

Volume 12, issue 1, March 2001 | Articles originaux

Transforming growth factor-b inhibits interleukin-10 synthesis by human monocytic cells.

Abstract

Transforming growth factor-b (TGF-b1) enhances interleukin-10 (IL-10) synthesis by mouse monocytes/macrophages, suggesting a potential role of IL-10 in mediating some of the anti-inflammatory properties of TGF-b1. Since differences exist between the transcriptional regulation of human and mouse IL-10, the studies reported here examined whether TGF-b1 up-regulated IL-10 production by human monocytes/macrophages as well. Exposure of PMA-differentiated U. 937 promonocytic cells to TGF-b1 resulted in an unexpected,

dose-dependent decrease in IL-10 production as assessed by specific ELISA. TGF-b1 was effective when added at the time of the PMA stimulus or 6 hours after. In addition, TGF-b1 suppressed induction of IL-10 by three different stimuli other than PMA. TGF-b1 inhibition of IL-10 protein release was associated with proportional changes in IL-10 mRNA accumulation as assessed by quantitative kinetic ELISA PCR. This would result from a decrease in IL-10 gene transcription as TGF-b1 did not affect IL-10 mRNA stability, and TGF-b1 limited the luciferase activity in cells transfected with reporter gene constructs containing 1,308 bp of the 5' non-coding sequence of human IL-10 gene. Blocking tumour necrosis factor-a (TNF-a) with neutralizing anti-TNFa antibody did not modify the response to TGF-b1, indicating the involvement of TNF-a-independent mechanisms in the overall process. Thus, the present study provides the first evidence that TGF-b1 prevents IL-10 production by human monocytic cells at a transcriptional level.

Full text

INTRODUCTION

In addition to its role in development, cell proliferation, cell differentiation and extracellular matrix production, TGF-beta exerts key anti-inflammatory properties. *In vitro* studies have demonstrated that TGF-beta1 suppresses the capacity of monocytes/macrophages to release reactive oxygen intermediates [1], reactive nitrogen intermediates [2] and proinflammatory cytokines [3, 4]. *In vivo*, TGF-beta1-null mutation in mice causes dramatic inflammatory lesions with massive infiltration of lymphocytes and macrophages in tissues such as heart and lungs [5, 6]. Conversely, gene transfer of plasmid DNA encoding TGF-beta1 suppresses inflammatory lesions as seen in an arthritis model [7]. TGF-beta1 appears to share a number of anti-inflammatory properties with IL-10 [8, 9]. The importance of IL-10 in inhibiting inflammation is indicated by the phenotype of IL-10-null mice, which develop inflammatory lesions, mainly in the intestinal tract [10]. In addition, both gene transfer of plasmid DNA encoding IL-10 and administration of recombinant IL-10-blunt inflammatory lesions, for instance in glomerulonephritis models [11].

Recently, TGF-beta1 has been shown to enhance IL-10 synthesis by mouse cells, suggesting an involvement of IL-10 in the anti-inflammatory activities of TGF-beta1. Firstly, studies from our laboratories have demonstrated that TGF-beta1

increases LPS-induced IL-10 generation by mouse mesangial cells [12]. TGF-beta1 has been shown to also up-regulate IL-10 synthesis by mouse macrophages [13, 14] and rat hepatic stellate cells [15]. Whether TGF-beta1 also enhances IL-10 synthesis by human monocytes/macrophages remains to be confirmed.

To this end, we evaluated the influence of TGF-beta1 on IL-10 synthesis by U. 937 cells, a human promonocytic cell line. In addition, we examined the possible mechanisms by which TGF-beta1 may exert its influence. The results provide the first evidence that TGF-beta1, instead of increasing, dramatically decreases IL-10 release from human monocytes/macrophages. This regulation appears to be mediated, at least in part, *via* inhibition of IL-10 gene transcription.

