Review

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# Recessive mutations and chromosome deletions leading to cancer

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*This review examines the effect that a small chromosome deletion affecting a specific DNA sequence may have in producing a state of 'hemizygosity' for a gene or genes, and so triggering malignancy of the cells concerned. The association between such deletions and a variety of cancers will be considered and the implications for clinical practice will be outlined.*

**Keywords:** Cancer, chromosome deletions, oncogenes

The involvement of genetic factors in the aetiology of cancer was first clearly stated by Boveri in 1914[1], who had observed that abnormalities of the mitotic cycle of sea urchin eggs frequently preceded abnormal growth. Later, in 1930, Winge[2] suggested that a population of cancer cells represents the result of a single genetic event, and proposed the 'stem cell' concept. Many years had to pass before cytogenetic[3,4] and biochemical analysis[5] of cancer cells made it possible to demonstrate conclusively that all cells of a tumour are cloned from a single cell and that, in the course of their proliferation, they may acquire new characteristics and ultimately differ from the parental cells.

The concept that tumorigenesis is a multistage process, which involves changes at gene level, has gained new emphasis with the discovery of the oncogenes and their role in the transformation of normal cells[6,7].

The purpose of this article is to review briefly a single aspect of the association between chromosome abnormalities and cancer: the effect that a small chromosome deletion may have in producing a state of 'hemizygosity' for a gene (or genes), thus triggering malignancy of the affected cells. These recent discoveries have been made possible by the collaboration of oncologists, surgeons and geneticists as many of these small deletions can only be detected when genetic probes are used to test freshly collected cancer cells. Awareness of the unique chromosome deletions associated with each type of cancer and a close working relationship between oncologists, surgeons and geneticists should improve diagnosis and prognosis of cancer patients and, at least in some cases, allow for more effective prevention of the disease in their relatives.

## Major types of chromosome abnormalities in cancer cells

At present, several types of chromosome abnormalities have been shown to be associated with cancer (*Table 1*). The most frequent are: (a) reciprocal translocation with or without apparent loss of DNA sequence; (b) non-reciprocal translocation with loss of genetic material; (c) duplication or amplification of chromosomal DNA sequences; (d) deletion of a small chromosome segment resulting in hemizygosity of an allele at one locus[8,9].

Before discussing this last type of abnormality, we will briefly analyse a few examples of the other genetic defects.

Chronic myeloid leukaemia was the first disorder found to be associated with a reciprocal chromosome translocation with no apparent loss of DNA sequence. About 90 per cent of chronic myeloid leukaemia patients have a population of lymphocytes with a small chromosome, 'Philadelphia' ($Ph^1$), which results from the translocation of a segment of the long arm of chromosome 22 to, usually, chromosome 9. Appreciable loss of DNA in these leukaemic cells could not be detected by conventional techniques[10–14].

Several other types of leukaemia have been shown to be characterized by unique reciprocal translocations[9,15,16]. In acute promyeloblastic leukaemia, for example, the translocation involves the transfer of the short arm (p) of chromosome 15 to the long arm (q) of chromosome 17: t(15p+;17q−). In acute myelogenous leukaemia the defect involves a translocation between chromosome 8 and 21: t(8q−;21q+).

Perhaps the most investigated tumour involving a translocation is Burkitt's lymphoma, where the translocation occurs between chromosome 8 and either chromosome 14, 2 or 22, carrying respectively the genes for the heavy (14) or light (2 and 22) chains of the immunoglobulin gene[13,16,17]. The breakpoints of some of the reciprocal translocations observed in human carcinoma are often very near an oncogene. This has lent support to the hypothesis that, in these patients, tumorigenesis results from the activation of an oncogene, but how this occurs has not yet been established[16].

In some of these reciprocal translocations, genetic material is lost to a varying extent. Other tumours are characterized instead by a duplication of a chromosome or part of it. In many cases, duplications are seen in cancer cells from patients at the terminal phase of their disease, such as in patients with chronic myeloid leukaemia, where, in addition to the $Ph^1$ chromosome, an extra chromosome 8 or segments of chromosome 17 can be identified by cytogenetic analysis. Partial trisomies have also been observed in solid tumours[8], probably as a result of repeated mitotic abnormalities. As it is not possible to identify a uniform pattern of duplication of DNA segments in these cancers, the present view is that the genes involved in the duplications are not cancer-specific. Consistent with this suggestion is the fact that patients with trisomies of (or part of) chromosomes 8, 9 and 18 do not show an increased incidence of cancer[8]. An exception

