SUPPRESSION OF NATURAL ANTI-TUMOR MECHANISMS BY TUMOR-PROMOTING AGENTS

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The process of chemical carcinogenesis is considered to proceed in various tissues in at least 2 sequential stages : initiation and/or transformation by solitary carcinogens, producing irreversible tissue alterations, and enhancement of outgrowth of transformed cells by tumor-promoting agents. However, the mechanisms by which solitary carcinogens and tumor promoters lead to oncogenesis are insufficiently defined. In showing that tumor-promoting polyfunctional diterpene derivatives of the tigliane, ingenane and daphnane type prevent the enhancement of natural cytotoxicity in resting macrophages (activation step) and suppress the manifestation of natural cytotoxicity by previously activated macrophages (effector step) and by "Natural Killer" cells, and moreover enhance tumor growth in vivo, the present findings lend support to the concept that tumor promoters function primarily via interference with natural antitumor effector systems. Solitary carcinogens exerted little or no activity in these experimental systems.

ULTRASTRUCTURE OF HUMAN NATURAL KILLER CELLS

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In an effort to better define the morphological characteristics of natural killer (NK) cells, freshly isolated human peripheral blood mononuclear cells (MNC) were depleted of T lymphocytes as well as of phagocytic or plastic-adherent cells. The resultant fractions showed high levels of cytotoxicity to a human hypernephroma cell line (as high as 98 % specific 51-Chromium release at a 4:1 MNC-to-target cell ratio) and, therefore, represented populations enriched for NK activity. In these cultures, MNC adhering to living or glutaraldehyde-fixed tumor cells were assumed to be predominately NK cells and were examined by scanning and transmission electron microscopy. Adherent cells were round (approx. 4 μm dia.) and possessed variable numbers of microvilli. Internally, these cells possessed a large, heterochromatic nucleus (nucleus:cytoplasm ration $>$ 1) and a cytoplasm containing numerous mono- and polyribosomes, a few large mitochondria, an occasional electron-dense granule, a well developed Golgi apparatus and a variable number of clear vesicles near the cell surface. Microvilli of these cells contained only cytosol and were often branched. At areas of NK-tumor cell contact, the target cell's surface was indented by pseudopodia of the NK cell. Although intimate contact was achieved, an intercellular space of irregular width was always maintained and no focal plasmalemmal alterations such as specialized junctions, membrane fusions or deletions were observed. Furthermore, the cytoplasm within the NK cells' pseudopodia did not differ significantly from the cytoplasm in the remainder of the cell. Intercellular contacts were similar irrespective of whether the tumor cell was viable or glutaraldehyde-fixed. Thus while we can now define the essential morphology of cells which in all probability are natural killer cells, the structural basis of NK-mediated cytotoxicity remains unclear. The mechanism appears to involve no alteration of the component plasmalemmas of either cell or the release of lysosomal enzymes by NK cells at the zones of contact.

IN VITRO SENSITIVITY OF HUMAN TUMOR CELLS TO SPONTANEOUS CELL MEDIATED CYTOTOXICITY (SCMC)

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The correlation between in vitro sensitivity of tumor cell lines to spontaneous cell mediated cytotoxicity (SCMC) or natural killer activity (NK) and in vivo tumor formation in transplantation experiments in mice indicates that SCMC might be involved in the early stages of tumor development. Whereas the effector mechanisms of SCMC were extensively analysed, few data exist on susceptibility of uncultured human tumor target cells from different origin.
In a short term 51-Cr release assay we tested freshly seperated, shortly incubated as well as frozen tumor cells from the same patients with hematologic neoplasia and solid tumors for their susceptibility to NK-lysis from healthy unprimed donors with a high lytic capacity. Solid tumors were separated by enzyme treatment avoiding