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Clinical and biological significance of chromosome aberrations in leukemia and lymphoma*

Hansjakob Müller

Summary

Clonal chromosome aberrations have been found in several malignancies, especially in leukemia and lymphoma. Their exact characterization has diagnostic, therapeutic and prognostic significance. Consistently occurring translocations have been found in several subsets of acute non-lymphocytic leukemia and in chronic myeloid leukemia as well as in lymphoid neoplasms.

These aberrations tend to affect only certain chromosomes. Specific segments along these chromosomes are preferentially involved in structural aberrations. This may imply that these chromosomes carry genetic material of special importance for malignancies. Cancer genes known as "oncogenes" have been identified within affected chromosomal segments. By pooling the data about the chromosome aberrations and malignancy it becomes apparent that there might be at least two main genetic mechanisms operating in human neoplasia. In the majority of the reported solid tumors as well as in some leukemias and lymphomas there is a loss of specific chromosome material implying that in these malignancies there might be a critical loss of genetic information. In most leukemias and lymphomas a reciprocal translocation with precise breakpoints occurs; in this case it is possible that a cancer gene (oncogene) becomes activated as a result of the genetic rearrangement. Therefore, one common pathway to cancer may involve the direct activation of oncogenes; but there is also another pathway involving a loss of activity of genes whose function might be the induc-

tion of final differentiation. It has been suggested that the oncogenes are the driving factors of proliferation and that differentiation is controlled by a different group of genes which – in effect – act as anti-oncogenes (Knudson, 1982).

Zusammenfassung

Klonale Chromosomenaberrationen wurden in verschiedenen malignen Neubildungen, vor allem in Leukämien und Lymphomen, nachgewiesen. Ihre exakte Charakterisierung hat diagnostische, therapeutische und prognostische Bedeutung. Spezifische Chromosomentranslokationen wurden bei verschiedenen Formen der akuten nichtlymphatischen Leukämie, der chronisch myeloischen Leukämie, aber auch bei bösartigen Neubildungen des lymphatischen Gewebes gefunden.

Von solchen Aberrationen werden bestimmte Chromosomen und oft sogar nur Chromosomensegmente betroffen. Dies ist ein Hinweis dafür, dass dort Gene lokalisiert sein müssen, die eine entscheidende Rolle bei der Entstehung eines bösartigen Tumors spielen. Tumorgene, die Onkogene genannt werden, kommen in solchen Regionen vor. Die Vermehrung oder auch Aktivierung von Onkogenen führt wahrscheinlich zu unkontrollierter Proliferation. Zahlreiche Neoplasien sind aber durch einen Verlust von Chromosomenmaterial gekennzeichnet. Demzufolge muss es noch Erbfaktoren geben, deren Verlust im Zusammenhang mit der Tumorgenese von Bedeutung ist. Es könnte sich dabei um Erbfaktoren handeln, die für die endgültige Differenzierung der Zellen verantwortlich sind. Knudson (1982) hat die einfache Hypothese aufgestellt, dass Tumoren aus einem Missverhältnis der Aktivität der Onkogene und solcher Differenzierungsgene resultieren, die er Anti-Onkogene nennt.

*This paper is dedicated to Professor Dr. G. Stalder, Director of the University Children's Hospital, Basel, in honour of his 60th birthday.

Our own investigations on chromosomes in malignancies were supported by the Swiss Cancer League.

Introduction

An association between chromosome aberrations and neoplastic transformation has long been mooted (Bovery, 1914) since chromosomal abnormalities have been found in cells of a variety of malignancies. With the new banding techniques cancer cytogenetics has become a rapidly expanding branch of everyday oncology. Consistently occurring clonal chromosome aberrations have been found to be associated with specific types of leukemia and lymphoma (Rowley, 1980). Although such findings do not directly prove the hypothesis that chromosomal changes represent a major step in carcinogenesis, a remarkable concordance between the chromosomal location of cellular oncogenes and the chromosomal segments involved in such aberrations is becoming apparent. In this review the clinical and biological significance of chromosomal rearrangements in leukemic cells will be discussed.

1. Clinical significance

Several major types of chromosome abnormalities have been identified in human leukemias and lymphomas. They have been found to exhibit a wide range of defects, i.e. a gain or a loss of entire chromosomes or parts of chromosomes and also structural rearrangements such as reciprocal translocations. Certain chromosomes are preferentially affected. Their identification refines the classification of the malignancies.