METHODS

Cells. The promonocytic U. 937 cell line was purchased from the American Type Culture Collection (Rockville, MD, USA) and maintained in RPMI 1640 supplemented with 10% FCS, 10 mM HEPES and antibiotics (culture medium) in a humidified incubator (95% air and 5% CO_2). These cells were differentiated to a mature macrophage-like phenotype, as previously described [16]: 0.5×10^6 cells per ml were pretreated for 24 hours with 1.2% DMSO, washed twice with PBS and resuspended at 10^6 cells, in 0.5 ml per well of culture medium (24-well plates). They were stimulated by either PMA (50 ng/ml; Sigma Chemical Co., St Louis, Mo, USA), *Escherichia coli* LPS (serotype 026B6 10 mug/ml; Sigma), TNF-alpha (5 ng/ml; Genzyme, Cambridge, MA, USA) or dibutyryl-cAMP (100 muM; Sigma) with or without ultrapure natural human TGF-beta1 (0-50 ng/ml; Genzyme) and polyclonal neutralizing antibody to TNF-alpha (Genzyme). The effects of agents either on cell growth and cell viability were determined by measuring cell number with a hematocytometer, and cell exclusion of trypan blue dye, respectively. Monocytes were obtained by plastic adherence of peripheral blood mononuclear cells from healthy volunteers, as previously described [17].

ELISA for IL-10. The supernatants were harvested after 24 hours, centrifuged to remove cell debris, and stored at - 70° C until they were analyzed for IL-10. Concentrations of IL-10 were measured by ELISA (PeliKine Compact human IL-10 ELISA kit, CLB, Amsterdam, The Netherlands). The minimum detectable concentration was 3 pg/ml.

Quantitative ELISA-polymerase chain reaction at saturation for IL-10 mRNA. Total cellular RNA was extracted from 0.1 x 10^6 cells using the RNAble kit (Eurobio, Les Ulis, France) with a co-precipitant (Pellet Paint, Novagen, Madison, WI, USA) according to the protocol of the supplier. RNA was resuspended in 40 mul and reverse transcription carried out on 10 mul of RNA in a volume of 20 mul using random hexamers and oligo-dT and avian myeloblastosis virus transcriptase (Promoga, Madison, WI, USA) as described [18]. Quantitative PCR was carried out using an homologous DNA internal standard (IS) as described in ref 19, with the primers described in ref 18 and 20. Briefly, the IS was spiked in the PCR mix and an external scale, made of serial dilutions of purified cDNA amplicons (GAPDH or IL-10), was amplified in every experiment. After 42 PCR cycles, the amount of cDNA and of IS was quantified by a luminometric ELISA system [18]. The ratios of the cDNA/IS signals of the unknowns were compared to those of the scale by linear regression, allowing absolute values to be found. The ratio of IL-10 to GAPDH were computed for each sample, to normalize for RNA yield and RT efficiency and the duplicate values were averaged.

Cell transfection and reporter gene assay. The effect of TGF-beta1on IL-10 gene transcription was analyzed by transiently transfecting U. 937 cells with an IL-10 promoter-luciferase reporter plasmid (a kind gift of Dr. H.D. Volk, Humboldt University, Berlin, Germany). This plasmid contains a 1,308-bp fragment from the 5' non-coding sequence of the human IL-10 gene that was subcloned into the *Kpnl* and *Pst I* sites of the luciferase reporter vector pGL2-Basic (Promega) to generate the construct pGL2-IL-10 [21]. After 24 hours of DMSO pretreatment, U. 937 cells in suspension were transfected with 2.5 mug plasmid DNA per 10^7 cells using the DEAE-dextran procedure, as described elsewhere [22]. At 2 hours after transfection, U. 937 cells were plated onto 6-well plates at a density of 4 x 10^6 cells/well and stimulated with PMA (50 ng/ml) or dibutyryl cAMP (100 muM) together with or without TGF-beta1 (1 ng/ml) for 24 hours. Luciferase activity was measured as previously described [22].

Statistics. Results are presented as the mean ± SD from *n* determinations. Differences between groups were assessed by Student's *t*-test. Statistical significance was set at $p < 0.05$.

