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Review

Tumour morphology – interplay between chromosome aberrations and founder cell differentiation

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Summary. Studies of haematological neoplasms have shown that alterations in structure and/or expression of transcription factor genes may play a crucial role for transforming stem cells or progenitor cells into malignant cells. These mutations typically arise through balanced translocations and appear to induce a block in cellular differentiation. The impact of the transforming mutation is highly dependent on the lineage of the founder cell and each specific translocation is limited to one or a few morphological subtypes. Originating from immature cells, these neoplasms have a high self-replicative capacity and are already before transformation protected from senescence by constitutive telomerase expression. Most solid tumours, on the other hand, probably originate from cells at higher levels of differentiation and require multiple mutations in oncogenes and tumour suppressor genes for neoplastic transformation. Absence of telomerase activity in the tumour-founding cell line predisposes to abnormal shortening of telomeric repeats in these cells during early clonal expansion. In turn, this triggers chromosomal breakage-fusion-bridge events through which the tumour genome is constantly reorganised, resulting in a complex and heterogeneous pattern of chromosome aberrations in the tumour cell population; the abnormal mitotic processes also give rise to cellular pleomorphism and nuclear atypia. Tumour morphology thus appears to be determined not only by the lineage of the transformed cell but also by its propensity for chromosomal instability.

Key words: Morphology, Chromosome instability, Telomere, Differentiation, Stem cell

Introduction

Clonal chromosome aberrations have been found in all malignant tumours. In haematological neoplasms and some bone and soft tissue tumours, a strong correlation exists between tumour morphology and cytogenetic changes. These neoplasms typically contain balanced translocations, which directly correlate to pathogenetic events at the molecular level. Classical examples are the 9;22-translocation in chronic myelogenous leukaemia and the 11;22-translocation in Ewing sarcoma. However, the majority of epithelial and mesenchymal tumours exhibit a highly complex pattern of genetic abnormalities. Although these tumours show a clearly non-random distribution of chromosome breakpoints, characteristic cytogenetic aberrations are rarely found (Heim and Mitelman, 1995). Instead there is a vast heterogeneity in the karyotypic profile within histopathological subgroups (Lleonart et al., 2000). There is also strong evidence that the cytogenetic changes evolve extensively over time, in parallel to tumour progression, so that high-grade solid tumours exhibit a higher number of aberrations than low-grade lesions of the same histological subtype (Gisselsson et al., 2001a). Why a certain tumour cell develops according to one or the other of these two modes of cytogenetic evolution has not been established. This is an attempt to summarise some of the established relations between cytomorphology and chromosome mutations. Based on these data, it is hypothesised that not only the lineage of the tumour-founding cell, but also its propensity for cytogenetic instability play a decisive role for the morphological characteristics of neoplastic lesions.

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Do chromosome aberrations affect tumour morphology or *vice versa*?

Leukaemic cells frequently contain chromosome aberrations that are specific for one or a few morphological subtypes. Most of these subtypes have normal counterparts at various stages of bone marrow differentiation and it has been proposed that the role of chromosome aberrations is to block differentiation towards mature blood cells (Klein and Klein, 1986). For instance, the M3 subtype of acute myeloid leukaemia typically carries a translocation between chromosomes

15 and 17, leading to fusion of the PML gene in chromosome 15 with the retinoic acid receptor alpha gene RARA in chromosome 17 (Rowley et al., 1977; Cleary, 1991). The resulting PML/RARA fusion protein is thought to act in a dominant fashion, inhibiting either the transcription factor activity of PML or the receptor function of RARA, thereby blocking differentiation beyond the promyelocyte stage (Grignani et al., 1993).

Similar mechanisms have been revealed in soft tissue tumours. Both benign and malignant lesions of soft tissues may show characteristic translocations leading to fusion or dysregulated expression of genes (Mandahl, 1996). For instance, common lipomas often show rearrangement of the long arm of chromosome 12, leading to abnormal expression of the gene *HMGA2* (Ashar et al., 1995; Schoenmakers et al., 1995). The HMGA2 protein is a so-called architectural transciption factor, normally expressed only in embryonal and other fetal cells. The ectopic expression of HMGA2 in adult mesenchymal stem or progenitor cells is thought to contribute to uncontrolled cellular proliferation in a so far unknown manner. In the malignant myxoid liposarcomas, on the other hand, a translocation between chromosomes 12 and 16 is typically observed, leading to fusion of *CHOP* in chromosome 12 with *TLS* in chromosome 16 (Crozat et al., 1993). In this case, a structurally abnormal TLS/CHOP fusion protein disrupts the normal transcription factor activity of CHOP. Whereas lipomas are morphologically identical to mature adult fat, the myxoid liposarcomas consist of lipoblasts at various stages of differentiation (Enzinger and Weiss, 1994). Analogous to the situation in haematological neoplasms, it is thought that the molecular rearrangements in these soft tissue tumours block the normal differentiation of cells. Consequently, myxoid liposarcomas should arise from cells at early stages of lipoblastic differentiation, whereas lipomas should originate from more mature cells of the same lineage. But why do translocations at all exhibit this type of lineage restriction? There are several alternative explanations:

