Oncogenes and Cancer: Genomic Instability in Experimental Tumors

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ABSTRACT

Cancer is a complex disease associated with uncontrolled cell growth and the stepwise acquisition of genetic alterations. Through such acquisitions, tumors become genomically unstable. Tumors usually contain several types of genomic lesions, including subtle DNA sequence changes as well as cytogenetically visible changes such as aneuploidy, translocations and amplifications.

Some types of cancer have been shown to be dependent on the initial lesion of an oncogene or tumor suppressor gene. Through the use of animal models for human cancer, the role of specific genes in tumor development can be thoroughly studied. In addition, individual differences in genetic susceptibility and exposure to environmental factors can be minimized, facilitating the identification of genes important in tumor development.

To examine the role of oncogenes in tumorigenesis, several approaches were taken. As a first step, several cancer-related genes were physically mapped in the rat by FISH. Subsequently, a detailed cytogenetic map was developed for rat chromosome 6q14-q16, which had previously been shown to be frequently involved in a chromosomal amplification in rat endometrial carcinoma. Southern blot analysis and different fluorescent *in situ* hybridization techniques implicated that the oncogene *Mycn* was the target gene of amplification in two out of ten tumors. RT-PCR showed that the gene was overexpressed in both these tumors and in two additional tumors.

Next, genomic events associated with *MYC*-induced tumorigenesis were revealed by spectral karyotypic analysis of 27 primary and relapsed reversible *MYC*-induced mouse lymphomas. All the tumors were shown to be karyotypically unstable. In addition, relapsed tumors exhibited a previously unidentified jumping translocation involving mouse chromosome 3, where parts of different donor chromosomes had translocated to the telomeric end of chromosome 3.

To study how *MYC* might induce genomic instability, different assays for measuring DNA damage were used in normal human fibroblasts overexpressing *MYC*. Overexpression of *MYC* induced chromatid breaks and chromosomal translocations and impaired the repair of DNA double-strand breaks by interfering with both homologous recombination and non-homologous end joining. The results imply a new role for oncogenes in the initiation of tumorigenesis.

Keywords: amplification, animal models, cancer, DNA repair, endometrial cancer, FISH, *Mycn*, *MYC*, oncogenes, overexpression, reversible lymphoma, SKY, translocation

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