

Volume 12, issue 4, December 2001 | Articles originaux

Reduced adrenal response and increased mortality after systemic Klebsiella pneumoniae infection in interleukin-6-deficient mice

Abstract

During bacterial infections, both the immune system and the hypothalamus-pituitary-adrenal (HPA) axis are activated. The role of IL-6 in the activation of the HPA axis during bacterial sepsis is not fully understood. The aim of the present study was to investigate the role of endogenous IL-6 in a potentially lethal infection with Klebsiella pneumoniae and the concomitant activation of the HPA

axis. We examined the mortality of IL-6-/- and IL-6+/+ mice after intravenous (i.v.) infection with K. pneumoniae as well as the bacterial outgrowth in several organs. Subsequently, the influence of endogenous IL-6 on the effect of i.v. administration of K. pneumoniae on the plasma levels of corticosterone and the pro-inflammatory cytokines TNF-alpha and IL-1alpha was investigated in these mice. The present study demonstrates that IL-6-/- mice are more susceptible than IL-6+/+ mice to a systemic Gram-negative infection with K. pneumoniae, leading to increased outgrowth of microorganisms in the organs of the mice. Moreover, this infection is associated with a reduced adrenal response in IL-6-/- mice. We conclude that IL-6-/- mice are more susceptible to Gram-negative bacterial infections, which is mainly due to an impaired recruitment of granulocytes to the site of infection in the absence of IL-6. Furthermore, the reduced adrenal response may be an explanation for the strong inflammatory response with higher TNF-alpha plasma levels in IL-6-/- mice.

Full text

INTRODUCTION

During bacterial infections, both the immune system and the hypothalamus-pituitary-adrenal (HPA) axis are activated [1, 2]. Sepsis due to infection with Gram-negative bacteria is often related to high circulating levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha), interleukin-1alpha (IL-1alpha) and interleukin-6 (IL-6) [3, 4]. It has been shown that lipopolysaccharide (LPS) from Gram-negative bacterial cell walls induces the release of these cytokines [5-7]. Furthermore, LPS induces an increase in plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone, which is characteristic of an activated HPA axis [5, 8, 9]. Cytokines and glucocorticoid hormones are believed to integrate an immuno-regulatory feedback circuit: TNF, IL-1 and IL-6 stimulate ACTH and corticosterone release [10-14], whereas glucocorticoids suppress immune cell functions and production of cytokines, thereby protecting the organism against a harmful overshoot of immune reactions [10, 15-18].

IL-6 reportedly plays a pivotal role in the interaction between the immune system and the HPA axis [19]. This pleiotropic cytokine is produced both by immune cells and by cells in endocrine tissues [20]. IL-6 has an inhibitory effect

on the secretion of TNF and IL-1 [6, 21], and a direct stimulatory effect on glucocorticoid release by the adrenal gland [22, 23].

Evidence for a protective role of IL-6 during infection was obtained by investigating mice that are genetically deficient in the production of IL-6 [24]. IL-6-deficient (IL-$6^{-/-}$) mice have been shown to be more susceptible than wild-type (IL-$6^{+/+}$) control mice to infections caused by a variety of microorganisms [25-30]. In a previous study, we have shown that IL-$6^{-/-}$ mice were not able to mount an efficient neutrophil response during the infection with *Candida albicans*, explaining why the IL-$6^{-/-}$ mice are more susceptible to disseminated candidiasis [30].

The role of IL-6 in the activation of the HPA axis during bacterial sepsis is not fully understood. The aim of the present study was to investigate the role of endogenous IL-6 in a potentially lethal infection with *K. pneumoniae* and the concomitant activation of the HPA axis. We examined the mortality of IL-$6^{-/-}$ and IL-$6^{+/+}$ mice after an intravenous (i.v.) infection with *K. pneumoniae*, as well as the bacterial outgrowth in several organs, and the recruitment of polymorphonuclear neutrophils (PMN) to the site of *Klebsiella* injection. Subsequently, the influence of endogenous IL-6 on the effect of i.v. administration of *K. pneumoniae* on the plasma levels of corticosterone, and of the pro-inflammatory cytokines TNF-alpha and IL-1alpha, was investigated in these mice.

MATERIALS AND METHODS

Animals

Breeding pairs from the mixed (C57Bl/6 **x** 129/Sv) F2 generation of both IL-6-deficient (IL-$6^{-/-}$) and wild-type control (IL-$6^{+/+}$) mice were obtained from the Max-Planck-Institut für Immunbiologie, Freiburg, Germany [24]. Homozygous IL-$6^{-/-}$ and IL-$6^{+/+}$ mice were housed under specific pathogen-free conditions (according to FELASA recommendations [31]), at the Central Animal Laboratory of the University of Nijmegen.