1. Mutation promoted by differentiation

Some chromosome mutations may preferentially occur during certain periods of cellular differentiation. Evidence of such a mechanism has been demonstrated in lymphomas and lymphatic leukaemias. B-cell neoplasms frequently carry translocations affecting the immunoglobulin loci in chromosomes 2, 14, and 22. Through these rearrangements, oncogenes are brought under the influence of the highly active promoters and enhancers of the immunoglobulin loci. The DNA sequence at the translocation breakpoint indicates that these rearrangements may depend on physiological VDJ rearrangements, somatic hypermutation, and isotype switching, probably during the pre-B cell stage of differentiation (Kuppers and Dalla-Favera, 2001). It is notable that isotype switching and somatic hypermutation are most frequently seen in lymphomas arising from germinal centre cells; these are also the cells where such recombination events occur during normal B cell development. In T cell malignancies, on the other hand, the T-cell receptor loci in chromosomes 7 and 14 are involved in analogous rearrangements, most probably generated by RAG-dependent VDJ recombination (Hiom et al., 1998). In these neoplasms, the association between cytogenetic and morphological features thus could be caused by an increased frequency of certain chromosome aberrations during a normal, programmed cellular process.

2. Mutation selected through differentiation

This model assumes that chromosome aberrations occur spontaneously at a considerable rate. Every cell type may then potentially be afflicted by any type of cytogenetic abnormality. However, the physiological consequences of a chromosome translocation will have transforming effects only during a certain differentiational setting, a so-called"window of vulnerability" (Klein and Klein, 1986). The resulting morphology would then be determined primarily by the original features of the first transformed cell. If the mutation does not totally block the process of differentiation, but instead limits it to a few morphological stages, a tumour comprising cells at different stages of maturation could appear. Such a pattern is actually observed in a number of different tumours. An illustrative example is lipoblastoma – a rare tumour of infancy – where the tumour parenchyma completely simulates embryonal lipogenesis, from immature mesenchymal spindle cells to adipocytes (Enzinger and Weiss, 1994). Cytogenetically, these tumours are characterised by rearrangement of the *PLAG1* gene in the long arm of chromosome 8 (Hibbard et al., 2000). The rearrangement is present in all the morphological components: polyvacuolar and monovacuolar lipoblasts, mature adipocytes, and fibroblast-like mesenchymal spindle cells (Fig. 1A-C). *PLAG1* rearrangements thus appear to be compatible with a complete program of embryonal lipogenesis; the tumours never progress beyond the benign stage and the mature adipocytes appear to be their differentiational endpoint. Interestingly, *PLAG1* is also rearranged in another tumour, pleomorphic adenoma of the salivary gland (Kas et al., 1997). Here, the morphological variation is even more striking, as these lesions contain both an epithelial and a mesenchymal component; overexpression of PLAG1 has been detected in both these cell types (Debiec-Rychter et al., 2001).

A similar scenario has been observed in leukaemic cells. Just like in the lipoblastomas, the pathogenic translocations are here thought to occur at the stem cell level. Still, many hematological neoplasms exhibit features of considerable cellular differentiation (Shteper and Ben-Yehuda, 2001). In bone marrow from patients with chronic myeloid leukaemia, the Philadelphia

chromosome has been detected in pluripotent stem cells, in myeloid cells at different stages of maturation, and in B-cell and NK cell progenitors (Miura et al., 2000). However, mature NK cells or B-cells with the BCR/ABL fusion gene cannot be detected, indicating that the mutation is compatible only with certain lines of differentiation. Furthermore, some studies have shown that the BCR/ABL fusion product may be detected at trace levels in blood also from healthy individuals and that the frequency of the mutation increases with age (Biernaux et al., 1996). This indicates that tumour-associated chromosome aberrations may occur in a number of cell types without causing transformation. Conversely, only one or a few stages of differentiation will support neoplastic transformation through a certain translocation.

