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Cytogenetic basis of human cancer

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Introduction

In considering the role of heredity in the etiology of cancer, it is customary to recognize two levels of genetic change. One is alterations in germ-line heredity that manifest as increased predisposition to cancer development in individuals with certain genotypes and the other is alterations in somatic cell heredity that initiate cancer development irrespective of germ-line genotype. The former may be in the form of recessive, dominant, multifactorial, or chromosomal factors (for a review of formal genetics of cancer, see Chaganti and German 1985). The latter, first recognized during the early part of this century by Boveri (1914) and others as chromosome change involves mutation, deletion, recombination, amplification, transposition, and activation of certain classes of genes, frequently in association with change in chromosome number (Chaganti and Jhanwar 1985, review). Study of the cellular genetics of cancer has advanced rapidly during the past fifteen years, spurred first by the advances in methods of chromosome analysis that took place in the early 1970s and more recently by the integration of molecular genetics with cytogenetics. The current dogma of cancer etiology recognizes it as a multistep process that requires at least two genetic alterations in order for a normal cell to be converted to a malignant cell. The nature of these genetic changes and their hypothetical role in triggering carcinogenesis are the subjects of this review.

Chromosome changes in neoplastic cells

The large body of cytogenetic literature pertaining to human and animal tumors that has accumulated over the past several years allows the following conclusions to be made: (1) chromosome changes can be seen to characterize virtually all tumors when studied with appropriate techniques, (2) such changes generally affect chromosomes nonrandomly, often showing considerable specificity which correlates with histologic subtypes and/or etiologic factors, and (3) tumor progression is accompanied by karyotypic evolution. The chromosome changes include the entire spectrum of aberrations resulting from abnormal anaphase segregation as well as breakage and reunion of broken ends of chromosomes. The former results in chromosome numbers in tumors that range from monosomy and trisomy to haploidy and polyploidy, and the latter results in deletion, duplication, inversion and translocation of chromosomal regions. Thus, the genetic system of a tumor cell becomes unstable, probably early in its

history, and remains so throughout its life, which is the source of variation for tumor evolution. The significance of this change to the genetic organization of the transformed cell and the establishment, survival, and spread of the tumor that derives from it has been discussed by many investigators. An obvious conclusion from descriptive cytogenetics was that specific position effects cause disruption in the normal dosage or alignment and coordinated function of some important genes (e.g., those that control cell proliferation and cell function), thereby setting the stage for abnormal proliferation and/or development (Chaganti 1983a, b; Levan and Mitelman 1977; Rowley 1977).

Data from a variety of tumors indicates that rearrangements affect a limited number of sites within the genome, numbering less than 100 (Chaganti 1983b; Mitelman 1984). These sites, which are also called specific breakpoints, are shown in figure 1. Verification of the role of the position effect in gene regulation stated above requires a knowledge of the genes that are situated at these breakpoints and their fate in rearrangements. The first such verification came recently with the study of Burkitt's lymphoma (BL), a tumor of B cells, which exhibits three specific translocations, one standard and two variant. The standard translocation involves chromosomes 8 and 14 with breakpoints in bands 8q24 and 14q32, and the variant translocations involve chromosomes 2 and 8 in one and 8 and 22 in the other. The breakpoint in chromosome 8 in all cases is in band 8q24 whereas the breakpoints in chromosomes 2 and 22, respectively, are in bands 2p12 and 22q11 (Lenoir *et al* 1982). Gene localization studies have shown that the breakpoints do indeed correspond with the positions of a most interesting set of genes. Thus, chromosomes 14, 2 and 22 carry, at their breakpoints, the determinants for the immunoglobulin heavy chains, kappa light chains, and lambda light chains, respectively (Kirsh *et al* 1982; Malcolm *et al* 1982; McBride *et al* 1982). The breakpoint in chromosome 8 carries c-*myc* (Neel *et al* 1982), which belongs to a class of genes known as cellular oncogenes (see below). In these translocations, c-*myc* rearranges with the immunoglobulin genes and, although constitutively inactive in nonembryonal tissues, it undergoes activation in the translocation-carrying cells, presumably under the influence of the immunoglobulin genes that are normally active in these cells (Erikson *et al* 1983). The demonstration that a cellular oncogene undergoes activation and that a change in position is associated with such activation thus led to an intense effort to identify genes situated at the breakpoints.

