The following full text is a publisher's version.

For additional information about this publication click this link.  
http://hdl.handle.net/2066/27165

Please be advised that this information was generated on 2019-11-02 and may be subject to change.
β-GLUCANS MODULATE ALVEOLAR MACROPHAGE RESPONSE TO BACTERIAL LIPOPOLYSACCHARIDE. QA 
Hoffman, JE Standing, AH Limper, Thoracic Disease Research Unit, Mayo Clinic and Foundation, Rochester MN.

Tumor necrosis factor-alpha (TNFα) is a potent proinflammatory cytokine believed to play a central role in the pathogenesis of endotoxin-induced shock and the adult respiratory distress syndrome. Pretreatment of animals with β-glucan prior to bacterial challenge reduces detectable TNFα and lethal infection (J. Cell. Biochem., 1991; 46: 60). We therefore hypothesized that β-glucan might directly regulate TNFα secretion from alveolar macrophages (AMS) in response to lipopolysaccharide (LPS). Rat AMS were cultured in the presence of increasing concentrations of β-glucan alone and TNFα secretion quantified using a sensitive L929 cytotoxicity assay. Whereas unstimulated AMS released 22.7 ± 5.3 pg/ml of TNFα, addition of β-glucan at doses of 10 and 100 μg/ml resulted in increased TNFα release (113.1 ± 26.1 and 729.9 ± 294.3 pg/ml TNFα, respectively; p < 0.05 compared to controls). However, lower concentrations of β-glucan (≤ 500 μg/ml) resulted in suppression of TNFα release from AMS (15.0 ± 1.6 pg/ml; p = NS compared to controls). Furthermore, preincubation of AMS with 500 μg/ml of β-glucan also inhibited the secretion of TNFα induced by LPS (10 μg/ml). Whereas LPS-stimulated AMS released 13,407 ± 248 pg/ml of TNFα, AMS pretreated with β-glucan released only 4.0 ± 0.2 pg/ml. Additionally, interferon-gamma (IFN) (10 ng/ml), a potent activator of TNFα expression, failed to overcome the inhibition of TNFα release induced by β-glucan. Our study demonstrates that β-glucan regulates the secretion of TNFα from AMS. Lower concentrations of β-glucan actually stimulate TNFα release, however, whereas higher concentrations of β-glucan inhibit TNFα secretion. Furthermore, AMS suppressed by β-glucan are also refractory to further stimulation by LPS even following IFN priming. These data suggest an immunomodulatory role of β-glucan which may explain its beneficial effect in models of sepsis.

POTENTIAL, INDIRECT ANTI-INFLAMMATORY EFFECTS OF IL-4: STIMULATION OF HUMAN MONOCYTES, MACROPHAGES, AND ENDOTHELIAL CELLS BY IL-4 INCREASES AMINOPEPTIDASE-N-ACTIVITY (CD13; EC 3.4.1.12).

P.Th.W. van Halt1, J.P.M. Hopstaken-Broos1, A. Prens1, H.G. Hoogsteden2, R.J.F. Jansen1, C.G. Fijten3, and C. Hilvering4

Depts. of Immunology1 and Pulmonary Medicine2, Erasmus University and University Hospital Dijkzigt, Rotterdam; Dept. of Immunology3, Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands.

IL-4 up-regulates various monocyteic properties, which are associated with proinflammatory functions. Paradoxically, IL-4 may also act as an anti-inflammatory agent by down-regulating the production of several inflammatory mediators. Studies have already been started to examine these properties in vivo. As the activity of some mediators has recently been shown to be regulated by peptidases, we examined whether IL-4 was able to modulate the expression of a cell membrane associated peptidase, aminopeptidase-N (CD13).

Monocytes were isolated from healthy volunteers, purified by centrifugal elutriation, and cultured under non-adherent conditions in Teflon bags. Expression of cell surface antigens was analysed with a FACScan. IL-4 caused a dose-dependent increase of the expression of CD13 Ag on these cells. Maximal expression was observed around 48 h of culture. This IL-4-induced increase was completely blocked by anti-IL-4 antisemur. Furthermore, the increase in surface expression was preceded by increased mRNA levels of CD13, which was maximal around 24 h of culture. We also observed that CD13-mediated leucine-aminopeptidase activity of monocytes was induced by IL-4. Also other CD13-expressing cells were sensitive to IL-4, since CD13 Ag expression and CD13 mRNA levels were up-regulated in human alveolar macrophages and endothelial cells upon IL-4 treatment.