Only healthy male offspring of 10-16 weeks old, weighing 20-30 grams, were used. Mice were housed in groups of 4 to 10 animals per cage. Mice were kept under a 12/12 hours dark/light cycle (lights on at 0700 hours) and received

acidified water and standard food (Hope Farms, Woerden, The Netherlands) *ad libitum*.

Materials

Klebsiella pneumoniae (ATCC 43816), a strain that can produce lethal infection in mice [21], was cultured overnight, and suspensions were washed in sterile physiological saline (0.9% NaCl) and subsequently diluted to the appropriate concentration immediately before use. Lipopolysaccharide (LPS *E. coli* 0111:B4) was purchased from Sigma (St. Louis, MO, USA).

Experimental protocols

Lethal K. pneumoniae infection model and lethal endotoxemia model

K. pneumoniae were injected intravenously (i.v., 100 mul) into the retro-orbital plexus of IL-$6^{-/-}$ and IL-$6^{+/+}$ mice under mild ether anesthesia. Doses of either 10^2, 10^3 or 10^4 colony-forming units (CFU) were injected at 10 a.m. Injections with sterile physiological saline were used as controls. Survival was assessed twice daily in 4 to 11 IL-$6^{-/-}$ or IL-$6^{+/+}$ mice per group for 14 days. Each experiment was performed 3 or 4 times.

LPS, dissolved in physiological saline, was injected intraperitoneally (i.p., 200 mul) at 9 a.m. doses of 250, 500, 1,000 or 2,000 mug per mouse. Survival was assessed daily in 2 to 7 animals per group for 14 days. Each experiment was performed 2 to 5 times.

Outgrowth of K. pneumoniae *in organs and blood*

A *K. pneumoniae* suspension of 10^2 CFU was injected i.v. (100 mul) into IL-$6^{-/-}$ and IL-$6^{+/+}$ mice (8 or 9 mice per group). After 24 hours, mice were anaesthetized with ether, a blood sample was taken from the orbital plexus, and organs (liver, lung, spleen, kidney) were removed aseptically, cleared of adhering fat, weighed, and homogenized in sterile physiological saline in a tissue grinder. Outgrowth of the microorganisms in the organs and blood of the animals was quantified by plating serial dilutions of the homogenized tissues or blood samples on sheep blood agar plates, and counting the number of CFU after overnight incubation at 37° C.

Recruitment of neutrophils

To investigate the recruitment of PMN at the site of *Klebsiella* infection, groups of four IL-$6^{-/-}$ and IL-$6^{+/+}$ mice were injected intraperitoneally with 10^7 CFU/ml heat-killed *K. pneumoniae*. Before injection and 4, 8, and 24 hours thereafter, peritoneal cells were collected in sterile saline containing 0.38% sodium citrate, and the total cell number was counted. The percentage and the absolute number of neutrophils were determined in Giemsa-stained cytocentrifuge preparations [30].

Plasma glucocorticoid and cytokine levels during K. pneumoniae *infection*

At 4, 8 or 24 hours after i.v. injection of *K. pneumoniae*, mice were decapitated to obtain trunk blood for determination of plasma corticosterone, TNF-alpha and IL-1alpha levels (7 to 11 mice per group). Blood was collected on ice in (K_3) EDTA Monoject Samplette whole blood collector tubes (Sherwood Medical, St.Louis, MO) to which 250 KIE aprotinine (25 mul, Trasylol, Bayer AG, Leverkusen, Germany) was added. Collected blood was centrifuged for 10 min at 1,500 **x** g (4° C), and plasma was separated and stored at - 20° C until assayed.

Corticosterone and cytokine assays

Corticosterone levels were determined by radioimmunoassay (RIA) after extraction with dichloromethane as described before [13]. Mouse TNF-alpha and IL-1alpha antigen values were measured by specific RIA [32]. The detection limits of the cytokine assays were 0.04 and 0.02 ng/ml, respectively.

Statistical analysis

Survival data were analyzed using the Kaplan-Meyer log rank test. Differences in outgrowth of the microorganisms from organs and blood, and for recruitment of neutrophils, were analyzed using the Mann-Whitney U test. Differences were considered significant at $P < 0.05$. For blood sample data for corticosterone, TNF-alpha and IL-1, a 2-way analysis of variance (2-way ANOVA) was performed where appropriate. Further comparisons of group means by 1-way ANOVA were carried out, using Bonferroni corrections to maintain the overall level of significance at $P < 0.05$. The statistical analysis package SPSS version 6.1.3 (SPSS, Gorinchem, The Netherlands) was used.

