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Review

Chromosomal Instability in Cancer: Causes and Consequences

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Summary

Many human malignant tumours exhibit abnormal chromosomal segregation at cell division. It is believed that these anomalies play a role in tumorigenesis by increasing the rate of chromosome mutations, including deletion and amplification of genes involved in cellular proliferation and/or survival. *In vitro* experiments have also shown that mitotic instability may be a mechanism for developing resistance to cytotoxic drugs. Abnormal mitotic mechanisms may result in numerical or structural aberrations in the daughter cells. Numerical aberrations can be caused either by the loss of chromosomes at metaphase/anaphase or by multipolar divisions associated with abnormal number or structure of centrosomes. Structural rearrangements have been associated with chromosomal breakage-fusion-bridge (BFB) cycles that can be initiated by telomeric dysfunction, giving rise to unstable dicentric or ring chromosomes. In most tumours exhibiting chromosomal instability, including high-grade malignant pancreatic, ovarian, and head- and neck carcinomas, as well as osteo- and soft tissue sarcomas, the two types of instability occur together. However, in some low-grade mesenchymal and neuroglial tumours, rarely showing numerical changes, BFB events involving telomeric associations and ring chromosomes dominate the mitotic process. At progression towards higher malignancy in these tumours, complex structural and numerical aberrations become more frequent. This may be explained by a process initiated by telomeric dysfunction and anaphase bridging, which, in turn, may give rise to an increased frequency of multinucleated cells through failure of cytokinesis. These cells will contain an abnormal number of centrosomes leading to multipolar mitotic figures at the next cell division. Further understanding of these events may lead to novel strategies for detection and treatment of malignancy.

Introduction

All malignant tumour types have been shown to contain chromosomal aberrations. The pattern of abnormalities varies greatly between malignancies, ranging from simple balanced rearrangements to complex abnormalities affecting both chromosome structure and number (Mitelman Database of Chromosome Aberration in Cancer 2001). In haematological neoplasms, certain abnormalities are often strongly associated with specific diagnostic entities. Typically, these changes are reciprocal translocations such as the t(9;22) in chronic myelogenous leukaemia (Heim and Mitelman, 1995). Similar genetic abnormalities are seen in some solid tumours, e.g. the 11;22 translocation in Ewing sarcomas and the inversion of proximal 10q in papillary thyroid carcinomas (Vecchio and Santoro, 2000). Such subtype-specific chromosomal abnormalities often correspond to distinct molecular genetic alterations, including the formation of fusion gene products, or the swapping of promoter elements leading to dysregulated gene expression (Åman, 1999). The majority of malignant solid tumours, however, exhibit a complex pattern of chromosomal abnormalities, rarely showing any direct association with specific morphological or prognostic subgroups. Many common aggressive epithelial tumours, such as high-grade pancreatic, ovarian, and lung cancer, fall within this category (Pejovic et al., 1992; Johansson et al., 1995; Gorunova et al., 1998). So do many

sarcomas, such as osteosarcoma, leiomysorcoma, and malignant peripheral nerve sheath tumour (Mandahl, 1996). The molecular genetic alterations corresponding to these complex cytogenetic anomalies are not well characterised, although abnormal activation of oncogenes and losses at tumour suppressor genes are common. These changes are rarely subtype specific. However, as a rule, the total number of chromosomal aberrations is roughly proportional to the risk of metastasis (Mitelman et al., 1997).

What is chromosomal instability?