1.1. Chronic myeloid leukemia (CML)

The Philadelphia (Ph¹)-chromosome in CML was described in 1960 by Nowell and Hungerford. On the basis of banded karyotypes, this aberration was first interpreted as a 22q-deletion (Caspersson et al, 1970) and was subsequently found to involve primarily a translocation between a chromosome No. 9 and a No. 22: t(9;22)(q34;q11) (Rowley, 1973). Approximately 90% of all patients suffering from CML show the presence of the Ph¹-chromosome.

Patients with the Ph¹-negative form tend to be older than those with the Ph¹-positive form. They are predominantly male and have a smaller leukocyte increase and more pronounced thrombocytopenia. As a general rule the Ph¹-negative patients show a poor response to therapy, so that survival time is shorter (Ezdinli et al, 1970). After a period of three years 84% of 23 of our own patients with a Ph¹-positive CML were still alive, compared with only 60% of 8 patients with the Ph¹-negative form (unpublished results).

At the time of blast crisis about 75% of all patients develop additional chromosome aberrations, superimposed on the karyotype with only the Ph¹-chromosome (Mitelman and Levan, 1981). The predominant aberrations are a gain of a second Ph¹-chromosome or of one or more chromosomes No. 8, or the formation of an isochromosome No. 17. Altogether, at least one of three changes occurs alone or in combination in more than 80% of the karyotypically abnormal CML-patients.

Table 1. Consistent structural chromosome aberrations in acute non-lymphocytic leukemia

Type of ANLL	Translocation/Inversion	Clinical, cytological and other findings
Acute myeloblastic leukemia, AML M2	t(8:21) (q22;q22)	Low onset age, good response to treatment, 2/3 of myeloblasts with Auer rods, low alkaline phosphatase
Acute promyelocytic leukemia, APL M3 and variant M3	t(15:17) (q22:21)	Hypergranular promyelocytes, tendency to intravascular coagulation, poor morphology of the chromosomes
Acute monocytic leukemia AMoL M5 (auch M4)	11q- (q23-24) (q13-14) translocation variable	Most frequently in children with type a
Acute myelocytic leukemia M1	t(9:22) (q34;q11) Philadelphia chromosome	Poor response to therapy, short survival time
Acute myelomonocytic leukemia AMMoL M4	inv(16) and del (16)(q22)	Increased number of eosinophils, good prognosis

In a 17-year old female patient with a Ph¹-positive CML a deletion of the long arm of one chromosome No. 11 was found in an acceleration phase of the disease which did not turn into a typical blast crisis, but led to death.

1.2. Acute non-lymphocytic leukemia (ANLL)

Abnormal karyotypes have been reported in approximately 50% of all patients with ANLL (Sandberg, 1980). Analysis of metaphase plates alone showed clonal aberrations in 25 of 55 of our own patients (unpublished results). However, the incidence of chromosomal aberrations may be significantly greater when new techniques for obtaining prometaphase chromosomes are applied (Yunis et al. 1981).

The specific chromosome aberrations which are most commonly found in ANLL have been reviewed extensively (Mitelman and Levan, 1981; Sandberg, 1980). Therefore, only the translocations will be presented that are specifically associated with particular types of ANLL.

There seem to be at least five clinical subtypes of ANLL that can be identified by the type of chromosome rearrangement found (see tab. 1).

One group has a translocation involving the long arm of chromosomes No. 8 and 21 and represent about 10 to 15% of all ANLL patients with chromosomal aberrations (Kamada et al, 1968; Rowley, 1973). They have the hematological picture of an acute myelogenous leukemia M2 and are recognized from the low onset age of the leukemic process. The myeloblasts often have Auer rods and a low alkaline phosphatase activity. Patients with this disorder respond well to

therapy and have a relatively good prognosis. Experienced cytologists recognise this type as a special entity because of the specific morphologic features of the leukemic cells.

A second group is characterized by a structural rearrangement between chromosomes No. 15 and 17. This translocation is unique to acute promyelocytic leukemia (M3 and M3 variant) (Rowley et al. 1977).

