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

Abstract

Growing evidence shows that cytokines of the IL-6 family play an important regulatory role in heart physiology such as inducing cardiomyocyte hypertrophy. The purpose of this study was to see if IL-6 and its soluble receptors (sIL-6R and sgp130) could be detected in pericardial fluids, and to see if they are produced by the pericardium. We report that human pericardial fluid from patients with coronary pathologies contained IL-6, sIL-6R, and sgp130. However, the levels present in sera and pericardial fluid did not correlate, which suggests local

production. This observation was confirmed by in vitro studies demonstrating massive IL-6 production by cultured pericardial samples, which could be strongly inhibited by methylprednisolone. RT-PCR studies revealed that IL-6 was weakly expressed in fresh tissues and strongly induced after culture. In situ hybridisation and immunohistochemical analysis showed that IL-6 and gp130 were mainly present in mesothelial cells. sIL-6R and sgp130 were also produced by pericardium in vitro, and their synthesis was upregulated by methylprednisolone. Taken together, these results demonstrate that IL-6 is present in pericardial fluid and that its presence could be due to synthesis by pericardial tissue. In vitro studies suggest that IL-6 production by this tissue could be strongly induced and regulated. A potential paracrine role of these factors in cardiomyocyte functions in normal or pathological conditions is discussed.

Full text

INTRODUCTION

IL-6 is a cytokine involved in the regulation of a variety of cellular responses. It plays a key role in the induction and maintenance of inflammatory responses by promoting the synthesis by hepatocytes of acute phase proteins such as the C-reactive protein (CRP) [1]. It is a potent inducer of cardiomyocyte hypertrophy [2, 3]. IL-6 exerts its function through a cell surface receptor composed of two trans-membrane proteins belonging to the type I cytokine receptor family, a 80 kDa ligand-binding subunit designated IL-6R (CD126), and a transducing 130 kDa glycoprotein (gp130, CD130) [4]. Binding of IL-6 to IL-6R triggers the association of IL-6R and gp130, forming a high-affinity binding site able to transduce activation signals *via* the Jak/STAT activation pathways. gp130 is also involved in the signaling pathway of leukemia inhibitory factor (LIF), oncostatin-M (OSM), ciliary neurotrophic factor (CNTF), IL-11, cardiotrophin-1 (CT-1) and cytokine-like factor-1/cardiotrophin-like cytokine (CLF/CLC) [5-7] which explains the overlapping properties of these cytokines. Studies of gp130-knockout mice demonstrated that the cytokines of the IL-6 family might play a critical role in heart development and in muscle cell survival during the onset of heart failure during biochemical stress [8, 9]. Furthermore, *in vivo*, continuous activation of gp130 causes myocardial hypertrophy in mice [2].

Whereas serum IL-6 levels are low (< 20 pg/ml) or undetectable in normal subjects, high levels have been reported in several inflammatory diseases, acute

myocardial infarction, severe congestive heart failure, haematological diseases, and a variety of tumours including cardiac myxoma [10]. IL-6 has also been detected in other biological fluids such as synovial fluid of rheumatoid arthritis and in the urine of recipients of kidney transplants before rejection [11]. We and others have also demonstrated that pleural or peritoneal effusions contain large amounts of IL-6 [5, 6, 12-14]. Despite previous contradictory reports, we have demonstrated that the IL-6 levels in pleura were independent of underlying diseases [12]. Pleural IL-6 levels, 16 to 2,500 fold higher than serum levels led us to hypothesize a production and a sequestration of IL-6 in the pleural cavity [12]. Pleura and peritoneum are serosal membranes lined by mesothelium. Peritoneal mesothelial cells produced IL-6 spontaneously or after activation by growth factors and cytokines [15]. Parietal and visceral pericardium are also covered by mesothelium, delimiting a cavity containing 20-25 ml of serous fluid in physiological conditions.

The aim of this work was to see if pericardial tissue produces IL-6 that could exert paracrine actions on cardiac myocytes. We compare IL-6 and soluble IL-6 receptor levels in pericardial fluids and in sera of patients undergoing open heart surgery (heart valve disease, congenital heart defects and chronic ischemic heart disease). We also analysed IL-6 and gp130 expression by pericardium and the *in vitro* ability of pericardial samples to produce IL-6 and its soluble receptors.

MATERIALS AND METHODS

Patients

Twenty-two patients undergoing surgery in the cardio-thoracic surgery unit (Poitiers Hospital, France) were enrolled in the study between October 1998 and March 1999. Patients with preoperative inflammatory disease, previous cardiac surgery or referred as emergencies were excluded. Two patients were suffering from heart valve disease, and 20 patients suffered from chronic ischemic heart disease. Subjects were prepared for surgery in a similar way. None of these patients had large pericardial effusion. Pericardial patches were removed as part of the surgical repair procedure. Unused samples were kept for this study. Additional samples were not required other than those necessary for the normal management of patients as approved by the Ethics Committee of Poitiers

Hospital. Control adult sera were collected from 30 randomly chosen blood donors.

