yet been accomplished.

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IDENTIFICATION OF HUMAN UROTHELIAL CELLS PROPAGATED IN CULTURE

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Cell lines derived from non-malignant and malignant human urothelium have been established. These cell lines have a human karyotype, express keratin and react with monoclonal antibodies against either normal urothelium or bladder tumour associated antigens. The human and epithelial origin of these cell lines was further confirmed by studies of species specific isozymes, by electron microscopy and by tumour histology. Based on life-span in culture, tumourigenicity in nude mice, the cell lines have been classified into three diffeent categories of transformed cells. Ongoing research aims at characterizing the cell lines with respect to isozyme phenotype and karyotype. These characteristics will be compared with the tissue-type of the cell lines in order to evaluate the value of isozyme phenotyping and chromosomal characteristics as methods for the identification of established cell lines.

ACTIVATION OF THE ras-GENE: TRUNCATION INSTEAD OF POINT MUTATION

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Identically to the transforming cellular ras genes detected by gene transfer assay in 3T3 cells, Harvey-ras in Harvey sarcoma virus and Balb sarcoma virus is thought to be activated by point mutations at codon 12 (Balb SV), or 12 and 59 (HaSV) of the transforming protein p21. To test this hypothesis, we have exchanged parts of viral ras containing codons 12, or codons 12 and 59, or the complete coding region with the corresponding regions of normal rat proto-ras 2 or proto-ras 1 respectively. Viruses generated from the proviral clones all showed efficient transforming function in vitro and in vivo. Sequence comparison between normal and viral Harvey-ras genes revealed a previously undetected 5' exon termed exon (-1) that is contained in normal proto-ras but is always truncated in transforming viral ras genes. Because of the uncertainty of the 5' ends of ras, transforming cellular ras genes are also possibly truncated. We conclude that point mutations are not necessary for the transforming function of ras and propose that truncation of the normal gene activates the Harvey-ras gene. We have reisolated a few of the recombinant viruses and have obtained sequence data. The transforming function of new recombinant viruses containing upstream sequences of proto-ras which are truncated in the wild type virus has been investigated.

INDUCTION OF THE AROMATIC HYDROCARBON (AH) RECEPTOR AND OF DRUG METABOLIZING ENZYMES BY VARIOUS AROMATIC AMINES IN RAT LIVER

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The aromatic amines 2-acetylaminofluorene (AAF), transacetylaminostilbene (AAS) and 2-acetylaminophenanthrene (AAP) have different carcinogenic properties in rat liver. Only AAF is a complete carcinogen and exerts promoting effects. These have not yet been defined on a molecular basis. We have now studied interactions with the Ah receptor which has been suggested to play a role in promotion. The amines (100 µmol/kg, AAS 20 µmol/kg) and 3-methylcholanthrene (MC) as a control were administered by intraperitoneal injection into female Wistar rats daily for 5 days, for induction of ornithine decarboxylase (ODC) for one day. In addition to ODC activity and the hepatic Ah receptor level, the activity of Ah receptor controlled drug metabolizing enzymes and of microsomal epoxide hydrolase (EHm) were determined. All amines tested induced ODC in rat liver. The time course of this induction differed. AAs increased both the hepatic Ah receptor level and EHm 2-fold. AAF and AAP stimulated ethoxyresorufin-O-deethylase activity maximally by 4.2-fold, which is a small effect in comparison to the 80-fold increase by MC. The results indicate that AAF and AAP, but not AAS, may interact with the Ah receptor in vivo. AAS, however leads to other specific biological responses.

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