The large number of chromosomal changes frequently seen in malignant solid tumours has brought forth the suggestion that an abnormally high rate of chromosome mutations occurs in neoplastic cells (Nowell, 1976). Tumours exhibiting a large number of chromosomal abnormalities usually also show considerable intratumour variability in the pattern of genetic rearrangements. In most cases, a subset of these abnormalities are shared by all cells of a tumour, indicating that a step-wise accumulation of cytogenetic changes have occurred during tumour growth (Heim et al., 1988). Chromosomal instability may be defined as a state of continuous formation of novel chromosome mutations, at a rate higher than in normal cells. Strictly, this implies that neither cytogenetic complexity, nor cytogenetic heterogeneity *per se*, should be used as evidence of chromosomal instability, as these states may both be attained through a single mutagenic insult. In practice, instability may be assessed by following the evolution of cytogenetic abnormalities in a tumour cell population over time and by comparing the rate of chromosome mutations with that in a normal cell population (Lengauer et al., 1997). Alternatively, the mutation events can be monitored directly by quantifying the incidence of chromosomal losses, gains, and structural rearrangements at cell division. However, none of these strategies is sufficient to fully evaluate the mechanisms of chromosomal instability. Normally, cells that have undergone DNA breakage are prevented from further proliferation by a number of cell cycle check points. A continuous accumulation of chromosome changes in a cell population may thus arise either through an elevated mutation frequency, a decreased tendency of self-elimination among mutated cells, or both. The scenario is further complicated by the influence of environmental factors on experimental systems (Johansson and Mertens, 1986).

Mechanisms of chromosomal instability

Structural chromosome instability

An elevated frequency of structural chromosome aberrations could be directly caused by an abnormally high incidence of DNA double-strand breaks. Chromosomal breakage can result in a number of different structural rearrangements, some of which give rise to abnormalities of chromosomal segregation at mitosis. For example, terminal deletions due to a break of a single chromatid will result in a centric derivate chromosome plus an acentric fragment. Because of its failure to bind the mitotic spindle, the fragment may be permanently lost in the subsequent cell division, and may be seen as a lagging chromatin body at metaphase or anaphase. Such lagging is a common finding in cell populations exposed to ionising radiation (Natarajan et al., 1996). It has also been described in a number of solid tumours, such as head and neck, and breast carcinomas (Hansemann, 1891; Steinbeck, 1997).

In normal cells, DNA lesions are detected and repaired by a sophisticated physiological machinery. An essential component of this is the BRCA1-associated genome surveillance complex (BASC), including the BRCA1, BRCA2, MSH2, MSH6, MLH1, ATM, BLM proteins, as well as the RAD50 - MRE11 - NBS1 complex (Wang et al., 2000). So far, germ-line mutations of *BRCA1*, *BRCA2*, *MSH2*, *MLH1*, *ATM*, and *BLM* have been found to cause inherited syndromes with an increased tumour incidence (Meyn, 1997). Also, somatic mutations of these genes occur in sporadic tumours, e.g. *MSH2* and *MLH1* in colorectal carcinomas (Gafa et al., 2000), *ATM* in lymphomas (Meyn, 1997), and *BRCA1* in mammary cancer (Meje, 1995). Both the Bloom syndrome and ataxia telangiectasia exhibit an increased level of spontaneous chromosomal aberrations in somatic cells. Still, the incidence of chromosomal instability far exceeds the frequencies of somatic *ATM* and *BLM* mutations in sporadic cancers, indicating that other mechanisms are primarily responsible.

Genomic integrity is also under surveillance from a system of cell cycle checkpoints, preventing cells that have sustained DNA damage from proliferating further. For instance, double-strand DNA breaks induced by clastogenic agents, such as radiation or reactive oxygen species, may lead either to cell cycle arrest or apoptosis by a mechanism including activation of the TP53 and p21 proteins (Kastan et al., 1991; Bunz et al., 1998; Rotman and Shiloh, 1998; Morrison et al., 2000). Factors involved in this cell cycle checkpoint system are frequently deregulated or inactivated in tumour cells. Mutations of *TP53* are responsible for the Li-Fraumeni tumour syndrome and also occur at a frequency of approximately 50% in sporadic malignant tumours. The gene for the TP53-inhibitor MDM2 is amplified in another 10%-20% of bone and soft tissue tumours (Toguchida et al., 1992; Wang et al., 1995; Miller et al., 1996; Lonardo et al., 1997; Yoo et al., 1997). Inactivation of TP53 in immortalised cells results in a marked instability of chromosome structure, including translocations, deletions, telomeric associations, and ring chromosomes (Agapova et al., 1996; Meyn, 1997). A similar pattern of aberrations is typically seen in pancreatic carcinomas and poorly

differentiated sarcomas with mutations in *TP53* or genomic amplification of *MDM2* (Gisselsson et al., 1998; Gisselsson et al., 2000).