The third group shows a typical Philadelphia chromosome; the patients suffer from AML with a poorer response to therapy. It is not known why the same translocation, occurring probably in similar stem cells, leads to different hematological pictures, not only CML and AML but also ALL.

In patients with acute myelomonocytic leukemia (M5) and also acute promyelocytic leukemia (M4) a translocation is observed to involve the long arm of chromosome No. 11 (Berger et al. 1980).

Finally, an inversion (Inv 16) is found in patients with acute monocytic leukemia (M4).

All these abnormalities occur preferentially in children and younger adults, indicating that the aetiological factors responsible for these types of leukemia differ from those associated with leukemia in older adults. Instead of having a specific translocation the latter show a variety of numerical and also structural defects, especially of chromosomes No. 5, 7, or 8.

Non-random chromosomal changes have been observed in the marrow cells of patients who have acute non-lymphocytic leukemia secondary to treatment with irradiation or cytotoxic drugs. These aberrations consist of a loss of the entire chromosome or part of the long arm of chromosomes No. 5 and/or 7 (Colomb et al. 1982). Patients who have been occupationally exposed to some potential mutagenic agents (petroleum products, chemical solvents or pesticides) were more likely to have chromosomally abnormal leukemic cells than non-exposed persons. The incidence of certain chromosome changes, such as of No. 5, 7 or 8 was much higher in the exposed than in the unexposed population (Mitelman et al. 1978).

Several of these chromosome aberrations show an uneven geographic distribution. Such geographic heterogeneity may be taken to indicate heterogeneity in the distribution of aetiological agents.

Table 2. Median survival time and cytogenetic pattern in 241 patients with ANLL*.

Cytogenetic pattern	No. of patients	Median survival in months	Alive after 1 year No.	%
Normal	102	6	21	21
Normal and abnormal	80	5	17	21
Abnormal	59	4	3	5

* Results based on an analysis by the First Internal Workshop on Chromosomes in Leukemia (1978).

With a successful antileukemic therapy patients having cells with normal karyotypes are capable of repopulating their marrow with these elements when the leukemic ones disappear.

In addition chromosomal aberrations present in leukemic cells can be used to monitor a specific leukemic cell clone during the whole course of the disease. This is of considerable importance in phases such as clinical remission or relapse. In our hospital we profited very much from the information gained from cytogenetic analysis in different stages of the disease (Müller and Stalder, 1976). New sub-clones, carrying new chromosomal abnormalities, often acquire new phenotypic properties and are responsible for minor changes in the course of the disease.

Secondary chromosome aberrations may arise in malignancies through disturbance of mitosis in rapidly dividing cells. Also such secondary changes that happen to enhance the effect of the primary ones have a selective value and thus will accumulate in the cell population that means in subclones.

1.3 Lymphoid neoplasms

The karyotypic aberrations in many lymphoid neoplasms appear multiform with no evident consistent pattern. However, the different specific chromosome translocations have been identified in ALL: t(9;22), t(4;11), t(8;14) (Sandberg, 1980). These are the most common structural rearrangements as shown in table 3. As in ANLL the presence

of aneuploid clones is a significant negative prognostic factor. The importance of diagnosing Ph⁺-positive ALL both in children and in adults is now universally recognized. Most cases of lymphoma and B-cell ALL have a 14q-abnormality, the donor chromosome most frequently being No. 2, 8, 11, 22 or the other No. 14. The prognostic importance of the specific donor chromosome is not clear, but may correlate with specific immunoglobulin light or heavy chains found on the malignant cell surfaces (Croce et al. 1979; Erikson et al. 1981; McBride et al. 1982; Kirsch et al. 1982).

2. Biological significance

The genetic alteration responsible for the initiation of a malignancy probably does not take place at the chromosomal level but at the gene or DNA level. The origin and the role of the chromosome aberrations in this process are still matters of scientific debate. However, the facts that consistent chromosomal abnormalities occur in a high percentage of patients with certain types of cancer and that the chromosomal abnormalities affect only certain chromosomes or even chromosomal segments contradict the opinion that they represent only a symptom or an incidental phenomenon of the disease and have nothing to do with its initiation or progression.