RESULTS

Lethal K. pneumoniae *infection model*

Survival after i.v. infection with *K. pneumoniae* was significantly lower in IL-$6^{-/-}$ mice when compared to IL-$6^{+/+}$ mice (Figure 1). After injection of 10^2 CFU, only 4% of the IL-$6^{-/-}$ mice survived, whereas survival of IL-$6^{+/+}$ mice was 43% ($P < 0.0001$). Mortality in IL-$6^{-/-}$ mice was 100% within 2 or 3 days after injection of 10^4 CFU (data not shown). Of the IL-$6^{+/+}$ mice, however, 27% survived after injection of 10^4 CFU ($P < 0.0001$).

Lethal endotoxemia model

Survival after 14 days did not differ significantly between IL-$6^{-/-}$ mice and IL-$6^{+/+}$ mice after i.p. injection of 0.25 mg to 2 mg LPS (Figure 2).

Outgrowth of K. pneumoniae *in organs and blood*

To assess whether the increased mortality of the IL-$6^{-/-}$ mice in the lethal *K. pneumoniae* infection model was associated with a higher bacterial load in the organs, groups of IL-$6^{-/-}$ and IL-$6^{+/+}$ mice were sacrificed 24 hours after i.v. injection with 10^2 CFU of *K. pneumoniae*. The outgrowth of microorganisms in all of the specific organs, including peripheral blood, was significantly higher in IL-$6^{-/-}$ mice than in IL-$6^{+/+}$ mice (Figure 3).

Recruitment of polymorphonuclear neutrophils

To investigate the recruitment of neutrophils at the site of a *Klebsiella* infection, groups of IL-$6^{-/-}$ and IL-$6^{+/+}$ mice were injected intraperitoneally with 10^7 CFU/ml heat-killed *K. pneumoniae*, and exudate peritoneal neutrophils were harvested and counted before injection, and 4, 8, and 24 hours later. IL-$6^{-/-}$ mice had a reduced influx of neutrophils compared with IL-$6^{+/+}$ mice, most prominently at 8 hours after injection of the microorganisms ($P < 0.05$; Figure 4).

Plasma glucocorticoid and cytokine levels during K. pneumoniae *infection*

To investigate the role of IL-6 in the activation of the HPA axis and in the release of pro-inflammatory cytokines during an ongoing Gram-negative infection, trunk blood was collected from IL-$6^{-/-}$ and IL-$6^{+/+}$ mice at 4, 8 and 24 hours after i.v. injection with saline or with 10^2 CFU of *K. pneumoniae*. After injection of saline, plasma corticosterone levels did not differ between the two mouse strains (Figure 5A). After injection of bacteria into IL-$6^{+/+}$ mice, corticosterone levels increased within 4 hours, with highest levels observed at 8 hours, and subsequently decreased. In IL-$6^{-/-}$ mice, corticosterone levels were significantly lower, compared to IL-$6^{+/+}$ mice, at 4 and 8 hours after the injection of 10^2 CFU of *K. pneumoniae* ($P < 0.05$). No differences in corticosterone response between IL-$6^{-/-}$ and IL-$6^{+/+}$ mice were found after 24 hours (Figure 5A). TNF-alpha plasma levels in IL-$6^{-/-}$ and IL-$6^{+/+}$ mice, increased within 4 to 8 hours after the onset of the infection with *K. pneumoniae* (Figure 5B). IL-$6^{-/-}$ mice had higher TNF-alpha levels than IL-$6^{+/+}$ mice at 8 and 24 hours after injection of *K. pneumoniae* ($P < 0.05$). Figure 5C shows that IL-1alpha levels in both mouse strains increased only marginally after infection with *K. pneumoniae*.

DISCUSSION

The present study demonstrates that IL-$6^{-/-}$ mice are more susceptible than IL-$6^{+/+}$ mice to a systemic Gram-negative infection with *K. pneumoniae,* and that this infection is associated with a reduced adrenal response in IL-$6^{-/-}$ mice. Previous studies using Gram-negative bacteria *(E. coli)* [26], and other microorganisms *(L. monocytogenes, M. tuberculosis, C. albicans, S. pneumoniae)* [25, 27-30], also demonstrated the protective role of IL-6 during lethal infections. In our study, the increased mortality in IL-$6^{-/-}$ mice was accompanied by a 10- to 100-fold increased outgrowth of *K. pneumoniae* in all of the organs analyzed. This difference between IL-$6^{-/-}$ and IL-$6^{+/+}$ mice was already found at 24 hours after the i.v. injection of the microorganisms. The outgrowth of microorganisms in the first 1 to 3 days seems to determine the outcome of the survival of IL-$6^{-/-}$ and IL-$6^{+/+}$ mice after 14 days, in three different infection models that were studied in our group: *K. pneumoniae* (present study), *C. albicans* [30], and *Y. enterocolitica* (J.H.A.J. Curfs, F.H.J. van Enckevort, J.F.G.M. Meis, CGJ Sweep, A.R.M.M. Hermus, J.A.A. Hoogkamp-Korstanje, *Yersinia enterocolitica* infection in IL-6-deficient mice. Abstract 13th British Scandinavian Conference on Infectious Diseases, 1997). In general, the early host response during the first days of bacterial and fungal infection is mediated by neutrophils, and a defective response may be explained by either a reduced recruitment of

neutrophils at the site of infection or an impaired phagocytosis and intracellular killing of the organism. In the present study, the IL-$6^{-/-}$ mice displayed a reduced capacity to recruit neutrophils to the site of a *Klebsiella* injection. This is in agreement with earlier observations, showing that the recruitment of neutrophils is dependent on IL-6 in models of *C. albicans* infection [30] or peritoneal infection with *S. epidermidis* [33].