Included in the genomes of retroviruses (RNA tumor viruses that cause rapid transformation of vertebrate cells) are genes that determine their oncogenic property (viral oncogenes or v-*onc* genes). The genomes of host vertebrate species contain genes that are homologus to v-*onc* genes which in turn are called cellular oncogenes (or c-*onc* genes). C-*onc* genes are highly conserved throughout vertebrate evolution (Bishop 1981, 1983; Hayward 1985). Until recently their function was unknown, although it had been suggested that they may be part of the cell's genetic machinery responsible for the control of proliferation and/or differentiation. More recent experimental data support such a view. Thus, c-*myc* has been shown to play a role in the control of cell proliferation (Kelly *et al* 1983) and c-*sis* and c-*erb-B* have been shown to be homologous to the genes that encode platelet derived growth factor (PDGF) (Waterfield *et al* 1983) and the receptor for epidermal growth factor (EGF) (Downward *et al* 1984), respectively. Finally, various lines of evidence indicate that vertebrate c-*onc* genes are also capable of inducing transformation under appropriate conditions (Cooper 1982).

Although the retrovirally related c-*onc* genes have classically been identified by their

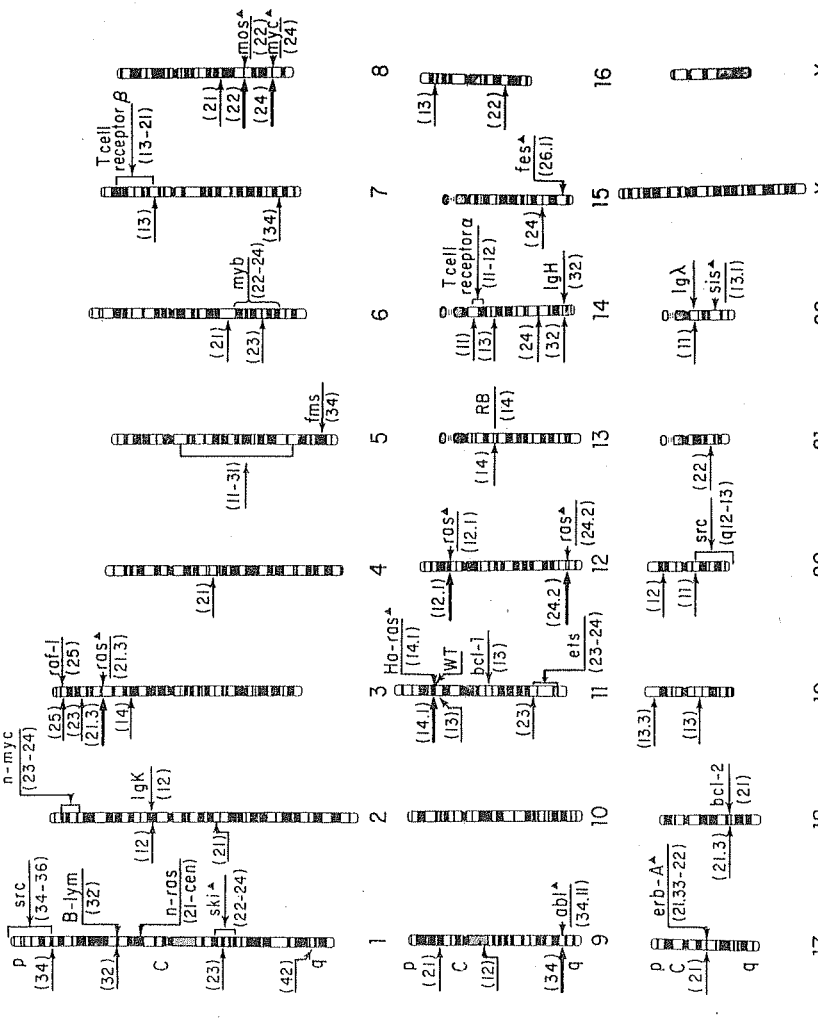

Figure 1. Banded idiogram of human chromosomes showing oncogene localizations and non-random breakpoints reported in neoplastic cells (*c* centromere; *p* short arm; *q* long arm). Oncogene localizations are indicated by arrows on the right side of each relevant chromosome with specific band designation shown in parentheses below the arrow. Breakpoints are indicated by arrows on the left side of each chromosome with the specific band designation shown in parenthesis above the arrow (from: Chaganti and Jhanwar 1985).

