TRANSFORMING GENES OF RETROVIRUSES AND HUMAN CANCER CELLS
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An approach towards understanding mechanisms involved in processes leading to malignancy has come from studies of acute transforming retroviruses. These viruses have arisen in nature by recombination of replication-competent type C RNA viruses with a limited set of evolutionarily well-conserved cellular genes. When incorporated within the retrovirus genome, such transduced cellular (onc) sequences acquire transforming properties. To investigate the role of onc-related genes in human cancer, we have utilized molecular cloning techniques to isolate the human cellular homologues of retroviral onc genes. These genes are often actively transcribed in human tumour cells. We have mapped the chromosomal locations of onc-related genes in human cells and shown that in some cases such genes are involved in highly specific translocations associated with certain cancers. Using DNA-mediated gene transfer techniques, transforming genes, or oncogenes, have been detected in human tumours and tumour cell lines. By transfection analysis we have detected three distinct but related oncogenes in tumours of many tissue types. These oncogenes are also related to the onc genes of a small family of acute transforming retroviruses comprised of BALB, Harvey and Kirsten murine sarcoma viruses. Thus, our findings potentially link a small group of retroviral onc related genes in processes that can lead normal human cells toward malignancy.

ABSENCE OF ADAPTIVE RESPONSE TO ALKYLATING AGENTS IN V79 CHINESE HAMSTER CELLS.
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Numerous observations support the hypothesis that alkylation of the O^6-position of guanine may be a significant lesion in both mutagenesis and carcinogenesis. The finding that a repair pathway, specific for this lesion, is induced in bacteria by low doses of alkylating agents raised the question of whether pre-exposure to low doses also protects mammalian cells against genetic and carcinogenic injuries.

Despite negative biochemical evidence for such an adaptive response in Chinese hamster cells(1), decreased cytotoxicity and mutagenicity in V79 and CHO cells pre-exposed to low levels of methylating agents has been reported(2). In contrast to these reports, we present data showing that pre-treatment with both methylating and ethylating agents does not protect V79 cells against the lethal and mutagenic effects of higher doses of the same agents. In fact, with some induction protocols, the genetic effects are even enhanced, possibly due to saturation of the constitutive level of O^6-methyltransferase.

1) Waldestein, E.A. et al., Proc.Nat.Acad.Sci. USA, 79, 5117, 1982
2) Samson, L. and J.L. Schwartz, Nature, 287, 861, 1980; Kaina, B., Mut.Res.93,195,1982.

EXCISION OF BENZO(a) PYRENE-DIOL-EPOXIDE-DNA ADDUCT IN RAT SKIN.
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Early attempts have shown the rat skin epidermis to be resistant to benzo(a) pyrene (BP) carcinogenesis. The persistence of BP bound adducts to DNA is related to carcinogenesis in mouse epidermis. The important question remains: what is the fate of these adducts in the epidermis of species resistant to BP tumourogenesis? (^{3}H)BP (2.5 Ci/mmole) was applied topically (1 µMole in 200 µl per rat) to the shaved areas (6 x 6 cm) of 10 male WAG rats in resting phase. One group of rats was killed at 18 hr and the other 3 weeks after treatment and the epidermis was removed. The epidermal DNA was isolated, enzymatically degraded and modified deoxyribonucleosides determined by HPLC. At the 18 hr end-point, the (+) anti-BP diol epoxide was the major adduct from the total methanol soluble material. 9-OH-BP-4,5-oxide-DNA ($\pm$) syn-BPDE,($\pm$) anti BPDE-dA and BP-4,5-oxide-DNA were also observed. Very slight radioactivity was present in modified deoxyribonucleoside sample after 3 weeks (~0.01 pMoles/mg DNA or 0.1% of the level observed at 18 hr). In comparison with mouse epidermis (~5%, Cancer Letters 16 247-251 1982), rat epidermis shows 50 times greater excision rate. The disappearance of BP-DNA adduct formation from rat epidermal DNA 3 weeks after application of BP appears to correlate with the relative resistance to tumourogenesis of rat skin.