RELATIONSHIP BETWEEN CHROMOSOMAL INSTABILITY AND LEUKEMIA

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Since Th. Boveri put forth his famous hypothesis in 1914 that malignant cells are mutant clones with a genetically unbalanced chromosome complement, many scientists were able to show examples for such origin of tumors.

Tumor cells usually contain marker chromosomes which point to chromosomal rearrangements in the very beginning of malignant growth. Numerical alterations of the karyotype are very often observed in tumor cells. Both, the markers and the additional chromosomes characterize each individual tumor independent of type or site of the neoplasia.

There are two exceptions: the Philadelphia chromosome which is a delted chromosome No. 22, in the majority of cases with chronic myelogenous leukemia, and the other constant, interindividual chromosome aberration is the missing G-chromosome in meningioma.

These cytogenetic findings, the marker chromosomes and the two constant aberrations in chronic myelogenous leukemia and meningioma clearly indicate a clonal origin of the neoplasias. Biochemical studies of tumor tissues offer another argument for the clonal origin of many different tumors. One of the two X-chromosomes is genetically inactive in female cells, which occurs randomly and early in embryogenesis and is fixed from then on through life. This leads to two types of somatic cells: one population with the paternal, the other with the maternal X-chromosome active. Tumors always exhibit only one type of X-chromosomal enzyme in cases where the femal is heterozygote for different types of an X-chromosomal enzyme. This is also true for leukemic cells.

There are, however, tumors and leukemic cells with an apparently normal karyotype. One explanation is that subtile aberrations may not be detectable by the present techniques. On the other hand it is possible that there are changes like point mutations which are responsible for the unrestrained growth or other properties of cancer cells.

A certain sequence of events which finally cause the transformation into a cancer cell has not yet been determined. However, the fact, that cancer cells derive very often from a single cell with a visible chromosome rearrangement draws the attention to a few inherited diseases with high incidence of leukemia and cancer. These diseases also have an increased spontaneous chromosomal instability in common: Fanconi anemia (FA), Bloom's snydrome (BS) and Ataxia telangiectasia (AT). Clinically they are very different syndromes. FA is known as a pernicious-like

aplastic anemia in childhood, BS is characterized by stunted growth, sun-sensitivity of the skin and telangiectasia in exposed areas. AT is a neurological disease combined with telangiectasia.

A fourth recessive trait, Xeroderma pigmentosum, belongs to this group of diseases. The genetic defect is known: the UV specific endonuclease necessary for the first step in dark repair is missing so that UV induced damages in the DNA are not being repaired. The UV exposed skin of the patients is covered with lesions and later in life with multicentric cancers.

The spontaneous chromosome instability in FA, BS and AT is present in cultures from peripheral blood cells and from skin biopsies, in direct preparations of bone marrow cells or even in bone marrow smears. Cultured cells from patients with XP show increased breakage after UV irradiation. Although the genetic defects in FA, BS or AT are unknown, they are responsible for the chromosomal instability in each disease. James German and I were able to show that the genetic defects causing FA and BS act differently at the cellular level, i. e. the different genes express themselves very different cytogenetically. For instance, FA-cells show almost exclusively chromatid interchanges between non-homologous chromosomes. BS-cells, in contrast, have almost exclusively chromatid interchanges composed of homologous chromosomes, and in addition, the breaks occur seemingly at the same loci. Studies of the sites of breakage demonstrated a non-random distribution over the entire karyotype in both, FA and BS. In BS there are distinct sites of certain chromosomes which are far more involved in breakage and rearrangement than others. FA does not show such a clear pattern of breakage and reunion as BS does, however, there are also preferences for breakage at certain chromosome regions. Differences like that might indicate that the damage due to the genetic defect occurs at different times in the cell cycle in FA and BS. No study comparable with this has been made with AT-cells or XP-cells after UV irradiation. Both cell types grow very poorly in vitro.

The consequence of such aberrations are unbalanced karyotypes in the daughter cells after mitosis. This certainly leads to cell death in many instances. It also can lead to a surviving single cell which gives rise to a clonal cell population and eventually becomes malignant.

Hence, in these diseases the steps from chromosome mutation, the survival of a mutant cell, the development of a clonal cell population into the established tumor cells or leukemic cells can be observed.

Actually, in all four diseases, cell clones with rearrangements have been found:

In FA in bone marrow and lymphocyte cultures, in BS and XP in fibroblast cultures and in AT in lymphocyte cultures.

These findings are comparable with what is known about the effects of ionizing irradiation in man, the only situation where cell clones with abnormal chromosomal complements have been found in vivo. X-ray induces chromosomal breakage and predisposes to cancer and leukemia. A-bomb survivors in Japan were found with mutant cell clones in their peripheral blood cells showing stable chromosome rearrangements. The oncogenic implication of X-ray induced chromosomal breakage, of UV-light induced damage in the DNA of XP patients and of the chromosomal instability found spontaneously occuring in FA, BS and AT is one and the same.

Chromosomal instability appears characteristic of cell damage caused by irradiation or by genetic defects – from which cancer is likely to emerge. In the diseases discussed here, the incidence of cancer or leukemia is about 10 % in FA and BS, maybe less in AT, however, it is 100 % in XP patients. For FA it can be predicted that hormone therapy for treatment of the aplastic amenia will help the patient to survive longer in future, long enough to most probably experience leukemia.

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