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ISOFLAVONIC PHYTOESTROGENS IN HUMANS, -IDENTIFICATION AND METABOLISM

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Naturally occurring isoflavonic phytoestrogens and metabolites thereof have been investigated in connection with breast cancer and other estrogen dependent diseases because of their possible role as estrogens and/or antiestrogens. Human subjects, particularly vegetarians, excrete in comparison with estrogens high amounts of phytoestrogens in urine. The lowest amount of phytoestrogens were found in urine of postmenopausal breast cancer patients. During the course of the present investigation on the influence of diet on estrogen metabolism we identified by combined gas chromatography-mass spectrometry the following isoflavonic compounds in human urine: Formononetin (For), Daidzein (Da), Intermediate-E (I-E), Intermediate-O (I-O), O-desmethylangolensin (ODma), Equol (Eq), Methylequol (Meq) and Genistein (Ge). Naturally occurring For is metabolized by intestinal bacteria to either Da or in smaller amounts to Meq. Da which also occurs in foodplants is metabolized either via I-E to Eq (70%) or via I-O to ODma (5 to 20%). Ge is known to occur in plants but may also be a metabolic product of naturally occurring Biochanin A. It is concluded that the metabolism of isoflavonic phytoestrogens in human subjects is similar to that in animals.

CONTRIBUTION OF ras ONCOGENES TO NEOPLASTIC DEVELOPMENT

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Chemical and physical carcinogens have been implicated in the etiology of human cancer. Most of these carcinogens interact with DNA and have mutagenic properties. Whereas the majority of carcinogen-induced mutations have no serious consequences to the host, a small number of them are thought to be responsible for neoplastic development. The recent discovery that oncogenes, in particular those of the ras gene family, are reproducibly activated in carcinogen-induced tumours has made it possible to establish a correlation between those mutations responsible for the malignant activation of these oncogenes and the known mutagenic properties of the initiating carcinogens. These studies have indicated that initiation of neoplasia may involve the activation of oncogene(s) by the direct mutagenic action of certain carcinogens. In the present study, the contribution of normal developmental programmes to the phenotypic expression of oncogenes and the involvement of additional genetic events in the development of the full enoplastic phenotype has been investigated.

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ASSOCIATION IN THE EXPRESSION OF Ki-ras ONCOGENE AND MHC CLASS I ANTIGENS IN FIBROSARCOMA TUMOUR CELL VARIANTS EXHIBITING DIFFERENT METASTATIC CAPABILITIES

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The present study is aimed to investigate the expression of proto-oncogenes in the T-10 fibrosarcoma lines that exhibit distinct metastatic properties in correlation with the expressed H-2 antigens. The major oncogene which showed differential expression in the T-10 clones is the Ki-ras. The amounts of specific Ki-ras M-RNA and the Ki-ras p21 protein are expressed in elevated levels in the H-2D^{k} negative non-metastatic clones in comparison with low level of expression in the H-2D^{k} positive highly metastatic clones. Expression of H-2K antigens following transfection with cloned H-2K genes had no effect on the expressed Ki-ras oncogene in the T-10 clones. However, transfection of the non-metastatic cells with cloned H-2D^{k} gene resulted in shifting the cells to highly metastatic phenotype and in reduction of the expressed c-Ki-ras oncogens.

HISTOLOGICAL MARKERS USED TO FOLLOW-UP THE PROGRESSION OF SOFT TISSUE SARCOMAS

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Some histopathological factors (tumour differentiation, degree of cellularity, nuclear polymorphism, mitosis count, tumour

necrosis, structure of tumoural vascular pattern, vascular emboli and reticular tumoural stroma) had been chosen to estimate the histological degree of malignancy, for all soft tissue sarcomas treated at the Oncological Institute of Cluj-Napoca, Romania, since 1979.

Using a multiple linear regression analysis, according to the Armitage and Gehen model, we selected six factors which showed the best correlation with patient survival in the majority of histologic types of soft tissue sarcomas. Among these, cellularity, mitotic index, polymorphism and macrosis were found essential and sufficient to determine the tumour grade, but tumoural vascular and stromal patterns also proved of important prognostic value in assessing the cancer progression.

EFFECT OF KETOTIFIN (K) ON ADRIAMYCIN (A)-INDUCED HISTAMINE RELEASE AND TOXICITY

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K is an anti-anaphylactic drug which acts in part, similarly to sodium cromoglycate, by inhibiting mediator release from mast cells. However it has been shown that K induces also a non-cytotoxic histamine release from mast cells. We have recently demonstrated that sodium cromoglycate inhibits A-induced histamine release from rat mast cells and limits its cardiotoxicity. The aim of this study was therefore to test the effect of K on A-induced histamine release and the toxicity in mice. The intraperitoneal (i.p.) injection of various concentrations of K (from 2.1 to 25 mg/kg) induced significant histamine release from mast cells. 30 min afterwards, microscopic observation revealed that these cells were completely degranulated and no more histamine was present in the peritoneum. When administered i.p. to mice 30 min before A (15 mg/kg i.p.), K significantly ameliorated the survival time and reduced the cardiotoxicity. On the contrary, when given simultaneously, K increased the toxic effect of A. These data support the hypothesis that histamine release could play a role in the pathogenesis of A cardiotoxicity.

CHARACTERIZATION OF SERUM IMMUNE COMPLEXES ISOLATED BY SEPHAROSE PROTEIN-A IN GASTROINTESTINAL TUMOURS

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Circulating immune complexes (CIC) were analyzed in some gastrointestinal tumours to characterise their antigenic components. CIC were isolated from sera by 3.5% PEG precipitation and then purified on Sepharose 4BCL Protein-A followed by acid elution (glycine-HCl buffer). Molecular weight determination of the antigens was then obtained by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) with discontinuous buffers. Different molecular patterns of migration were shown from various patients. A preliminary analysis of the antigenic components was then undertaken in order to detect those factors being either different from, or in common with, the features displayed from a pool of control sera (normal healthy blood donors).

SERIAL ASSAY OF CIRCULATING IMMUNE COMPLEXES, CEA AND CA 19-9 IN GASTROINTESTINAL CANCER PATIENTS DURING CHEMOTHERAPY OR CLINICAL FOLLOW-UP

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Circulating immune complexes (CIC) have been proposed as prognostic markers in human neoplasms even though conflicting results have been reported so far. Very little information is also available on their behaviour during the natural history of the disease as well as during chemotherapy. In this study, at least 4 serial assays of CIC have been performed in 14 patients with advanced gastrointestinal tumours during chemotherapy and in 2 patients with surgically resected colon cancer at intervals of 1 to 3 months. CEA and CA 19-9 were simultaneously assayed. The disease was monitored by CEA in 10 patients, by CA 19-9 in 9 and by CIC in 8. It should be emphasized that high levels of CIC predicted progression of disease in 6/16 patients, recurrence in 1/2 and, in 2 subjects, CIC were the only useful serum marker.

NITROSAMINE EXPOSURE IN SUBJECTS AT RISK FOR CANCER OF THE MOUTH, STOMACH, OESOPHAGUS AND URINARY BLADDER

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