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MOLECULAR ANALYSIS OF THE ONCOGENE V-HA-RAS.

Berthe Marie Willumsen, Mikrobiologisk Institut, Københavns Universitet, Øster Farimagsgade 2A, 1353 K.

The gene c-Ha-ras has been shown to be involved in the etiology of 10 - 15 % of human cancers; involved in the sense that the genetic material of the tumor cells have a transforming version of the gene. The gene becomes transforming by mutations, such that when the activated gene is transferred to non-tumorigenic cells, they become tumorigenic. The transforming gene was first found on a sarcomagenic mouse virus, Harvey sarcoma virus (the v-Ha-ras gene).

One approach to understand the mechanisms that change cells from a normal to a transformed state is to analyze the biochemical and biological differences between normal and activated oncogenes, as well as determining which components of the cell interact with the oncogene products.

Using molecular genetics I have, in collaboration with Dr. D. Lowy at the National Cancer Institute, defined the portions of the protein encoded by the v-Ha-ras gene that are necessary for its biological functions as well as for its biochemical activities. Using this information, we have developed assays that attempt to measure the normal function of the gene as well as constructed mutants that can aid in elucidating the function of the normal protein.

We (and others) conclude that the activated protein is locked in an exited state which transmits signals to the cell nucleus that cell division is to occur. A large part of the normal protein is devoted to, in a controlled, physiological manner, bring the protein into and out of the exited state that the transforming versions display. We have defined the part of the protein which anchors the protein at the plasma membrane, as well as the part which is involved in the interaction with the molecule(s) which result in the growth signal transduction.

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COMBINED HIGH-DOSE CARBO- AND CISPLATIN IN OVARIAN CANCER PATIENTS. B. Lund, M. Hansen, O. P. Hansen, H. H. Hansen. The Finsen Institute, Bispebjerg Hospital, Copenhagen, Frederiksborg Hospital, Hillerød, Denmark.

Carbo- (C) and Cisplatin (P) are both highly active agents in ovarian carcinoma (OC). Their different toxicity makes a combination feasible, and thus also the administration of a higher total dose of platin. Between 01.02.-01.11.1987 37 previously untreated patients (pts.) with residual disease of epithelial OC were treated with C 300 mg/m² i.v. day 1 and P 50 mg/m² i.v. day 2 and 3 q 4 weeks. Second-look laparotomy was performed after 6 cycles. Patient characteristics: Median age: 56 years; FIGO stage IIB: 4 pts., IIIA: 3, IIIB: 3, IIIC: 19, IV: 8; clinically evaluable: 22 pts. vs 15 non-evaluable. A total of 183 cycles was given. Preliminary clinical response rates: CR + PR: 14/23 = 61% (CR = 43%). Pathological response rates: PCR + PPR: 10/19 = 53% (PCR = 26%). 5 pts. have died, 4 due to PD, and 1 early death. Gastrointestinal toxicity grade 2-3 was seen in 53% of the pts., hairloss grade 1 in 77%. Paraeesthesias developed in 27%; nephrotoxicity occurred in 32% with a decrease of 51Cr-EDTA-clearance of in median 33%(10-75%) below normal values; ototoxicity in 48%. Hematological toxicity grade 3-4 developed in 21%: Hgb, 38%; WBC, 74%; platelets. In median 90% C (66-125%) and 94% P (0-125%) was given in the 3rd cycle, 67% C (33-150%) and 67% P (0-150%) in the 6th cycle. In conclusion high-dose carbo- and cisplatin is highly active, and the toxicity is manageable.

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A COMPUTER PROGRAM FOR DETERMINATION OF MEAN GROWTH CURVES AND CALCULATION OF RESPONSE TO THERAPY OF SOLID TUMOR XENOGRAFTS.

Kåre Rygaard & Mogens Spang-Thomsen, University Institute of Pathological Anatomy, Copenhagen Denmark.

From growth recordings of tumor xenografts the "GROWTH" program determines mean growth curves for tumor area, tumor volume, and for a rectilinear growth description according to a transformed Gompertz function. In therapy experiments the response, i.e. growth delay and specific growth delay, is calculated, and in specified pre- and post-therapeutic intervals the volume doubling time and growth rate are determined for the individual treatment groups. Linear regression analysis on growth data of the individual tumors enables statistical comparison of growth curves. All mean growth data of treated and untreated tumors are presented graphically. GROWTH was designed in the Lotus Symphony(R) spreadsheet and is easily operated by a menu system. The necessary prerequisites for using GROWTH are an IBM PC/PS2 or compatible, the Lotus Symphony(R) program, and a basic knowledge of how to use Symphony(R). GROWTH can be obtained on request for a handling fee.

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THE DANISH CASE-CONTROL STUDY OF SKIN MELANOMA - IMPORTANCE OF SUN EXPOSURE

A. Østerlind
Danish Cancer Registry, Copenhagen, Denmark.

The aim of this study is to identify risk factors in the causation of cutaneous malignant melanoma and this presentation focus on the importance of sun exposure.

All incident cases of skin melanoma, excluding lentigo maligna melanoma, diagnosed from October 1st, 1982 to March 31st, 1985, were identified in the Danish Cancer Registry. Of the eligible cases, 474 of 516 (92%) were interviewed. Sex and age stratified controls were selected at random from the same population, drawn from the National Populations Register. Response rate among the controls was 82%.

Sunbathing is associated with a relative risk (RR) of 1.7 (95% C.I.; 1.2-2.6), after controlling for major host factors. There is a clear association between multiple sunburns in childhood (age < 15), while sunburns in adult life were less important. A significant dose-response relationship is found (p < 0.001) with the risk associated with > 5 sunburns rising to 2.7. Various leisure time activities were investigated. Only boating and skiing resulted in significant increased risks. Constant sun exposure due to work outside in summer was associated with a decrease in risk in men, RR = 0.7 (95% C.I., 0.50.9).

In conclusion, our results suggest that short-term exposure to intense sunlight increases the risk of melanoma while constant exposure seems to protect against melanoma development.