homology to v-*onc* genes, more recently, c-*onc* genes with either no known homologies to v-*onc* genes or showing varying degrees of divergence from v-*onc* genes have been isolated from tumor cells in one of three ways: (1) by their ability to transform *in vitro* rodent fibroblast cells (NIH/3T3) following introduction of tumor DNA as calcium phosphate precipitate, indicating that the oncogene in question is in an activated state in the given tumor (example: B-*lym* [Diamond *et al* 1983]), (2) by isolating DNA sequences that occur amplified severalfold in tumor cells and comparing their organization with that of known oncogenes (example: n-*myc* [Kohl *et al* 1983]), and (3) by identifying the sequences translocated into genes with known organization such as the immunoglobulin determinants [example: *bcl*-1 (Tsujimoto *et al* 1984)].

The number of already known c-*onc* genes is impressive although the total number of such genes present in the human genome is currently unknown. So far, c-*onc* genes have been mapped to about 18 sites in the human chromosomal complement. With the exception of a few (e.g. c-*fes* at 15q26·1 and c-*sis* at 22q13·1), the positions of most correspond to those of specific breakpoints reported in rearrangements seen in tumor cells (figure 1). Whether all or most of these chromosome rearrangements also represent gene rearrangements, and if so with what consequence to the development of the tumor, is an issue of considerable fundamental importance.

Pathways of genetic changes in neoplastic cells

The data discussed above show that gene action associated with tumorigenesis is modulated by more than one mechanism. The major documented consequence of somatic cellular alterations is activation, overproduction or production of aberrant products of cellular oncogenes. A discussion of the mechanisms that bring about these phenomena will follow.

Mutation

Mutational activation of three closely related *ras* family oncogenes (c-*Ha-ras*, c-*Ki-ras*, and c-*N-ras*) has been reported in a number of human and animal tumors (Cooper 1982; Der *et al* 1982; Parada *et al* 1982; Shimizu *et al* 1983; Santos *et al* 1982). The 21kd *ras* proteins bind guanine nucleotides, and at least one has been shown to have GTPase activity (Shih *et al* 1980; McGrath *et al* 1984; Feramisco *et al* 1984). The proteins encoded by mutant *ras* alleles differ from their wild type counterparts frequently at residues 12 or 61 (Santos *et al* 1982; Tabin *et al* 1982; Taprowisky *et al* 1982; Fasano *et al* 1984).

Rearrangement

The classical example of oncogene activation by rearrangement is the activation of c-*myc* during the induction B cell lymphomas in chicken by the slowly transforming avian leukosis virus (AVL). AVL lacks the oncogene (v-*myc*) of its rapidly transforming retroviral counterpart (MC29); however, transformation occurs in AVL infected cells when the viral long terminal repeat (LTR) sequences containing the viral promoter

integrate upstream from cellular *myc* (c-*myc*) and cause its activation. A 30 to 100-fold increase in c-*myc* activity has been observed in transformed cells (Hayward *et al* 1981). The BL translocations in which c-*myc* activation is brought about by its translocation to the immunoglobulin genes is analogous to the promoter insertion that takes place in avian bursal lymphomas. Another example of a rearrangement that causes gene activation is the 9/22 translocation which leads to the formation of the Philadelphia (Ph^1) chromosome seen consistently associated with chronic myelogenous leukemia (CML) (Nowell and Hungerford 1960). The c-*abl* oncogene has been mapped to the breaksite on chromosome 9 (9q32·1) (Jhanwar *et al* 1984). It translocates to the Ph^1 chromosome (de Klein *et al* 1982; Bartram *et al* 1983) and the leukemic cells have been shown to produce a novel *abl* MRNA of a size larger than that seen in cells expressing normal c-*abl* as well as a mutant *abl* protein (Canaani *et al* 1984; Collins *et al* 1984; Konopka *et al* 1984). Specific rearrangement, especially translocation, is a diagnostic feature of several tumor types (Sandberg 1985; Testa and Misawa 1985). The above examples strongly indicate the importance of rearrangement in mediating tumorigenesis.