RESULTS

*TGF-*beta*1 inhibits IL-10 production in PMA-differentiated U. 937 cells*

To determine if TGF-beta1 affects IL-10 production by PMA-differentiated U. 937 cells, DMSO-treated cells were stimulated with PMA together with or without different concentrations of TGF-beta1 for 24 hours. Supernatants were harvested at this time point and tested for IL-10 using a specific ELISA. The addition of TGF-beta1 dose-dependently decreased the IL-10 concentration (Figure 1). At the highest dose, IL-10 synthesis was suppressed by more than 90%. Under these conditions, cell number and cell viability were not decreased (97.6 ± 1.5% and 95.1 ± 0.8% cell viability after 24 hours exposure to 0 and 50 ng/ml TGF-beta1, respectively). In a further set of experiments, the time dependence of the TGF-beta1 inhibitory effects was examined. TGF-beta1 was effective when added at the time or up to 6 hours after cell stimulation with PMA (Figure 2).

To determine whether different pathways of IL-10 induction were susceptible to inhibition by TGF-beta1, undifferentiated U. 937 cells were stimulated with LPS, TNF-alpha or dibutyryl cAMP (Figure 3). All agents induced IL-10 expression, as shown previously [23]. The addition of TGF-beta1 dose-dependently inhibited this induction. This is consistent with TGF-beta1 having a broad effect on various pathways of IL-10 induction rather than a specific effect on PMA-signaling.

To further investigate the effect of TGF-beta1 on IL-10 production by human monocytes/macrophages, a subset of experiments was repeated using blood monocytes. Exposure of these cells to 10 ng/ml TGF-beta1 for 24 hours caused a 34.1 ± 13.7% decrease in IL-10 production (Table 1).

*TGF-*beta*1 inhibits IL-10 mRNA expression in PMA-differentiated U. 937 cells*

To determine whether IL-10 inhibition by TGF-beta1 was regulated at the transcriptional level, total RNA was isolated form U. 937 cells stimulated with PMA together with or without different concentrations of TGF-beta1 for 3 hours, and quantitative kinetic ELISA PCR was performed. The addition of TGF-beta1 dose-dependently decreased IL-10 mRNA expression (Figure 4A). The inhibition reached 92% at 5 ng/ml TGF-beta1 . The mechanisms whereby TGF-beta1 decreased IL-10 mRNA may include a decrease in IL-10 gene transcription and/or a decrease in IL-10 mRNA stability. To address this issue, the half-life of IL-10 mRNA was determined by measuring the IL-10 mRNA level after cell exposure to 5,6-dichloro-1-beta-D-ribofuranosyl benzimidazole (DRB), a specific RNA polymerase II inhibitor. As shown in Figure 4B, the decay of IL-10 mRNA was fast

after DRB addition and obviously not accelerated by TGF-beta1. Thus TGF-beta1 effect on IL-10 mRNA levels may possibly be due to an effect on IL-10 gene transcription.

To further evaluate whether IL-10 mRNA expression was transcriptionally regulated by TGF-beta1, transient transfection assays were performed with a promoter-luciferase gene construct containing a IL-10 promoter fragment (1,308 bp upstream from the start codon). The levels of luciferase activity were determined after stimulation of U. 397 cells with either PMA or dibutyryl cAMP, in the absence or presence of TGF-beta1 (Figure 5). A low level of luciferase activity was detected in unstimulated U. 937 cells. Either PMA or dibutyryl cAMP stimulated the promoter activity of the construct. This response was completely suppressed by the addition of 1 ng/ml TGF-beta1.

*TGF-*beta*1 inhibits IL-10 production in PMA-differentiated U. 937 cells through TNF-*alpha*-independent mechanisms*

TGF-beta1 has previously been demonstrated to blunt the release of TNF-alpha from mononuclear cells [3]. Since TNF-alpha plays a predominant role in human monocyte IL-10 synthesis [24], this suggests that a decrease in TNF-alpha availability might participate in the TGF-beta1-mediated inhibition of IL-10 production. Therefore, in a further set of experiments, this possible action of TNF-alpha was prevented by the addition of neutralizing anti-TNF-alpha antibody (Figure 6). This slightly reduced IL-10 production by PMA-differentiated U. 937 cells but did not affect the response of these cells to TGF-beta1. Thus, TNF-alpha limitation is not involved in IL-10 decrease after cell exposure to TGF-beta1.

