Guest editorial

Chromosomes in orthopedic tumors

Merely a generation ago, it was a major scientific achievement to just count normal human chromosomes; in 1956, Tjio and Levan determined that man has 46 chromosomes. Today, the ability to identify chromosome aberrations, even minor structural rearrangements, holds promise to be of clinical significance in the treatment of orthopedic tumors.

The findings that characteristic chromosome changes in various hematologic malignancies reflect specific molecular genetic events have turned cancer cytogenetics from being a philately type of collecting strange aberrations to a science (1).

Cytogenetic studies of solid tumors are technically more difficult and are still largely at the descriptive stage, but the hope is that the chromosome changes will prove as useful, from a clinical point of view, as are the aberrations in hematologic malignancies.

At present, some 400 bone and soft tissue tumors have been analyzed. As early as 1984, Aurias, Turc-Carel, and their coworkers (2, 3) reported a consistent translocation t(11;22) in Ewing's sarcoma. This tumor type is now the most extensively (80 cases) cytogenetically studied sarcoma, and the 11;22 anomaly has turned out to be present in four fifths of the tumors. However, the aberration is not exclusive to Ewing's sarcoma; cytogenetically identical translocations have been found in Askin's tumor, peripheral neuroepithelioma, esthesioneuroblastoma, and in one case of small-cell osteosarcoma, indicating that these are related tumors; whether there is also a molecular or a functional identity remains to be seen. In a small subset of tumors, the t(11;22) is the sole anomaly, indicating that it may be a primary aberration, whereas in many tumors, additional, secondary aberrations are present. Some of the latter are also nonrandom.

Consistent aberrations have been identified also in other sarcomas, t(2;13) in rhabdomyosarcoma, t(X;18) in synovial sarcoma, and t(12;16) in myxoid liposarcoma. These rearrangements have all been present as the sole anomaly in a substantial number of tumors, and have not been found as consistent changes in any other tumor type.

Most malignant fibrous histiocytomas (4) and osteosarcomas have high chromosome numbers and extremely complex aberrations; most leiomyosarcomas and chondrosarcomas are less complex. In malignant fibrous histiocytoma, some consistent aberrations have been identified, including particular segments of chromosomes 1, 3, 11, and 19. Ring chromosomes are also common anomalies. A set of different tumors of borderline or of low malignancy, including atypical lipoma/well-differentiated liposarcoma (which are probably from a biologic point of view the same type of neoplasia), dermatofibrosarcoma protuberans, neurofibrosarcoma, and malignant fibrous histiocytoma, have been found to be characterized by supernumerary, unidentifiable ring chromosomes as the sole aberration or as one of a few aberrations.

Not long ago, some favored the opinion that chromosome changes were principally a characteristic of malignant tumors; the few known benign tumors displaying consistent aberrations being merely exceptions. It now seems clear that such aberrations—mostly less complex—are regularly present also in benign tumors. Chromosome changes have been found in 70 of the 100 lipomas cytogenetically investigated (5). The chromosome segment most often involved is 12q13–15, however, never as the t(12;16) characteristic of myxoid liposarcoma. Interestingly, the same segment of chromosome 12 is involved in consistent aberrations in subsets of uterine leiomyomas (6) and pleomorphic adenomas of the salivary gland. If molecular studies show that the same gene on chromosome 12 is affected in both lipomas and liposarcomas, they could constitute an excellent system to study mechanisms of benign and malignant cell proliferations.

Few data are yet available on molecular-level genetic changes in musculoskeletal tumors. Gene loss or loss of activity of tumor suppressor genes are common in osteosarcoma and possibly also in other sarcomas. Two genes, the retinoblastoma gene on chromosome 13 and the p53 gene on chromosome 17, are frequently involved. Only sporadic studies on changes of oncogenes have been reported, but search for the genes affected by consistent translocations is going on. It seems likely that some of these genes are oncogenes that, through the rearrangement, might be activated in similar ways as have been found in Burkitt's lymphoma and chronic myeloid leukemia.

Tumor progression is associated with acquisition of additional genetic changes, leading to a clonal evolution, with emergence of genetically partly different cell populations. Sarcomas frequently have areas with different macroscopic and microscopic morphology. Little is known whether this morphologic heterogeneity is related to a genetic heterogeneity. Cytogenetic and histologic characterization of samples from different parts of the same tumor may be informative (7). First, in tumors that usually have multiple, complex aberrations, it might be possible to identify the early ones, which would correspond to changes that are present in all the clones. Secondly, specific aberrations might be related to different histologic features. Thirdly, by combining these heterogeneity studies with longitudinal studies of the primary tumor, local recurrence, and distant metastases, particular aberrations associated with a tendency to relapse, might be more easily sorted out. Molecular analyses of the identified aberrations may give a deeper understanding of tumorigenesis and tumor progression.

The diagnostic and prognostic importance of cytogenetic analyses of musculoskeletal tumors is still small. However, the type of aberration is already of some diagnostic utility in atypical lipoma, myxoid liposarcoma, Ewing's sarcoma, synovial sarcoma, and rhabdomyosarcoma. In a series of malignant fibrous histiocytomas, we have recently found that tumors with rearrangement of chromosome band 19p13 relapsed more often than tumors without this anomaly (8). Prognostic correlations in other sarcomas have not been found.

The histologic classification of musculoskeletal tumors has become increasingly refined by different stainings, electron microscopy, and immunohistochemistry. Over 100 different entities have so far been identified. Moreover, several of the sarcoma types are further subclassified into different malignancy grades. For obvious reasons the histopathologic classification is still used as the gold standard when determining associations between cytogenetic changes and tumor type. Inevitably, however, there will be found cytogenetically identical aberrations in histologically different tumor types (there are already examples of this, most notably the t(11;22) and supernumerary ring chromosomes but also for t(X;18)), and different cytogenetic aberrations in tumors with similar histology. When more tumors have been cytogenetically analyzed, it might be of interest to group muculoskeletal tumors on the basis of a cytogenetic classification to see whether genomic changes could discriminate between musculoskeletal tumors better than the phenotypic characteristics.

It is likely that cytogenetic analysis will add substantial clinical information about musculoskeletal tumors and will, in conjunction with molecular genetic studies, increase the understanding of their biology.

References

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