susceptibility to cancer by Krontiris et al (Nature, 313: 6369, 1985). We studied the DNA from normal leukocytes of a group of fifty melanoma patients and of fifty healthy individuals and failed to find any significant association between melanoma and rare alleles defined by MspI/HpaII digestion. We have recently described a new polymorphism in the VTR region of H-ras-1 based on the presence of additional TaqI restriction sites (Pierotti et al, Nucleic Acid Research, 14: 4379, 1986). Digesting our DNA samples with TaqI, we observed that the frequency of the allelic variant containing TaqI restriction sites within the VTR region was three fold higher in melanoma patients than in unaffected individuals.

EXPRESSION OF THE c-Ha-ras GENE IN DMBA-INDUCED RAT MAMMARY TUMOURS TREATED WITH A NOVEL ANTIESTROGEN COMPOUND TOREMIFENE

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Rat mammary tumours were induced by DMBA in 8 week-old female Sprague-Dawley rats. The tumours were allowed to develop for approximately 8 weeks whereafter toremifene treatment (15 mg/kg daily) was initiated. Control rats were exposed similarly to DMBA but did not receive toremifene. Total RNA was isolated from 6 control tumours, 8 hormone-independent, and 10 hormone-dependent tumours. Total RNA was also isolated from the liver and uterus of control rats. The expression of c-Ha-ras gene was studied by Northern blot analysis using BS-9 probe (a clone specific for rat Ha-ras oncogene). The following conclusions were made: (1)The amount of Ha-rasmRNA did not differ significantly between the control group and the tumours insensitive to toremifene treatment. (2)In hormone sensitive tumours the expression of Ha-ras was reduced by approximately 40% when compared to the two other groups. (3)The amount of Ha-ras mRNA in liver was of the same order to magnitude as that in hormone dependent tumours whereas in the uterus the expression was somewhat lower.

NUCLEAR UPTAKE OF NGF, EGF, PDGF AND INSULIN, BINDING TO CHROMATIN RECEPTORS IN TUMOUR CELL LINES

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The mechanism of action of growth factors is unclear,although interaction with the surface receptors and internalization are generally accepted. We have found that NGF, EGF, PDGF and insulin, taken up by cells bearing appropriate surface receptors, are tightly and specifically bound to chromatin. All growth factors tested have been isolated from chromatin as non-degraded. Binding of growth factors to the isolated chromatin has been inhibited by MAbs directed against the surface receptor. NGF chromatin receptor has been immunoprecipitated by MAb 20.4 from Eco RI-digested chromatin of melanoma HS 294 (230 kd), proliferating in the presence of TPA melanocytes (230 kD) and colorectal SW 707 cells (35 kd).

MAb 425, anti-EGF receptor has been taken up and incorporated into the chromatin of A 431, SW 948 and WI 38 cells, while another MAb, Br 15-6A only in SW 948 cells. Chromatin binding of anti-EGF receptor antibodies seems to explain an agonistic or antagonistic effect on growth factors of some antibodies through direct action on gene regulation. We suggest that chromatin receptors for growth factors may be of special importance for intracellular activation of autonomic growth of tumour cells.

A 3T3-CELL DERIVED FACTOR TRIGGERS THE RELEASE OF A SELF MITOGEN FROM FcγRECEPTOR EXPRESSING T CELLS

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We tested the possibility of a proliferative response of Fcγ receptor (FcγR) expressing T cells to signal emitted by precancerous or cancerous non-lymphoid cells, as an attempt to explain the observed increase in the number of FcγR T suppressor cells in cancer patients. Hypotonic cell extracts derived from H-ras transformed and non-transformed NIH 3T3 cells, triggered a mitogenic response of FcγR positive T2D4 hybridoma T cells, originating from density arrested cultures. Kinetic studies indicated that the 3T3 cell derived factor (3T3-F) triggers the release of a self autocrine growth factor from the T2D4 target cells. While 60 to 120 min were required for a proliferative response to T2D4 cells to the signal emitted by 3T3-F, supernatants

of T2D4 cells exposed to the 3T3-F were capable of transmitting the proliferative signal to naive T2D4 cells, within 15 min. The possibility of a relationship between the fast acting mitogen (FAM) in the T2D4 supernatants and immunoglobulin binding factor (IBF) was tested. IBF is a soluble form of FcR, released by T2D4 cells, with culture conditions similar to those allowing the release of FAM. Indeed, the exposure of T2D4 cells to the 3T3-F enhanced the release of IBF, shown to be acting as a self mitogen.