DISCUSSION

A number of previous studies have documented the induction of IL-10 in mouse monocytes/macrophages following either *in vitro* or *in vivo* exposure to TGF-beta1 [12-14]. Thus, at the start of these studies, we hypothesized that TGF-beta1 would stimulate IL-10 synthesis by human monocytic cells as well. This did not, however, prove to be true. On the contrary, the studies demonstrate that TGF-beta1 rather prevented IL-10 synthesis by U. 937 monocytic cells. Such opposite effects can not be explained by differences in the treatment of cells by TGF-beta1. In the present study as in previous studies [12, 14, 15], effective

concentrations of TGF-beta1 ranged between 0.1 and 50 ng/ml. Concentrations of TGF-beta1 ranging between 0.001 and 0.05 ng/ml were without effect (data not shown). In addition, this result does not reflect a cytotoxic effect of TGF-beta1 against U. 937 cells as the viability of these cells was not decreased even at the highest TGF-beta1 concentration tested. This is in agreement with previous studies showing that TGF-beta1 does not affect proliferation and viability of U. 937 cells up to a concentration of 10 ng/ml [25].

The present study also shows that TGF-beta1 suppressed IL-10 mRNA expression in U. 937 cells to the same extent as IL-10 protein release. This is presumably the result of transcriptional inhibition rather than mRNA decay. Indeed, TGF-beta1 which did not modify IL-10 mRNA drops after inhibition of RNA *de novo* synthesis, decreased IL-10 promoter activity. The molecular mechanisms that account for such a decrease have not been identified. One likely possibility is that TGF-beta1 exerts a direct effect on the regulation of IL-10 gene transcription. Cloning and sequencing of the 5' regulatory region of the human IL-10 gene have revealed numerous sequence elements potentially involved in that regulation [21, 26, 27]. They include TATA box, IFN-enhancer core sequence and responsive elements to glucocorticoid, cAMP, AP-1, AP-2 and Sp1. Since both AP-1 and Sp1 participate in the transcriptional responses to TGF-beta1 [28], the cognate responsive elements could be particularly involved in the suppression of IL-10 gene transcription. Interestingly, the Sp 1 recognition site is located in a promoter region that suppresses IL-10 expression in B cells [26]. Thus, it may be speculated that Sp 1 induction is key event underlying TGF-beta1-suppression of IL-10 gene transcription in U. 937 monocytic cells. Alternatively, TGF-beta1 might interfere with the cAMP signaling pathway that participates in PMA-induced differentiation of U. 937 cells [29]. This mechanism is supported by the results demonstrating that TGF-beta1 also suppressed IL-10 release from U. 937 cells stimulated with dibutyryl cAMP instead of PMA.

A second possibility is that TGF-beta1 suppresses IL-10 mRNA expression indirectly by limiting the availability of other cytokines responsible for IL-10 induction. Prominent in this regard is the importance of TNF-alpha. TNF-alpha has been previously identified as the main inducer of IL-10 in human monocytes [24]. Our studies add to this data by demonstrating that a neutralizing anti-TNF-alpha antibody significantly decreased IL-10 induction in PMA-differentiated U. 937 cells. However, while TGF-beta has been shown to limit TNF-alpha synthesis in human mononuclear cells [3], this inhibition was not mandatory for IL-10

suppression in PMA-differentiated U. 937 cells. Indeed, no change in the response of these cells to TGF-beta1 has been observed upon exposure to neutralizing anti-TNF-alpha antibody. Thus, more experiments are needed to determine if an indirect mechanism is involved in the regulation of IL-10 suppression by TGF-beta1.

The *in vitro* and *in vivo* relevance of TGF-beta1-induced IL-10 suppression remains to be established. TGF-beta1 and IL-10 may constitute a cascade of cytokines produced sequentially to limit the development of inflammatory responses. The results of studies analyzing TGF-beta1 and IL-10 expression at different time points of human monocyte differentiation into macrophages have demonstrated a progressive inability of the cells to produce TGF-beta1, in contrast to an intact ability to produce IL-10 [30]. Our study suggests that the lack of TGF-beta1 is potentially critical to that prolonged expression of IL-10.

CONCLUSION

Acknowledgments. This work was supported by INSERM and the Faculté de Médecine Saint-Antoine. We thank C. Platzer and H.D. Volk for the generous gift of pGL2-IL-10 construct, Joëlle Perz for technical assistance and N. Ourtirane for secretarial assistance.

