Chromosomes and Neoplasia

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ABSTRACT

Specific chromosome changes are consistently observed in numerous types of neoplasms. These chromosome changes are generally seen only in malignant cells and are not present in somatic cells. Associations of an increased incidence of cancer following exposure to certain chromosome breakage agents, in chromosome instability syndromes, and in patients with gene or constitutional chromosomal imbalances, suggest that chromosomal changes play a role in the etiologies of malignancies. The purpose of this paper is to review briefly chromosomal aberrations in cancer in relation to etiology. Awareness of the probable multiple causes of human cancer and the importance of multidisciplinary collaboration in the investigation of these diseases are essential for a better understanding of this complex group of diseases.

Introduction

Interest in the field of human cancer cytogenetics increased in 1960 when the association of the Philadelphia chromosome with chronic myelogenous leukemia was first described. This discovery evoked and supported the idea that some tumors were derived from a single abnormal cell and were clonal in origin. Approximately 12 years ago, the introduction of various chromosome banding techniques paved the way for much more detailed cytogenetic analysis of malignant cells. These techniques not only enabled the exact identification of each chromosome but also allowed for the detection of relatively small structural abnormalities of individual chromosomes. It is now possible for cytogenetic laboratories to detect deletions, partial trisomies, translocations, and other structural chromosome abnormalities.

Boveri's hypothesis, published in 1914, states first that malignant cells have an abnormal chromosomal constitution and, second, that any event leading to an abnormal chromosome constitution will result in a malignant tumor. Nearly 70 years after Boveri's hypothesis was published, the role of chromosome changes in oncogenesis is still met with controversy.

Since the advent of banding procedures, the information relevant to chromosome changes in neoplasms has become voluminous and most investigators agree that chromosomal changes in the development of neoplasia are important. Specifically relevant to the hematologic malignancies is the fact that cytogenetic observations often assist in a specific di-
agnosis and can aid the clinician in providing prognostic information in some situations.2,9,16,24,25

This paper will not attempt to document specific chromosomal changes which have been reported with certain neoplasms; instead, an attempt will be made to present an overview of chromosomes as related to the neoplastic process (table I).

Agents and Diseases which Predispose to Cancer

Agents Which Cause Chromosome Breakage (Clastogens)

Certain chemicals, viruses, and ionizing radiation have been shown to initiate chromosome damage and some of these have been implicated as being carcinogens; these topics have been extensively reviewed.4,5,10,21 It is the opinion of this author that most carcinogens or their metabolites probably cause chromosomal breakage (viz clastogenic).

Chromosome Instability Diseases

Three autosomal recessive diseases, Fanconi’s anemia, Bloom syndrome, and ataxia telangiectasia,7,8,12,20 are characterized by increased spontaneous chromosome breakage in cultured lymphocytes and fibroblasts. All three of these diseases involve a defect in deoxyribonucleic acid (DNA) repair and an increased incidence of malignancy, primarily of the lymphatic system; however, these neoplasms also occasionally involve the myeloid system. Siblings with Fanconi’s anemia who both developed acute myelogenous leukemia associated with monosomy for chromosome No. 7 in malignant cells were recently studied by us. Also of interest and of possible relevance is the fact that these three chromosome instability syndromes involve an immune deficiency during the course of the disease.

Constitutional Chromosomal Anomalies

An increased association of leukemia in children with Down syndrome is well established. Children with Down syndrome have a 1/95 risk of developing leukemia13 compared to 1/3,000 in other white children.1 There is also an established increased incidence of breast carcinoma in Klinefelter (47,XXY) patients.11 A probable increased incidence of leukemia in Klinefelter8 and Turner (45,X) patients16 has also been reported as has an increased incidence of gonadoblastoma in XY females.18 There is a suggested predisposition to malignancy in general for patients who have trisomy 8 mosaicism.22 An interstitial deletion of chromosome 13 has been associated with retinoblastoma20 as has a deletion of chromosome 11 with aniridia and Wilms’ tumor.23

Tumor Cell Cytogenetics

When human malignant cells are analyzed by early metaphase (figure 1) or prometaphase procedures and when one can be reasonably confident that tumor
cells are being examined, neoplastic cells usually have chromosome abnormalities. Utilizing these high resolution cytogenetic procedures, new abnormalities are being detected,\textsuperscript{27} and it has been suggested that most neoplastic cells may have a chromosome abnormality.\textsuperscript{29} In the exceptions to this, the question remains as to whether or not abnormalities are present but not detectable by current techniques.

Knudson's "two hit" theory of carcinogenesis\textsuperscript{14,15} proposes the presence of two mutational events in order for tumorigenesis to occur. If the "first hit" were represented by an inherited gene or chromosome disorder, a "second hit" would be much more likely to cause cancer in this situation than in a person not having a "first hit" at the time of conception. Likewise, increased chromosomal breakage in the chromosome instability syndromes and breakage induced by exposure to clastogenic agents would increase the chance for two critical mutational events. This would result in a higher incidence of cancer, which is observed in these syndromes and in clastogenic exposures.

**Current and Future Emphasis**

Existing data suggest that chromosome abnormalities are involved in predisposition, causation, or are perhaps sometimes secondary to the neoplastic
References