**Table 1** *Examples of chromosomal abnormalities in human cancer cells*

| Abnormality | Examples and comments |
|---|---|
| Point mutation | Cancer of bladder and several other tumours |
| Deletion | Retinoblastoma, Wilm's tumour, cancer of lung |
| Translocation | Burkitt's lymphoma, and at least ten other different cancers |
| Inversion | Usually associated with other abnormalities |
| Amplification | Neuroblastoma: double minutes |
| Breakages, duplication, trisomies | Usually observed in advanced stages of neoplasms |

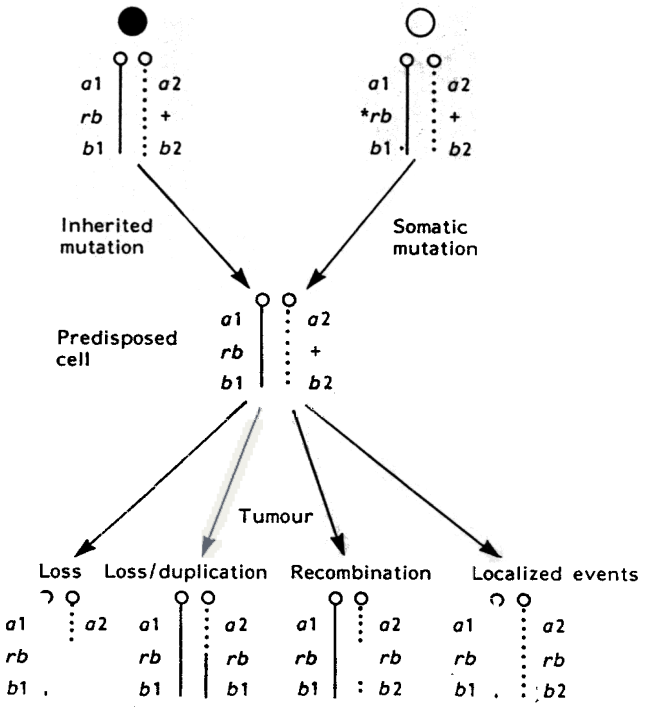


**Figure 1** *Schematic mechanisms which can unmask a recessive gene* (rb) *predisposing for retinoblastoma. Patient* ● *has inherited the abnormal gene* (rb), *while patient* ○ *has acquired it in some cells by somatic mutation. Loss of part of the chromosome containing the normal gene* (+) *and a closely linked gene* (b2) *results in hemizygosity for the abnormal* rb *gene. Loss followed by duplication results in the presence of two copies of the* rb *gene. A recombination event may also duplicate the* rb *gene. Finally, a localized mutation may be responsible for the loss of the normal* (+) *gene, leaving the cell with two* rb *genes. In all these instances the regulatory influence of the normal gene* (+) *on the* rb *gene is lost, resulting in cancer of the affected cell. DNA sequences at some distance from the inherited mutation (e.g. sequence for* a *or* b *loci) defined by restriction fragment length polymorphism can be employed to detect the deletion of the 'cancer' gene*

is trisomy 21, as patients with Down's syndrome have an increased predisposition to leukaemia or other haematological disorders[18,19].

Other duplications are unique to certain types of tumours. For example, neuroblastoma cells may contain several small chromosome segments with unique staining properties. Referred to as homogeneously staining regions or double minute segments, they contain multiple copies of several genes or even a single gene, often conferring resistance to drugs[8,20]. Duplication of oncogenes in double minute segments has also been shown to take place[17,21,22], and this, for example, has been held responsible for causing malignancy in patients with neuroblastoma.

## DNA deletions and cancer

The fourth type of abnormality observed with increased frequency in cancer cells is a small deletion affecting a specific DNA sequence. This abolishes the state of heterozygosity of the cell for allelic genes at one locus, and results in a condition of hemizygosity. The gene (or genes) present in the DNA sequence homologous to the deleted chromosome segment will thus be present in single 'dose' in the affected cell, and hence the hemizygotic state (*Figure 1*).