References

1. Tsunawaki S, Sporn M, Ding A, Nathan C. 1988. Deactivation of macrophages by transforming growth factor-beta. *Nature* 334: 260.

2. Boutard V, Havouis R, Fouqueray B, Philippe C, Moulinoux J P, Baud L. 1995. Transforming growth factor-beta stimulates arginase activity in macrophages. Implications for the regulation of macrophage cytotoxicity. *J. Immunol.* 155: 2077.

3. Chantry D, Turner M, Abney E, Feldmann M. 1989. Modulation of cytokine production by transforming growth factor-beta. *J. Immunol.* 142: 4295.

4. Maltman J, Pragnell IB, Graham GJ. 1996. Specificity and reciprocity in the interactions between TGF-beta and macrophage inflammatory protein-1alpha. *J. Immunol.* 156: 1566.

5. Kulkarni AB, Huh C G, Becker D, Geiser A, Lyght M, Flanders K C, Roberts A B, Sporn M B, Ward J M, Karlsson S. 1993. Transforming growth factor-beta1 null mutation in mice causes excessive inflammatory response and early death. *Proc. Natl. Acad. Sci. USA* 90: 770.

6. Kulkarni A B, Karlsson S. 1993. Transforming growth factor-beta1 knock-out mice. A mutation in one cytokine gene causes a dramatic inflammatory disease. (Review) *Am. J. Pathol.* 143: 3.

7. Song X Y, Gu M, Jin W W, Klinman D M, Wahl S M. 1998. Plasmid DNA encoding transforming growth factor-beta1 suppresses chronic disease in a streptococcal cell wall-induced arthritis model. *J. Clin. Invest.* 101: 2615.

8. Bogdan C, Nathan C. 1993. Modulation of macrophage function by transforming growth factor-beta, interleukin-4, and interleukin-10. *Ann. N.Y. Acad. Sci.* 685: 713.

9. Bogdan C, Vodovotz Y, Paik J, Nathan C. 1992. Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-beta and interleukin-10. *J. Biol. Chem.* 267: 23301.

10. Kühn R, Löhler J, Rennick D, Rajewsky K, Müller W. 1993. Interleukin-10 deficient mice develop chronic enterocolitis. *Cell* 75: 263.

11. Baud L, Fouqueray B, Bellocq A. 1998. Switching off renal inflammation by anti-inflammatory mediators: the facts, the promise and the hope. (Review) *Kidney Int.* 53: 1118.

12. Fouqueray B, Boutard V, Philippe C, Kornreich A, Marchant A, Perez J, Goldman M, Baud L. 1995. Mesangial cell-derived interleukin-10 modulates mesangial cell response to lipopolysaccharide. *Am. J. Pathol.* 147: 176.

13. Maeda H, Kuwahara H, Ichimura Y, Ohtsuki M, Kurakata S, Shiraishi A. 1995. TGF-beta enhances macrophage ability to produce IL-10 in normal and tumor-bearing mice. *J. Immunol.* 155: 4926.

14. d'Orazio T J, Niederkorn J Y. 1998. A novel role for TGF-beta and IL-10 in the induction of immune privilege. *J. Immunol.* 160: 2089.

15. Wang S C, Ohata M, Schrum L, Rippe R A, Tsukamoto H. 1998. Expression of interleukin-10 by *in vitro* and *in vivo* activated hepatic stellate cells. *J. Biol. Chem.* 273: 302.

16. Brigino E, Haraguchi S, Koutsonikolis A, Cianciolo G J, Owens U, Good R A, Day N K. 1997. Interleukin-10 is induced by recombinant HIV-1 Nef protein involving the calcium/calmodulin-dependent phosphodiesterase signal transduction pathway. *Proc. Natl. Acad. Sci. USA* 94: 3178.

17. Philippe C, Roux-Lombard P, Fouqueray B, Perez J, Dayer J M, Baud L. 1993. Membrane expression and shedding of tumour necrosis factor receptors during activation of human blood monocytes: regulation by desferrioxamine. *Immunology* 80: 300.

