MOLECULAR ANALYSIS SHOWS A COMMON DELETION IN THE MAJOR TYPES OF LUNG CANCER

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Chromosome studies of 5 SCLC cell lines revealed a common deletion of chromosome 3 with bands p21-p23 as the shortest region of overlap. Hybridization with a polymorphic 3p21 probe (minor allele frequency almost 0.5) revealed no heterozygosity in 15 SCLC cell lines. All those SCLC patients who were found to be heterozygous for this probe in blood DNA gave homozygous patterns when their tumour DNA was analyzed. Hybridization of DNA from 17 squamous- and 6 adenocarcinomas revealed 13 and 3 cases, rspectively, with only one band in the autoradiograph. The others showed two bands of unequal intensities. For 12 heterozygous control DNAs, the intensity ratios of the two bands varied between 1.20 and 0.80. For all tumours, except for one squamous- and one adenocarcinoma, the ratio was significantly outside this range. The presence of low intensity bands can be attributed to an admixture of normal tissue with the tumour, as was confirmed by histologic examination. The common occurrence of the 3p21 deletion in all lung cancers suggests that it is one of the essential events in the development of this tumour.

BIOLOGICAL CHARACTERISTICS OF HUMAN MALIGNANT MELANOMA CELL LINES AND ITS POSSIBLE CLINICAL APPLICATION

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Cellular heterogeneity of human tumours is considered responsible for different sensitivity to chemotherapeutic drugs; a characteristic which has great clinical significance. In order to achieve an accurate study of the biological properties of histologically verified human cutaneous melanoma, four cell lines were characterized using antimelanoma monoclonal antibodies, examined morphologically and by karyotype analysis. Different degrees of immunofluorescent staining have been detected in primary tumour continuous cell lines compared to cloned cell lines obtained from the same primary culture by colony selection or micromanipulation. Metastaic melanoma cell line from the same patient differed in immunofluorescence from primary and cloned cell lines. Morphological analysis showed variability within the primary, as well as metastatic cell culture, while cloned cell lines were morphologically more uniform. Chromosome analysis revealed abnormalities in ploidy, different rearrangments and three shared characteristic markers. Such characterization of tumour cell lines could be used in planning therapy for individual patient with single or metastatic tumours.

9-AMINOACRIDINE-4-CARBOXYAMIDES INDUCE COVALENT INTERSTRAND DNA CROSS-LINKING IN TUMOUR CELLS

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We have shown previously that such classical intercalators as 1-nitroacridines exert their cytotoxic and antitumour activity by covalent DNA cross-linking which occurs after metabolic activation in the cell. On this basis, we anticipated that some other highly active antitumour drugs which are believed to act via intercalation might, in fact, cross-link cellular DNA. This hypothesis has been confirmed in our laboratory for some anthracyclines and anthracenediones. Recently, we have also found that 9-aminoacridine-4-carboxyamides, a new class of antitumour compounds synthesized at the Univeristy of Auckland, New Zealand, induce interstrand cross-links in DNA of tumour cells in dose-dependent manner. The ability to form interstrand DNA cross-links depends on both cytotoxic activity of the compounds studied and their chemical structure.

HUMAN LYMPHOMA XENOGRAFTS IN DRUG SCREENING

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Three human non-Hodgkin lymphomas (B-cell origin) were established as transplantable xenografts in artificially immune-suppressed CBA mice. (None of the samples from Hodgkin-lymphomas had taken.)

All of them preserved the phenotypic characteristics of the original tumour (morphology, Ig patern) even after several passages. Drugs which are involved in clinical schedules were screened. The transplantable tumours were highly sensitive to cyclophosphamide and methotrexate, reflecting the results obtained in patients' treatment. Other agents including alpha-inteferon produced no or slight response.

2'-5' OLIGO(A) SYNTHETASE LEVELS AND PROTEIN KINASE IN INTERFERON-SENSITIVE OR -RESISTANT BREAST CANCER CELLS

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The levels of 2'-5'oligo(A) synthetase have been studied in three breast cancer cell lines. The activity of 2'-5' oligo(A) synthetase has been measured, both in control and interferon or interferon inducer-treated cells, by two different assays. The activity of this enzyme is increased 20-fold when T47D cells are treated with human interferon or with interferon inducers. In contrast, MCF-7 and BT-20 cells treated or not with interferon, exhibit low activity of 2'-5' oligo(A) synthetase.

The profiles of protein kinase are presently under further investigation.

MARKERS OF HUMAN MAMMARY GLAND DIFFERENTIATION AND THEIR EXPRESSION IN BREAST TUMOURS

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To relate the tumour phenotype to the framework of normal mammary gland differentiation, we compared phenotypic features of the human resting, pregnant, lactating and regressing breast epithelium with those of more thatn 200 benign and malignant breast lesions. Monoclonal antibodies to cytokeratins No. 19, 18, 8 and 7 to epithelial membrane antigens and secreted molecules were produced and employed in immunohistochemistry combined with 1-D and 2-D gel immunoblotting. The results revealed several distinct sub-populations in normal epithelium pertinent to differentiation stage. The phenotypes of benign lesions mainly resembled the resting or pregnant epithelium, whereas some features of late pregnancy and lactation were observed in carcinomas though lacking the co-ordinate expression seen in normal differentiation. The antibodies also proved to be useful in identification of micrometastases and for the differential diagnoses of some human malignancies.

NEOPLASTIC-GROWTH CHANGES IN NON-HISTONE CHROMATIN PROTEINS

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Two fractions of non-histone chromatin proteins (NHCP1 and NHCP2) isolated by a hydroxyapatite procedure were obtained from nuclei of Kirkman-Robbins hepatoma at the 4th, 7th and 9th day of its growth. Electrophoretic (one- and two-dimensional analyses followed by Coomassie Brilliant Blue and silver staining) and immunological (Western blots) techniques revealed some specific non-histone polypeptides (within MW ranges of 16,000-25,000 and 80,000-85,000 in the NHCP1 as well as 17,000-28,000 and 35,000-42,000 in the NHCP2) observed during neoplasia. The growth of neoplastic tissue is accompanied by increase, decrease (or disappearance) of some non-histone components.

POTENTIATION OF ANTITUMOUR EFFECT OF CYCLOPHOSPHAMIDE BY DL-α -DIFLUOROMETHYLORNITHINE (DFMO)

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Potentiating effect of DL-α-difluoromethylornithine (DFMO) in combination with different cytotoxic agents has been reported in experimental and clinical cancer chemotherapy. In order to clarify the mode of action, normal control and P388 leukaemia-bearing mice were treated with DFMO continuously and/or with a single dose of cyclophosphamide. Effects of singular and combined treatments were monitored by determination of metabolite concentrations in blood, urine, liver and tumour cells with respect to the conversion of ornithine into polyamines and urea cycle. Urinary excretion of natural and acetylated polyamines was measured during tumour growth