The infection with *K. pneumoniae* was accompanied by higher levels of the pro-inflammatory cytokine TNF-alpha in IL-$6^{-/-}$ mice than in IL-$6^{+/+}$ mice, at 8 and 24 hours of the infection. Firstly, this could be explained by the diminished adrenal response in the first 8 hours in IL-$6^{-/-}$ mice, resulting in a reduced glucocorticoid suppression of immune cell functions and production of cytokines. Secondly, in the absence of endogenous IL-6 in these mice, a putative, direct inhibiting effect of IL-6 on the release of TNF-alpha and IL-1alpha is absent [6, 21], leading to higher levels of cytokines during the course of the infection. Thirdly, during sepsis and endotoxic shock, macrophage migration inhibitory factor (MIF) is induced, which acts to override the glucocorticoid inhibition of the production of cytokines (TNF-alpha, IL-1alpha and IL-6) in macrophages and T cells [34-36]. As IL-6 is an inhibitor of the release of MIF, we suggest that in IL-$6^{-/-}$ mice MIF levels are higher, which also may account for a reduced inhibition of cytokines by endogenous glucocorticoids in IL-$6^{-/-}$ mice. Most importantly, the higher bacterial load in IL-$6^{-/-}$ mice found at 24 hours of the infection may account for inducing more TNF-alpha and IL-1alpha.

The role of IL-6 in the activation of the HPA axis during septic shock or bacterial sepsis is not fully understood. In a previous study we showed that IL-6 deficiency in mice results in a reduced adrenal response after injection with a single dose of purified LPS, although the plasma levels of TNF-alpha and IL-1alpha did not differ between IL-$6^{-/-}$ and IL-$6^{+/+}$ mice in that model [37]. Injection of a single dose of LPS resulted in a fast cytokine response with a peak of TNF-alpha within 1 hour. The present results show a diminished corticosterone response until 8 hours after infection with *K. pneumoniae*, accompanied by higher TNF-alpha levels in IL-$6^{-/-}$ mice. However, at 24 hours of infection, corticosterone levels were equally high in IL-$6^{-/-}$ mice and in IL-$6^{+/+}$ mice, where corticosterone levels had already started to decrease, while TNF-alpha levels were still higher in IL-$6^{-/-}$ than in IL-$6^{+/+}$ mice. On the basis of these results we suggest that IL-6 is important in the response of the HPA axis, and is a distinct mediator of the cytokine response to an infection with live microorganisms.

To assess whether the increased bacterial outgrowth *per se*, or the associated bacterial endotoxins induce the higher mortality of IL-$6^{-/-}$ mice during the infection with *K. pneumoniae*, purified LPS was injected into IL-$6^{-/-}$ and IL-$6^{+/+}$ mice. In contrast to infection with *K. pneumoniae*, injection of mice with doses of 1 or 2 mg LPS led to no difference in mortality rates between IL-$6^{-/-}$ and IL-$6^{+/+}$ mice, which is in accordance with the study by Dalrymple *et al.* [26]. Moreover, in contrast to the higher levels of TNF-alpha found in IL-$6^{-/-}$ mice during the infection reported here, no difference in TNF-alpha levels was found between IL-$6^{-/-}$ and IL-$6^{+/+}$ mice after injection of LPS [37]. Therefore, the difference in mortality between the two mouse strains during the infection with *K. pneumoniae* is not mediated by LPS. Rather, the impaired neutrophil recruitment, leading to increased outgrowth of microorganisms in the absence of endogenous IL-6 is the main cause of the increased mortality in IL-$6^{-/-}$ mice.

CONCLUSION

We conclude that IL-$6^{-/-}$ mice are more susceptible to Gram-negative bacterial infections and to infections with live microorganisms in general, due to a defective migration of neutrophils to the site of infection and increased outgrowth of microorganisms in the organs of the mice. Furthermore, the reduced adrenal response may be an explanation for the strong inflammatory response with higher TNF-alpha plasma levels in IL-$6^{-/-}$ mice.

