

Volume 12, issue 2, June 2001 | Compte-rendu

Serum levels of interleukin-18 in patients with uncomplicated Plasmodium falciparum malaria

Abstract

Interleukin (IL)-18, a newly discovered cytokine produced primarily by macrophages, has been shown to induce gamma interferon (IFN-g) production by natural killer cells, to induce the T helper type 1 response. To further elucidate the role of this cytokine in uncomplicated malaria caused by Plasmodium falciparum, serum levels of IL-18, and gamma interferon (IFN-g), determined by an immunoenzymatic assay, were analyzed in 40 adult patients, and in 15 healthy control subjects. A significant increase in serum levels of IL-18 was

observed in patients with uncomplicated P. falciparum malaria on admission, whereas serum levels of IFN-g tended to increase although not significantly. Serum levels of IL-18 decreased three days later, but still remained significantly high, whereas IFN-g levels returned to normal levels compared to the controls. No significant correlation was found between parasitemia and serum levels of IL-18 and IFN-g. The increase of IL-18 levels during acute and recovery phases of uncomplicated P. falciparum malaria may reflect a proinflammatory role of IL-18 in these patients. An early and effective immune response regulated by proinflammatory Th1 cytokines, including tumor necrosis factor (TNF), interleukin (IL)-12, and possibly IFN-g may limit the progression from uncomplicated malaria to severe and life-threatening complications.

Full text

INTRODUCTION

Infection with *Plasmodium falciparum*, a causative agent of uncomplicated and severe clinical malaria, continues to be a global health concern [1]. Impairment of cell-mediated immunity, with specificity for both parasite and non-parasite antigens is a peculiar feature of acute *P. falciparum* infection [2, 3]. Stevenson *et al.* [4] have shown that the preferential activation of a Th1 response in mice is related to resistance to blood-stage *Plasmodium chabaudi* AS infection. Several studies have shown that administration of interleukin (IL)-12 before infection of mice with *Plasmodium yoelii*, or of rhesus monkeys with *Plasmodium cynomolgi*, provides full protection in both animal models, through a gamma interferon (IFN-gamma)-dependent antiplasmodial mechanism [5, 6]. In addition, Stevenson *et al.* [7] demonstrated that the IL-12-induced protection against the blood stage of *P. chabaudi* AS, is mediated by upregulation of IFN-gamma and tumor necrosis factor (TNF), at least in part by the generation of high levels of nitric oxide. Thus, these studies suggest that the protective immunity to malaria is mediated by activation of Th1 cytokines, including IL-12, IFN-gamma and TNF.

Interleukin(IL)-18, formerly interferon gamma-inducing factor, is an 18- to 19-KDa cytokine with multiple biological functions, and is produced by several cell types, including activated mononuclear cells and epidermal cells, in response to bacterial and inflammatory stimuli [8, 9]. Furthermore, IL-18 induces production of gamma interferon (IFN-gamma) by natural killer cells and antigen or mitogen-stimulated Th1 cells, and upregulation of interleukin-2 receptor on T cells [10, 11].

IL-18 and IL-12 have a synergistic effect on the induction the production of IFN-gamma by T cells, probably due to the upregulation of IL-18 receptors by IL-12 [11, 12]. IL-18 has been recently shown to induce the production of tumor necrosis factor (TNF) by human natural killer and T cells [13]. More recently, Pirhonen *et al.* [14] have demonstrated that during influenza and Sendai virus infections, human monocytes and macrophages are able to produce IL-18 in response to viral infection.

To confirm experimental and clinical results, and to gain further insight into the role of IL-18 in *P. falciparum* malaria, we evaluated circulating levels of IL-18 and IFN-gamma in patients with uncomplicated malaria caused by *P. falciparum.*

METHODS

The study was carried out at the Division of Infectious Diseases, Varese, and at the Institute of Infectious Diseases, University of Brescia, Italy.

Forty adult patients (32 male, 8 female; mean age: 37.7 ± 5.9 years) were admitted to the hospitals of Varese and Brescia, with a diagnosis of uncomplicated *P. falciparum* malaria. All patients were African immigrants. Malaria was diagnosed by examination of thick and thin blood films. All patients received adequate antimalarial treatment, most of them received treatment with quinine, given intravenously or orally. Uncomplicated malaria was defined as *P. falciparum* parasitaemia (1,000 to 10,000 parasites/muL) with Hb > 8.0 g/dL, glycemia > 60 mg/dL, and no signs of severe malaria. Fifteen healthy Caucasian subjects (10 male, 5 female; mean age: 32.1 ± 5.9 years) served as a negative control group.