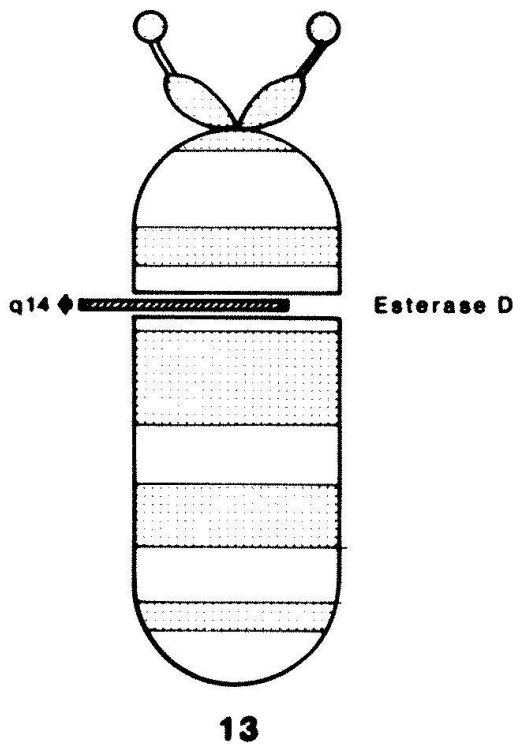
When considering the genetic effects of chromosome breakage and rearrangement, it is important to bear in mind that despite the improved resolution achieved by new banding techniques human chromosome bands are far removed from single genes.

The human haploid genome contains some 3×10^9 nucleotide pairs. An average sized metaphase band therefore contains around 10^7 nucleotide pairs. This amount of DNA would be enough to code some 5000 different mRNA transcripts, each originally two kilobases long. The increased resolution obtained by investigating prometaphases represents a significant advance, but if there are some 40000 or so genes in the genome, then these 800 bands will relate to 50 or so units of information (Evans, 1982). Cancer genes, which are known as oncogenes (onc), are one of the "hottest" areas of current cancer re-

Table 3. Consistent chromosome abnormalities in lymphoid neoplasms

Chronic lymphocytic leukemia (B cells)	14q + + 12
Plasma cell leukemia (multiple myeloma)	14q +
ALL (B-cells)	14q + t(8;14) t(8;22) t(11;14) t(4;11)
Various lymphomas	
a) endemic and non-endemic Burkitt's	14q + t(8;14) t(2;8) t(8;22)
b) non-Hodgkin's, non-Burkitt's	14q +
c) malignant (follicular) lymphoma	t(14;18)

RETINOBLASTOMA



WILMS' TUMOR

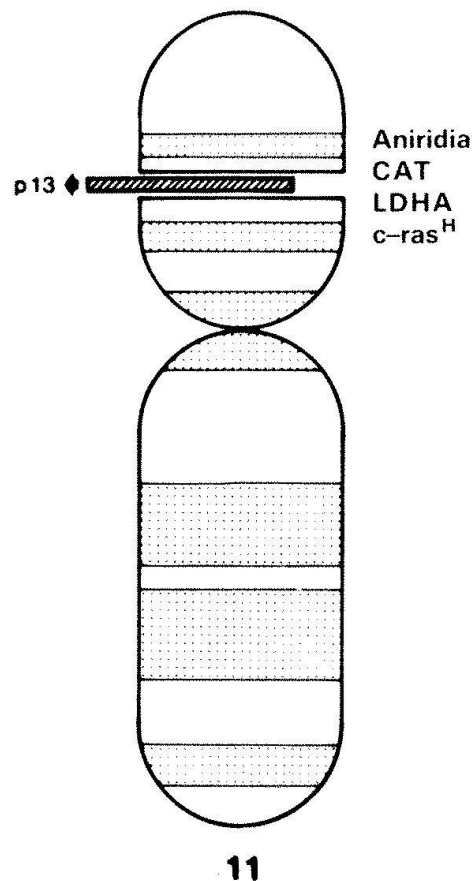


Fig. 1. Schematic representation of chromosome Nos. 11 and 13. Chromosomal assignment of the lost or inactivated genes for retinoblastoma and Wilms'tumor as well as of linked loci (see also: McKusick, 1983).

search. The 20 or so viral oncogenes have normal cellular counterparts. Sixteen such oncogenes have been identified within the last few months and the location of nine of them on the chromosomes has been identified (Bristol-Myers-Symposium, Chicago, October 1982). One of these oncogenes, known as "myc" is associated with an abnormal chromosome translocation that is found in almost all cases of Burkitt's lymphoma (Manolova et al, 1979). The end of chromosome No. 8 which contains the myc oncogene is translocated to the long arm of one No. 14 chromosome where the immunoglobulin heavy chain gene cluster is located. It is now assumed that this relocation of the myc oncogene affects its expression by the neighbouring active immunoglobulin genes (Croce et al, 1983). Loss of the normal regulatory control of the c-myc oncogene may cause malignancy. The specific association of certain translocations with particular leukemia and lymphoma suggests that some alterations in gene func-

tion give a proliferative advantage to specific groups of cells such as the B cells in the case of the myc oncogene.