Acknowledgements. The authors gratefully acknowledge Dr. M. Kopf (Basel Institute for Immunology, Basel, Switzerland) for providing the breeding couples of IL-$6^{-/-}$ and IL-$6^{+/+}$ mice. We thank Yvette Brom, Gerry Grutters and Geert Poelen for assistance with the animal experiments, and Ineke Verschueren for measuring cytokine levels.

References

1. Chrousos G P. 1995. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. (Review) *N. Engl. J. Med.* 332: 1351.

2. Tilders F J, DeRijk R H, Van Dam A M, Vincent V A, Schotanus K, Persoons J H. 1994. Activation of the hypothalamus-pituitary-adrenal axis by bacterial

endotoxins: routes and intermediate signals. (Review) *Psychoneuroendocrinology* 19: 209.

3. Hack C E, de Groot E R, Felt-Bersma R J, Nuijens J H, Strack Van Schijndel R J, Eerenberg-Belmer A J, Thijs L G, Aarden L A. 1989. Increased plasma levels of interleukin-6 in sepsis. *Blood* 74: 1704.

4. Lynn W A, Cohen J. 1995. Management of septic shock. (Review) *J. Infect.* 30: 207.

5. Givalois L, Dornand J, Mekaouche M, Solier M D, Bristow A F, Ixart G, Siaud P, Assenmacher I, Barbanel G. 1994. Temporal cascade of plasma level surges in ACTH, corticosterone, and cytokines in endotoxin-challenged rats. *Am. J. Physiol* 267: R164.

6. Schindler R, Mancilla J, Endres S, Ghorbani R, Clark S C, Dinarello C A. 1990. Correlations and interactions in the production of interleukin-6 (IL-6), IL-1 and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood* 75: 40.

7. Zuckerman S H, Shellhaas J, Butler L D. 1989. Differential regulation of lipopolysaccharide-induced interleukin-1 and tumor necrosis factor synthesis: effects of endogenous and exogenous glucocorticoids and the role of the pituitary-adrenal axis. *Eur. J. Immunol.* 19: 301.

8. Dunn A J. 1993. Role of cytokines in infection-induced stress. (Review) *Ann. N. Y. Acad. Sci.* 697: 189.

9. Rivier C, Chizzonite R, Vale W. 1989. In the mouse, the activation of the hypothalamic-pituitary-adrenal axis by a lipopolysaccharide (endotoxin) is mediated through interleukin-1. *Endocrinology* 125: 2800.

10. Besedovsky H, del Rey A, Sorkin E, Dinarello C A. 1986. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* 233: 652.

11. Katsuura G, Gottschall P E, Dahl R R, Arimura A. 1988. Adrenocorticotropin release induced by intracerebroventricular injection of recombinant human

interleukin-1 in rats: possible involvement of prostaglandin. *Endocrinology* 122: 1773.

12. Naitoh Y, Fukata J, Tominaga T, Nakai Y, Tamai S, Mori K, Imura H. 1988. Interleukin-6 stimulates the secretion of adrenocorticotropic hormone in conscious, freely-moving rats. *Biochem. Biophys. Res. Commun.* 155: 1459.

13. Sweep C G, van der Meer M J, Hermus A R, Smals A G, van der Meer J W, Pesman G J, Willemsen S J, Benraad T J, Kloppenborg P W. 1992. Chronic stimulation of the pituitary-adrenal axis in rats by interleukin-1 beta infusion: *in vivo* and *in vitro* studies. *Endocrinology* 130: 1153.

14. van der Meer M J, Sweep C G, Rijnkels C E, Pesman G J, Tilders F J, Kloppenborg P W, Hermus A R. 1996. Acute stimulation of the hypothalamic-pituitary-adrenal axis by IL-1beta, TNF-alpha and IL-6: a dose response study. *J. Endocrinol. Invest.* 19: 175.

15. del Rey A, Besedovsky H, Sorkin E, Dinarello C A. 1987. Interleukin-1 and glucocorticoid hormones integrate an immunoregulatory feedback circuit. *Ann. N. Y. Acad. Sci.* 496: 85.

16. Fantuzzi G, Ghezzi P. 1993. Glucocorticoids as cytokine inhibitors: role in neuroendocrine control and therapy of inflammatory diseases. *Mediators in Inflammation* 2: 263.

17. Harbuz M S, Lightman S L. 1992. Stress and the hypothalamo-pituitary-adrenal axis: acute, chronic and immunological activation. (Review) *J. Endocrinol.* 134: 327.

18. Turnbull A V, Rivier C L. 1999. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. (Review) *Physiol. Rev.* 79: 1.

19. Papanicolaou D A, Wilder R L, Manolagas S C, Chrousos G P. 1998. The pathophysiologic roles of interleukin-6 in human disease. (Review) *Ann. Intern. Med.* 128: 127.