Blood samples were taken on day 0 (before start of the treatment) and on day 3 of the disease.

After centrifugation, sera were immediately aliquoted and stored at - 80° C until tested.

IL-18 was measured by a sandwich enzyme-linked immunosorbent assay. The assays use a monoclonal antibody specific for human IL-18 (Euroclone, Devon, UK), and a monoclonal antibody specific for human IFN-gamma (Euroclone). The optical density was read at 450 nm.

IL-18 and IFN-gamma concentrations (in picograms per millilitre) were determined by comparison with the standard curve. The lower detection limit for the IL-18 and the IFN-gamma immunoassays was 45 pg/mL, and 5 pg/mL respectively.

Data are expressed as mean and standard deviation. For multiple comparison, the Kruskal-Wallis nonparametric ANOVA test was used. Coefficients of correlations were calculated using the Spearman rank test. p values are considered significant when $p < 0.05$.

RESULTS

To evaluate the role of IL-18 during the course of uncomplicated *P. falciparum* malaria, serum levels of IL-18 and IFN-gamma were tested in 40 adult patients, and were compared with those detected in 15 seronegative healthy donors. A significant increase of serum levels of IL-18 were observed in patients with uncomplicated malaria on admission (876.2 ± 467.9 pg/mL: controls: 160.3 ± 63.9 pg/mL, $p < .0001$), whereas three days later IL-18 levels had decreased, but still remained significantly higher than the controls (636.7 ± 367.5 pg/mL, $p < .0001$) (Figure 1). However, our patients quickly improved after antimalarial treatment (quinine or mefloquine), which was started at admission, and all patients recovered completely from the infection within 7-10 days. Furthermore, we determined circulating levels of IFN-gamma in these patients. As shown in Figure 2, a moderate, but not significant increase of IFN-gamma levels was only observed on admission (24.0 ± 48.8 pg/mL; controls: 7.0 ± 5.6 pg/mL; $p = .0921$).

We also determined correlation between serum levels of IL-18, IFN-gamma and parasitaemia. Parasitaemia show-ed no association with either serum levels of IL-18 or IFN-gamma levels ($r = 0.02667$, $p > 0.05$ and $r = 009018$, $p > 0.05$ respectively).

It is interesting to note that patients with higher levels of IL-18 at days 0 and 3 demonstrated elevated levels of IFN-gamma concomittantly.

DISCUSSION

The present study demonstrates for the first time, elevated levels of IL-18 in adult patients with uncomplicated *P. falciparum* malaria, which decrease

concomittantly with improvement and recovery from the disease. In addition, in these patients, serum levels of IFN-gamma did not significantly change. A peculiar feature of acute *P. falciparum* malaria is impairment of cell-mediated responses. The pathogenesis of both cerebral malaria and severe malarial anemia appear to involve dysregulation of the cytokine arm of the immune response to the infection.

Winkler *et al.* [15] have shown a more pronounced Th2-driven immune response during acute untreated and uncomplicated malaria caused by *P. falciparum*, with a shift towards Th1 responsiveness induced by parasite clearance. During the early stage of mild *P. falciparum* malaria there is activation of the monocyte/macrophage system, which leads to an increase in TNF-alpha, IL-6, and IL-10 [16]. IL-18 is mainly produced by monocytes/macrophages in response to bacterial stimuli [8, 9], and it is considered a proinflammatory cytokine along with TNF and IL-6, especially during the early stages of the infection. In addition, IL-18 has been shown to stimulate production of TNF from T cells [13]. The increased production of IL-18 observed in our patients with uncomplicated *P. falciparum* malaria, followed by reduction of IL-18 levels during the recovery phase of the disease, may represent an efficient and persistent stimulation of Th1 response against malaria infection. In fact, IL-18 is an effective costimulatory factor in the activation of Th1 cells, inasmuch as it is able to induce production of IFN-gamma by natural killer cells and antigen or mitogen-stimulated Th1 cells [10]. In a previous study, circulating levels of IFN-gamma were not increased in patients with uncomplicated malaria [17].

However, patients with higher production of IL-18 at days 0 and 3 also had increased levels of IFN-gamma. It is conceivable that an early production of Th1 cytokines such as IL-12, IFN-gamma and IL-18 is crucial to a better response and resolution of malaria infection.

In this study, we confirmed that IFN-gamma levels were not significantly increased in uncomplicated *P. falciparum* malaria.