18. Alard P, Lantz O, Sebagh M, Calvo CF, Weill D, Chavanel G, Senik A, Charpentier B. 1993. A versatile ELISA-PCR assay for mRNA quantitation from a few cells. *Biotechniques* 15: 730.

19. Taoufik Y, Froger D, Benoliel S, Wallon C, Dussaix E, Delfraissy J F, Lantz O. 1998. Quantitative ELISA-polymerase chain reaction at saturation using homologous internal DNA standards and chemiluminescence revelation. *Eur. Cytokine Netw.* 9: 197.

20. Taoufik Y, Lantz O, Wallon C, Charles A, Dussaix E, Delfraissy J F. 1997. Human immunodeficiency virus gp120 inhibits interleukin-12 secretion by human monocytes: an indirect interleukin-10-mediated effect. *Blood* 89: 2842.

21. Platzer C, Meisel C, Vogt K, Platzer M, Volk H D. 1995. Up-regulation of monocytic IL-10 by tumor necrosis factor-a and cAMP elevating drugs. *Int. Immunol.* 7: 517.

22. Bellocq A, Suberville S, Philippe C, Bertrand F, Perez J, Fouqueray B, Cherqui G, Baud L. 1998. Low environmental pH is responsible for the induction of nitric-oxide synthase in macrophages. Evidence for involvement of nuclear factor-kappaB activation. *J. Biol. Chem.* 273: 5086.

23. Meisel C, Vogt K, Platzer C, Randow F, Liebenthal C, Volk H D. 1996. Differential regulation of monocyte tumor necrosis factor-alpha and interleukin-10

expression. *Eur. J. Immunol.* 26: 1580.

24. Wanidworanun C, Strober W. 1993. Predominant role of tumor necrosis factor-alpha in human monocyte IL-10 synthesis. *J. Immunol.* 151: 6853.

25. Kamijo R, Takeda K, Nagumo M, Konno K. 1990. Effects of combinations of transforming growth factor-beta1 and tumor necrosis factor on induction of differentiation of human myelogenous leukemic cell lines. *J. Immunol.* 144: 1311.

26. Kube D, Platzer C, von Knethen A, Straub H, Bohlen H, Hafner M, Tesch H. 1995. Isolation of the human interleukin-10 promoter. Characterization of the promoter activity in Burkitt's lymphoma cell lines. *Cytokine* 7: 1.

27. Eskdale J, Kube D, Tesch H, Gallagher G. 1997. Mapping of the human IL-10 gene and further characterization of the 5' flanking sequence. *Immunogenetics* 46: 120.

28. Heldin C H, Miyazono K, ten Dijke P T. 1997. TGF-beta signalling from cell membrane to nucleus through SMAD proteins. (Review) *Nature* 390: 465.

29. Nambu M, Morita M, Watanabe H, Uenoyama Y, Kim K M, Tanaka M, Iwai Y, Kimata H, Mayumi M, Mikawa H. 1989. Regulation of Fcg receptor expression and phagocytosis of a human monoblast cell line U. 937. Participation of cAMP and protein kinase C in the effects of INF-gamma and phorbol ester. *J. Immunol.* 143: 4158.

30. Toossi Z, Hirsch C S, Hamilton B D, Knuth C K, Friedlander M A, Rich E A. 1996. Decreased production of TGF-beta by human alveolar macrophages compared with blood monocytes. *J. Immunol.* 156: 3461.

Figures

























Table 1
Inhibition of IL-10 production by TGF-beta1 in human monocytes[a]

Addition of TGF-beta 1 (ng/ml)	Concentration of IL-10 (pg/ml)
0	58.0 ± 2.0
10	38.0 ± 6.9[b]

[a] Monocytes were incubated with the indicated concentrations of TGF-beta1 for 24 hours. IL-10 concentration in culture supernatant samples was assessed using a specific ELISA. Results are expressed as the mean ± SD of values obtained in 3 individual experiments.
[b] $p < 0.01$ as compared with TGF-beta1-untreated cells.

Authors

S. Suberville, A. Bellocq, I. Peguillet, O. Lantz, P. Stordeur, B. Fouqueray, L. Baud

Service d'Explorations Fonctionnelles Multidisciplinaires, Hôpital Tenon, 4, rue de la Chine, 75020 Paris, France.

