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1007

MECHANISM(S) OF ANTITUMOR EFFECT OF INDOMETHACIN (IMC)

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Previous results have shown that sensitivity of mouse tumors to IMC correlates with ability of tumors to synthesize PGE ex vivo. In these experiments we investigated the mechanisms of antitumor of IMC on a sensitive methylcholantrene-induced tumor. The results obtained so far can be summarized as follows. 1. IMC significantly enhanced the antitumor resistance of suboptimaly immunized mice. 2. The antitumor effect of IMC is significantly higher in normal than in T cell-deficient mice. 3. IMC had no effect on specific antitumor immunity in Winn's assay, but enhanced cytotoxicity of peritoneal macrophages against L929 cells. 4. IMC had no significant influence on growth of tumor cells in vitro. These data show that antitumor effect of IMC in vivo is indirect, i.e. mediated most probably by modulation of host immune antitumor response

1.008

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MHC class II expression and tumorigenicity in ras transformed fibroblasts.

Murine fibroblasts in the absence of cytokines express low or undetectable levels of MHC antigens, but after treatment with IFN-gamma express high levels of class I antigen and often class II also. The introduction of activated ras oncogenes into such cells modulates the induction of class II antigens: in established fibroblast lines (Balb/c 3T3, C3H 10T½) it is inhibited, but in early passage fibroblasts (EPFs; 3 independent lines) it is augmented. EPFs transformed with ras however lose class II inducibility after a few in vitro passages; and class II inducible cells may be back-selected from ras transformed established fibroblasts. The non-inducible cells are clearly more tumorigenic than inducible cells, and upon one or two passages as tumours class II inducibility is lost. The failure to express class II antigens and augmented tumorigenicity may be correlated with TGF-beta production.

1.009

CHANGES OF LYMPHOCYTES SUBSETS AFTER NEOADJUVANT CHEMOTHERAPY FOR HEAD AND NECK CANCERS.

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61 patients received a chemotherapy combining bleomycin, etoposide, cis platinum, fluorouracile and ifosfamide prior to radio-surgical treatment. Significant variations were observed between percentages of lymphocytes subsets analyzed by flow cytometry.In proportion of baseline values, CD4 increased of 15%, CD3+ DR- of 10% and CD3+ DR+ of 24%; B cells decreased of 40% and null cells of 26%. Reduction of tumour burden, amplification of T lymphocytes functions with increase of H/S ratio and fall in percentage of null cells seem to be linked. The possible immunosuppressive effect of neoadjuvant chemotherapy appears limited to B cells population.

1.010

LYMPHOCYTES INFILTRATING MELANOMA METASTASIS: IN VIVO MODULATION DURING SUBCUTANEOUS TREATMENT WITH RECOMBINANT INTERLEUKIN-2 AND INTERFERON ALFA.

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Lymphocytes isolated from a voluminous lymphonodal metastasis of melanoma, have been examined before and after a cycle of subcutaneous treatment with recombinant human interleukin-2 (rIL-2)(CETUS) and interferon alfa 2b (IFN alfa 2b). Surface marker analysis have been carried out on lymphocytes isolated from the metastasis (pre and post therapy)and on peripheral blood lymphocytes (PBL) of the same patient (pre therapy, post pulse, post 1 week of therapy, post 6 weeks of therapy). Subcutaneous treatment of rIL-2 + IFN alfa, totally subverted PBL phenotype, showing,during the 6 weeks of therapy, a remarkable increase of Natural Killer and Cytotoxic/Suppressor populations, to the prejudice of all T Lymphocytes and T Helper. These lymphocyte subsets did not show the same quantitative modifications in the metastasis; instead, there was an evident increase of lymphocytes with low affinity IL-2 receptor and of all T cells. A chromium-51 release cytotoxicity assay was performed using K562 cells and NK resistant IGROV ovarian cancer cells at different effector/target ratios (ranging from 50:1 to 1.5:1). The post-treatment NK and LAK activity in lymphocytes isolated from metastasis was depressed significantly, compared with those produced in PBL. The substantial discordance in percentage of B lymphocytes among the effector cells (lower in PBL), does not justify the difference in cytotoxicity assay results. These preliminary data warrant further investigations to confirm and determine explanations for the decreased cytotoxic activity in lymphocytes infiltrating neoplasm.

1.011

HSPs CAN BE EXPRESSED AT THE SURFACE OF TUMOR CELLS IN ASSOCIATION WITH HLA CLASS I ANTIGENS.

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Heat Shock Proteins (HSPs) are a highly conserved group of proteins constitutively present in the cytoplasm of normal cells and whose synthesis is increased in response to a variety of stimuli, including malignant transformation. It has been suggested that members of HSP families represent the surface target of immune responses leading to tumor rejection in mice. Here we describe that, compared to normal cells, tumor cell lines constitutively expressed higher levels of HSP90 in the cytoplasm;moreover, in the absence of environmental stress, two lines (out of six) expressed the "inducible" HSP72. The protein appeared diffusely distributed in the cytoplasm of most cells,albeit some exibited a nuclear localization. This was possibly due to a cell cycle-regulated expression of HSP72. Heat shock caused an increased synthesis of HSP72 in most tumor cell lines, as well as in normal cells.Conversely, other stress stimuli,such as irradiation and lymphokine treatment,only slightly affected HSP synthesis. It is of note that we could detect both HSP90 and,to a lesser extent,HSP72 at the surface of some tumor cell lines in association with MHC class I products.We conclude that tumor cells differ in their pattern of HSP expression from normal cells and this might be responsable for the induction of an immune response.

1.012

DIFFERENT MIGRATION PATTERNS OF THE MAIN LYMPHOCYTE SUBPOPULATIONS DURING IN VIVO IL2 ADMINISTRATION.

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We have monitored the blood distribution of the main T-lymphocyte subsets and NK cells and their in vitro proliferation and the activation of NK/LAK precursors after 3 day of culture with rIL2 (1000 U/ml).Advanced renal cancer pts. received IL2 (18 MIU/m2/day) in constant i.v. administration for 5 consecutive days.Patients'PBMC were collected before starting the therapy,24 and 96 hrs after the infusion was started and 2 days after the end of the infusion.A dramatic reduction of the in vitro NK/LAK precursors activity is evident after 24 hr of IL2 infusion,while goin on with the infusion and 2 day after the end of the infusion the precursors'activity return to the basal value.Cell proliferation,evaluated after 3 day of in vitro stimulation with lectins,is also reduced during all the infusion time.The lymphopenia induced by the systemic infusion of IL2 is characterized by a marked decrease of the % of CD4+ lymphocytes,while CD8+ cells remain unchanged.Conversely,the % of NK (CD3-CD 56+) cells increases.The lymphocytosis followed from the suspension of IL2 treatment is mainly due to the increase of the % of CD4+ lymphocytes.Most of them are activated cells expressing the CD25 and CD29 surface antigens and belong to the CD45RO subset.These data seem to corroborate the idea of different migration patterns of CD4 and CD8 lymphocytes and NK cells.Finally,we have not observed a strict correlation between the % of peripheral blood NK cells and the in vitro activation of NK/LAK precursors.When a dramatic reduction of the NK/LAK activation is evident the % of the NK cells is like to the basal value,as well as at the end of the infusion cycle, when the % of NK cells is much higher than the basal value,the NK/LAK precursors activity return to the baseline.These data seem to suggest that some inhibitory factors might be released in the serum of the patients submitted to immunotherapy.