Winkler *et al.* [18] have demonstrated that children with severe *P. falciparum* malaria have significantly lower levels of IFN-gamma-secreting CD4 T cells in the peripheral blood than children with uncomplicated malaria. More recently, the same investigators have also demonstrated reduced activity of IL-12 in children with severe *P. falciparum* malaria. These investigators postulate that reduced T

cell mediated IFN-gamma activity in the peripheral blood of these children may be directly implicated in the reduced plasma IL-12 levels observed in the same patients [19]. In our previous study [17], serum levels of IFN-gamma in patients with uncomplicated malaria are neither decreased nor increased. Even though it is well known that IL-18 and IL-12 synergize to stimulate production of IFN-gamma [11, 12], the role of IFN-gamma, as a proinflammatory Th1 cytokine, in acute mild, uncomplicated malaria caused by *P. falciparum* has not yet been clarified. In addition, inability to mount and maintain an adequately balanced immune response, particularly a Th1 cytokine response, may underlie the progression from uncomplicated *P. falciparum* malaria to that with severe complications.

CONCLUSION

In conclusion, the results of this study strongly suggest a role of IL-18 in uncomplicated *P. falciparum* malaria as a proinflammatory Th1 cytokine, since the elimination of intracellular pathogens, including *P. falciparum*, requires activation of Th1 cells with consequent production of Th1 cytokines to initiate an early and prompt cell-mediated immune response.

References

1. World Health Organization. World malaria in 1994. 1997. *Weekly Epidemiol. Rec.* 72: 269.

2. Brasseur P, Agrapart M, Ballet J J, Druilhe P, Warrell M J, Tharavanij S. 1983. Impaired cell-mediated immunity in *Plasmodium falciparum*-infected patients with high parasitemia and cerebral malaria. *Clin. Immunol. Immunopathol.* 27: 38.

3. Riley E M, Andersson G, Otoo L N, Jepsen S, Greenwood B M. 1988. Cellular immune responses to *Plasmodium falciparum* antigens in Gambian children during and after acute attack of *Falciparum malaria*. *Clin. Exp. Immunol.* 73: 17.

4. Stevenson M M, Tam M F. 1993. Differential induction of helper T cell subsets during blood-stage *Plasmodium chabaudi* AS infection in resistant and susceptible mice. *Clin. Exp. Immunol.* 92: 77.

5. Hoffman S L, Crutcher J M, Puri S, Ansari A A, Villinger F, Franke E D, Singh P P, Finkelman F, Gatelx M K, Sedegah M. 1997. Sterile protection of monkeys against malaria after administration of interleukin-12. *Nature Med.* 3: 80.

6. Sedegah M, Finkelman F, Hoffman S L. 1994. Interleukin-12 induction of interferon-gamma-dependent protection against malaria. *Proc. Natl. Acad. Sci. USA* 91: 10700.

7. Stevenson M M, Tam M F, Wolf S F, Sher A. 1995. IL-12-induced protection against blood-stage *Plasmodium chabaudi* AS requires IFN-gamma and TNF-alpha and occurrs *via* a nitric oxide-dependent mechanism. *J. Immunol.* 155: 2545.

8. Okamura H, Tsutsui H, Komatsu T, Youtsudo M, Hakura A, Tanimoto T, *et al.* 1995. Cloning a new cytokine that induces IFN-gamma production by T cells. *Nature* 378: 88.

9. Stoll S, Muller G, Kurimoto M, Saloga J, Tanimoto T, Yamauchi H, Okamura H, Knop J, Enk A H. 1997. Production of IL-18 (IFN-gamma-inducing factor) messenger RNA and functional protein by murine keratinocytes. *J. Immunol.* 159: 298.

10. Kohno K, Kataoka J, Ohtsuki T, Suemoto Y, Okamoto Y, Usui M, Ikeda M, Kurimoto M. 1997. IFN-gamma-inducing factor (IGIF) is a costimulatory factor on the activation of Th1 but not Th2 cells and exerts its effect independently of IL-12. *J. Immunol.* 158: 1541.

11. Takeda K, Tsutsui H, Yoshimoto T, Adachi O, Yoshida N, Kishimoto T, Okamura H, Nakanishi K, Akira S. 1998. Defective NK cell activity and Th1 response in IL-18-deficient mice. *Immunity* 8: 383.

