the production of IFN-γ in tumor environments were evaluated by ELISA and confirmed by RT-PCR.
Using specific inhibitors, we investigated the mechanisms underlying synergistic enhancement of IFN-γ expression in murine macrophage by TNF-α and 3LL. Since TNF-α is sufficient to activate nuclear factor κB (NF-κB) and several mitogen-activated protein kinase (MAPK) pathway, the inhibitor SN50, which specifically blocked NF-κB pathway and the inhibitor SB203580, which specifically inhibited enzymatic activity of cellular p38 MAP Kinase were utilized. Inhibition of p38 MAP Kinase activation abolished 3LL and TNF-α stimulated IFN-γ production for 20 hr treatment, but inhibition of NF-κB did not. In addition, inhibition of JAK-2 activity with the specific inhibitor AG-490 prevented the expression of IFN-γ mRNA for 20 hr treatment. Furthermore, the ability of TNF-α and 3LL to enhance IFN-γ production appears to require new TNF-α stimulated gene expression, because it is blocked by the reversible protein synthesis inhibitor cycloheximide.
Our data suggest that enhancement of IFN-γ production by TNF-α is mediated p38 in early time, and JAK-2 in late time, and TNF-α stimulated IFN-γ production in tumor environment requires new protein synthesis.

[PB4-15] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Functional Importance of TRAF6-Binding Motif in IL-1 Mediated Signal Transduction

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Crystal structure of TRAF6 in complex with TRAF6-binding sites from CD40 was previously determined. The structure revealed a distinct TRAF6-binding groove of CD40, the key structural determinant of interaction. The structural information leads to a proposed TRAF6-binding motif. This allows the identification of TRAF6-binding sequences in the hIRAK protein, whose functional requirement in IL-1 mediated signal transduction is further demonstrated using site-directed mutagenesis. The mutational effects of hIRAK on the down-stream NF-κB signaling shows the importance of the TRAF6 interface for signaling by IL-1.

[PB4-16] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Modulation of the activity of ex vivo cultured leukemic-DC by L-ascorbic acid (LAA)

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L-ascorbic acid (LAA) was shown to modulate the in vitro growth of leukemic-colony forming cells from patients with acute myelogeneous leukemia (AML). Dendritic cells (DCs) were successfully cultured from the leukemic blasts by us and others. The effects of LAA on the ex vivo cultured leukemic-DC were studied. Plastic adherent cells from the leukemic blasts were cultured with GM-CSF and IL-4 (each 103 U/ml) with or without LAA (300 uM) for 7 days and harvested. Surface marker phenotyping indicated the cultured leukemic-DCs were HLA-DR+++, CD1a++, and CD80+ (98.86%, 23.46% and 13.35%, respectively). LAA reduced the proportion of HLA-DR+ (48.60%) and CD1a+ cells (11.84%). LAA lowered the leukemic-DC stimulated proliferation of cord blood cells (849.47% vs. 2685.16% of responder only) and CTL activity against HL-60 (38.9% vs. 71.7% cytotoxicity at E:T ratio 50:1). These data together with the reduction of leukemic-DC production of IL-12 by LAA suggest that the LAA may suppress the leukemic-DC activation.

Poster Presentations - Field C1. Biochemistry

[PC1-1] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]