The BFB cycle - a chain reaction of chromosomal breakage

Concurrent breaks in two different chromosomes may either give rise to translocations or dicentrics. Whereas translocation derivatives are stably transmitted through cell division, the dicentric chromosomes may be stretched out between the spindle poles to form bridges at anaphase (Figure 1A). These bridges may subsequently break, and the chromosomes are transmitted to the daughter cells with broken ends that may recombine further during the subsequent interphase (McClintock, 1940). Similarly, ring chromosomes having undergone sister chromatid exchange, may be stretched out at anaphase, break, and then be transmitted to the daughter cells as broken chromosomes (Figure 1B; McClintock, 1938). The broken chromosome ends may fuse into novel dicentrics and rings, which may again break at the next cell division. Thus, chromosomal damage may not only result in static aberrations, such as translocations, inversions, deletions, and duplications; it may also result in mitotically unstable chromosomes, which may trigger a series of breakage-fusion-bridge (BFB) events. Such BFB cycles have been shown to occur in many malignant solid tumours with complex chromosome abnormalities, including head and neck, pancreatic, and ovarian carcinomas, as well as leiomyosarcoma, osteosarcoma, malignant fibrous histiocytoma, and atypical lipomatous tumours (Gisselsson et al., 2000; Saunders et al., 2000). Data from *in vitro* and animal studies indicate that the BFB cycles may be initiated by shortening of telomeric repeat sequences, leading to impaired integrity of chromosome termini and telomeric associations between chromosomes (Artandi and DePinho, 2000). It is probable that similar mechanisms are responsible for the high frequency of BFB instability in human malignancies (Gisselsson et al., unpublished data).

Numerical instability

Already at the end of the 19th century, Hansemann observed aberrations of the mitotic apparatus in

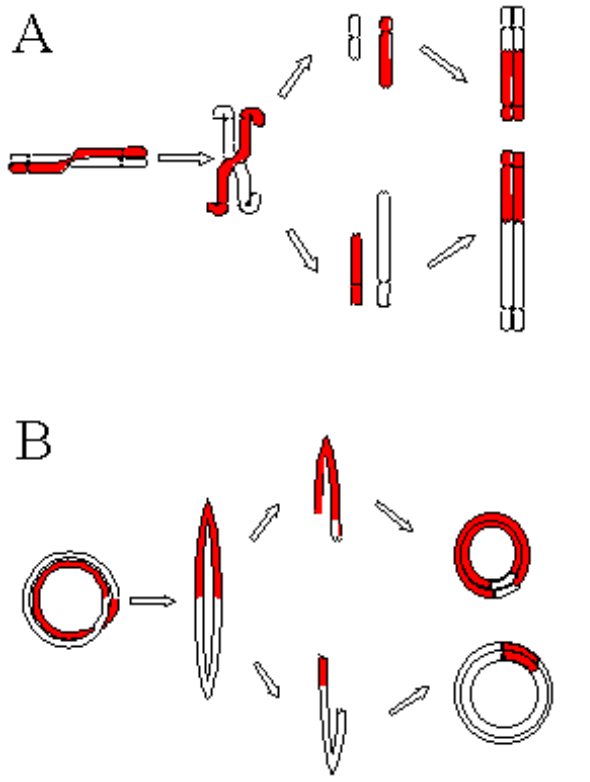

Figure 1: Chromosome breakage-fusion-bridge (BFB) cycles: Dicentric (A) and ring (B) chromosomes may form bridges at anaphase and the broken ends of the two chromatids (red and white) may fuse into novel dicentric and ring-shaped structures in the daughter cells.