So far, at least 15 neoplasms have been found to be often associated with an unique type of deletion, some of which are shown in *Table 2*. The best known examples are retinoblastoma and Wilm's tumour, which occur in both sporadic and hereditary forms[28]. A genetic basis for retinoblastoma has been apparent for many years, even though only about 10 per cent of patients have a positive family history[29]. In patients with a family history of the disease, inheritance occurs in a simple autosomal dominant fashion. Furthermore, in about 30 per cent of patients with a new mutation, the disease is transmitted to about 50 per cent of the offspring. In 1971, Knudson[30] suggested a provocative theory, that the disease is triggered by two hit-processes, two events affecting the genome of a cell and resulting in its malignancy. Recent studies have clarified the situation and basically confirmed the hypothesis advanced by Knudson: both alleles of the gene must be altered in order for the disease to develop. The first studies were based on cytogenetic analysis of cells from patients in whom retinoblastoma was associated with multiple malformations and mental retardation. These patients were shown to have a deletion in the long arm of chromosome 13 (Reference 31). Further investigations showed that a deletion of the band at q14 of chromosome 13 (13q14) could be seen in retinoblastoma cells of patients without the malformation syndrome[32,33]. These and other observations have provided evidence that retinoblastoma results from the inheritance of a germinal mutation which does not, in itself, cause malignancy but predisposes to it, and that a second 'hit' is necessary to trigger malignancy. According to the theory, an individual may inherit the predisposing abnormal gene (*rb*, first hit), but only when a second gene change, such as a deletion (second hit), occurs in a susceptible cell (e.g. retinal cell) will the cell become malignant.

The story with Wilm's tumour began with the recognition that cancer cells from patients with a tumour of the kidney, associated with aniridia, had a deletion of the short arm of chromosome 11 at band p13 (11p13)[34]. Abnormality at this site is now considered to be the first event in the aetiology of Wilm's tumour and, as in retinoblastoma, the second event confers either hemizygosity for Wilm's gene (as a result of a deletion) or homozygosity for the abnormal gene (e.g. by mitotic recombination) (*Figure 1*).

The body of evidence assembled so far from the study of these two tumours has led to the hypothesis that they originate because one normal suppressor or regulatory gene is lost in the course of the second hit, leaving only the abnormal gene to trigger malignancy. Most recently, Whyte *et al.*[35] have isolated a $10{\cdot}5 \times 10^4$ protein as a product of the retinoblastoma gene. They postulate that this protein might be acting as an 'anti-oncogene' whose presence initiates suppression of cell division. To support this idea they have observed that a DNA tumour virus, adenovirus E1A, produces a protein which binds the normal $10{\cdot}5 \times 10^4$ protein gene product. Furthermore they speculate that the tumour-inducing properties of this virus lie in its ability to turn off normal cellular suppression by binding the host cell's normal suppressor protein. This idea is supported by the finding that a deletion in the DNA of the tumour virus in the gene which produces the binding protein destroys the tumour-inducing properties of the virus[35,36]. Using probes which identify polymorphic DNA sequences (restriction fragment length polymorphisms) linked to the tumour loci, two other embryonal carcinomas—rhabdomyosarcoma and hepatoblastoma—have

**Table 2** *Some deletions detected in human cancer cells*

| Tumour | Chromosomal abnormality | Reference* |
|---|---|---|
| Retinoblastoma | Chromosome 13 (13q14) | 23 |
| Wilm's tumour | Chromosome 11 (11p13) | 23 |
| Lung cancer (small cell type) | Chromosome 3 (3p21) | 23 |
| Colon cancer (familial adenomatous type) | Chromosome 5 (5q21 or 5q22) | 24 |
| Breast cancer | Chromosome 11 (short arm) | 25 |
| Renal carcinoma | Chromosome 3 (3p11.2 or 3p13) | 26 |
| Osteosarcoma | Chromosome 13 (13q14) | 27 |
| Neuroblastoma | Chromosome 1 (1p31) | 23 |

* Reference to reviews and recent papers

been shown to be due to genetic changes which result in hemizygosity or homozygosity for an abnormal gene[37].

During the last 2 years, other tumours have been found to be associated with unique types of chromosome deletions, which could only be detected using restriction fragment length polymorphisms. In the absence of any knowledge of the gene responsible for a specific tumour, the polymorphism of DNA sequences closely linked to the cancer gene can be exploited to establish the presence or absence of a deletion (see *Figure 1*). This strategy has been employed, for example, to investigate oncogenesis in patients with cancer of the lung, the colon or the breast.

A small deletion of chromosome 3 is the most constant finding in cancer of the lung tissue. Using a large panel of lung cancer cell lines representing all the different histological types (squamous or epidermoid carcinoma, adenocarcinoma, small cell carcinoma, and combined type) Minna *et al.*[38] were able to identify a gene on the short arm of chromosome 3 which may predispose to cancer of the lung. According to this hypothesis, individuals at risk would be heterozygous for this recessive gene, carrying one mutant and one copy of a normal functional gene in each cell. In these individuals environmental factors, in particular cigarette smoke, may produce somatic changes—such as a deletion or a mutation of the normal gene—in a lung cell, thus unmasking the abnormal gene. Loss of the normal gene is suspected to deregulate the expression of a proto-oncogene of the c-*myc* family or other gene controlling the synthesis of growth factor.