In this issue

Regulation of interferon-g receptor (INF-gR) chains: a peculiar way to rule the life and death of human lymphocytes.

P. Bernabei, A. Allione, L. Rigamonti, M. Bosticardo, G. Losana, I. Borghi, G. Forni, F. Novelli
human, IFN-g, IFN-g receptor, signal transduction, cellular proliferation, apoptosis.

The interleukin-6 cytokine system in embryonic development, embryo-maternal interactions and cardiogenesis.

P. Seiler, G. Plenz, M.C. Deng
interleukin-6, embryo, blastocyst, endometrium, heart, gp130.

Role of cytokines in the modulation of nitric oxide production by cyclic AMP.

Z. Zidek
cyclic AMP, prostaglandins, nitric oxide, interleukin-10, tumor necrosis factor-a, interferon-g.

The 3' untranslated region of tumor necrosis factor-a is highly conserved in idiopathic pulmonary fibrosis (IPF).

R.W. Freeburn, H. Kendall, L. Dobson, J. Egan, N.J. Simler, A.B. Millar
TNF-a, idiopathic pulmonary fibrosis, polymorphism.

Endogenous interferon-g impairs bacterial clearance from lungs during Pseudomonas aeruginosa pneumonia.

M.J. Schultz, A.W. Rijneveld, P. Speelman, S.J.H. van Deventer, T. van der Poll
interferon-g, cytokines, host defense, Pseudomonas aeruginosa, pneumonia.

Development of allergic contact dermatitis requires activation of both tumor necrosis factor-receptors.

F.M. Becke, T. Hehlgans, G. Brockhoff, D.N. Männel
allergic contact dermatitis, p75TNF receptor, p55TNF receptor, Langerhans cells, dendritic cells.

Transforming growth factor beta-1 and interferon-alpha in the aids dementia complex: possible relationship with cerebral viral load?

O. Perrella, P.B. Carreiri, A. Perrella, C. Sbreglia, F. Gorga, D. Guarnaccia, G. Tarantino
transforming growth factor-beta1, HIV-RNA, AIDS-dementia complex, interferon-alpha.

Interferon-beta (INF-b) antibodies in interferon-b1a- and interferon-b1b-treated multiple sclerosis patients. Prevalence, kinetics, cross-reactivity, and factors enhancing interferon-b immunogenicity in vivo.

P. Perini, A. Facchinetti, P. Bulian, A.R. Massaro, D. De Pascalis, A. Bertolotto, G. Biasi, P. Gallo
interferon-beta, natural autoantibodies, multiple sclerosis.

The promoter polymorphism of the interleukin-6 gene regulates interleukin-6 production in neonates but not in

adults.

S. Kilpinen, J. Hulkkonen, X.Y. Wang, M. Hurme
interleukin-6, cord blood, gene polymorphism, inflammatory mediators.

The hepatitis C virus (HCV) induces a long-term increase in interleukin-10 production by human CD4+ T cells (H9).

O. Delpuech, D. Buffello-Le Guillou, E. Rubinstein, C. Féray, M.A. Petit
HCV-RNA, interleukin-10, H9 T cells, CD81, capsid mutation, protein kinase C.

Retrovirus-mediated gene transfer of the cytokine genes interleukin-1b and tumor necrosis factor-a into human neuroblastoma cells: consequences for cell line behavior and immunomodulatory properties.

C. Coze, T. Leimig, M.T. Jimeno, P. Mannoni
neuroblastoma, immunotherapy, gene therapy, cytokine, IL-1b, TNF-a.

Characterisation of cytokine mRNA expression in tumour-infiltrating mononuclear cells and tumour cells freshly isolated from human colorectal carcinomas.

A. Csiszar, T. Szentes, B. Haraszti, W. Zou, D. Emilie, G. Petranyi, E. Pocsik
colorectal cancer, tumour-infiltrating lymphocytes, cytokines, gene expression, RT-PCR.

Analysis of interleukin-18, interleukin-1 converting enzyme (ICE) and interleukin-18-related cytokines in Crohnís disease lesions.