malignant tumours, including abnormal mitotic polarity and an unequal segregation of chromosomes at anaphase (Hansemann, 1891). A few decades later, Boveri suggested that abnormalities in mitotic polarity could be caused by an abnormal number of centrosomes - the organelles responsible for organisation of the mitotic spindle (Boveri, 1914). Today it is well established that many epithelial tumours exhibit an asymmetrical segregation of chromosomes at the metaphase-anaphase transition, resulting in an aberrant distribution of the genetic material to the daughter cells (Steinbeck, 1998). Also, abnormalities in the number and structure of centrosomes have been observed in malignancies with aneuploid chromosome numbers, including cancers of the breast (Lingle and Salisbury, 1999), colon (Ghadimi et al., 2000), and the head and neck region (Saunders et al., 2000). These changes in centrosomal configuration have been correlated with a number of molecular genetic abnormalities, including amplification of *STK15* (Zhou et al., 1998), mutations in *TP53* (Carroll et al., 1999), and inactivation of *BRCA1* (Xu et al., 1999), *BRCA2* (Tutt et al., 1999), and *GADD45* (Hollander et al., 1999).

Abnormal centrosomal function may also be induced *in vitro* by expression of the papilloma virus genes E6 and E7, inhibiting normal TP53 and RB1 activity, respectively (Duensing et al., 2000). This is particularly

interesting since multipolar mitoses and other manifestations of chromosomal instability are hallmarks of malignant progression in HPV-related cervical carcinomas (Duensing and Münger, 2001). It has also been suggested that inactivation of genes that control the timing of mitotic chromosome segregation may contribute to numerical instability. However, only rare examples of such aberrations have so far been identified (Cahill et al., 1998).

Sine qua non or side effect?

Although chromosomal instability is a common finding in malignant tumours, its precise pathogenetic role remains to be established. Rapid cellular proliferation would undoubtedly be of selective value in a developing tumour. It is likely that cells could increase their mitotic frequency by decreasing the cell cycle intervals spent on DNA repair. An impaired control of cell cycle progression, such as disrupted TP53 or RB1 function, could thereby be coupled to a higher rate of proliferation. These proteins are also involved in the control of genomic integrity and the uncoupling of mitosis from genomic integrity could then merely be a side effect of selection for cells with a high mitotic rate. In this case, a continuous rearrangement of the chromosome complement may even impose a burden on the cell population, and efficient growth would be dependent on a delicate balance between proliferation rate and mutation rate. Functions that stabilise the chromosome complement, while still allowing a permanent disruption of cellular check points, would then be highly favourable for efficient tumour development. It has been suggested that abnormal activation of telomerase could stabilise inherently unstable genomes by synthesising novel telomeric repeats at broken chromosome ends (Artandi and DePinho, 2000). Indeed, telomerase activity has been detected in the majority of malignant epithelial tumours (Krupp et al., 2000).

On the other hand, genomic instability may actually have a selective value *per se*. An increased rate of chromosomal mutations will result in an elevated frequency of other genetic abnormalities, some of which may directly promote tumour cell proliferation and viability. Such an elevated frequency of chromosomal mutations may even be a prerequisite for oncogenetic processes requiring multiple genetic steps, such as the inactivation of tumour suppressor genes and amplification of oncogenes (Lengauer et al., 1998). Many of the tumours showing genomic instability typically have loss of heterozyogosity for many loci. Also, in tumours showing genomic amplification, BFB events occur at a high frequency. For instance, in head and neck cancer, amplification of the *CCND1* gene, located in 11q13, is associated with anaphase bridging of chromosome 11 material (Shuster et al., 2000). These tumours also show loss of heterozyogsity at various tumour suppresser loci, including *FHIT* in 3p14, *INK4A* in 9p21, and *TP53* in 17p13 (Scully et al., 2000). In atypical lipomatous tumours carrying amplified sequences from 12q13-15, including the *SAS*, *CDK4*, HMGIC, and *MDM2* genes, the majority of anaphase bridges contain sequences from this particular chromosome segment (Gisselsson et al., 1999). Furthermore, a number of *in vitro* systems have shown that amplification of genes conferring resistance to cytotoxic drugs may occur through BFB events (Smith et al., 1992; Ma et al., 1993; Coquelle et al., 1997). This suggests that a state of chromosomal instability may not only be crucial for tumour development, but may also play a role in resistance to chemotherapy.

