MEETING ABSTRACTS

HORMONE SENSITIVITY OF OVARIAN AND BREAST CANCER COLONY FORMING CELLS

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Fifty-nine primary ovarian tumour samples and twenty-four primary breast tumour samples formed colonies in semi-solid medium which is supplemented with 5% foetal calf serum. Progesterone and 17-beta-oestradiol were tested by continuous exposure. Ovarian cancer cells exposed to 10^{-6} to 10^{-8}M 17-beta-oestradiol were significantly inhibited (less than 30% growth compared to control) in only 7 instances. Similar data was observed with 10^{-6} to 10^{-7}M progesterone. Colony formation was enhanced by 17-beta-oestradiol in eleven instances. These data suggest that hormonal manipulations should have little clinical benefit in ovarian cancer. Breast cancer samples that grow in our assay system represent a subgroup of particularly aggressive tumours unrelated to the presence of estrogen receptors. Only 3/24 samples were affected by 17-beta-oestradiol. Thus it appears that colony-forming cell assays detect a subgroup of estrogen-receptor positive breast cancers that may respond poorly to hormone treatment.

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QUALITY CONTROL OF COLONY FORMING CELL (CFC) ASSAYS

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The EORTC CASSG is comprised of laboratories in nine European countries. One of the aims of the group is to examine the reliability and explore potential clinical applications of CFC assays. We have completed two studies in which a single cell-line (colon, WiDR) was sent to each participating laboratory from a central laboratory (JFE, ISREC, Epalinges). The cells were tested with each laboratory's own assay system to determine the linearity and plating efficiency of the cell line. The effects of adriamycin and cisplatin were also tested at several concentrations. The results of the dose-response curves were somewhat different between individual laboratories. The overall results were remarkably reproducible from experiment to experiment. The results with cisplatin showed the dependence of this drug's effects on the culture medium used. These quality control studies have pointed out several methodological questions, which individual laboratories have taken the initiative to investigate. We conclude that a group of laboratories using CFC assays can rapidly provide reliable drug screening results.

MODULATION OF EXPRESSION OF CLASS I MHC GENES IN RODENT CELLS TRANSFORMED BY HUMAN ADENOVIRUSES WHICH DIFFER IN THEIR ONCOGENIC POTENTIAL.

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Relative levels of MHC class I mRNAs and proteins have been determined in a range of human Adenovirus (Ad)-transformed rodent cell lines, in hamster tumours induced by Ad-transformed cells and in cells derived from such tumours. Results obtained show that cellular transformation by highly oncogenic Ad12 completely abrogates expression of class I MHC genes, whereas transformation by non-oncogenic Ad2 or Ad5 results in no significant reduction of class I expression.

Since co-recognition of viral antigen and self-MHC determinants is required for attack by cytotoxic T lymphocytes, this modulation of MHC gene expression may allow tumour cells to evade immune surveillance in the host. A very low level of class I mRNA was found in Ad12-induced hamster tumours. Interestingly, in hamster tumours induced by Ad5-transformed cells, relatively high levels of class I mRNA were detected in actively growing solid tumours.

Studies on the levels of nuclear class I pre-mRNA and on the mechanism of transcription of class I genes in Ad-transformed cells have also been performed.

ASSOCIATION OF DIET AND SEX HORMONES IN RELATION TO BREAST CANCER

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Earlier studies indicate that dietary fiber intake correlates negatively and fat intake positively with plasma estrone and estradiol (E2) levels in young women. Decreasing fat intake lowers plasma testosterone (T), free T(FT) and percentage FT in men. We have studied 27 postmenopausal women [9 vegetarians (VG), 10 omnivores (OG) and 8 healthy women with surgically removed breast cancer (BC)] 4 times during one year, with intervals of about 18 weeks. Each time, diet was recorded during 3 days and blood samples were drawn on all 3 days. Analysis of variance showed statistically significant differenes between the groups for androstenedione (A), T, % FT, FT, % FE2 and sex hormone binding globulin binding capacity (SHBG). High protein and fat and low grain, carbohydrate, total and grain fiber intake were associated with high A, T, % FT, FT and % FE2 and low SHBG. All parameters showed this pattern in BC, but only two, SHBG and % FE2, differed significantly between BC, and OG and VG (non-paired t-test), the other differing significantly only from those of VG. It is concluded that a "Western type diet" is associated with high % FT and % FE2 and low SHBG and thus probably increases BC risk and risk for other sex hormone dependent cancers.

CORRELATIONS BETWEEN URINARY EXCRETION OF LIGNANS AND PHYTOESTROGENS AND PLASMA NON-PROTEIN BOUND SEX HORMONES AND SEX HORMONE BINDING GLOBULIN.

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During the last 7 years a number of biologically active compounds, belonging to the classes of lignans (Ligs) and isoflavonic phytoestrogens (Ph-ES), have been identified in human urine. These hormone-like compounds are products of intestinal bacterial action on dietary precursors. Urinary excretion of Ligs is particularly low in postmenopausal (pmp) breast cancer patients (BC) and correlates with fiber intake. It has been shown that the Ph-Es and Ligs are both estrogenic and antiestrogenic. Some are also moderate aromatase inhibitors. In the present study, the excretion of 2 Ligs and 3 Ph-Es was determined in the urine of 34 young women, including BC and in 20 pmp women. Preliminary results indicate that the lowest mean excretion of these compounds occur in BC and the highest in vegetarians. Positive correlations were found between urinary excretion of the lignan enterolactone, total Ligs and Ligs+Ph-Es, and fiber intake and plasma SHBG, and negative correlations with percentage free (F) estradiol (E2), FE2 and free testosterone ($p<0.05-<0.001$). It is concluded that intake of a fiber-rich food is associated with low non-protein bound sex hormone levels, probably due to stimulation of SHBG synthesis in the liver by these weak estrogens, entering portal circulation from the intestine.

ANTI-COLLAGENOLYTIC ACTIVITY OF TAMOXIFEN ON HUMAN K 562 CELLS

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Collagenolytic activity has been demonstrated in the human leukaemic cell line K 562 by employing Macartney's fluorescamine technique (FEBS Lett. 119: 327,1980) with fibrillar collagen I as substrate. The enzymes are either free or membrane bound and the total activity is 0.60 ± 0.06 mU/10^6 cells. Main enzymatic parameters including optimum pH, Ca-dependence, trypsin activation have been defined. Among various effectors studied, tamoxifen (Txf), a well-known antiestrogenic compound, exhibited a strong inhibitory effect. After 3 days of culture in the presence of 10^{-7}M of Txf, 75% of the collagenolytic activity was inhibited. Hydroxy-Txf and N-demethyl-Txf are equally potent inhibitors though devoid of any direct cytotoxic effect.

K 562 cells have no binding sites for estrogens but they possess high affinity membrane-bound binding sites for H-Txf (31 femtomoles/mg protein). These findings have been evaluated with respect to their significance in the prevention of metastases.

KINETICS OF HYDROLYSIS OF NORNITROGEN MUSTARD, A METABOLITE OF PHOSPHORAMIDE MUSTARD AND CYCLOPHOSPHAMIDE

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Nornitrogen mustard (NOR) and phosphoramide mustard (PAM) are important metabolites of cyclophosphamide. A gas chromatographic (GC) method was developed