20. Muramami N, Fukata J, Tsukada T, Kobayashi H, Ebisui O, Segawa H, Muro S, Imura H, Nakao K. 1993. Bacterial lipopolysaccharide-induced expression of interleukin-6 messenger ribonucleic acid in the rat hypothalamus, pituitary, adrenal gland, and spleen. *Endocrinology* 133: 2574.

21. Aderka D, Le J M, Vilcek J. 1989. IL-6 inhibits lipopolysaccharide-induced tumor necrosis factor production in cultured human monocytes, U937 cells, and in mice. *J. Immunol.* 143: 3517.

22. Päth G, Bornstein S R, Ehrhart-Bornstein M, Scherbaum W A. 1997. Interleukin-6 and the interleukin-6 receptor in the human adrenal gland: expression and effects on steroidogenesis. *J. Clin. Endocrinol. Metab.* 82: 2343.

23. Salas M A, Evans S W, Levell M J, Whicher J T. 1990. Interleukin-6 and ACTH act synergistically to stimulate the release of corticosterone from adrenal gland cells. *Clin. Exp. Immunol.* 79: 470.

24. Kopf M, Baumann H, Freer G, Freudenberg M, Lamers M, Kishimoto T, Zinkernagel R, Bluethmann H, Köhler G. 1994. Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* 368: 339.

25. Dalrymple S A, Lucian L A, Slattery R, McNeil T, Aud D M, Fuchino S, Lee F, Murray R. 1995. Interleukin-6-deficient mice are highly susceptible to *Listeria monocytogenes* infection: correlation with inefficient neutrophilia. *Infect. Immun.* 63: 2262.

26. Dalrymple S A, Slattery R, Aud D M, Krishna M, Lucian L A, Murray R. 1996. Interleukin-6 is required for a protective immune response to systemic *Escherichia coli* infection. *Infect. Immun.* 64: 3231.

27. Ladel C H, Blum C, Dreher A, Reifenberg K, Kopf M, Kaufmann S H. 1997. Lethal tuberculosis in interleukin-6-deficient mutant mice. *Infect. Immun.* 65: 4843.

28. Romani L, Mencacci A, Cenci E, Spaccapelo R, Toniatti C, Puccetti P, Bistoni F, Poli V. 1996. Impaired neutrophil response and $CD4^+$ T helper cell 1 development in interleukin-6-deficient mice infected with *Candida albicans. J. Exp. Med.* 183: 1345.

29. van der Poll T, Keogh C V, Guirao X, Buurman W A, Kopf M, Lowry S F. 1997. Interleukin-6 gene-deficient mice show impaired defense against pneumococcal pneumonia. *J. Infect. Dis.* 176: 439.

30. van Enckevort F H, Netea M G, Hermus A R, Sweep C G, Meis J F, Van der Meer J W, Kullberg B J. 1999. Increased susceptibility to systemic candidiasis in interleukin-6 deficient mice. *Med. Mycol.* 37: 419.

31. Rehbinder C, Baneux P, Forbes D, van Herck H, Nicklas W, Rugaya Z, Winkler G. 1996. FELASA recommendations for the health monitoring of mouse, rat, hamster, gerbil, guineapig and rabbit experimental units. *Lab. Anim.* 30: 193.

32. Netea M G, Demacker P N, Kullberg B J, Boerman O C, Verschueren I, Stalenhoef A F, Van der Meer J W. 1996. Low-density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe gram-negative infections. *J. Clin. Invest.* 97: 1366.

33. Hurst S M, Wilkinson T S, McLoughlin R M, Jones S, Horiuchi S, Yamamoto N, Rose-John S, Fuller G M, Topley N, Jones S A. 2001. Il-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. *Immunity* 14: 705.

34. Bozza M, Satoskar A R, Lin G, Lu B, Humbles A A, Gerard C, David J R. 1999. Targeted disruption of migration inhibitory factor gene reveals its critical role in sepsis. *J. Exp. Med.* 189: 341.

35. Calandra T, Bernhagen J, Metz C N, Spiegel L A, Bacher M, Donnelly T, Cerami A, Bucala R. 1995. MIF as a glucocorticoid-induced modulator of cytokine production. *Nature* 377: 68.

36. Calandra T, Echtenacher B, Roy D L, Pugin J, Metz C N, Hultner L, Heumann D, Mannel D, Bucala R, Glauser M P. 2000. Protection from septic shock by neutralization of macrophage migration inhibitory factor. *Nat. Med.* 6: 164.

