EDITORIALS

Clinical Correlations of Chromosome Change in Human Solid Tumors: The Tip of the Iceberg?

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It is now clearly recognized that a large variety of human cancers (including many solid tumors) display recurring chromosome abnormalities. However, what is the biologic significance of these findings? How do these chromosomal changes relate to changes in expression of important growth regulatory genes, e.g., cellular oncogenes? What clinical significance, if any, do specific cytogenetic abnormalities have, particularly for solid tumors, in which they are often found against a background of other genetic alterations? These and other related questions have received a significant amount of attention over the past 5 years. In general, it appears that recurring sites of chromosome change may indeed represent the byproduct of molecular events, which themselves may participate in the generation or progression of human cancers. Our recognition and ultimately our molecular understanding of chromosome abnormalities will unquestionably provide further insights into neoplasms generally and solid tumors particularly.

The diversity of structural chromosome alterations across the spectrum of human cancers is enormous and increasing rapidly. Information on cancer-associated chromosome alterations is currently accumulating at a rate in excess of 2,000 new cases per year, with well over 15,000 cases of chromosome abnormalities in cancers now reported in the literature (1,2). Recent attempts of a special committee (2) to summarize this immense amount of technical information has resulted in the identification of 149 nonrandom chromosome changes involving 43 types of neoplastic disorders, including many benign proliferations (2). These changes include a plethora of genomic alterations including deletions, translocations, isochromosomes, insertions, inversions, etc. Taken together, every human chromosome except the Y can now be included in some form of neoplasia-associated alteration.

With the explosion in our knowledge base of human chromosome alterations in neoplasia has come the widespread acceptance of the clinical value of chromosome analysis in studies of human hematologic cancers. Specifically, chromosome analysis of malignant cells from patients with hematopoietic cancers provides diagnostic and equally important prognostic information independent of other laboratory and clinical features of disease (3-5). What is interesting is that, despite solid tumors being infinitely more common than the blood-borne cancers of man and that they add significantly more to morbidity and mortality than hematologic neoplasms, by comparison surprisingly little is known of the chromosome changes and especially their clinical importance in solid tumors.

The article by Bosl and colleagues (6) in this issue indicates that cytogenetic information may be a useful clinical marker for the diagnosis and prognosis of male germ cell tumors (GCTs). The rationale for this study was essentially that these tumors represented an ideal model in which a remarkably specific cytogenetic alteration could be related to the diagnosis and prognosis of individual patients. Ultimately, investigators hoped to find that chromosome abnormalities would provide a new marker to stratify patients clinically into good- versus poor-risk treatment categories. The most frequent chromosome alteration in GCTs that previously has been recognized to occur in 50% or more of GCTs (7-9) is the formation of an isochromosome for the short arm of chromosome 12 [i(12p)]. An isochromosome is produced when the centromere of a chromosome splits transversely instead of longitudinally. The net result is the arms are generally of equal length, but more importantly, they are genetically identical. The net result is a doubling of the genetic information of the duplicated arm, concomitant with the loss of genetic information on the other arm of the chromosome.

This paper makes two major points regarding the i(12p) and GCTs. First, the finding of an i(12p) may be a diagnostically useful marker in GCTs. The author and associates (6) observed i(12p) in 100% of the patients with GCTs who were studied and also identified it accompanying leukemia cells in some patients, which suggested a common cell lineage. A reflection of the specificity of this alteration was shown in their cytogenetic analysis of 3,500 non-GCT-related tumors over a 5-year period. No example of an i(12p) was found in any non-GCT-related tumor. The second major point is that the presence of multiple copies of the short arm of chromosome 12 may predict treatment outcome. Specifically, the authors suggest that the presence of three or more additional copies of 12p was associated with a statistically significant, greater likelihood of treatment failure.

The report of Bosl et al. (6) does appear to provide new information that may have clinical relevance. Nevertheless, their report raises as many questions as it answers. For example, many of the patients in the current study did not have tumor cytogenetics performed before treatment, and few early stage tumors or seminomas were evaluated. Furthermore, because few primary tumors were studied, the possibility exists that heterogeneity of chromosome alterations associated with

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tumor progression, compounded by a relatively small number of cells per tumor analyzed, could have influenced the outcome of this research. Finally, the study was not designed to address the mechanism underlying the proposed clinical effect of i(12p). Thus the results should be viewed with some caution and will require corroboration. However, based on the aforementioned evidence of clinical and biologic usefulness of cytogenetic alterations in hematologic cancers, it seems that these results will be clinically valuable.

The study of Bosl and colleagues is unquestionably an important step in the right direction. However, a significant amount of work remains to be done before the full potential of this technology will be logically extended to other, more common, solid tumors. Almost 30 years have passed since the initial discovery of the first recurring chromosome abnormality in a human cancer, the Philadelphia chromosome in chronic myelogenous leukemia (10). Clinical use of chromosome change in hematopoietic tumors has been recognized for over 20 years (11). With the publication of this report and others, which are beginning to appear in the literature for other solid tumors, the future integration of cancer cytogenetics into the clinical management of patients with solid tumors appears likely.

As suggested in the title of this editorial, these beginning studies on clinical correlation of chromosome change in solid tumors may merely represent the tip of the iceberg!

References

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