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Review

Cytogenetics and genetics of human cancer: methods and accomplishments

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Abstract Cytogenetic and related changes in human cancer constitute part of a constantly developing and enlarging continuum of known genetic alterations associated with cancer development and biology. The cytogenetic component of this continuum has fulfilled much of its pioneering role and now constitutes a small but dynamic segment of the vast literature on cancer genetics, in which it has played an important if not initiating role. The goals of this article are (a) to address historical and methodological aspects of cancer cytogenetics; (b) to present information on diagnostic translocations in leukemias, lymphomas, bone and soft tissue tumors, and carcinomas; (c) to connect some of these chromosomal aberrations with their molecular equivalents; and (d) to describe anomalies in some solid tumors indicative of the complexity of the genomic alterations in cancer. We also look at a few of the more recent genomic developments in cancer and offer an opinion as to what all these findings add up to.

1. Introduction

Since its first application to the study of cancer, cytogenetics has taken us from a state of virtually no knowledge of the chromosome changes in human cancer to a point at which a staggering body of information is available. The latter is evidenced by the nearly 55,000 leukemic and tumor karyotypes now included in the Mitelman Database of Chromosome Aberrations in Cancer [1]. Now more than half a century old [2], the field of cancer cytogenetics has more than lived up to its envisioned task of finding recurrent or specific abnormalities associated with cancer, and continues to provide crucial diagnostic and prognostic information. In current practice, cytogenetic data often serve as a guide in other studies, ranging from the exploration of cytogenetic findings with various methodologies, singly or in combination, including fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), or microarray-based technologies such as comparative genomic hybridization to the use of immunohistochemical techniques by the pathologist. Cytogenetic data also provide key background information for the recognition and identification of genes (and their networks) involved in cancer and for their subsequent application in therapeutic development.

Progress in understanding the cytogenetic and molecular basis of neoplastic transformation has strengthened the conception of cancer as a genetic disease. Thus, the finding of apparently normal karyotypes in abnormal cells (as is seen in leukemias and various solid tumors) presents an enigma. It can be assumed that cryptic genetic changes are involved in such cases, as has been shown in some tumors and leukemias. These cryptic changes are not discernible with routine cytogenetic methods, but can be studied with special FISH methods (e.g., spectral karyotyping [SKY] and multiprobe FISH [M-FISH]) or, if a specific karyotypic change is suspected, with appropriate cosmid probes or other molecular means. Indeed, newer technologies promise to shed light on the more complicated and perplexing aspects of cancer that have eluded more traditional cytogenetic studies. For example, molecular studies have demonstrated fusion genes associated with prostate cancer and lung cancer that are not discernible cytogenetically. These findings raise the strong possibility that more epithelial carcinomas, which are usually associated with numerous or complex karyotypic alterations, will be shown to have cryptic primary genetic alterations.

Given the daunting quantity of cytogenetic and molecular genetic information on cancer gleaned through the past