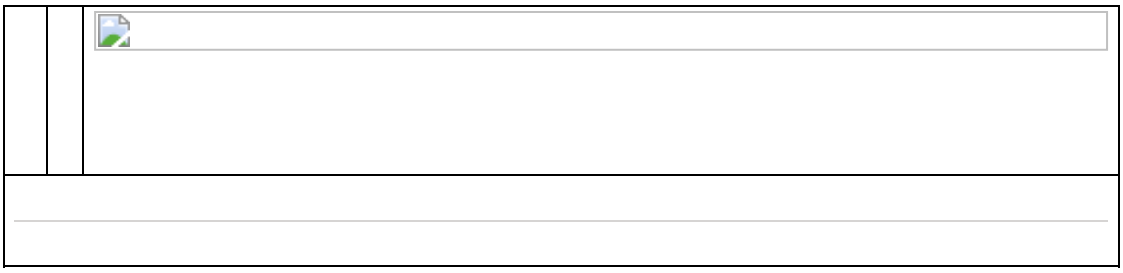
37. van Enckevort F H, Sweep C G, Span P N, Demacker P N, Hermsen C C, Hermus A R. 2001. Reduced adrenal response to bacterial lipopolysaccharide in interleukin-6-deficient mice. *J. Endocrinol. Invest.* 24: 786.

Figures

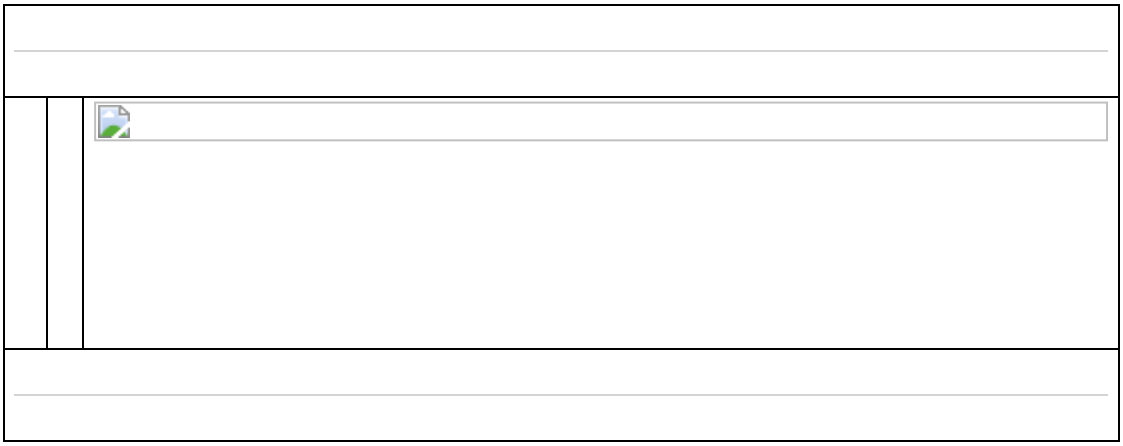




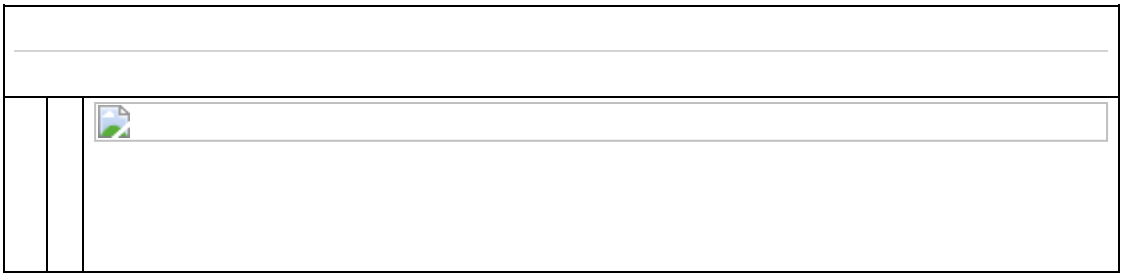




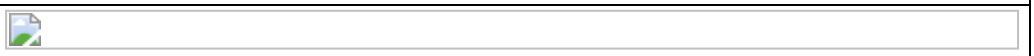












Authors

Frank H.J. van Enckevort, C.G.J. Sweep, Paul N. Span, Mihai G. Netea, Ad R.M.M. Hermus, Bart Jan Kullberg

Department of Endocrinology (531), Nijmegen University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

In this issue

Monocyte chemotactic protein-3

Patricia Menten, Anja Wuyts, Jo Van Damme
MCP-3, induction, diseases, structure, receptors.

Adenoviral supply of active transforming growth factor-beta1 (TGF-beta1) did not prevent lethality in transforming growth factor-beta1-knockout embryos

Hedia Chagraoui, Stéphane Giraudier, William Vainchenker, Françoise Wendling
TGF-beta1, cytokine, knockout mice, gene therapy, adenovirus.

Absence of endogeneous interleukin-10 enhances the evolution of murine type-II collagen-induced arthritis

Salvatore Cuzzocrea, Emanuela Mazzon, Laura Dugo, Ivana Serraino, Domenico Britti, Massimo De Maio, Achille P. Caputi
collagen, inflammation, nitric oxide, peroxynitrite, superoxide dismutase, IL-10.