12. Ahn H J, Maruo S, Tomura M, Mu J, Hamaoka T, Nakanishi K, Clark S, Kurimoto M, Okamura H, Fujivara H. 1997. A mechanism underlying synergy between IL-12 and IFN-gamma-inducing factor in enhanced production of IFN-gamma. *J. Immunol.* 159: 2125.

13. Puren A J, Fantuzzi G, Gu Y, Su M S, Dinarello C A. 1998. Interleukin-18 (IFNgamma-inducing factor) induces IL-8 and IL-1beta *via* TNF-alpha production

from non-CD14^{+} human blood mononuclear cells. *J. Clin. Invest.* 101: 711.

14. Pirhonen J, Sareneva T, Kurimoto M, Julkunen I, Matikainen S. 1999. Virus infection activates IL-1beta and IL-18 production in human macrophages by a caspase-1-dependent pathway. *J. Immunol.* 162: 7322.

15. Winkler S, Willheim M, Baier K, Schmid D, Aichelburg A, Graninger W, Kremsner P G. 1998. Reciprocal regulation of Th1-and Th2-cytokine-producing T cells during clearance of parasitemia in *Plasmodium falciparum* malaria. *Infect. Immun.* 66: 6040.

16. Baptista J L, Vanham G, Wery M, Van Marck E. 1997. Cytokine levels during mild and cerebral falciparum malaria in children living in a mesoendemic area. *Trop. Med. Int. Health* 2: 673.

17. Torre D, Ferrario G, Matteelli A, Speranza I, Giola M, Pugliese A, Cantamessa C, Carosi G, Fiori G P. 1998. Levels of circulating nitrate/nitrite and gamma interferon not increased in uncomplicated malaria. *Infection* 26: 301.

18. Winkler S, Willheim M, Baier K, Schmid D, Aichelburg A, Graninger W, Kremsner P G. 1999. Frequency of cytokine-producing T cells in patients of different age groups with *Plasmodium falciparum* malaria. *J. Infect. Dis.* 179: 209.

19. Luty A J, Perkins D J, Lell B, Schmidt-Ott R, Lehman L G, Luckner D, Greve B, Matousek P, Herbich K, Schmid D, Weinberg J B, Kremsner P G. 2000. Low interleukin-12 activity in severe *Plasmodium falciparum* malaria. *Infect. Immun.* 68: 3909.

Figures

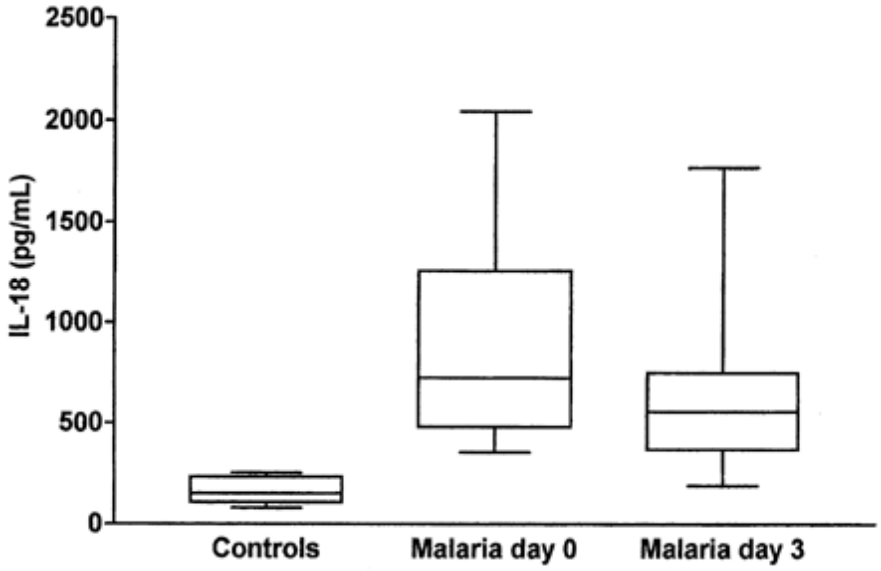


Figure 1

Serum levels of IL-18 in 40 patients with uncomplicated *P. falciparum* malaria, and in 15 healthy control subjects.

Patients had significantly higher levels of IL-18 than healthy controls at day 0 and day 3 ($p < 0.0001$; Kruskal-Wallis nonparametric ANOVA test). The line in the box and whiskers means median value.

