

Dendritic Cell as an effective cancer immuno-cell therapy module I. : Anti-tumor effect of cultured DCs in murine leukemia model

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As a potent antigen presenting cells and a powerful inducer of antigen specific immunity including cytotoxic T cell activity, dendritic cells(DCs) are being considered as a promising anti-tumor therapeutic module. Unlike solid tumors, leukemia is the hematologic malignancy involving immune effector cells. The expected usage of DCs in leukemia is the treatment of minimal residual disease(MRD) after the remission or stem cell transplantation . In this study ,syngeneic leukemia cells were inoculated intra-venously into the mouse (WEHI-3 into the Balb/c), and the autologous tumor cell lysate pulsed DCs were injected as a therapeutic module twice in two weeks. To mimic the minimal residual disease (MRD), one day before the first DC injection (3~5 X10⁵ DCs/mouse,i.p.), 5X10⁴ WEHI-3 cells inoculated i.v. Three weeks after final DC injection, the tumor formation and the growth were observed as well as the DC-induced systemic anti-tumor immunity with the splenic lymphocyte. Bone marrow origin mouse myeloid-DCs were cultured with GM-CSF and IL-4 for 7 days and pulsed with leukemic cell lysate (50ug/ml protein , for 18hrs). Compared to the saline treated group, DC or pulsed DC injected group did not make the tumor as observed by gross or microscopic section of tissues. Tumor specific T cell proliferations were significantly increased in DC or pulsed-DC injected group as were measured by CFSE-staining . The proportion of IFN- γ producing CD8+ cells(flow cytometry) and the IFN- γ production(ELISA) were increased significantly in DC treated group .The data indicating the promising anti-leukemic effect of cultured DCs in MRD model by inducing the tumor specific immunity.

[PB4-4] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Immunodulatory activity of betulinic acid from *Lycopus lucidus* in murine macrophage RAW 264.7 cells

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Betulinic acid (BA), a pentacyclic triterpene isolated from *Lycopus lucidus*, has been reported to be a selective inducer of apoptosis in various human tumor cells. It also exhibits anti-inflammatory and immunomodulatory properties. Due to its high level of these activities and lack of toxicity, BA is an attractive and promising compound as a new drug and recently undergoing preclinical development as an immunomodulators. How BA mediates these matters is not known yet. Because of the critical role of the monocytes and tissue macrophages in inflammatory and immune responses, we postulated that BA modulates the activity of its immunomodulatory properties at least two groups of protein mediators of inflammation, Interlukin-1 β (IL-1 β) and the Tumor necrosis factor- α (TNF- α). In this study we investigated the effect of BA on murine macrophage RAW 264.7 cells to activate macrophage at low concentration (2.5 μ g/ml) and induced pro-inflammatory cytokines. The enhanced surface CD40 molecule was expressed on the resting cells at 2.5 μ g/ml of BA or LPS/BA. Furthermore, BA enhanced TNF- α induced apoptosis. Overall, our results indicated that BA induced activation of macrophage and pro-inflammatory cytokines. This may provide a molecular basis for the ability of BA to mediate macrophage, suppress inflammation, and modulate the immune response.

[PB4-5] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

The Effect of allicin on radiation-induced expression of ICAM-1 and activation of JNK and p38 MAP kinase pathway in human endothelial cells.

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Inflammation is a frequent radiation-induced following therapeutic irradiation. Since the upregulation of adhesion molecules on endothelial cell surface has been known to be associated with inflammation, interfering with the expression of adhesion molecules is an important therapeutic target. We examined the effect of allicin, a major component of garlic, on the induction of intercellular adhesion molecule-1 (ICAM-1) by gamma-irradiation and the mechanisms of its effect in gamma-irradiated human umbilical vein endothelial cells (HUVECs). The inhibitory effect of allicin on ICAM-1 expression in gamma-irradiated HUVECs was assessed by ELISA and RT-PCR analysis, respectively. Also, the effects of allicin on transcription factors were determined by electrophoretic mobility shift assay (EMSA). Our data indicated that allicin significantly inhibited the surface expression of ICAM-1 and ICAM mRNA in a dose dependent manner. In EMSA analysis, AP-1 was activated in HUVECs by gamma-irradiation, whereas NF- κ B was not. In addition, treatment with allicin resulted in the decrease of AP-1 activation. The data showed that treatment of JNK and p38 inhibitors were decreased radiation-induced expression of ICAM-1 by Western Blotting. We further investigated the effect of allicin on JNK and p38 MAP Kinase, and demonstrated that ICAM-1 expression induced by gamma irradiation was reduced by allicin in a dose dependant manner. And allicin decreases the level of p-p38 and p-pJNK in gamma-irradiated HUVECs. These results suggest that allicin modulates expression of ICAM-1 via AP-1 dependent pathway in gamma-irradiated HUVECs and has therapeutic potential for the treatment of various inflammatory disorders associated with an increase of endothelial leukocyte adhesion molecules.

[PB4-6] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Enhancing Effect and Action Mechanism of Interleukin-4 Production in Activated T Cells by Phytoestrogens

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Phytoestrogens are naturally occurring compounds derived from plants. Structurally, some phytoestrogens resemble endogenous estrogen of humans and animals. Phytoestrogens exhibit estrogen agonist/antagonist properties and have many biological effects such as prevention of hormone-dependent breast cancer, anti-oxidative activity, inhibition of tyrosine kinase activities and inhibition of angiogenesis. In this study we investigated whether biochanin A, a phytoestrogen, and its metabolites such as genistein, p-ethylphenol and phenolic acid affect IL-4 production in EL-4 thymoma cell-line and primary lymph node cells. Biochanin A, genistein and p-ethylphenol significantly enhanced PMA-stimulated IL-4 production from EL-4 T cells in a dose-dependent manner while phenolic acid did not. This effect was not observed in primary lymph node cells. Biochanin A, genistein and p-ethylphenol induced IL-4 promoter activity in EL-4 T cells transiently transfected with IL-4 gene promoter constructs, but this effect was impaired in EL-4 T cells transfected with an IL-4 promoter construct deleted of P4 site carrying NF-AT and AP-1 binding sites. Furthermore, biochanin A, genistein and p-ethylphenol increased both NF-AT and AP-1 DNA binding activities, as demonstrated by electrophoretic mobility shift assay. The enhancing effects on IL-4 production and NF-AT/AP-1 DNA binding activities were, respectively, abrogated by specific inhibitors for PI3-K, PKC and p38 MAPK, indicating that biochanin A, genistein and p-ethylphenol might enhance IL-4 production by cross-talk between NFAT and AP-1 through PI3K/PKC or PKC/p38 MAPK signaling pathway. These results suggest that phytoestrogens and some their metabolites may increase allergic responses via enhancement of IL-4 production in T cells.

[PB4-7] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

A small carbohydrate fraction from Artemisia Folium suppresses death of the mouse thymocytes in vitro by down-regulating the Fas death receptor gene

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Artemisia Folium is a preparation of dried leaves from Artemisia species and has been used traditionally to prevent or treat various kinds of woman's diseases. A similar preparation called Chinese Moxa has been used to