and this close proximity activates the c-abl oncogene giving rise to disordered proliferation of white cells resulting in chronic myeloid leukaemia.

CONCLUSION

Cytogenetics will have a greater role to play in malignancies as improved cytogenetic methods will enable subtle chromosome defects to be defined. The full significance of these chromosomal abnormalities eg translocation or deletions which involve oncogenes and malignant transformation is an important area of ongoing cancer research and further studies will provide us with a better understanding in malignancy. It is timely that a report on the experience of the cytogenetic findings from a laboratory in our region is being published.

REFERENCES

1. Nowell P.C., Hungerford D.A. : A minute Chromosome in human chronic granulocytic leukaemia. Science 1960, 132:1497.
2. Yunis J.J. : High resolution of human Chromosomes Science 1976, 191:1268–70.
3. Yunis J.J., Bloomfield C.A., Ensrud K. : All patients with acute non lymphocytic leukaemia may have a chromosomal defect New Engl. J. Med., 1981, 305:135–9.
4. Yunis J.J.: The chromosomal basis of human neoplasia Science 1983, 221:227–235.
5. Weatherall D.J. — The New Genetics and Clinical Practice — 2nd Edition.
6. Potter A.M., Watmore A.E. et al.: Significance of Non Standard Philadelphia Chromosomes in Chronic Granulocytic Leukaemia British Journal of Haematology 1985, 60:457–467.