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Letter to the Editor

Genomic instability in context of the chromosomal theory *

Sir,

Cancer cells differ from normal cells in karyotype, cell morphology, invasive or non-invasive growth, development of metastases, primary and acquired drug resistance, and in expression of genes and proteins. The mechanisms of carcinogenesis remain unclear and the prevailing gene mutation theory explaining carcinogenesis by a sequence of mutations has not really solved the problem. Key features of cancer are not explained by mutations such as carcinogenesis by non-mutagenic carcinogens, the absence of carcinogenic genes in cancer in spite of tremendous efforts over the years to show their existence, the lack of explanation for neoplastic latency after carcinogen exposure, dependence on phenotype alterations in cancers on unrealistically high mutation rates or the absence of heritable cancer in spite of heritable mutations in cancer cells.

An explanation of these features is offered by the chromosomal theory [1]. According to this theory, carcinogens induce non-specific chromosomal alterations which unbalance thousands of genes, destabilize the genome and encourage the evolution of neoplastic cells. Induced chromosomal alterations generate abnormal phenotypes via abnormal dosages of genes. Cancer cells, by chromosomal constitution, are new species with non-random specific chromosomal alterations, but instable karyotypes [2]. The higher the ploidy-factor, the more instable is the karyotype. Maximal instability is observed with triploidy and decreases towards tetraploidy [3]. Since aneuploidy disrupts interactions of multiple genes, enzymes, and proteins, alters gene dosage effects and is ubiquitous in cancer it is one of the most plausible explanations for the inherent genetic instability of cancer cells.

What are the mechanisms for the induction of such aneuploidies? Centrosome aberrations and defects of spindles have been implicated in the causation of chromosome aberrations. We therefore analyzed chromosomes and centrosomes in CD34 positive CML cells along the course of CML. Numerical and structural centrosomal aberrations were observed in chronic phase and decreased in blast crisis. The centrosomal alterations correlate with chromosomal aberrations. It was assumed that BCR-ABL expression is involved in centrosome aberrations. This was analyzed in a BCR-ABL p210 transfected, tetracycline inducible cell line (U937-P210$^{\text{BCR-ABL}}$/c6). After induction with tetracycline, the increase in BCR-ABL transcript level correlated with centrosome aberrations [4].

Concerning the analysis of spindle defects, the observation was used that tyrosine kinase inhibitors induce spindle aberrations in normal human cells. Using this approach, centrosome and chromosome aberrations were found to correlate with defects of mitotic spindles. In conclusion, alterations of centrosomes and spindles (spontaneous or induced) correlate with chromosomal aberrations and may represent a mechanism for the cause of aneuploidy [5].

The degree of aneuploidy, chromosome non-disjunction or structural alteration is paralleled by increasing genetic instability and by preneoplastic and neoplastic phenotypes of increasing malignancy. Alterations of centrosome and of spindles structure may be mechanisms involved in the generation of aneuploidy. These findings may have far reaching implications for prevention and early diagnosis of cancer.

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