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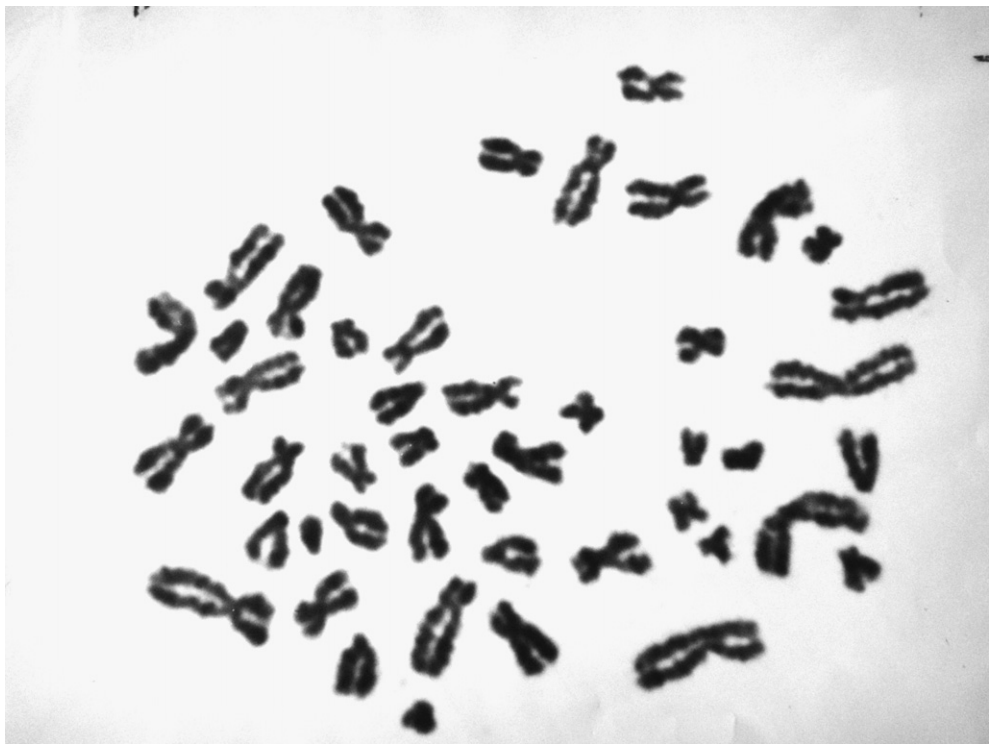

Fig. 1. Metaphase of a cultured cell, as shown in the classic 1956 article by Tjio and Levan [6], containing 46 chromosomes and establishing that number as characteristic of the human normal chromosome complement. Reproduced with permission of the publisher.

half-century of research and clinical application, we cannot in an article cover the myriad known chromosome changes associated with cancer or their downstream effects. Rather, our goal is to focus on some particular conditions that bear directly on a few of the more complicated and perplexing aspects of cancer genetics.

2. Cytogenetic methodologies in cancer

2.1. Historical facets of cytogenetic methodologies

In 1956, Tjio and Levan [6] confirmed the correct number of human chromosomes as 46 and established their karyotypic constitution in somatic cells (Fig. 1). Within a few years, the first meaningful chromosomal changes in human cancer were reported in leukemias [3−5]. A historical survey of some of the cytogenetic methodologies introduced over the years is presented in Figures 1−10. Each new method widened the recognition of karyotypic changes, increasing the resolution of cytogenetic details until the limits of microscopic visualization were reached. The evolution of cytogenetics presented in Figures 1−10 encompasses also molecular approaches such as FISH and array comparative genomic hybridization (aCGH). These techniques have revealed novel and otherwise cryptic rearrangements, as well as providing chromosome information for cases in which conventional cytogenetic analysis is not possible.

2.2. Special requirements and limitations of cancer cytogenetic studies

Cytogenetic techniques require the presence of dividing cells (preferably in the metaphase stage) for the visualization of chromosomes. Thus, fresh specimens are necessary for establishing short-term cultures (in the case of marrow) or long-term cultures (in the case of solid tumors) cultures. Although uncultured marrow often contains sufficient dividing cells for cytogenetic studies, short-term culture allows for more efficient analysis [2,7−9].

The cytogenetic information in hematologic conditions has become so crucial to clinicians that chromosomal analysis is performed in almost all cases of leukemias and lymphomas. This is not yet true of solid tumors, in which the specimens are often fixed before a small portion is obtained for chromosome analysis. Nevertheless, useful genetic information (and including partial cytogenetic information) can be obtained from fixed specimens with appropriate FISH or other molecular techniques [7]. With increasing appreciation of the value of chromosome findings in the clinical and pathologic aspects of epithelial tumors, we can hope that surgeons and pathologists will become accustomed to securing fresh-frozen tumor tissue suitable for cytogenetic analysis.

Cytogenetic studies also fail to provide the immediacy of pathologic examinations because of the long time required for culture, assay performance, and interpretation of results.