VBR 18

THE IMPORTANCE OF LOW PLASMA CEA VALUES IN HEALTHY SMOKERS FOR THE SENSITIVITY OF CEA ASSAYS IN TUMOR PATIENTS

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Application of monoclonal antibodies for plasma CEA immunoassays enable further improvement of epitope specificity. As a result, an increased sensitivity for oncologic patients might be achieved compared to immunoassays in which polyclonal antibodies are used. It was, however, observed that the monoclonal antibody assays did not differ significantly from the former polyclonal CEA assays. Recent introduction of a new monoclonal CEA test applying three monoclonal antibodies (Pharmacia RIA, test prototype) seems to have significantly changed the present standard of diagnostic quality.
Three poly- and eight monoclonal CEA immunoassays were used simultaneously to determine the plasma levels in healthy individuals (n=149; 74 smokers and 75 non-smokers) and tumor patients (n=92). The results as per assay were transformed into inverse distribution curves and receiver operator characteristic (ROC) curves to determine sensitivity and specificity of the assays.
Only one of the monoclonal CEA tests showed a superior sensitivity compared to all the other tests. Further analysis of our data revealed that the improvement of discrimination was not due to increased sensitivity for tumor patients but to better specificity in the control group. The antibodies applied did not lead to as many elevated CEA values for smokers as those of the other tests. With the monoclonal CEA-MARIA test prototype from Pharmacia we found a 100% increase of sensitivity compared to the other CEA test kits. This result shows that exclusion of "false positive" CEA values in the control group is important for increasing the discriminating power of a tumor marker assay.

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VBR 19

DEMONSTRATION OF CARCINOGENIC AND MUTAGENIC ACTIVITY OF AIRBORNE PARTICULATES (CITY SMOG) FROM POLLUTED AREA USING HUMAN AND RODENT TISSUE CULTURE CELLS

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Sample of city smog (No. 18) was collected in the Rhine-Ruhr-area, extracted by cyclohexane and the global extract (GEX) was quantitatively transferred to dimethylsulfoxide(DMSO) for tissue culture experiments.
Extract of city smog No. 18 induced in a dose-dependent manner an increase of "sister chromatid exchanges" in human lymphocyte cultures. It is remarkable that amounts of substances found in 1 cbm of air were already effective. Similar results were obtained using the Chinese hamster lung cell line V 79.
"Point mutations" at the HGPRT-locus induced by global extract in exposed cultures of V 79 cells were demonstrable by appearance of 8-azaguanine resistant mutants. Mutants were induced with concentrations of global extract equivalent to amounts of substances from 4 and 8 cbm of air, respectively.
In cell transformation experiments logarithmically growing cultures of Syrian hamster kidney cells were exposed to various concentrations of global extract and after 18 hours infected with SV-40 (MOI 500 ID50).
A dose-dependent increase of malignant cell transformation was observed. Already small amounts of global extract, equivalent to air volumes of 0,5 - 1 cbm led to a significant "enhancement" of cell transformation.

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VBR 20

HISTOGENESIS OF THE BRONCHIOLO/ALVEOLAR CARCINOMA RESULTING FROM MODIFICATION OF N-NITROSO-DI-N-BUTYLAMINE ORGANOTROPISM BY DISULFIRAM

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N-Nitroso-di-n-butylamine induces tumors of the esophagus, liver and bladder in the rat. Earlier investigations revealed that the respiratory system is also a target organ for the carcinogen when it is applied concomitantly with disulfiram. In the present study, N-nitroso-di-n-butylamine (750 mg/l drinking water) and disulfiram (200 mg/kg diet) were applied to 244 female SIV 50 rats. The stages of development of the resulting bronchiolo/alveolar carcinoma were studied using lightmicroscopy, transmission- and scanning- electron microscopy. The initial alteration after the onset of exposition is focal lipoproteinosis in the vicinity of interstitial vessels. This alteration may be interpreted as a toxic-degenerative lesion of previous studies of the metabolism of the present carcinogen constituting a proliferative stimulus. In the second stage Type II pneumocytes proliferate within, or at the periphery of the lipoproteinosis foci. In the third stage such sites of "bronchiolo/alveolar" hyperplasia increasingly reveal destruction of the alveolar architecture, transformation to adenomas and adenocarcinomas.
The modification of the carcinogenic effect of nitrosamines by xenobiotics and thereby induction of tumor in the respiratory tract by previously "unsuspected" carcinogens appears to be of great significance. The relevance of such effects is particularly evident when disulfiram is combined with the above carcinogen. In addition to use of disulfiram in the treatment of chronic alcoholism, large amounts of the compound are employed as an accelerator in the rubber industry.

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VBR 21

AMPLIFICATION AND EXPRESSION OF PROTO-ONCOGENES IN SMALL CELL LUNG CANCER CELL LINES (SCLC)

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Proto-oncogenes are normal cellular genes, highly conserved in evolution, which were found because of their relationship to transforming oncogenes in retroviruses. These parts of retroviral genomes can cause a malignant transformation in some in vitro systems and may play a role in the induction of tumors in several animal species. In many human tumors these proto-oncogenes are mutated or expressed on a higher level than in normal cells (Slamon et al. Science 224, 256, 1984). Despite these findings, still no conclusive proofs exist that proto-oncogenes are a necessary or even a sufficient condition for the induction and/or the maintenance of malignant transformation (Duesberg Science 288, 669, 1985). In order to study the role of some oncogenes in small cell lung cancer, we examined five SCLC cell lines in comparison to two acute myelogenous leukemia cell lines for DNA amplification and elevated levels of expression of oncogenes.

Cell lines	PDT (hr)	myc DNA	myc RNA	myb DNA	myb RNA	fos DNA	fos RNA	N-ras DNA	N-ras RNA	Ki-ras DNA	Ki-ras RNA	Ha-ras DNA	raf DNA	raf RNA	fms RNA
SCLC-16H	65	++++	++++	++	+	+++	++	-	+++	+	-	+	+	+	+++
SCLC-22H	75	++	++++	+	+	+	+	+	++	+	-	+	+	+	+
NCI-H82	45	++++	+++	+++	++++	+++	++	+	+++	+	+	+	+	++	+
NCI-H417	40	++++	++	+	+	+	+	+	++	+	+	+	+	+++	+++
NCI-H526	65	++	+	++++	++++	+	+	+	+++	+	+	+	+	+	+
HL 60		++	++++	++	+	+	+	+	+	+	+	+	+	+	+
K6 1		++	+++	++	+	+	+	+	+	+	+	+	+	+	n.d.

The quantification of RNA and DNA specific for oncogenes was determined by dot-blot and Southern-blot techniques. Our results suggest that a large number of proto-oncogenes seem to be amplified and expressed at high levels in SCLC. An apparent proto-oncogene pattern for SCLC, however, does not seem to exist. Whether high levels of proto-oncogene expression or amplification are associated with the malignant behaviour of tumor cells (here indicated by the population doubling time) cannot be decided yet due to the small number of cell lines up to date.

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