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EVIDENCE SUPPORTING H19 AS A TUMOR SUPPRESSOR GENE IN HYDATIDIFORM MOLE BUT NOT IN CHORIOCARCINOMA CELL LINE.

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The H19 transcript is one of the most abundant mRNAs in human placenta and embryonal tissues. It has been previously shown to be parentally imprinted (i.e. genomic expression based on the gamete of origin), yet it's function has not been clearly elucidated. Recent data associating H19 with IGF-II, a known growth factor/proliferation gene, has led to the speculation that H19 may counterbalance these proliferative effects via suppressor activity. We examined for the expression of mRNA H19 in native placental tissue, hydatidiform mole, and the JAr choriocarcinoma cell line using northern blotting. These tissues were selected because of their common cell of origin, but different genomic compositions (gynecogenic/androgenic, androgenic only, and androgenic with chromosomal translocation, respectively). In 1st and 3rd trimester placentae, H19 was expressed to a similar extent. The highest expression was noted in the JAr cells. H19 was absent, or minimally expressed in the molar tissue. The low levels of expression in this latter tissue was shown to be due to decidual contamination. IGF-II was expressed in all tissues examined except in JAr. These data suggest that the imprinted H19 gene may function in the capacity of a suppressor gene in normal placental tissue, and that the absence of this expression (due to alterations in genomic makeup) leads to cell proliferation in hydatidiform mole. Conversely, other mechanisms can also result in uncontrolled cellular proliferation of this same cell type, even with the functional expression of this gene.

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PROGNOSTIC IMPORTANCE OF P53 AND EGFR IN CERVICAL CARCINOMA

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A significant proportion of stage I and II cancers of the cervix relapse rapidly, yet are not predicted by currently used clinico-pathological prognostic factors, such as stage, size and grade of tumour. In a preliminary study, immunocytochemical staining was carried out on 46 paraffin-embedded cervical tumours, using antibodies to p53 (CMI) and EGFr (F4). Staining was assessed on a semi-quantitative three point scale for intensity and distribution by three independent observers, without knowledge of outcome. Overexpression of p53 protein was found in 37% of tumours, while overexpression of EFGr was found in 76% of tumours. 28% of tumours exhibited overexpression of both protein markers. Of these, 35% were moderately differentiated and 29% poorly differentiated. None of the well differentiated tumours exhibited these staining patterns. HPV status and sub-type analysis is being assessed by in-situ hybridisation and the polymenase chain reaction techniques, and the numbers extended to 100 cases.

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FLOW CYTOMETRY DNA PLOIDY AND N MYC GENOMIC CONTENT AS PROGNOSTIC INDICATORS IN NEUROBLASTOMA

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Neuroblastoma is an enigmatic tumor representing 10% of all malignancies of childhood. Although some neuroblastoma mature or regress spontaneously, others are highly aggressive. Cytogenetic abnormalities, N myc gene amplification, and DNA ploidy have been suggested to be reliable prognostic predictors. The aim of the study was to assess the DNA content with other prognostic factors. 25 children were studied: all with DI 1.3-1.6, are well with no evidence of disease. One infant, with stage IV-S DI 1.52 - regressed spontaneously. 2 stage III: with DI 1.39, 1.55 - alive with disease. Stage IV - 12 patients: 11 of whom older than 1 year. DI - 10 <1.2 of whom 3 expired, 2 relapsed, 3 on therapy, one NED. Two with DI of 1.38 - responding to therapy. One with DI of 2 - NED following BMT. N myc amplification was detected in only 5 out of 21 stage IV studied and one in stage III. The results obtained indicate that DNA ploidy may serve as an important prospective prognostic factor and may help to delineate the individual child with adverse prognosis.

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ALTERATION OF THE PROTO-ONCOGENE HER2/neu IN CORRELATION TO THE CLINICAL PATHOLOGICAL FACTORS IN GASTROINTESTINAL ADENOCARCINOMA

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The equivalent of the neu transforming gene, coded for 185 kd phosphoprotein, identified first in rats' ganglioneuroblastomas genome, and then in human was designated HER2 or c-erbB-2. HER2/neu gene is amplified and/or highly expressed in human tumor cell lines, mainly breast and ovarian cancer, and was reported to be altered in gastrointestinal tumors. The correlation found between the occurrence of specific proto-oncogene abnormalities and the clinical course signify the importance of combining the detection of these molecular events with the clinical-pathological assessment of malignant diseases. The level of the HER2/neu protein and the gene copy number in a cohort of 106 tumor specimens, representing gastric and colorectal adenocarcinoma, were evaluated and compared to the clinical-pathological factors of the patients. Even though the amplification of the HER2/neu is rare, it may become a tool to predict the clinical outcome than the high expression of the gene. It could become a molecular marker in some of the malignant diseases, and a helpful method to determine the therapeutic regimen in specific cases.

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P53 PROTEIN AND ANTIBODIES TO P53 IN PRIMARY BRAIN TUMORS. RESULTS FROM A NEWLY DEVELOPED LUMINOMETRIC ASSAY FOR P53 COMPARED TO IMMUNO-HISTOCHEMISTRY.

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Overexpression of, mainly mutated, p53 protein is found frequently in a wide variety of human malignant tumors. A newly developed sandwich type immunoassay has been used to measure both wild-type and mutant p53 protein in extracts from tumor tissues from 35 well documented patients suffering from different forms of brain tumor. In this study the results from the quantitative luminometric assay correlate well with the semiquantitative immunohistochemical analysis of paraffin sections from the same tumors. Studies on circulating levels of p53 and autoantibodies to p53 were performed on serum samples drawn at the time of the removal of the tumor. The study indicates that current technique can reliable access the p53 status of a tumor. The prognostic and therapeutic impact of such an assessment remain to be elucidated.

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EFFECT OF RECOMBINANT β-INTERFERON ON ONCOGENE EXPRESSION IN HUMAN BREAST CANCER CELLS

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The c-myc and c-erb B2 oncogenes are frequently amplified and/or overexpressed in human breast carcinoma. There is increasing evidence that interferon (IFN) inhibits cell proliferation in different experimental models through a series of mechanisms which include regulation of oncogene expression. We studied the effect of recombinant β-IFN (rβ-IFN) on the level of the proteins encoded by c-myc and c-erb B2 in an estrogen-sensitive variant of MCF-7 cells, named CG-5, which is responsive to the antiproliferative activity of this type of IFN. CG-5 cells were grown in different culture conditions and were tested with the growth-inhibiting dose of rβ-IFN of 1000 IU/ml. The response, at the oncoprotein level, was analyzed at time intervals ranging from 4 to 120 hours, by Western blot technique. Relative amounts of c-myc and c-erb B2 proteins were determined by densitometric scanning of the oncoprotein specific bands. In 3 experiments no relevant difference was found up to 72 hours, whereas after 120 hours of rβ-IFN treatment the protein level of c-myc and c-erb B2 appeared to be reduced. To our knowledge this is the first evidence of in vitro down-regulation of these two oncogenes by rβ-IFN in estrogen receptor-positive breast cancer cells.