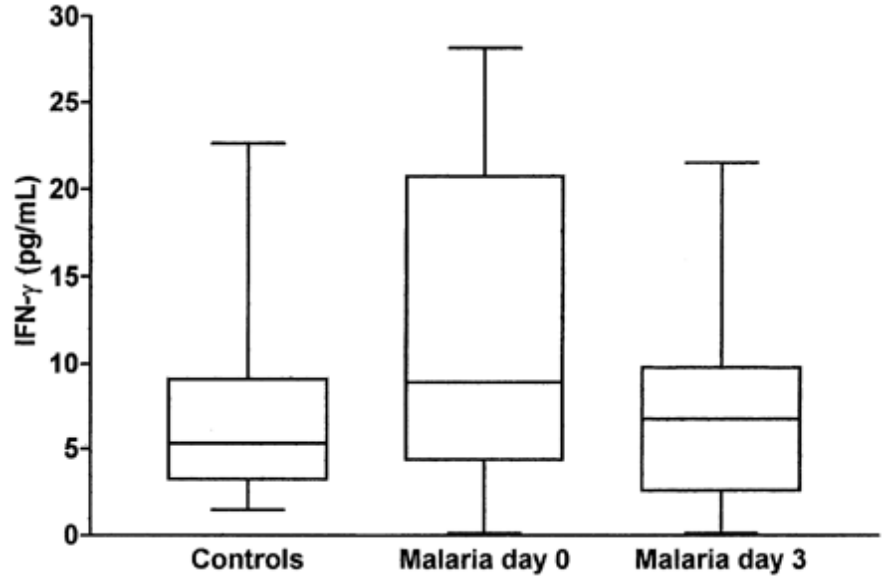


Figure 2

Serum levels of IFN-gamma in 40 patients with uncomplicated *P. falciparum* malaria, and in 15 healthy control subjects.

IFN-gamma levels were not significantly increased at day 0 and day 3 ($p > 0.005$; Kruskal-Wallis nonparametric ANOVA test). The line in the box and whiskers means median value.

Authors

D. Torre, M. Giola, F. Speranza, A. Matteelli, C. Basilico, G. Biondi

Division of Infectious Diseases, Regional Hospital, Viale Borri 57, 21100 Varese, Italy.

In this issue

Regulation of helper T cell responses to staphylococcal superantigens

S.B. Cameron, M.C. Nawijn, W.W.S. Kum, H.F.J. Savelkoul, A.W. Chow
cytokines, Th1, Th2, Tr1, IL-10, staphylococcal superantigens.

Fibronectin increases the migration induced by stromal cell-derived factor-1a (SDF-1a) in pre-B acute lymphoblastic leukemia cells

E. Sbaa-Ketata, M. Vasse, B. Lenormand, P. Schneider, C. Soria, J.P. Vannier
acute lymphoblastic leukemia, SDF-1a, CXCR-4, VLA-4, VLA-5, fibronectin.

Hematopoietic growth factors in patients receiving intensive chemotherapy for malignant disorders: studies of

granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-3 (IL-3) and Flt-3 ligand (Flt3L)

O. Bruserud, B. Foss, H. Petersen
chemotherapy, acute leukemia, G-CSF, GM-CSF, IL-3, Flt3L.

Can interleukin-2 reverse anthracyclin chemoresistance in metastatic soft tissue sarcoma patients. Results of a prospective phase II clinical trial

G. Gravis, M. Mousseau, J.Y. Douillard, T. Dorval, M. Fabbro, B. Escudier, L. Mignot, P. Viens
immunotherapy, soft tissue sarcoma, interleukin-2, chemoresistance, anthracyclin.

Activation of two distinct anti-proliferative pathways, apoptosis and p38 MAP kinase-dependent cell cycle arrest, by tumor necrosis factor in human melanoma cell line A375

T. Hattori, H. Hayashi, T. Chiba, K. Onozaki
melanoma, tumor necrosis factor, apoptosis, cell cycle arrest, p38 MAPK.

Impaired interleukin-5 (IL-5) production by T cells as a prognostic marker of disease progression in human immunodeficiency virus type 1 (HIV-1)-infected children

S. Resino, S. Sanchez-Ramon, J.M. Bellon, J.L. Jimenez, M.A. Munoz-Fernandez
HIV-infected children, cytokine production, interleukin-5, PBMC, prognostic markers.

Cytokine-mediated inflammatory hyperalgesia limited by interleukin-13

B.B. Lorenzetti, S. Poole, F.H. Veiga, F.Q. Cunha, S.H. Ferreira
inflammatory hyperalgesia, interleukin-13, tumour necrosis factor alpha, interleukin-1b, interleukin-8, prostaglandin E2.