Different mechanisms or steps in a single process?

In most tumours exhibiting chromosomal instability, BFB events and centrosomal abnormalities occur together (Saunders et al., 2000; Gisselsson et al., unpublished data). In analogy, most malignant tumours exhibit both structural and numerical chromosome abnormalities (Mitelman Database of Chromosome Aberrations in Cancer 2001). However, in many low-grade mesenchymal and neuroglial tumours, BFB events involving telomeric associations and ring chromosomes are seen at mitosis, in the absence of major numerical changes (Sawyer et al., 1992, 1998, and 2000; Gisselsson et al., 1999). However, at progression of these tumours towards higher malignancy, numerical aberrations as well as highly complex structural aberrations become more frequent (Mitelman Database of Chromosome Aberrations in Cancer 2001; Rosai et al., 1996). This implies a sequence of parallel cytogenetic and molecular steps, where telomeric dysfunction and BFB events occur at an early stage, and numerical instability develops later. First, a continued proliferation of cells with reduced telomere length (beyond the Hayflick limit) requires an inhibition of cell cycle control mechanisms. *In vitro*, this may be induced by partial inhibition of normal TP53 and RB1 function, for instance by SV40 transfection (Jha et al., 1998). The corresponding *in vivo* changes remain to be elucidated, although recent findings indicate that some cell types, such as human