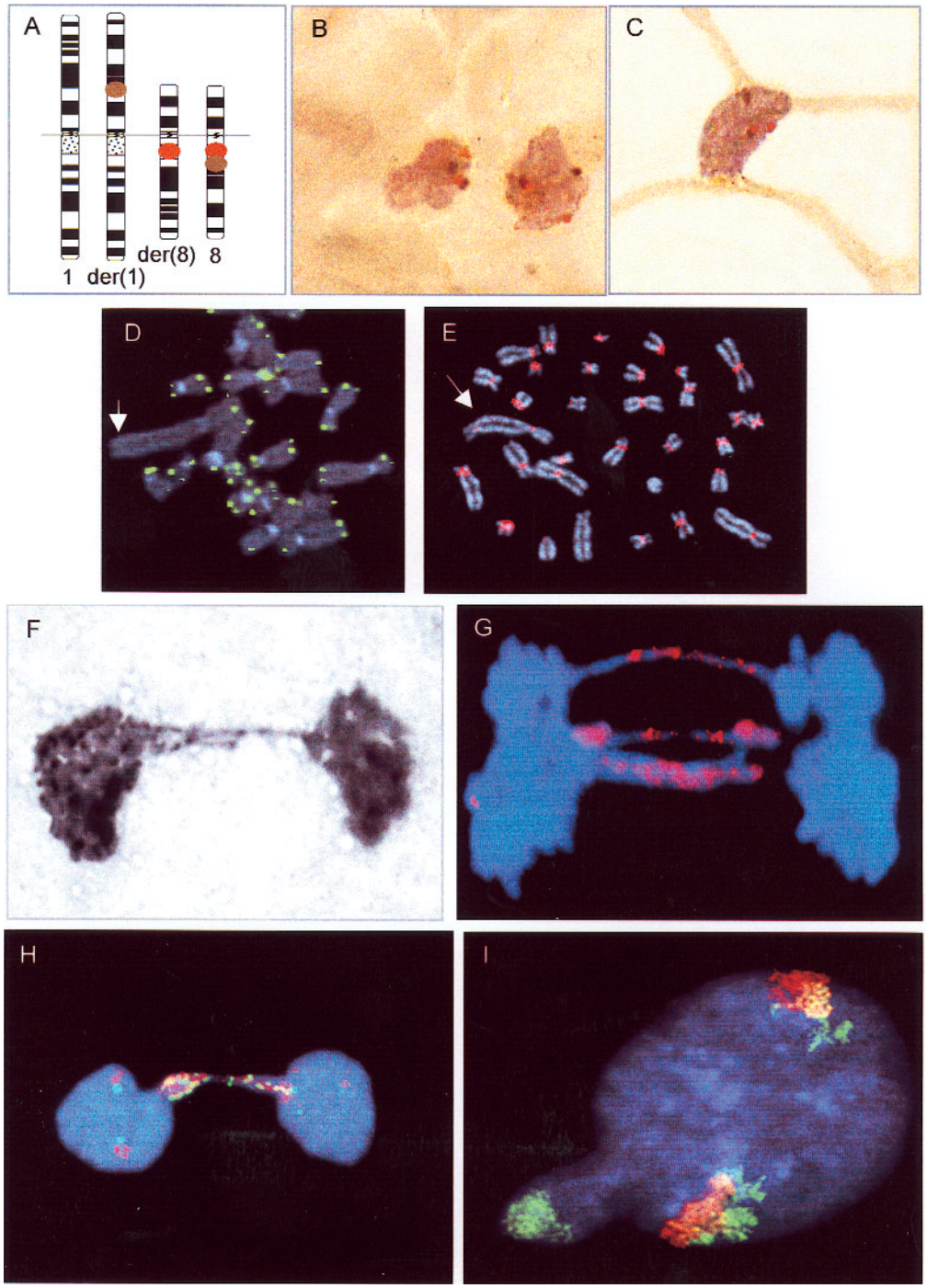

Fig. 1. In situ hybridisation (ISH) of the *PLAG1* region in 8q11-12. The gene is flanked proximally and distally by single-copy probes detected by red and brown chromogens, respectively. Rearrangement of the gene causes splitting of the red and brown signal between the derivative chromosomes, shown schematically in **A.** In tissue sections from a lipoblastoma with a 1;8-translocation, split red and brown signals are observed in nuclei of both the fibrous **(B)** and adipocytic components **(C)** of the tumour, indicating that this mutation is associated with a spectrum of cellular phenotypes rather than a complete differentiation block. **D-I.** ISH showing absence of telomeric TTAGGG repeats (green) in a pancreatic carcinoma **(D)**, leading to formation of dicentric chromosomes **(E)**, which may form bridges between the poles at anaphase **(F)**. Anaphase bridge in liposarcoma containing sequences from chromosome 12 (**G**; red); after telophase, remnants of the bridge remain in interphase nuclei as chromatin strings (**H**; chromosome 12 sequences in read and green) and nuclear blebs (**I**; chromosome 12 sequences in green).