Expression of thrombopoietin by umbilical vein endothelial cells

A. El Andaloussi, P. Duchez, J. Rieffers, J. Ripoche, C. Grosset
thrombopoietin, umbilical vein endothelial cells.

Production of cytokines by immature erythroid cells derived from human embryonic liver

S.V. Sennikov, S.V. Krysov, T.V. Injelevskaya, A.N. Silkov, V.A. Kozlov
erythroid progenitor, IL-1b, IL-2, IL-4, IL-6, fetal liver.

Inflammatory cytokine production in interferon-g-primed mice, challenged with lipopolysaccharide. Inhibition by SK&F 86002 and interleukin-1b-converting enzyme inhibitor

S. Spinelle-Jaegle, P. Devillier, S. Doucet, S. Millet, C. Banissi, A. Diu-Hercend, E. Ruuth
interferon-g, lipopolysaccharide, interleukin-1b, cytokine, interleukin-1b-converting enzyme inhibitors.

The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines

V. Barak, T. Halperin, I. Kalickman
Sambucol, inflammatory cytokines, IL-1b, TNF-a, IL-6, IL-8.

Interferon (IFN)-g and Herpes simplex virus/tumor necrosis factor-a synergistically induce nitric oxide synthase 2 in macrophages through cooperative action of nuclear factor-kB and IFN regulatory factor-1

S.R. Paludan, L. Malmgaard, S. Ellermann-Eriksen, L. Bosca, S.C. Mogensen
macrophages, NOS2, Herpes simplex virus, NF-kB, IRF-1.

Negative regulation of onconstatin M signaling by suppressor of cytokine signaling (SOCS-3)

F. Magrangeas, O. Boisteau, S. Denis, Y. Jacques, S. Minvielle
cytokine signaling, inhibition, Jak-STAT pathway.

Increased expression of interleukin-8 and aminopeptidase N by cell-cell contact: interleukin-8 is resistant to degradation by aminopeptidase N/CD13

A. Kehlen, I. Egbert, K. Thiele, K. Fischer, D. Riemann, J. Langner
cell co-culturing, leucine aminopeptidase, plasma membrane preparations, CD13, proteolysis of IL-8, interleukin-8.

Functional characterization of the mouse lymphotoxin-beta receptor promoter

P. Muller, D.N. Männel, T. Hehlgans
LTbR-promoter, transcriptional activation, dexamethasone.

Glucose potentiates interleukin-1b (IL-1b)-induced p38 mitogen-activated protein kinase activity in rat pancreatic islets of Langerhans

A.M.E. Sprinkel, N.A. Andersen, T. Mandrup-Poulsen
interleukin-1b, p38, ERK1/2, JNK, nitric oxide, diabetes mellitus.

Sustained parasite burden in the spleen of Leishmania infantum-infected BALB/c mice is accompanied by expression of MCP-1 transcripts and lack of protection against challenge

D. Rousseau, S. Demartino, F. Anjuère, B. Ferrua, K. Fragaki, Y. Le Fichoux, J. Kubar
murine leishmaniasis, acquired immunity, inflammation, chemokines, spleen cell subpopulations.

Effects of cytokines and prolactin on the replication of Toxoplasma gondii in murine microglia

N. Benedetto, A. Folgore, C. Romano-Carratelli, F. Galdiero
T. gondii, cytokine, PRL, MGC.

Strip test for bedside detection of interleukin-6 in cervical secretions is predictive for impending preterm delivery

H. Trébéden, F. Goffinet, G. Kayem, F. Maillard, E. Lemoine, D. Cabrol, B. Weill, F. Batteux
cytokine, IL-6, prematurity, cervicovaginal secretions, strip test.

Serum levels of interleukin-18 in patients with uncomplicated Plasmodium falciparum malaria

D. Torre, M. Giola, F. Speranza, A. Matteelli, C. Basilico, G. Biondi
interleukin-18, malaria, Plasmodium falciparum, gamma interferon.

The ecdysone inducible gene expression system: unexpected effects of muristerone A and ponasterone A on cytokine signaling in mammalian cells

S. Constantino, R. Santos, S. Gisselbrecht, F. Gouilleux

ecdysone, PI 3-kinase, AKT, survival.

Presence of estrogen receptors in human myeloid monocytic cells (THP-1 cell line)

M. Cutolo, B. Villaggio, A. Bisso, A. Sulli, D. Coviello, J.M. Dayer

THP-1 cells, macrophages, estrogen receptors, estrogens, monocytes.

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



