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Some Karyotypic Aspects of Human Leukemia

H. Van den Berghe and C. Mecucci [1]

A. Introduction

Chromosome abnormalities are found in the vast majority of hematologic malignancies. A great number of these changes are very specific, and some unambiguously identify the nature and type of the malignant disorder in which they are found.

The purposes of this paper are (a) to update the list of characteristic chromosome changes occurring in human hematologic neoplasia; (b) to bring together data presently known about the nature of trisomies found in these disorders; and (c) to review which genes, other than oncogenes, located near the chromosomal breakpoints may play a role in the cellular proliferation and differentiation, as well as in some other phenotypic manifestations.

B. Recently Discovered Characteristic Chromosome Changes in Human Hematologic Malignancies

I. Lymphoproliferative Disorders

Six anomalies are to be added to the existing list of characteristic chromosome changes in lymphoid proliferations (Table 1). A t(1;19) characterizes some cases of pre-B-ALL [1]. All other specific changes were found in T-cell leukemias and lymphomas. The 9p anomaly is found predominantly in childhood ALL [2]. Lymphomas with 9p are found in adults [3]. The T-cell lymphomas with involvement of 6p23 [4] might be the counterpart in man of a T-cell lymphoma occurring in mice with activation of the *pim*-oncogene after insertion of Moloney murine leukemia virus [5]. The other three chromosome changes have one breakpoint in common, 14q11, where the alpha chain of the T-cell receptor is located [6]. Finally, a t(2;5) clearly characterizes a subset of malignant histiocytic proliferations [7].

Table 1. Recently discovered chromosome changes

Lymphoproliferation	
pre-B ALL	t(1;19)(q23;p13)
T-ALL	t(11;14)(p13;q11)
T-cell proliferation	9 p-
T-cell proliferation	inv(14)(q11q32)
T-cell proliferation	t(14;...)(q11;...), several translocations possible
T-cell lymphoma	6p-/t(6;...)(p23;...)
Malignant histiocytosis	t(2;5)(p23;q35)
Myeloproliferation	
t(1;7)(p11;p11)	MDS, secondary
t(1;15)(q12;p11)	MDS
t(2;11)(p21;q23)	ANLL
Trisomy 4	ANLL
t(1;3)(p36;q21)	ANLL
t(3;5) (q21-q25;q35)	ANLL
t(3;17)(q26;q22)	Myeloproliferative syndromes

[1] Center for Human Genetics, University of Leuven, Herestraat 49, B-3000 Leuven, Belgium

II. Myeloproliferative Disorders

An even larger series of characteristic chromosome changes have been discovered recently in myeloproliferative disorders (Table 1). The first of these changes, t(1;7), is invariably found in myelodysplastic syndromes (MDS) occurring as secondary disorders (iatrogenic or environmentally induced). The long arm and centromere of chromosome 7 are lost; the remaining short arm is translocated on the remainder of a chromosome 1 which had lost the short arm. Furthermore, two normal no. 1 chromosomes are present. Therefore, the leukemic cells are trisomic for 1q and monosomic for 7q:t(1;7)(p11;p11) [8]. Partial trisomy of chromosome 1 is also seen in another anomaly, but this time the long arm is translocated upon the short arm of chromosome 15. This t(1;15)(q12;p11) is found in MDS [9].

Chromosome 1 is involved in a t(1;3)(p35;q21), but this time in an apparently balanced rearrangement, found in acute myelogenous leukemia (ANLL) [10]. Two other balanced translocations show a rearrangement between chromosome 3 and either chromosome 5 or chromosome 17. The t(3;17) is found in myeloproliferative syndromes (MPS) and the t(3;5) in ANLL [11, 12].

Some ANLL are characterized by a t(2;11), with the breakpoint in chromosome 11 being at q23 as in monoblastic and myelomonocytic leukemia [13] and also in the t(4;11), which is by now a well-known entity frequently occurring as a congenital leukemia. A very remarkable anomaly is trisomy 4 occurring as the sole anomaly [14]. It is associated with a myelomonocytic leukemia and very clearly constitutes a new entity which, remarkably, was not discovered earlier, despite its conspicuous chromosomal change. It is possible that this type of leukemia may only recently have arisen.

C. Nature of Trisomy Occurring as the Sole Anomaly in Hematologic Malignancies

Trisomy 8 is found ubiquitously in myeloid proliferation and more rarely in lymphoid malignancies. It is found as the sole anomaly in 10% of de novo ANLL; it appears in transformation of CML, as well as in a number of other hematologic conditions.