3. Mutation leading to a shift in morphology

Finally, the occurrence of a chromosome mutation could directly lead to alterations in cellular morphology. *In vitro* transfection and/or abnormal expression of genes involved in morphogenesis, such as the homeobox genes could radically change the morphology of cells (Boukamp, 1995). Translocations involving homeobox genes have indeed been found in some tumours. For instance, in T cell acute lymphoblastic leukaemia, a 10;14-translocation leads to overexpression of the *HOX11 gene* in 10q24 (Hatano et al., 1991). Still, no evidence exists that these mutations have any more radical effect on the tumour phenotype than those in (1) or (2) and it is quite possible that a differentiation block is the predominant mechanism also in these cases.

Chromosomal instability and nuclear atypia

The chromosome aberrations discussed so far have all been relatively simple, balanced translocations that give rise to gene-mediated alterations of global transcriptional activity. However, some chromosomal alterations appear to have a direct impact on tumour cell morphology. Contrary to the mechanisms described above, the underlying processes here appear to be mechanical rather than physiological.

Most malignant solid tumours contain a large number of complex chromosome changes. Some of these aberrations, such as ring and dicentric chromosomes fail to undergo normal cell division (McClintock, 1938, 1940). Instead of normal sister-chromatid separation at anaphase, the chromosomes will be suspended as anaphase bridges, which may break and generate distinct alterations in shape of interphase nuclei, including blebs and micronuclei (Fig. 1D-I; Gisselsson et al., 2001b). Alternatively, the bridges will fail to break and then remain as chromatin strings between nuclei. These intact bridges may prevent the cell from undergoing normal cytokinesis and will thereby lead to polyploidisation, reflected in heterogeneity of nuclear size. This type of so-called breakage-fusion-bridge instability of chromosomes and the associated nuclear features have now been demonstrated in a number of malignant histopathological entities, including borderline and high-grade malignant bone and soft tissue sarcomas, and pancreatic, ovarian, and bronchial carcinoma (Gisselsson et al., 2000, 2001a,b).

What determines the direction of cytogenetic evolution?

There thus appears to be two mechanistically different connections between chromosome aberrations and morphology. Simple chromosomal changes may cause alterations in the pattern of DNA transcription, leading to disturbances of differentiation. Alternatively, chromosomal instability may alter mechanically the size and shape of the cell nucleus, giving rise to a pleomorphic population of cells with complex karyotypes and nuclear atypia. What is it then that determines whether a cell should follow one or the other pathway?

The stem cells or progenitor cells transformed by simple translocations exhibit a large self-replicative potential (Olsson et al., 1996). One characteristic of such cells is that they frequently express the enzyme telomerase, preventing shortening of the terminal TTAGGG repeats at DNA replication (Kolquist et al., 1998). The tumours with unstable karyotypes, on the other hand, often exhibit characteristics of cells at later stages of differentiation. For instance, some of the most complex cancer karyotypes have been observed in tumours derived from functional epithelium, such as pancreatic and ovarian adenocarcinomas (Pejovic et al., 1992; Gorunova et al., 1998) and squamous cell carcinomas of the head and neck (Saunders et al., 2000). Complex karyotypic patterns are also seen in mesenchymal tumours producing a matrix similar to that of adult tissues, such as chondrosarcomas and osteosarcomas (Mandahl, 1996). Compared to cells transformed by simple translocations, these cells should have a highly specialised phenotype and a low self-replicative potential. A genetic alteration causing a differentiation block would thus have a small or insignificant effect; other mechanisms are required for neoplastic transformation.

