Deep Insight Section

Cancer cytogenetics update 2005

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By January 2005, clonal chromosomal aberrations identified by various banding techniques had been reported in more than 47,000 human neoplasms (Mitelman et al., 2005a). An increasing number of the acquired abnormalities have now also been studied by various fluorescence in situ hybridization techniques, which have provided a new and powerful tool to identify abnormal chromosomes and to visualize very small rearrangements that escape detection by conventional chromosome banding. The new techniques have also added a further sophistication to the analyses in that breakpoints in structural aberrations can be delineated within specific genes. Furthermore, an ever increasing number of breakpoints of the cancer-associated chromosome abnormalities have been characterized at the molecular level, and the combined efforts of cytogeneticists and molecular geneticists over the past two decades have led to the identification of 275 genes rearranged as a consequence of chromosome aberrations in neoplasia (Mitelman et al., 2004).

Specific chromosomal rearrangements

The main conclusion from modern cancer cytogenetics is the realization that every tumor type that has been studied in a sufficient number to permit conclusions may be subdivided on the basis of characteristic chromosome abnormalities (Mitelman et al., 2005b). Many of these, in particular balanced rearrangements, most commonly translocations, are with remarkable specificity associated with distinct tumor subtypes. At present, almost 500 recurrent balanced neoplasia-associated aberrations have been identified. However, in spite of the very rapid, almost exponential, increase of information over the past decade, the available data are, due to technical difficulties, still heavily biased in favor of the hematological malignancies. Solid tumors constitute less than one-third of all cases with an abnormal karyotype reported in the literature. This is of course totally disproportionate in relation to their relative contribution to human cancer morbidity and mortality. For example, the malignant epithelial tumors, which cause 80% of human cancer deaths, constitute only 10% of the database. Thus, for most individual solid tumor types our knowledge is still only fragmentary.

In addition to the limited information on the cytogenetics of solid tumors, there are a number of analytical problems that diminish the value of the existing data. First, the chromosome quality in solid tumors, in particular epithelial neoplasms, is often suboptimal, and hence many of the published cases have actually only been partially karyotyped. Second, in contrast to the hematological disorders, which often contain few cytogenetic changes, most solid tumors have already at the time of diagnosis a multitude of aberrations acquired during tumor progression. This karyotypic complexity may be truly massive, rendering the identification of the various abnormalities practically impossible. So, even when the quality is good and each abnormality can be characterized, the distinction between primary, pathogenetically essential, changes and secondary evolutionary aberrations is as a rule more difficult in solid tumors than in hematological malignancies. Consequently, a large number of cytogenetically well-analyzed tumors of each entity is required in order to identify the relevant early abnormalities. Finally, clonal heterogeneity in the form of cytogenetically unrelated clones introduces a further dimension of complexity in the analysis of solid tumors, in particular as regards epithelial tumors. This phenomenon, seen in less than 5% of leukemias, lymphomas, and mesenchymal tumors, has been reported in up to 80% of various carcinomas. The aberrations are usually simple and balanced, the clones

are often small, but they may be numerous (Gorunova et al., 1998) and hence pose important analytical problems.

Obviously, more cytogenetic information is urgently needed, especially for many solid tumor types, in order to establish whether or not there are any principal tissue-specific differences in the mechanisms of aberration formation. The fact that tumors of various histologic derivations are characterized by, in principle, similar kinds of recurrent balanced abnormalities and that the fractions of recurrent balanced rearrangements are similar within different tumor classes (Mitelman et al., 2004) suggest that there may be no fundamental differences. There is one apparent quantitative difference in that the balanced, simple, and disease-specific changes are found in about one third of the acute leukemias and malignant lymphomas, 20% of the mesenchymal tumors, but in less than 5% of the epithelial tumors. What is the explanation for this uneven distribution? Does it reflect a true biologic difference or could it be that as yet unidentified primary balanced rearrangements are hidden in complex karyotypes and unrelated clones? Such aberrations may be individually very rare (Mitelman et al., 2005b). It has been proposed that balanced and unbalanced abnormalities most likely are functionally distinct – primary, pathogenetically essential, changes are cytogenetically balanced whereas the secondary, progression-related, aberrations are unbalanced (Johansson et al., 1996). This suggestion remains hypothetical, but it has a number of conceptual ramifications, in this context in particular that primary balanced rearrangements may be present when only unbalanced changes are detected.