Reduced adrenal response and increased mortality after systemic Klebsiella pneumoniae infection in interleukin-6-deficient mice

Frank H.J. van Enckevort, C.G.J. Sweep, Paul N. Span, Mihai G. Netea, Ad R.M.M. Hermus, Bart Jan Kullberg
corticosterone, cytokine, IL-6-deficient mice, granulocyte recruitment, survival.

Gamma-interferon induces apoptosis of the B lymphoma WEHI-279 cell line through a CD95/CD95L-independent mechanism

K.-E. Ben Jilani, K. Akarid, D. Arnoult, F. Petit, E. Baert, J.-P. Gaillard, J.-C. Ameisen, J. Estaquier
IFN-g, B cells, apoptosis, CD95, caspases, cytokines.

IFN-beta stimulates the production of beta-chemokines in human peripheral blood monocytes. Importance of macrophage differentiation

Laura Fantuzzi, Irene Canini, Filippo Belardelli, Sandra Gessani
MCP-1, MIP-1alpha, MIP-1beta, IFN-beta, monocytes/macrophages, differentiation.

Relationship between cell kinetics and apoptotic effects in TNF-alpha and IFN-gamma-treated human tumour cell lines

Heinz Baisch
apoptosis, c-Myc, cell cycle, cytokines, dual pathways.

L-Buthionine-(S,R)-sulfoximine, an irreversible inhibitor of gamma-glutamylcysteine synthetase, augments LPS-mediated pro-inflammatory cytokine biosynthesis: evidence for the implication of an IkappaB-alpha/NF-kappaB insensitive pathway

John J. Haddad
antioxidant, chemioxyexcitation, cytokines, glutathione disequilibrium, pharmacotherapy, reactive oxygen species, redox/thiol regulation.

Endotoxin regulates the maturation of sterol regulatory element binding protein-1 through the induction of cytokines

Luisa Diomede, Diego Albani, Marco Bianchi, Mario Salmona
SREBP-1, LPS, HepG2, liver, mice.

Regulation of Staphylococcus aureus-mediated activation of interleukin-18 in peripheral blood mononuclear cells

Ulrich Böcker, Tobias Manigold, Joanna M. Watson, Manfred V. Singer, Siegbert Rossol
human, cytokine, bacterial antigen, CD14, signal transduction.

Interleukine-6 (IL-6) synthesis and gp130 expression by human pericardium

Emmanuelle Menet, Pierre Corbi, Cécile Ancey, Franck Morel, Adriana Delwail, Martine Garcia, Anne-Marie Osta, John Wijdenes, Daniel Potreau, Jean-Claude

Lecron
IL-6, gp130, pericardium.

Plasmodium falciparum liver-stage antigen-1 peptide-specific interferon-gamma responses are not suppressed during uncomplicated malaria in African children

Adrian J.F. Luty, Martina Bongartz, Philipp Rezbach, Jean-Francois Faucher, Michael R. Hollingdale, Peter G. Kremsner
malaria, cytokine, interferon-gamma, liver.

Immunoexpressions of p21, Rb, mcl-1 and bad gene products in normal, hyperplastic and carcinomatous human prostates

Mar Royuela, María Isabel Arenas, Fermín R. Bethencourt, Manuel Sánchez-Chapado, Benito Fraile, Ricardo Paniagua
p21, Rb, mcl-1, bad, human prostate, benign prostatic hyperplasia, prostatic carcinoma.

Recombinant human interleukin-1 beta: new possibilities for the prophylaxis and correction of toxic myelodepression in patients with malignant tumors I. Phase I-II clinical trials of recombinant human interleukin-1 beta as a leukopoiesis stimulator in cancer patients receiving combination chemotherapy

M.L. Gershanovich, L.V. Filatova, S.A. Ketlinsky, A.S. Simbirtsev
human recombinant interleukin-1 beta, myelopoiesis, myelodepression, cancer chemotherapy.

Recombinant human interleukin-1 beta: new possibilities for the prophylaxis and correction of toxic myelodepression in patients with malignant tumors II. Phase II study of the protective effect of recombinant human interleukin-1 beta on myelodepression induced by chemotherapy in cancer patients

M.L. Gershanovich, L.V. Filatova, S.A. Ketlinsky, A.S. Simbirtsev
human recombinant interleukin-1 beta, leukopoiesis, myelodepression, cancer chemotherapy.

French society of immunology, cytokines

Eric Lelièvre, Isabelle Corre

Les éditions JLE

30 rue Berthollet, Bât. A,
94110 Arcueil, France

+ 33 (0)1 46 73 06 60

contact@jle.com

Publishing Policy

Books and e-books

Want to publish ?

Become a partner