35

THE PHORBOL ESTER, PMA, INCREASES CELLULAR LEVELS OF mRNA CODING FOR PLASMINOGEN ACTIVATOR INHIBITOR TYPE-1 (PAI-1) IN HUMAN NEOPLASTIC CELLS.

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Phorbol 12-myristate 13-acetate (PMA) which induces differentiation in HL-60 promyelocytic and U937 monocytic cell lines, caused a significant increase in PAI-1 protein level in the culture medium of these cells. Two other human neoplastic cell lines which do not undergo a PMA-dependent differentiation exhibited a similar stimulation of cellular and secreted PAI-1 level. This effect was transient and occurred at time- and concentration-ranges compatible with other known biological effects of PMA. Phorbols which are not tumor promoters or activators of protein kinase C failed to induce PAI-1. The stimulation was accounted for by an increased steady-state level of PAI-1 specific mRNA. Therefore, increased PAI-1 production is among the pleiotropic effects of tumor-promoting phorbol esters.

36

TUMOR NECROSIS FACTOR α REGULATES COMPONENTS OF THE PLASMINOGEN ACTIVATION SYSTEM IN HUMAN NEOPLASTIC CELL LINES.

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By the use of ELISAs,tumor necrosis factor α (TNFα) was found to cause several fold increases in the medium levels of urokinase-type plasminogen activator (u-PA) and type-1 plasminogen activator inhibitor (PAI-1) in some, but not all, of a number of tested human neoplastic cell lines. Studying the effect on PAI-1 in human HT-1080 fibrosarcoma cells in more detail, it was found that the effect on the medium level was preceded by a corresponding increase in the 3.1 and 2.2 kb PAI-1 mRNAs. In contrast, there was only a slight increase in the intracellular level of PAI-1, suggesting an effect on both the biosynthesis- and the secretion rate. We conclude that TNFα may regulate extracellular proteolysis around neoplastic cells by modulating the production of u-PA and PAI-1.

37

PRECLINICAL ACTIVITY OF THE INDOLOQUINONE EO-9 (NSC 382456) AGAINST HUMAN SMALL CELL LUNG CANCER (SCCL) CELL LINES

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Recently, a series of new indoloquinones, with the ability to act as bioreductive alkylating agents have been synthesized (Tetrahedron 43: 225,87). In the present study the activity was evaluated against 4 SCCL cell lines with clonogenic assay, flow cytometric DNA-analysis (FCM) and in nude mice. In the clonogenic assay, exponential dose-response curves were obtained on two cell lines (Oc-Nyh and Oc-Tol) with both one hour and continuous incubation, whereas only minimal cell kill was obtained with continuous incubation at the highest concentration used (.025ug/ml) in two other cell lines (NCI-N592 and NCI-H69). After exposure to EO-9, FCM showed a dose-dependent accumulation of cells in the S-phase and a concomitant decrease of cells in G_1. Based on the in vitro results, a sensitive and a resistant cell line were selected for testing in nude mice. Treatment with a non-toxic dose of EO-9 (5mq/kg day 1 and 7) caused a significant growth delay in the sensitive cell line whereas insignificant changes were encountered in the resistant cell line. These results suggest that EO-9 is active against SCCL. Furthermore, the results indicate the feasibility of selecting the most sensitive cell line in vitro before testing in vivo.

38

IN VITRO SENSITIVITYTESTING ON A PANEL OF HUMAN SMALL CELL LUNG CANCER (SCCL) CELL LINES FOR OPTIMIZING CHEMOTHERAPY

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A panel of SCCL cell lines has been established for evaluating the potential of in vitro sensitivitytesting by the clonogenic assay in the selection of new drugs or drug combination for improving the therapy of SCCL. Since the sensitivity has been shown to be dependent on the test conditions used, the comparison of ID_{50} values obtained for different drugs in different experiments is without much predictive value. One major application of the system is the comparison of drug analogues in simultaneously performed experiments. In the evaluation of drug combinations the addition of a second drug at a fixed concentration to the dose-response curves will enable the discrimination between antagonistic, additive or synergistic effect. In the selection of drugs for combination-chemotherapy the sensitivity profiles of the panel should be considered and drugs active against different cell lines should be combined.