F. Pagès, V. Lazar, A. Berger, C. Danel, S. Lebel-Binay, F. Zinzindohoué, P. Desreumaux, C. Cellier, N. Thiounn, D. Bellet, P.H. Cugnenc, W.H. Fridman
intestinal mucosa, Crohn's disease, interleukin-18, caspase-1/ICE, immunohistochemistry, reverse transcription polymerase chain reaction.

Daily production of human tumor necrosis factor in lipopolysaccharide (LPS)-stimulated ex vivo blood culture assays.

J.C. Aguillon, A. Escobar, V. Ferreira, A. Aguirre, L. Ferreira, M.C. Molina, A. Ferreira
TNF, cytokine, LPS.

Inducible nitric oxide synthase attenuates chronic colitis in human histocompatibility antigen HLA-B27/human b2 microglobulin transgenic rats.

H.S. Blanchard, E. Dernis-Labous, D. Lamarque, J. Tran van Nhieu, Z. Szepes, J.F. Fléjou, E. Wollman, B.J.R. Whittle, M. Breban
rodent, inflammation, nitric oxide, cytokines, in vivo animal models.

Up-regulation of mucin secretion in HT29-MTX cells by the pro-inflammatory cytokines tumor necrosis factor-a and interleukin-6.

M.G. Smirnova, S.L. Kiselev, J.P. Birchall, J.P. Pearson
MUC5AC, MUC5B, mucus-secreting cell line HT29-MTX.

A Jurkat T cell variant resistant to death receptor-induced apoptosis. Correlation with heat shock protein 27 and 70 levels.

J.E. Ricci, L. Maulon, V. Battaglione-Hofman, C. Bertolotto, F. Luciano, B. Mari, P. Hofman, P. Auberger
apoptosis, caspases, Hsp27, Hsp70, T lymphocytes.

Increased cell surface expression of histocompatibility class II IAd in c-FOS transfected clones of the P388D1 murine macrophage cell line.

Y. Le Garrec, E. Rouer, F. Conti, P. Michel, A. Pompidou
MHC class II antigens, murine macrophages, c-Fos.

Transforming growth factor-b inhibits interleukin-10 synthesis by human monocytic cells.

S. Suberville, A. Bellocq, I. Peguillet, O. Lantz, P. Stordeur, B. Fouqueray, L. Baud
transforming growth factor-b1, interleukin-10, U. 937 cells.

Evidence for tumor necrosis factor receptors (TNFRs) in human MRC5 fibroblast cells.

D. Derouich-Guergour, H. Pelloux, D. Aldebert, P. Demenge, P. Ambroise-Thomas
MRC5, fibroblasts, TNF receptor, RT-PCR, binding, flow cytometry.

Interleukin-9 induces 24P3 lipocalin gene expression in murine T cell lymphomas.

C. Orabona, L. Dumoutier, J.C. Renauld
cytokines, lipocalin, IL-9, 24P3.

Contrasting effect of interleukin-4 on the expression of cytosolic phospholipase A2, 5-lipoxygenase and 5-lipoxygenase-activating protein in peritoneal macrophages from control and ovalbumin-sensitized rats.

L. Escoubet-Lozach, C.F. M'Rini, A. Rey, M. Béraud, J.C. Lepert, J. Bernard, J.R. Mathieu, B. Pipy
cytokines, lipid mediators, macrophages, rat.

Fibrinogen cooperates with cytokines to induce interleukin-6 receptor mRNA expression in human hematopoietic CD34+ progenitors.

A. Hatzfeld, B. Panterne, N.O. Fortunel, M.N. Monier, J.A. Hatzfeld
human CD34+ cells, fibrinogen, competence factor, IL-6 receptor.

Balance between autocrine interleukin-1b and caspases defines life versus death of polymorphonuclear cells.

P. Bossù, E. del Grosso, M.P. Cesaroni, G. Maurizi, N. Balestro, A. Stoppacciaro, E. del Giudice, P. Ruggiero, D. Boraschi
apoptosis, interleukin-1, caspases, polymorphonuclear leukocytes, ICE.

Rat interleukin-10: production and characterisation of biologically active protein in a recombinant bacterial expression system.

V. Ball, S. Vigues, C.K. Gee, S. Poole, A.F. Bristow
IL-10, recombinant, rat, cytokines.

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