Trisomy 9 is more than occasionally found as an early event in polycythemia vera. Trisomy 12 characterizes chronic lymphocytic leukemia (CLL). Trisomy 4 identifies a subgroup of ANLL. In the light of oncogene activation by chromosomal changes, one does not readily see how chromosomal trisomies could be instrumental in this respect. Taking the example of chromosome 4, there are three genes on this chromosome which could be proliferation related: T-cell growth factor, epidermal growth factor, and the *Kit*-oncogene. Is a 50% increase in gene product sufficient to cause transformation or increased proliferation? Questions were raised, therefore, with regard to the nature of these trisomies. Could they not be in fact a triplication of one parental chromosome with the other parental chromosome missing? In trisomy 4 we used the G8 probe which detects an RFLP sequence linked to the Huntington gene on 4p and found a $2+1$ and not a 3×1 situation. By a similar approach it was shown in CLL with trisomy 12 that there was a similar situation of $2+1$. By morphological analysis of C-polymorphism in chromosome 9, we were able to show that in trisomy 9 also no parental chromosome was missing and that one of the homologs was duplicated. These preliminary data seem to indicate that if these trisomic changes are crucially important in the malignant process, it could be through a 50% increase of their gene products.

D. Chromosome Breakpoints Involving Genes of Specific Cell Differentiation and/or Functions

I. Differentiation Genes

It has been clearly demonstrated that chromosome breakpoints in B- and T-type lymphoproliferative disorders are related to two groups of genes specifically expressed in B- and T-cell differentiation; the immunoglobulin genes and the T-cell receptor genes. Some additional examples indicating a nonrandom involvement of differentiation genes

Table 2. Differentiation genes

Lymphocytic Cells (Burkitt's lymphoma; non-Hodgkin lymphoma-leukemia)		
B-type		
14q32	Heavy chain immunoglobulin	t(8;14)(q24;q32); t(11;14)(q13;q32); t(14;18)(q32;q21)
2p11	κ-chain immunoglobulin	t(2;8)(p11;q24)
22q11	λ-chain immunoglobulin	t(8;22)(q24;q11)
T-type (T-cell lymphoma-leukemia)		
14q11	α chain T-cell receptor	inv(14)(q11q32); t(11;14)(p13;q11)
7q35	β chain T-cell receptor	t(7; 14)
7p15	γ chain T-cell receptor	t(7;14)
11q23	T3 subunit of T3-T cell receptor	(1;6;11)(p33;q16;q23)
11q22	Thy-1 antigen	(1;6;11)(p33;q16;q23)
10q23	TdT	t(10;...)(q23;...)
2p11	T8 antigen	t(2;17)(p11;p11)
12	T4 antigen	
Erythrocytic cells (Erythroleukemia-ANLL, M6-FAB)		
11p15	β globin cluster	t(7;11)(q22;p15) t(9;11)(q11;p15)
16pter-p12	α globin cluster	t(16;17)(p13;q21)

in chromosome aberrations accompanying malignant T-cell proliferations are shown in Table 2.

A single patient with a T-cell lymphoma with T8-positive malignant lymphocytes and a t(2;17) translocation involving the region where the T8 antigen is located has been observed [15]. Additional breakpoints in T-cell lymphomas possibly corresponding to T-stage differentiation genes affect 11q23 at the level of or close to the genes for the T3 subunit of the T-cell receptor and the Thy-1 antigen. Moreover, more than one case has been observed with a chromosome rearrangement in 10q23, where the gene for terminal deoxynucleotydil transferase is located.

In addition, a few chromosome translocations involving the genes for α and β globin have been associated with acute leukemias

Table 3. Growth factors/growth factor receptors

Chromosome localization	Gene	Chromosome aberration	Malignant disorder
3q21-q26/3q26-qter	Transferrin/Transferrin receptor	inv(3)(q21q26)-3q-3q+	ANLL with thrombocytosis
10p14-p15	Interleukin 2 receptor	t(8;10)(q12;p14)	Malignant lymphoma
9pter-p13/p24-p13	Interferon α/β	t(9;11)(p21;q22)	ANLL, M5-FAB
4q25-q27/4q26-q28	EGF/Interleukin 2	trisomy 4	ANLL
19p13.3-p13.2	Insulin receptor	t(1;19)(q23;p13)	pre-B ALL
5q33/5q11-q13	GM-CSF/glucocorticoid Receptor	del(5)(q12q33)	MDS-ANLL
17q	Homeobox region	t(15;17)(q22;q21); iso(17q); t(3;17)(q26;q22)	ANLL-M3 FAB Acute myeloproliferative disorders

Table 4. Metal ions regulating genes

Chromosome localization	Gene	Chromosome aberration	Malignant disorder
16q22	Metallothionein genes	inv(16)(p13q22)	ANLL,M4 with eosinophilia
11q(13?)	Ferritin	del(11)(q14)/ del(11)(q14q23)	Acquired idiopathic sideroblastic anemia

characterized by predominant erythrocytic differentiation [16].