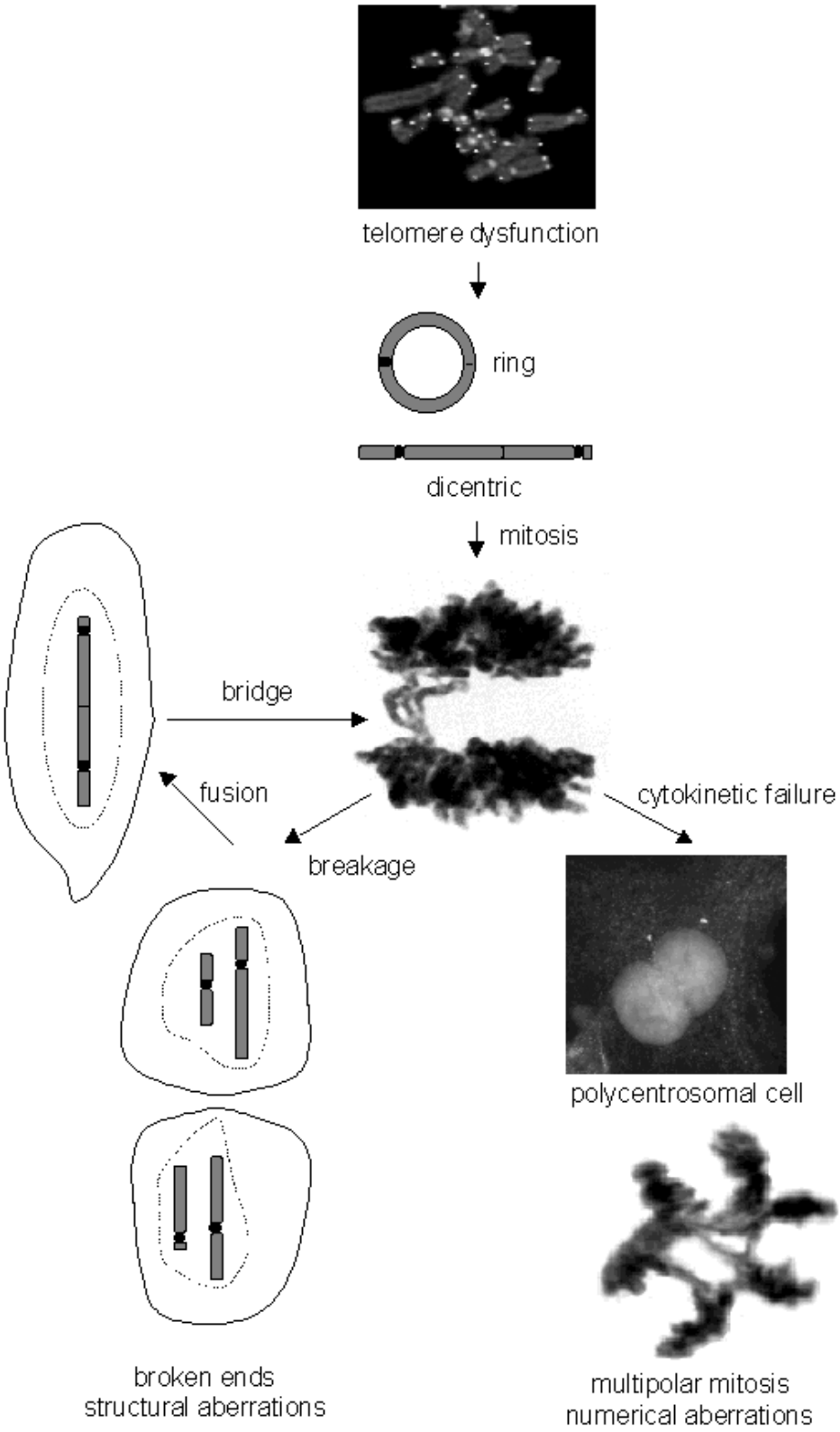

Figure 2; Hypothetical scenario of progressive mitotic instability: Telomere shortening, seen as absence of detectable TTAGGG repeats (top image; green fluorescence) may compromise the integrity of chromosome ends, leading to the formation of rings and dicentrics. These may form bridges at anaphase, which either breaks and initiate a series of BFB-events, or induce cytokinetic failure leading to the formation of binucleate cells with supernumerary centrosomes. Cells with an abnormal centrosome number (orange fluorescence) may form multipolar mitoses at the next cell division. Thus, telomeric dysfunction may result both in structural and numerical chromosome instability.

mammary epithelial cells, may spontaneously proliferate beyond the normal telomere length and acquire chromosomal changes such as dicentrics and rings (Romanov et al., 2001). Further survival of cell populations with disrupted telomeric integrity, resulting in frequent BFB events, would require additional impairment or total abrogation of the systems normally causing arrest or apoptosis in cells with double-strand DNA breaks. This step appears to be associated with inactivating mutations in *TP53* or high-level amplification of *MDM2* (Gisselsson, 2000). Also, the numerical chromosome instability associated with abnormal centrosome function indicates that highly malignant cells have acquired some tolerance to massive genomic imbalances.

The common concurrence of BFB instability and centrosome abnormalities suggests that these phenomena are mechanistically linked. Although it is true that both these instabilities may be associated with similar molecular genetic lesions, such as *TP53* mutation, their causal relationship, if any, remains unclear. There may be one rather straightforward relationship, however. It is well established that anaphase bridging may cause collapse of the cytokinetic process, leading to formation of cells with a duplicated genome (McClintock, 1938). Tumours with BFB events show a high frequency of binucleated cells (Gisselsson et al., 2001). These cells would not only carry the double amount of genetic material, but also twice the normal number of centrosomes. After the next round of replication, such cells may thus enter mitosis with abnormal centrosome configurations, leading to either tri- or tetrapolar cell divisions (Figure 2). Incomplete cytokinesis could then easily explain the connection between telomere shortening and BFB events, on one hand, and mitotic multipolarity, on the other hand.

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