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SYNERGISTIC INTERACTION OF RETINOIDS AND INTERFERONS IN BREAST CANCER.

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Combination of all-trans-retinoic acid (RA) with either interferon (IFN)-α or -γ results in a synergistic amplification of the anti-proliferative effect on cultured breast cancer cells. RA could be replaced by other biologically active retinoids. The synergism is also observed for the induction of 2'-5'-oligoadenylate synthetase, an enzyme which is involved in anti-viral activity of interferons and possibly in growth regulation of tumor cells. Comparing all-trans- with 9-cis-RA, the latter is more effective inhibiting tumor cell growth and in inducing synergism with IFN-γ. IFN-γ increases retinoic acid receptor-γ (RAR-γ) expression but had no influence on RAR-α, whereas RAR-β was not detectable in any of the examined breast cancer cell lines. RA-mediated increase of the cellular retinoic acid receptor binding protein-II (CRABP-II) was suppressed by IFN-γ. This observation indicates that IFN-γ-mediated increase in RAR-γ and suppression of RA-mediated CRABP-II activation may play a role in synergistic inhibition of proliferation in breast cancer cell lines.

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EFFECTIVE IL-2 THERAPY

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Locoregional cancer treatment with IL-2 induces good therapeutic effects without the toxicities associated with systemic application. We report on the following aspects:
I. PROTOCOL: Intra/peritumoral application of IL-2 is most effective in the dose range of 7,000-33,000 IU/day, injected for 5 consecutive days.
II. SENSITIVE TUMOUR TYPES: This therapy induced cures/complete remissions in mice with breast cancer, lymphosarcoma, fibrosarcoma, mastocytoma; rats with bladder carcinoma; guinea pigs with liver carcinoma; cattle with spontaneous ocular squamous cell carcinoma (OCC); horses with spontaneous sarcoids; human patients with T1/G1G2 marker lesions of superficial bladder carcinoma.
III. POTENCY OF IL-2 THERAPY: This therapy induces cures in mice with severely infiltrated and metastasized lymphosarcoma comprising at least 5% of the body weight and complete remissions of spontaneous OCC of up to 7 cm^2, and spontaneous sarcoids of up to 20 cm^2 surface in horses.
IV. TREATMENT OF HUMAN CANCER PATIENTS: Guinea pigs with an intracutaneous primary carcinoma and a metastasis in the draining lymph node can be cured by IL-2 treatment of the primary tumour. Cure was impossible after surgical removal of the primary. Probably the same will occur in human cancer patients.

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RECOMBINANT HUMAN ERYTHROPOIETIN-rHuEPO FOR ANEMIC CANCER PATIENTS ON COMBINATION CHEMOTHERAPY

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Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. Anemia in patients with advanced cancer has three features: a mild decrease in red blood cell survival, a decreased re-utilization of bone marrow iron stores and an inadequate erythropoietin (EPO) response to the degree of anemia. The inadequate EPO response to anemia consists of both a decrease in EPO production and a decrease in bone marrow responsiveness to EPO. Two cytokines, interleukin-1 (IL-1) and tumor necrosis factor-α (TNF), appear to play a vital role in this process. IL-1 stimulates T-lymphocytes to produce γ-interferon, whereas TNF stimulates bone marrow stromal cells to produce beta interferon. Both γ and β interferon are potent suppressers of early red cell precursors such as the colony forming unit-erythroid (CFU-E) cell. The erythroid inhibition caused by γ and β interferon can be overcome by the addition of rHuEPO to the culture medium. This observation supports the clinical finding that rHuEPO effectively treat the anemia of chronic disease. Until recently, transfusion has been the only option, but rHuEPO may provide an alternative to transfusion for some anemic cancer patients. Chemotherapy may cause or worsen anemia in patients with cancer. In can exert a direct cytotoxic effect on bone marrow erythroid progenitors and precursors: this mechanism, for example, typically operates in fluorouracil-induced anemia. Cisplatin appears to be peculiar in that this drug can blunt EPO production and cause prolonged anemia. In our trials Eprex (Epoietin-α) has been shown to increase hematocrit and decrease transfusion requirements after the first month of chemotherapy. The patients were randomly assigned to receive 150 U of Eprex per kilogram of body weight or placebo three times weekly by subcutaneous injection, with each dose separated from the next by at least 1 day. Dosing with the study medication was continued for 12 weeks or until hematocrit normalised (reached the target range of 38-40%). After the target hematocrit was attained, Eprex dose could be reduced to maintain the hematocrit at 38-40% for duration of the study. In all chemotherapy groups, there was noted a tendency for anemia to improve with Eprex administration.

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LEUCINE ZIPPER, NUCLEAR TARGETING AND P130 INTERACTION MOTIFS IN THE EPIDERMAL GROWTH FACTOR PRECURSOR: THE NUCLEOCRINE CONNECTION FURTHER UNVEILED

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Previous structural studies have unravelled the possibility of physical interactions between growth factors such as insulin or the insulin-like growth factors (IGF-I,-2) and tumor suppressors such as the retinoblastoma protein (RB) or the RB-related p107 gene product. These findings led to the view that insulin may be rapidly propelled from the extracellular space to the nucleus with the insulin-RB interaction as a direct link to gene expression. This shortcut of insulin has been perceived as the paradigm of a newly defined nucleocrine signal transduction pathway. This pathway encompasses complex formations of growth factors and/or their receptors with tumor suppressors taking place in the cell nucleus as a rule. The purpose of the present study was to ascertain whether there are also other growth factors which potentially enter this signal transduction highway. We first chose to look at the human epidermal growth factor (hEGF) since this molecule had previously been found to associate with nuclear chromatin. In line with the nucleocrine concept, we set out to detect structural hints which would predict an interaction of hEGF or its precursor with a tumor suppressor protein. Interestingly, we found that the complementary peptide for the human EGF precursor (hEGF-P) is similar to several nuclear proteins, most notably to the human p130 protein, an RB-like molecule. This result suggested that hEGF-P has the potential to specifically interact with human p130, thus paralleling the previously predicted complex formations between insulin/IGFs and RB/p107. To further substantiate our finding, we checked the hEGF-P amino acid sequence for structural hints which would indicate a nuclear localization for this molecule since p130, its presumed binding partner, acts in the cell nucleus. We identified in hEGF-P a possible nuclear localization signal (NLS) which is highly related to the NLS of the Tat protein of the human immunodeficiency virus (HIV)-1. Moreover, we found a leucine zipper-like motif and several S/TPXX motifs in hEGF-P suggesting that hEGF-P may be directly involved in nucleic acid binding and thus the control of gene expression. Taken together, this bioinformatics-based analysis of hEGF-P provides both a new perspective on the mechanisms of action of EGF by placing this important growth factor into the nucleocrine context and yet another platform for the design of antineoplastic compounds.