It is known that highly malignant tumours with complex karyotypes often contain a high number of molecular genetic alterations beside the cytogenetic rearrangements. These include activating point mutations of proto-oncogenes as well as inactivating mutations or losses of tumour supressor genes. Many of these genes are involved in the regulation of cell cycle progression. The TP53 protein, for instance, is a vital component of the DNA damage checkpoint machinery. This is particularly interesting since normal, highly differentiated cells neither express telomerase nor have activated any other known programme for avoiding cellular senescence. Clonal expansion of such cells would thus implicate extensive erosion of TTAGGG sequences at the chromosome ends. In turn, this leads to formation of mitotically unstable chromosomes and breakage-fusion-bridge instability (McClintock, 1940). In non-neoplastic cells the high frequency of chromosome breakage would trigger cell cycle arrest or apoptosis (Cohen-Jonathan et al., 1999; Gisselsson et al., 2001b). However, in TP53-deficient tumour cells, the cell cycle may proceed and additional chromosomal breakage may occur at subsequent mitoses. It has been demonstrated that inactivation of TP53 in mice with abnormally short telomeres leads to a high rate of epithelial malignancies with complex karyotypes (Artandi et al., 2000). There thus appears to be a cooperative relationship between dysfunction of DNA damage checkpoints and telomere dysnsfunction causing chromosomal instability. In each tumour, this allows the evolution of complex and heterogeneous cytogenetic

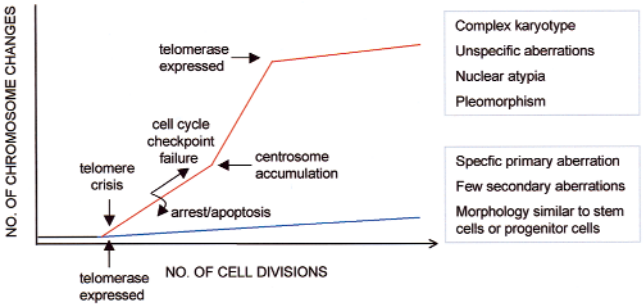

Fig. 2. Hypothetical view of two pathways of cytogenetic evolution and their morphological correlates. Immature cells expressing telomerase may be transformed by simple balanced translocations leading to fundamental shifts in transcription factor function; the genome is relatively stable and few additional changes will occur during clonal expansion (blue line). More mature cells not expressing telomerase will enter telomere crisis during clonal expansion, leading to breakage-fusion-bridge instability and accumulation of structural chromosome aberrations (red line); further growth is dependent on dysfunction of DNA damage and/or mitotic checkpoints. Also, failure of normal mitotic separation may result in accumulation of supernumerary centrosomes, multipolar cell divisions, and extensive changes in chromosome number. These processes may be partly counteracted by telomerase expression, leading to a moderate rate of cytogenetic evolution.

patterns on the one hand, and cellular pleomorhpism and nuclear atypia on the other.

Interestingly, it has been shown that telomerase is in fact activated at some point of neoplastic development in the vast majority of human tumours, including those with complex karyotypes. Most probably, this enzyme then stabilises the tumour genome to some extent, possibly facilitating the stable proliferation of clones with chromosome aberrations favourable to tumorigenesis (Rudolph et al., 2001). Of course, complex chromosome aberrations occurring as a result of chromosomal instability could, in their turn, have an impact on tumour morphology through changes in gene structure or expression – analogous to the situation in leukaemias. However, no such connection has so far been established experimentally.

Conclusion

Stem cells may be transformed by simple chromosomal rearrangements causing abnormal function and/or expression of transcription factors or other key enzymes. These cells have a high self-replicative capacity and maintain long telomeric repeats by constitutive telomerase expression. Tumour cell proliferation may thus occur without telomeric instability and the chromosome complement remains fairly stable, although some secondary cytogenetic changes, commonly trisomies, may occur during tumour growth (Heim and Mitelman, 1995). The transforming event is highly dependent on the state of cellular differentiation and a certain translocation is therefore present only in one or a few morphological subtypes. Mature cells, on the other hand, typically have a low self-replicative capacity. Due to the many cell divisions they have already passed through, they may have relatively short telomeres already before the initiation of neoplasia. Transformation implicates step-wise accumulation of mutations in oncogenes and tumour suppressor genes, allowing tumour growth despite further abnormal shortening of telomeric repeat sequences. This triggers massive mitotic instability and perturbations of nuclear shape. Usually either one or the other of these pathways of cytogenetic evolution is followed (Fig. 2). However, in rare cases, complex karyotypes and nuclear atypia are seen also in tumours with characteristic translocations. One example is adenocarcinoma arising from pleomorphic adenoma of the salivary gland, where the characteristic chromosome 8 rearrangements may be accompanied by other complex cytogenetic aberrations (Jin et al., 1998). It seems clear that the ontogeny, or histological lineage, of the founder cell is not the sole determinant of tumour cell morphology. The potential for generating genetic instability, as reflected by telomerase expression and telomere length, could also play a crucial role.

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