The increased expression of cell membrane aminopeptidase-N represents a potentially increased cellular activity to inactivate inflammatory mediators. Therefore, these findings nonspecifically suggest a variety of anti-inflammatory actions. We postulate that up-regulation of aminopeptidase-N expression may be an indirect working mechanism of IL-4 to modulate the action of bioactive peptides. This mechanism as such may also be relevant in studies on the anti-inflammatory effects of IL-4 in vivo.

Supported by Glaxo Holland b.v.

TGF-β and TNF-α INFLUENCE FIBRIN TURNOVER IN HUMAN TRACHEAL EPITHELIAL CELLS IN VITRO. Johnson, AR; Koenig, KB; and IdeI, S. University of Texas Health Ctr, Tyler, TX, USA.

Alveolar fibrin deposition characterizes alveolitis of severe forms of lung injury and may potentiate inflammation and subsequent alveolar organization. The epithelial lining of small airways and alveoli can influence local fibrin deposition via expression of procoagulant and fibrinolytic proteins. We used a human tracheal epithelial cell line (HEPC) to study cytokine influence on fibrin deposition. From recalcification times in factor-deficient plasmas we found that tissue factor (TF) accounts for most procoagulant activity of HEPC and confirmed this by direct and indirect binding studies with factor VII and neutralization with TF antibody. TGF-β and TNF-α stimulated release of TF into HEPC-conditioned media. HEPC expressed plasminogen-dependent fibrinolytic activity which, by fibrin enzymography, was primarily uPA; some remained in complex with inhibitor(s). TGF-β and TNF-α altered expression of fibrinolytic proteins and inhibitors in HEPC as measured by fibrin radio-assay and ELISAs. TGF-β depressed fibrinolytic activity in both cells and media. By contrast, TNF-α increased both cell-associated and media fibrinolytic activity. TNF-α also induced increased expression of uPA and tPA in HPEC, whereas TGF-β did not. TGF-β enhanced both cell-associated and media PAI-1. PAI-1 induction was not due to increased expression of fibrin enzymography. The disparate fibrinolytic response of HEPC to TGF-β and TNF-α differs from other human lung cells (mesothelium and fibroblasts) we studied previously. Although induction of procoagulant activity and depression of fibrinolysis by TGF-β favors fibrin deposition, induction of fibrinolytic activity by TNF-α could shift the balance towards fibrin clearance.

Supported by NIH grants HL45018, HL37770 and HL44473.

MODULATION BY IL-10, IL-4 and TGF-β OF TNFα, TGF-β AND T CELL PROLIFERATION INDUCED BY ALLOGENIC ALVEOLAR MACROPHAGES OR DERIVATIVES.

L.F. Nicol*, F. El Habra, J.-M. Dever

Division of Respiratory Diseases1 and Division of Immunology and Allergy, University Hospital, Geneva, Switzerland.

TNFα and TGF-β are powerful inflammatory and cytotoxic cytokines that may play a key role in acute or chronic lung rejection. We have studied their release during allogenic reactions induced by either human lung dendritic cells (DC) or alveolar macrophages (AM). The modulation of their production by IL-10, IL-4 or TGF-β was analyzed. DC were separated using their density, their size and their absence of autofluorescence. HEPC were then treated with DC and media and the TNFα or TNFβ during allogenic reaction. While TNFα or TNFβ during allogenic reaction. We found that tissue factor (TF) accounts for most procoagulant activity of HEPC and confirmed this by direct and indirect binding studies with factor VII and neutralization with TF antibody. TGF-β and TNF-α stimulated release of TF into HEPC-conditioned media. HEPC expressed plasminogen-dependent fibrinolytic activity which, by fibrin enzymography, was primarily uPA; some remained in complex with inhibitor(s). TGF-β and TNF-α altered expression of fibrinolytic proteins and inhibitors in HEPC as measured by fibrin radio-assay and ELISAs. TGF-β depressed fibrinolytic activity in both cells and media. By contrast, TNF-α increased both cell-associated and media fibrinolytic activity. TNF-α also induced increased expression of uPA and tPA in HPEC, whereas TGF-β did not. TGF-β enhanced both cell-associated and media PAI-1. PAI-1 induction was not due to increased expression of fibrin enzymography. The disparate fibrinolytic response of HEPC to TGF-β and TNF-α differs from other human lung cells (mesothelium and fibroblasts) we studied previously. Although induction of procoagulant activity and depression of fibrinolysis by TGF-β favors fibrin deposition, induction of fibrinolytic activity by TNF-α could shift the balance towards fibrin clearance.

Supported by NIH grants HL45018, HL37770 and HL44473.