Molecular consequences of chromosome rearrangements

All balanced structural abnormalities that have been characterized at the molecular level have been found to exert their action through one of two alternative mechanisms: deregulation, usually overexpression, of a gene in one breakpoint, or creation of a hybrid gene through fusion of parts of two genes, one in each breakpoint (Mitelman et al., 1997; Rowley, 2001; Helman & Meltzer, 2003). The first mechanism, common in lymphoid malignancies but seemingly quite rare in other tumor types, juxtaposes regulatory alements of a constitutively active gene, typically immunoglobulin and T-cell receptor genes, to the coding sequences of a normally silent target gene. More than 70 such gene rearrangements have now been documented (Mitelman et al., 2005a). The second mechanism, fusion of parts of various differentiation- and proliferation-regulating genes, often transcription control genes and genes encoding tyrosine kinases, has been described in hematological disorders, malignant lymphomas, and solid tumors. More than 200 different fusion genes are presently known (Mitelman et al.,

2005a). It is of interest in this context that some genes are highly promiscuous in that they may recombine with many different partners, usually within the same tumor entities, e.g., MLL in acute leukemias (Collins & Rabbitts, 2002), EWSR1 in bone- and soft tissue tumors (Helman & Meltzer, 2003), and RET in thyroid carcinomas (Pierotti, 2001). However, the same fusion gene may also give rise to tumors of totally different derivations, and one particular fusion gene, ETV6-NTRK3, has been described in entities as diverse as acute myeloid leukemia, infantile fibrosarcoma, mesoblastic nephroma, and breast carcinoma (Tognon et al., 2002). There are now also several examples where seemingly identical aberrations produce different fusion genes. One of the most common translocations in pre-B acute lymphoblastic leukemia, t(1;19)(q23;p13) leading to a TCF3/PBX1 fusion, may result in a chimeric transcript consisting of two entirely different genes, MEF2D in 1q23 and DAZAP1 in 19q13 (Yuki et al., 2004). Finally, several cryptic disease-specific rearrangements leading to fusion genes in cases with either normal karyotypes or with unbalanced changes have been reported (Romana et al., 1995; Pierotti, 2001). It thus seems reasonable to assume that the presently known gene rearrangements only represent the tip of an iceberg.

Conclusions

It now seems convincingly clear that the neoplastic phenotype is caused by a stepwise accumulation of genetic and epigenetic alterations (Hanahan & Weinberg, 2000; Vogelstein & Kinzler, 2004). The role played by genomic instability to initiate and promote the genetic variation is still controversial (Lengauer et al., 1998), but there is little doubt that the quantitative or qualitative gene changes caused by balanced cytogenetic abnormalities represent an important step in the initiation of the carcinogenic process. The identification of every recurrent cytogenetic change is therefore of great importance because the breakpoints point to the location of directly cancer-relevant genes. The alternative initiating mechanism - inactivation, often through mutations and deletions, of tumor suppressor genes - has been well documented in several familial cancer forms, in particular childhood tumors, e.g., retinoblastoma and Wilm's tumor (Knudson, 2001; Vogelstein & Kinzler, 2004), and similar mechanisms have also been implicated in, e.g., lung, breast, and kidney carcinoma. In these and several other common cancers of adult life, loss of tumor suppressor genes may be suspected because chromosomal regions are found to be consistently lost in the tumor cells (Mertens et al., 1997), but it is unclear what role, if any, such genes play in the initiation process of most sporadic cancers. Since most recurrent balanced cytogenetic abnormalities and genes rearranged as a consequence of such aberrations have been found in hematologic disorders and bone and soft tissue tumors, whereas

numerous genomic imbalances, but seemingly few balanced abnormalities, have been identified in epithelial tumors (Albertson et al., 2003; Futreal et al., 2004), it has become generally accepted that deregulation or fusion of genes as a consequence of balanced cytogenetic aberrations is the preferred initiating event in hematological disorders and mesenchymal tumors, whereas functional abrogation of tumor suppressor genes is of essence in epithelial carcinogenesis. It was, however, shown recently (Mitelman et al., 2004) that the ratios of the numbers of gene fusions and genes rearranged as a consequence of balanced rearrangements to the numbers of cytogenetically investigated cases are similar among tumor entities, irrespective of their histogenetic derivation. The obvious conclusion is hence that there may not be any fundamental tissue-specific differences in the genetic mechanisms by which neoplasia is initiated.

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