Amplification

Amplification of c-*onc* genes identified either as cytologically recognizable homogeneously staining chromosomal regions (HSR) and double minutes (DM), or simply as increased gene copy numbers in molecular assays has been reported in the case of a number of established tumor cell lines, and more recently in some fresh tumors as well; so far, in human tumors, amplification of c-*myc*, N-*myc*, and c-*abl* has been reported [Brodeur *et al* 1984; Collins and Groudine 1983; Kanda *et al* 1983; Kohl *et al* 1983; Montgomery *et al* 1983; Sakai *et al* 1985]. An interesting feature of amplification of these genes is that prior to amplification they frequently undergo transposition from their germ-line positions to other sites in the genome [Kanda *et al* 1983; Schwab *et al* 1983, 1984].

Oncogene amplification can be viewed as a very powerful mechanism by which tumor cells achieve their evolution. Amplification of proliferation-governing genes such as *myc* will place them at increasing growth advantage whereas amplification of some other genes may aid them in gaining resistance to cellular or iatrogenic factors that attempt to eradicate the tumor.

Non-disjunction

Non-disjunction leading to increase and decrease in chromosome number and hence gene copy number probably was among the first chromosome abnormality types to be recognized in tumor cells. Although rare subsets of tumors contain near-haploid or polyploid chromosome numbers (Testa and Misawa 1985), non-random loss or gain of specific chromosomes is the more usual observation (Testa and Misawa 1985). By definition, aneuploidy implies change in gene dosage; however, neither its mechanism of origin nor the genes whose dosage alteration plays a role in any form of tumorigenesis are known at present. Trisomy of chromosome 8 is a non-random change seen in a number of tumor types including acute non-lymphocytic leukemia (Testa and Misawa

1985). Although the oncogenes c-*mos* and c-*myc* have been localized on this chromosome, their activation status in these tumors is unknown. Thus, although gene dosage alteration brought about by chromosome non-disjunction is a well-documented genetic change in tumor cells, no examples of its specific role in tumor development have been discovered yet.

Hemizygosity and homozygosity

The so-called D-deletion retinoblastoma (RB) and the aniridia-Wilms' tumor association (AWTA) are characterized by deletions of chromosome bands 13q14 and 11p13, respectively (Yunis and Ramsay 1978; Riccardi *et al* 1978). In both cases, abnormal development affects multiple organ systems including those that act as targets for carcinogenesis (eye in RB and kidney in AWTA). The deletion in RB has been shown to vary in size ranging from a submicroscopic gene deletion to the loss of a segment of the long arm of chromosome 13, but always including band 13q14, thus localizing the RB gene to this band (Yunis and Ramsay 1978). The deletion in aniridia-Wilms' tumor association always includes the band 11p13, likewise localizing the Wilms' tumor (WT) gene to this band (Riccardi *et al* 1978). Thus, constitutionally these patients are hemizygous for certain key genes. Epidemiologic studies of familial and sporadic RB and WT, especially the former, were the basis for Knudson's genetic model of cancer origin according to which two mutations (in the broad sense of the word, including chromosome mutations) are required to bring about transformation (Knudson 1971, 1977). In the inherited forms of RB and WT, the first is transmitted through the germline (e.g., D deletion) and the second affects the homologous locus in the target somatic cells, thus rendering the cells recessive. In the sporadic forms of the disease, both mutations occur in the genetically normal cells of the patient. Recent molecular data indicate that RB and WT may attain homozygosity for the deletion through mechanisms such as non-disjunction or somatic recombination [Fearon *et al* 1984; Koufos *et al* 1984; Orkin *et al* 1984; Reeve *et al* 1984]. In these studies comparison of genotypes of constitutional and tumor cells with regard to restriction length fragment polymorphisms (RFLP) at a number of arbitrary loci flanking the gene in question (RB, WT) revealed that distal loci that were heterozygous in the germ-line cells became homozygous in the tumor cells. However, the key questions to be answered in this regard are whether or not the somatic events that affect these loci represent tumor-initiating changes, and if so, when during development and by what mechanisms are they triggered; and finally, what role does the developmental abnormality play in this process? In addition to RB and WT, a number of other cases of specific deletions have been described associated with neoplastic proliferations. These include the 5q-, 6q-, 7q-, and 20q- abnormalities reported in a number of myeloid and lymphoid neoplasms (Testa and Misawa 1985) and 1p- in neuroblastomas (Gilbert *et al* 1982).