DEVELOPMENT OF NON-TUMOURIGENIC HUMAN MESOTHELIAL CELL LINES WITH TRANSFECTED SV40 LARGE T ANTIGEN GENE

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Human mesothelial cells were obtained from pleural effusions or ascites fluids of patients with non-malignant conditions, and transfected with a plasmid, pRSV-T, containing the SV40 large T antigen gene and the Rous sarcoma virus long terminal repeat. Colonies of morhologically transformed cells occurred with a frequency of 1 to 2 x 10^{-4} transfected cells; transformed cells were not seen in control cultures. Individual colonies were isolated and cultured. These cells retained electron microscopic features of mesothelial cells, and all expressed keratin, vimentin and SV40 T antigen as detected by indirect immunofluorescence. The cells were aneuploid but most had near-diploid chromosome counts. For all cultures studied, the time to senescence was extended (60 to 70 population doublings (PD), 140 days) compared to normal mesothelial cells (15 PD, 30 days). For at least one culture, cells have escaped senescence and appear to be immortalized. Injection of 5 x 10^6 cells per site into nude mice has yielded no tumours after 6 to 12 months. Experiments are in progress to determine the response of these cells to asbestos and to transfection by other oncogenes and growth factor genes.

PHOSPHORYLATION OF L-TYPE PHOSPHOFRUCTO-KINASE IN HUMAN GLIOMAS

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The activity of the enzyme phosphofructokinase was decreased in human gliomas in comparison to normal brain. This decrease was accompanied by a relative increase in the expression of the L-type subunit of the enzyme. In addition, this particular subunit could be phosphorylated, most probably by a cAMP-independent protein kinase. This phosphorylation could not be detected in normal brain. The tumour enzyme appeared to be less sensitive to citrate inhibition and, more importantly, more sensitive to the activation by fructose--2,6-bisphosphate. The enzymes from tumour and normal brain showed no significant differences in their affinity towards the substrate fructose-6-phosphate. The results suggest an altered regulation of glycolysis in human gliomas by a reversible, cAMP-independent phosphorylation of phosphofructokinase.

DNA ADDUCTS IN MOUSE AND RAT EPIDERMIS VERSUS DERMIS AFTER TOPICAL APPLICATION OF (±)-TRANS7β,8α,-DIHYDROXY-9α,10α,-EPOXY-7, 8,9,10- TETRAHYDROBENZO(a)PYRENE AND (±) BENZO(a)PYRENE- 4.5-OXIDE

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Mice and rats were treated topically with the BP metabolites, (±)-7β,8α,-dihydroxy-9α,10α,-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (anti-BPDE) and (±) benzo(a)pyrene-4,5-oxide (BPO). Rat epidermal DNA was extensively modified by BPO, while mouse epidermal DNA was preferentially modified by anti-BPDE. Anti-dGuo adducts were observed only in mouse dermal DNA. DNA adducts were absent from the rat dermis. This adduct formation could produce the significantly different biological effects observed in vivo in the two species.

BREAST CANCER RISK FACTORS IN FINLAND AND THE UNITED STATES

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Breast cancer (BC) incidence is lower in Finland than in the United States, yet both popoulations have the same high dietary fat intake, a suspected risk factor for this tumour. To explore this discrepancy, other potential risk modifiers were compared in 286 healthy women and 124 BC patients in New York (NY) , and 163 healthy controls and 106