Cytogenetic Markers in Hematoproliferative Disorders

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Summary. In the last decade the improvement of methods of chromosome analysis has allowed new insights into the correlation of specific chromosome changes and certain types of malignant hematologic disorders. Even if a clear-cut correlation between a certain chromosomal marker and a certain malignancy is the exception, it is well established that specific chromosome aberrations occur nonrandomly in specific tumors. Moreover, it has been shown that so-called cellular oncogenes are located on those chromosome regions which are involved in translocations and other structural chromosome abnormalities in particular malignant tumors. The significance of chromosome alterations in leukemias and lymphomas is illustrated by examples concerning well-established data, on the one hand, and findings which have still to be confirmed, on the other. This may demonstrate that human tumor cytogenetics are a dynamically and vigorously developing branch of cancer research.

Key words: Leukemias – Lymphomas – Chromosome anomalies – Oncogenes

In the history of human tumor cytogenetics, i.e. in the search for particular and consistent chromosome abnormalities specific for a certain disease, several phases can be distinguished which are distinctly correlated with the development of cytogenetic techniques.

The first phase lasted from 1960 – the year of the discovery of the Philadelphia (Ph) chromosome in chronic myeloid leukemia (CML) [19] – to about 1970 and was characterized by a very restricted registration of only a few numerical and structural chromosome anomalies in association with human neoplasias. Most tumors, however, were judged to be chromosomally normal. The cause of these false negative findings was the lack of techniques for accurate chromosome preparation and differentiation which might have allowed the detection of subtle chromosome alterations, and the initial enthusiasm based on the detection of the Ph chromosome in CML was replaced by the disillusioning realization that chromosome anomalies might be rather secondary than primary phenomena in cancer development.

The second phase of tumor cytogenetics started with the development of chromo-
some banding techniques in the early seventies, allowing an accurate identification of each single chromosome and of its alterations. By application of these new chromosome staining techniques to tumor cells a series of new and specific chromosomal anomalies were found. This again led to the rash conclusion that each specific neoplasia is characterized by a certain chromosomal marker. But tumor cytogeneticists soon realized that the very same marker occurred in different tumors — as for example the Ph chromosome in CML, acute nonlymphocytic leukemia (ANLL) and acute lymphocytic leukemia (ALL). They further recognized that not all tumors of the same type demonstrated identical chromosome anomalies.

At present, we might be in the third phase of comprehension; we have learned to accept that a certain chromosome anomaly can be correlated to different malignancies and that this is not in contradiction to our view that chromosomal changes in tumor cells are non-random.

What expectations are placed on tumor cytogenetics and what strength of information is emerging from chromosome analyses of tumor tissues?

Cytogenetics can be helpful in diagnosis, staging, prognosis and therapy planning of hematological malignant disorders. This will be illustrated in the following by some selected examples rather than by a complete enumeration of tumor cytogenetical findings.

The Role of Cytogenetics in the Diagnosis of Hematoproliferative Diseases

Myeloproliferative Diseases

The best known example to demonstrate the value of chromosome analyses in the diagnosis of myeloproliferative disorders is the division of CML into two categories on cytogenetic basis: Ph-positive and Ph-negative. The determination as to whether a CML is Ph+ or Ph— is of more than academical interest, for the absence of the Ph is usually associated with a poorer prognosis than the Ph + disease, especially in the first year after diagnosis [15, 29].

Since the establishment of banding techniques in tumor cytogenetics a series of nonrandom numerical as well as structural chromosome abnormalities have been identified in association with certain types of myeloproliferative diseases.

Recently, a characteristic chromosomal change was found in the acute myelomonocytic or monocytic leukemia with eosinophilia in bone marrow — namely a pericentric inversion in a chromosome 16 [16] (Fig. 1). This structural chromosome aberration is detectable only by use of high resolution chromosome banding techniques; it is of significant value for the diagnosis of myelomonocytic or monocytic leukemia with abnormal eosinophils.

Other specific and characteristic gains and losses of chromosomes as well as translocations, inversions etc, nonrandomly observed in connection with CML and with subtypes of ANLL according to FAB criteria [2], are summarized in Table 1.

Besides these firmly established karyotypic changes, which have acquired well accepted diagnostic and prognostic value, a number of new associations between certain myeloproliferative disorders and specific chromosome abnormalities have been published. Two examples may illustrate the way to get information concerning the relationship between hematologic disorders and chromosome abnormalities.