II. Growth Factors and Growth Factor Receptors

There are two lines of evidence supporting an involvement of these genes in neoplastic processes (for review see Goustin et al. [17]).

First, c-*sis* and c-*erb*-B correspond to the platelet-derived growth factor and the epidermal growth factor respectively. Furthermore, it is known that tumor cells may "autocontrol" their own proliferation by producing specific growth-controlling polypeptides.

In the t(9;11) translocation associated with M5-FAB leukemias an oncogene, c-ets-1, moves to the short arm of chromosome 9, adjacent to interferon genes [18]. The insulin receptor gene on 19p13.3-p13.2 corresponds to the breakpoint of the t(1;19) translocation described in pre-B ALL [19].

Other well-established chromosome aberrations in malignant hematologic disorders that possibly involve genes controlling cell growth are indicated in Table 3.

III. Metal Ion Regulating Genes

In acute myelomonocytic leukemias (M4-FAB) with a high eosinophilic marrow component the typically associated pericentric inversion of chromosome 16, breakpoints in p13 and q22, involves the metallothionein genes, which, according to some authors, may be split by the chromosome rearrangement.

Another typical association has been found between a subgroup of myelodysplastic syndromes with sideroblastosis and a deletion of chromosome 11, with breakpoints apparently located in q14 and/or q23, close to the active gene for the subunit H of ferritin (Table 4).

These examples illustrate how several genes important for differentiation and cell proliferation are located on a number of chromosomes, in or near breakpoints specifically known to be involved in malignant hemopoietic cells. Some of these genes are very clearly involved in the mechanism(s) that govern the proliferation and phenotype of the malignant cell. Further work along these lines will undoubtedly lead to more insight into how these genes contribute to the malignant process or to its phenotypic expression.

References

1. Williams DL, Look AT, Melvin SL, Roberson PK, Dahl G, Flake T, Stass S (1984) Cell 36:101
2. Kowalczyk J, Sandberg AA (1983) Cancer Genet Cytogenet 9:383
3. Chilcote RR, Brown E, Rowley JD (1985) N Engl J Med 313:286
4. Mecucci C, Michaux JL, Tricot G, Louwagie A, Van den Berghe H (1985) Leuk Res 9:1139
5. Cuypers HT, Selten G, Quint W, Zijlstra M, Robanus-Maandag E, Boelens W, Van Wezenbeek P, Melief C, Berns A (1984) Cell 37:141
6. Human Gene Mapping 8 (1985) Cytogenet Cell Genet 40:1–4
7. Morgan R, Hecht BK, Sandberg AA, Hecht F, Smith SD (1986) New Engl J Med 314:1322

8. Scheres JMJC, Hustinx TWS, Hodrinet RSG, Geraedts JPM, Hagemeijer A, Van der Blij-Philipsen M (1984) Cancer Genet Cytogenet 12:283
9. Mecucci C, Tricot G, Boogaerts M, Van den Berghe H (1986) Br J Haematol 62:439
10. Bloomfield CD, Garson OM, Volin L, Knuutila S, de la Chapelle A (1985) Blood 66:1409
11. Mecucci C, Michaux JL, Broeckaert-Van orshoven A, Symann M, Boogaerts M, Külling G, Van den Berghe H (1984) Cancer Genet Cytogenet 12:111
12. Rowley JD, Potter D (1976) Blood 47:705
13. de la Chapelle A, Knuutila S, Elonen E (1986) Scand J Haematol 60 (suppl) 1:230
14. Mecucci C, Van Orshoven A, Tricot G, Michaux JL, Delannoy A, Van den Berghe H (1986) Blood 67:1328
15. Mecucci C, Van den Berghe H (1985) New Engl J Med 313:185
16. Kirsch IR, Brown JA, Lawrence J, Korsmeyer SJ, Morton CC (1985) Cancer Genet Cytogenet 18:159
17. Goustin AS, Leof EB, Shipley GD, Moses HL (1986) Cancer Res 46:1015
18. Diaz MO, Le Beau MM, Pitha P, Rowley JD (1986) Science 231:265
19. Yang-Feng TL, Francke U, Ullrich A (1985) Science 228:728