Tumor Cytogenetics

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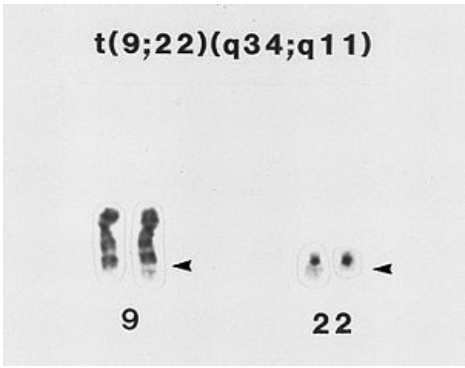
Introduction to tumor cytogenetics

We find numerous chromosomal changes in tumor cells, many of which are secondary to genomic instability in the tumor cell. Some chromosomal changes, such as those that alter the position of proto-oncogenes or exclude the tumor suppressor gene allele from function, are the primary change and the direct cause of the malignant process. The chromosomal abnormalities we find in tumors are changes in chromosome number, translocation, or other rearrangements, amplifications, and deletions. These abnormalities affect genes which are responsible for the regulation of cell division, with losses of genetic material leading to loss of tumor suppressor genes, gains of genetic material leading to excessive copies of oncogenes

Individual abnormalities

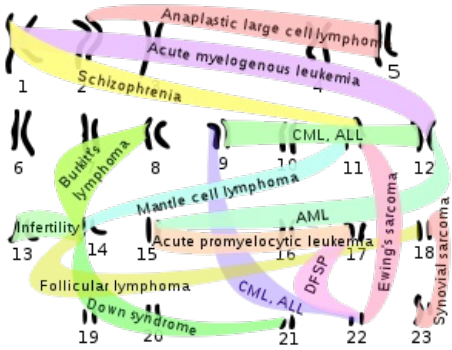
Translocations

Reconstructions (most often translocations) are relatively common in cancers with fractures within the introns of genes lying on different chromosomes, which then lead to the formation of fused genes producing abnormal - chimeric protein with increased activity (tyrosine kinase activity or transcription factor function). Such reconstructions are described in numerous hematopoietic malignancies, but also in solid tumors. An example of such a malignancy is chronic myeloid leukemia (CML). The cytogenetic abnormality observed in this disease (Philadelphia chromosome-Ph 1) is due to a balanced reciprocal translocation between chromosomes 9 and 22, in which the proto-oncogene abl (tyrosine kinase) is moved from its normal position on chromosome 9 to chromosome 22 to a breakpoint in the bcr gene. The fused gene (bcr/abl) then produces a chimeric protein with increased tyrosine kinase activity. Various breakpoints in the bcr region and alternative chimeric proteins then occur in chronic myeloid leukemia and acute lymphoblastic leukemia.



Philadelphia chromosome: t(9;22)(q34;q11)

Other translocations move the proto-oncogene to the vicinity of genes that encode **immunoglobulin** heavy or light chains or to the vicinity of T cell receptor genes. Here, the gene comes under another control **region, highly transcriptionally active,** and in this new position, the gene is over-transcribed, producing a normal protein but in an excessive amount. An example of such a translocation is **Burkitt's lymphoma** , in which the proto-oncogene is **myc** translocated from a normal position on chromosome 8 (8q24) to a distal locus for the immunoglobulin heavy chain locus on chromosome 14 (14q32) due to balanced translocation. Translocation is likely to result in gene transfer under the influence of an enhancer or other transcriptional activating sequence of immunoglobulin genes. Less frequently, translocations include this gene and immunoglobulin light chain genes on chromosome 2 or 22.



Scheme of various chromosomal translocations and their relation to selected diseases

Such a mechanism usually involves cells in which the genome undergoes **somatic recombination** . In the case of translocations of proto-oncogenes adjacent to immunoglobulin genes, somatic **recombination sites of the V (D) J segments** are thought to be a predisposing site for rearrangement. But fracture sites can also be random, and rearrangement can give the cell a selective advantage. For 9/22 translocation, the close position of the interphase chromosomes is indicated.

Amplification

Amplification of chromosomal parts manifests as "double minutes" - small circular structures containing copies of oncogenes and occurring in varying numbers in tumor cells. Sometimes amplified copies of oncogenes are tandemly integrated into the chromosome, then stained homogeneously on the striped chromosome and are called **HSR** (homogenously staining regions). Amplified copies of oncogenes are not mutated to produce normal protein, but there is an excessive amount of protein in the cell due to amplification

Deletions

Another chromosomal change that is directly related to tumor formation is the deletion of the region of the chromosome where the **tumor suppressor gene** lies (eg, in the retinoblastoma - RB1 gene on chromosome 13q14). Here, the deletion is one of two stages by which the tumor suppressor gene is excluded from its function (see **Knudson's two-step hypothesis** of tumor suppressor gene inactivation).

Syndromes with increased fragility of chromosomes and other diseases associated with an increased risk of cancer

In connection with chromosomal changes in tumors, other situations should be mentioned, such as autosomal recessive **syndromes associated with increased chromosomal fragility**, caused by **repair failure**, where the affected have a significantly increased percentage of cells with acquired aberrations in their cells as a result of damage and therefore also have a high risk of tumors. Also some imprinting syndromes, such as Beckwith-Wiedemann syndrome with deregulation of the imprinted region of IGF2 and H19, where chromosomal aberrations leading to duplication of the paternal IGF2 allele on paternal chromosome 11 or deletion or translocation of the maternal H19 allele leading to subsequent activation of the maternal IGF2 allele has increased consequences of tumor risk. Patients with Down syndrome (trisomy 21) also have an increased risk of cancer because their trisomic cells are increasingly sensitive to external mutagens. Thus, the association of chromosomal abnormalities with tumors is quite **diverse**.

Clinical significance

The study of chromosomal changes in tumors has contributed to the understanding of the mechanisms of tumor formation. For the patient and the doctor, it provides important prognostic information (certain chromosomal abnormalities mean a good, others a poor **prognosis**) and allows you to choose the appropriate method of **therapy** (some changes accompany the deterioration of the clinical condition and often even prevent this deterioration). Thus, cytogenetic examination is of great benefit for the treatment of the patient in many cancers.

Links

Related articles

- Characteristics of tumor transformed cells
- Chromosomal aberrations in the etiology of neoplasms
- Structural chromosomal aberrations

References

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