In malignant cells one can observe cytogenetic phenomena which rarely occur in normal cells such as double minute chromosomes or homogeneously staining regions. There are indications that both phenomena correlate with gene amplification. The functional significance of these chromosomal structures in malignant cells is at present unknown. Further characterization of the amplified sequences is needed. It could be that some of these represent amplified oncogenes.

The study of hereditary cancers in man indicates the existence of another class of genes, not yet defined in precise terms (Knudson, 1982). These genes are transmitted in a dominant fashion and predispose to specific cancers. Classical examples are hereditary retinoblastoma or Wilms' tumor (see fig. 1). These genes must differ from oncogenes because there is evidence that in

some instances the gene site is deleted. It is therefore the loss of gene activity that is important.

The retinoblastoma exists in both heritable and non-heritable forms. A small percentage shows a specific deletion of chromosome No. 13 (13q;14) in all somatic cells (Franke and Kung, 1976). The remaining hereditary cases, according to studies of linkage with the gene for esterase D, involve the same site on chromosome No. 13, although there is no visible chromosomal change. Since esterase D and the retinoblastoma genes are closely linked and since it is known that esterase D can be expressed in tumors, there should be cases in which there is no esterase D activity in the tumor. In one case examined for this possibility the karyotype of the individual was normal (Benedict et al. 1982). However, esterase D activity in somatic cells was 50% of normal suggesting that there was a sub-microscopic deletion of the 13q;14 site. In the tumor there was only one chromosome No. 13. Apparently the normal chromosome No. 13 was missing, because there was no measurable esterase activity in the tumor.

Pooling the data on chromosomal aberrations in leukemias and other malignancies the present information about oncogenes and genes which may act in hereditary tumors reveal at least two main genetic mechanisms operating in human neoplasms. In most leukemias and lymphomas a reciprocal translocation with precise breakpoints occurs; in these instances it is possible that a cancer gene becomes activated as a result of genetic rearrangement. Therefore it may be that one common pathway to cancer involves the direct activation of an oncogene while there is also an indirect pathway involving the loss of gene activity. This is indicated by the fact that in some leukemias and lymphomas and especially in the majority of the reported solid tumors, there is a loss of specific chromosomal segments, implying a critical loss of genetic information in these malignancies. The function of the lost genes may be to induce final differentiation. Knudson (1982) suggests that cell proliferation may be regulated by oncogenes and that differentiation may be controlled by a second set of genes which in effect are anti-oncogenes.

When compiling facts in a short summary we always run the risk of oversimplification.

However, it is felt that in such a complex field as oncology, simple hypotheses are needed which can be tested directly in order to make the necessary progress. There is no doubt that cytogenetic studies will become more and more useful in the clinical management of patients and that they may provide clues to the etiology of the disease and to the type of genes which are involved in malignancy.

Addendum

Since the article was first written in 1982 the recent application of DNA technology to tumor cytogenetics has provided a new insight into the nature of the chromosomal aberrations in leukemia and lymphoma. In the case of CML the oncogene c-abl is transferred from chromosome 9 to chromosome 22. Surprisingly, at the DNA level the breakpoints on the chromosomes vary considerably between individuals [Groffen et al. *Cell* 36, 93 (1984)]. The recombinant DNA techniques also permit the detection of somatic events leading to retinoblastoma and Wilms' tumor. Cavernee and colleagues (*Nature* 305, 139, 1983) have shown that at least in some tumors the malignant cells became homozygous for the chromosome 13 carrying the "retinoblastoma gene". Findings with Wilms' tumor also indicate that chromosomal mechanisms generating homozygosity may be important for tumor formation [Orkin et al. *Nature* 309, 172 (1984)].

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