Symposium no. 10: Gene Alterations in Human Cancer Cells

10.031

MUTATIONS OF THE P53 GENE IN HUMAN BRAIN TUMORS. Tenan M., Cajola B., Pollo B., Broggi G. and Finocchiaro G.- Istituto Nazionale Neurologico, 20133 Milano, Italy.

The p53 gene encodes a 53 kDa nuclear phosphoprotein involved in the control of cell proliferation. Several alterations of this gene have been found in human tumors. Among brain tumors p53 mutations have been only investigated and detected in glioblastomas. We want to investigate whether there are relationships between the localization of p53 mutations and: i. the tissue-specific development of tumors in brain; ii. the clinical evolution of these tumors.

We have amplified by polymerase chain reaction (PCR) a 2.9 kb region of the p53 gene in different brain neoplasis. This region contains exons 4 to 9, where p53 mutational hotspots have been detected. The PCR products were cloned and sequenced. No mutation of the p53 gene was found in one patient with grade II-III astocytoma. A mutation different from those previously described has been detected in exon 5 of one patient with glioblastoma. Other point-mutations are present in exon 8 of one patient with oligodendroglioma.

The sequence analysis of PCR products from other brain tumors is in progress.

10.032

K-ras MUTATION FREQUENCY IN PREMALIGNANT AND MALIGNANT COLONIC TISSUE OF THE SAME PATIENTS
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The frequency of K-ras mutations in codon 12 in the total population of colon tumour patients is 48% in the adenomas and 33% in carcinomas.We compared the progression of malignant transformation and the mutation frequency in this codon in the tissues from the same patient. DNA was isolated from paraffin-embedded"normal"(N),mildly to moderately dysplastic(AI-II),severly dysplastic (AIII) and carcinomatous (C) colonic tissue of 10 patients.K-ras sequences were amplified in the PCR and hybridised to radioactive probes complementary to non-mutated K-ras or to the four most frequent mutations in codon 12 (TGT,TGA,TTG or TAG instead of GGT).The frequency of the detected mutations was in N 30%,in AI-II 50%,in AIII 60% and in C 80%. These data suggest that in the total patient population not all carcinomas originate from AIII adenomas.

10.033

Loss of heterozigosity of 1p chromosome in neuroblastoma.

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More than 80% of advanced neuroblastoma (NB) show 1p ter deletion. Recently the region 1p36.6 has been indicated as the putative locus for NB suppressor gene. By a series of molecular probes including probes derived by microdissection and microcloning of 1p region. We have analysed loss of heterozigosity in 14 samples of NB. Preliminary results show LOH for the minisatellite probe MS1 in 4/14 patients (2 stage I, 1 stage II and 1 stage IV). Probe p1-31 (region 1p35.1) detected LOH in 1/5 patients in stage IV. Since MS1 encompasses the region 1p33-p35, MS1 analysis shows that deletion is more centromeric on respect the putative locus of NB suppressor gene. Our preliminary data suggest that LOH of 1p may be present in the localized as well in metastatic NB.

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10.034

Most ovarian cancers have deletion of chromosome 19 sequences

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The genetic scenario of the pathogenesis of ovarian cancer is beginning to be elucidated. Rarely oncogenes are activated in ovarian cancer. More often and in most ovarian cancers loss of genetic material as indicated by cytogenetics or examination with polymorphic probes, occurs. Chromosomes involved are 11p, 17p, 6q. It is assumed that tumor suppressor genes are located on these chromosomes and that their inactivation contributes part of the malignant phenotype. When using polymorphic probes of chromosome 19 as a control for loss-of- heterozygosity studies in ovarian cancer, we unexpectedly found loss of heterozygosity for chromosome 19 in 7 out of 13 (54%) of ovarian cancers, when comparing tumor DNA to constitutional DNA of informative patients. Previous cytogenetic work has never revealed involvement of chromosome 19 and the chromosome does not harbour any of the known tumor suppressor genes or suspected tumor suppressor genes in other tumors.

We conclude that gene(s) on chromosome 19 might be involved in the pathogenesis of a majority of human ovarian cancers.

10.035

C-FES DELETION IN HIGHLY MALIGNANT HYBRIDS CONSTITUTIVELY EXPRESSING THE C-FES GENE

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Highly metastatic hybridomas obtained from in vivo (ESb) and in vitro (EbF1 and EbF2-c4) fusion of the low metastatic T- lymphoma Eb and syngeneic macrophages, express several properties which were absent in the parental tumor Eb: macrophage antigenic and functional properties as well as c-fes and c-fos proto-oncogenes involved in the myelomonocytic pathway. Southern analysis of the c-fes DNA reveals that all the hybrids carry a 100 bp deleted c-fes gene; Eb DNA carries both the deleted band and the normal counterpart. Progressive digestions of the 1909 bp cDNA probe leads to a 240 bp fragment which still detects the lesion. Now a days results allow to map the deletion within a genomic region from a Bam HI site in the III intron to the Hinf I site within the IV exon, 30bp from the intron/exon splice junction

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