Deletion of a DNA sequence at the chromosomal region 3p21 in patients with lung cancer has been confirmed in a recent study[39]. In fact, using a molecular genetic approach, consistent deletion of the chromosome region 3p21 was observed not only in small cell lung cancer but also in all major types of lung cancer investigated. Part of the analysis was carried out using cell lines obtained from the tumours. A series of 16 biopsies from squamous cell carcinoma and 14 adenocarcinomas was also investigated. In several patients where heterozygosity for the selected DNA marker was detected using peripheral blood leucocytes, the tumour cells showed hemizygosity, thus revealing loss of the DNA region (3p21, locus DNF 15 5e). This confirms that somatic mutation of a gene at 3p21 is involved in the development of cancer of the lung.

In the case of cancer of the colon, a single patient was initially observed with a deletion of part of the long arm of chromosome 5 (5q), who, in addition to various developmental disorders, had multiple adenomatous polyps of the large bowel[40]. Linkage analysis of patients with cancer of the colon and their relatives, using a series of genetic probes defining polymorphic DNA segments (restriction fragment length polymorphisms) in the long arm of chromosome 5, has recently confirmed that indeed the familial adenocarcinomatous polyposis gene maps to chromosome 5 (5q21 or 22)[24,41]. In a parallel study, loss of heterozygosity in this DNA region was demonstrated in about 20 per cent of patients with spontaneous colon cancer[42]. Thus inherited and sporadic forms of cancer of the colon both result from mutation in the same gene, in analogy with the hypothesis advanced by Knudson[30] for retinoblastoma and Wilm's tumour[43]. Both these mutations act in a recessive form and both normal allelic genes must be altered for cancer to develop. In the sporadic cases both events occur somatically, whereas in the familial cases susceptibility is inherited through germ-line mutation and cancer develops after a somatic change in the homologous allele (*Figure 1*).

Somatic loss of heterozygosity for genes on chromosome 11 has also been observed in some patients with cancer of the breast[25]. Deletions of various DNA sequences of the short arm of chromosome 11 were observed in about 20 per cent of breast cancer tissue biopsies obtained from 56 patients tested, and a significant association was noticed with tumours that lacked oestrogen and progesterone receptors.

Renal carcinoma, the most frequent form of malignancy of the human kidney, usually occurs during the sixth and seventh decades of life. Most tumours are sporadic, but hereditary forms have been described and are characterized by an early onset and bilateral localization. Cytogenetic studies have indicated that the short arm of chromosome 3 (3p) is the most frequent site of non-random abnormalities in both hereditary and sporadic types[26,44]. A recent investigation by Kovacs *et al.*[45] has confirmed the high incidence of anomaly of chromosome 3, distal to band 3p11.2 or 3p13 manifested as a deletion. Restriction fragment length polymorphism analysis in patients with sporadic cancer of the kidney has shown loss of heterozygosity for one marker (D1S1) in 76 per cent of cases and for another marker (D3S2) in another 18 per cent of patients.

## Conclusions

At present, the prevailing working hypothesis about oncogenes is that they are involved in the process of tumorigenesis as a result of a mutation which may directly affect their function as growth factors or may activate a growth factor gene. This would induce a state of autocrine stimulation of the cell and consequently its abnormal proliferation. On the other hand a mutation of a specific receptor for a growth factor may induce autostimulation and consequent prolonged cell division. Another possibility is that the cell may be stimulated by the abnormal functional behaviour of a cell receptor via a mediator released in the cytoplasm by a cell receptor for a growth factor.

Finally, as already mentioned, the concept of the anti-oncogene and its role in tumorigenesis should be kept in mind[35,46]. The gene product of the antioncogene may act normally to suppress cell division. When this gene or its gene product is inactivated, uncontrolled proliferation occurs.

Probably the process of tumorigenesis is more complex than this, and the main question to answer is: why should a deletion such as 13q14 in an embryonal retinal cell result in a retinoblastoma while the same deletion in another type of cell does not induce malignancy? One possible explanation is that random deletions occur frequently in many cells and in most cases they may be either tolerated or lethal, but in some cells the same deletion induces abnormal growth and thus cancer. Further investigation should elucidate the role that genetic predisposition to a certain type of cancer, together with environmental agents, may have in triggering the disease and whether prevention can be achieved in relatives of the patient. It has been suggested, for example, that cancer of the lung is due to the presence of an abnormal recessive gene on chromosome 3 and that the deletion observed in this type of tumour (3p21) involving the normal gene may be induced by tobacco smoking. If this hypothesis turns out to be correct, patients at risk could be identified and preventive measures implemented. It is at this level of prevention that the close collaboration among oncologists, geneticists and surgeons is essential.

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