Radman has proposed that conversion of a "key" locus from a heterozygous to a homozygous state for a mutant allele by somatic recombination constitutes a promotional event in tumorigenesis (Radman and Kinsella 1980). Cytological demonstration of increased somatic crossing over in Bloom's syndrome, an inherited disorder that predisposes to leukemia and cancer (Chaganti *et al* 1974), provided support for this hypothesis. Recent molecular evidence for attainment of homozygosity for the chromosomal regions containing the RB and WT genes has been cited above. These data

clearly show that regions of chromosomes containing key genes can become homozygous by somatic recombination, one of the conditions predicted by Knudson's hypothesis of cellular recessivity as the genetic mechanism for induction of RB and WT (Knudson 1977). However, it is not clear how applicable this mechanism is to tumorigenesis *per se* nor has it been shown whether recombination precedes or follows the establishment of the tumor progenitor cells.

Another mechanism by which tumor cells attain homozygosity is parthenogenesis. This mechanism has been shown to be associated with the origin of two germ cell tumor types. The first is benign ovarian teratoma, a tumor that in many cases is derived from unfertilized secondary oocytes. These cells normally have completed first meiosis and are held in the ovary at the dictyate stage until postpubertal maturity and entry into the ovulatory cycle. Comparison of constitutional and teratoma cells at a number of fluorescent chromosomal heteromorphisms and enzyme polymorphisms revealed their parthenogenetic origin. In the case of chromosomal heteromorphisms, in which the constitutional cells were heterozygous, the tumor cells were always homozygous. In the case of the enzyme polymorphisms, however, proximal loci that were heterozygous in the constitutional cells were homozygous in the tumor cells, although some of the distal loci retained heterozygosity in the tumor cells because of crossing over between the gene locus and the centromere (Linder *et al* 1975). The other tumor type is the so-called complete hydatidiform mole. By comparison of chromosomal and enzyme markers of tumor cells with those of parental cells, it was shown that the majority of these tumors were homozygous for paternal markers, indicating that they were derived by parthenogenetic development of sperm nuclei that presumably underwent activation in defective or "empty" eggs (Jacobs *et al* 1980; Ohama *et al* 1981; Wake *et al* 1984). Both ovarian teratomas and complete hydatidiform moles are benign proliferations with normal chromosomal complements, although both carry high risk for further malignant transformation and concomitant karyotypic evolution. The molecular mechanisms involved in the development of either of these fascinating tumors are unknown at present.

The data discussed above clearly show that genetic changes comprise key events in cancer predisposition as well as cancer origin. Given the fact that the diversity of clinical cancer represents a multitude of phenotypic changes that affect virtually all the tissue and organ systems in the body, it is not surprising that the underlying genetic changes also are varied and complex. Some of the initial clues to the nature of these changes came from cytogenetic studies; the recent application of molecular genetic methods has provided some extraordinary insights into the nature of these changes and now offers the promise of a greater understanding of the nature of malignant change.

Conclusions

The significance of germ-line and somatic genetic changes to the etiology of cancer has been a subject of continuing interest for cancer cell biologists. Recognition of certain basic principles of cancer cell genetics such as the clonal nature of tumors and their dynamic genetic systems were the early results of these studies, which mainly related to chromosomes in tumor cells. Recent advances in techniques of chromosome analysis and the integration of tumor cytogenetics with immunology and molecular genetics have permitted extraordinary insights into the nature of the perturbations that gene

structure and function undergo in cancer cells. These developments have been reviewed here in so far as they address the central issue of cancer genetics, namely, the role of somatic and germ-line chromosome change in the origin and evolution of neopolastic cells.

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