Sera and pericardial fluids

Serum samples were obtained for routine biochemical analysis. Serum albumin and C-reactive protein (CRP) were measured by a laser nephelometry assay (Behring, Branchburg, NJ, USA) and the remaining serum was kept in aliquots frozen at - 20° C before ELISA. Prior to systematic aspiration of pericardial fluid, a sample was collected using a syringe, immediately after the opening of the parietal pericardium.

Pericardial tissue cultures

Pathological histopathology analysis of the pericardial fragments confirmed the absence of pathological lesions *i.e.* the absence of tumor or inflammatory cells. Normal pericardial samples of 25 mm^2 were obtained with a puncher in order to standardize the area of surface membrane. They were seeded in 6-well plates (Nunc, Intermed, Denmark), containing 5 ml of culture medium (RPMI 1640 [Gibco, Cergy-Pontoise, France], supplemented with 2 mM L-glutamine, 100 UI/ml penicillin, 100 UI/ml streptomycin, and 10% fetal calf serum [FCS] [Seromed, Berlin, Germany]) and then incubated at 37° C in a humidified atmosphere of 6% CO_2. When indicated, 10^{-5} M methylprednisolone (MP) was added to the cultures. Half of the supernatant was removed and replaced by fresh medium every day. IL-6, sIL-6R, OSM, CNTF and sgp130 of the supernatants were measured by ELISA.

IL-6, sIL-6R, OSM, CNTF and sgp130 measurements

IL-6, sIL-6R and sgp130 levels were measured by ELISA, as previously described [12]. Briefly, the IL-6 ELISA was performed using an anti-IL-6 purified monoclonal antibody (mAb) B-E8 (Diaclone, Besançon, France) as a capture mAb on 96-well flat-bottomed plates (Maxisorp, Nunc, Intermed, Denmark). The detection was achieved with an anti-IL-6 biotinylated mAb (B-E4, Diaclone) followed by detection with 33 mg/ml streptavidin-peroxidase (Dako, Trappes, France). sgp130 ELISA was performed using the anti-sgp130 mAb (B-P4) as a capture mAb, and the biotinylated anti-sgp130 mAb (B-T2) as a tracer mAb (Diaclone). sIL-6R ELISA was performed using the anti-sIL-6R mAb (B-N12) as a capture mAb

and the biotinylated anti-sIL-6R mAb (B-R6) as a tracer mAb (Diaclone). No interference was observed in the measurement of IL-6, sIL-6R and sgp130. OSM and CNTF ELISA were performed with mAbs from R&D (Duoset for CNTF and OSM, Abington, UK), and measurements were performed as recommended by this laboratory. The lowest detectable levels were 2 pg/ml for IL-6, 30 pg/ml for OSM and CNTF, 12 pg/ml for sIL-6R and 15 pg/ml for sgp130.

RT-PCR analysis

Total cellular RNA was extracted from approximately 100 mg of fresh or cultured pericardium as indicated, using the Trizol method (Gibco-BRL) according to the manufacturer's guidelines. cDNA was synthesized for 1 hour at 42° C using 3 mug RNA, 400 pg random primers and 200 U of SuperScript II reverse transcriptase (Gibco-BRL) in a total volume of 20 mul. The primers for the amplification of beta-actin or IL-6 transcripts consisted of the following: IL-6 sense ATGAACTCCTTCTCCACAAGTC, IL-6 antisense CTACATTTGCCGAAGAGCCCTCAGGCTGGACTG, beta-actin sense GTCGGGCGCCCCAGGCACCA and beta-actin antisense CTCCTTAATGTCACGCACGATTTC. The PCR amplification was carried out with 4 mul cDNA in a total volume of 25 mul PCR buffer, with 50 pmol of each primer, 200 muM nucleotides, 2 mM $MgCl_2$ and 1.5 U GoldTaq polymerase (Perkin Elmer). Thermal cycles performed in a PE9700 (Perkin Elmer) were: 94° C for 10 min, followed by 35 cycles at 94° C for 45 sec, 50° C for 30 sec and 72° C for 45 sec. Amplified products were electrophoresed on 2% agarose gel and stained with ethidium bromide. The lengths of specific products were 537 bp for beta-actin and 638 bp for IL-6.

In situ *hybridisation*

In situ hybridisation was performed on 4 mum, paraffin-embedded pericardial tissue sections. After deparaffinization and rehydration, deproteinization was carried out in 0.2 M HCl for 20 min at room temperature. Tissues were then digested at 37° C for 20 min in 150 mug/ml proteinase K (Gibco BRL) in PBS and fixed in 4% paraformaldehyde for 10 min. After rinsing twice with PBS, the slides were acetylated for 5 min in 300 ml of 0.1 mM triethanolamine-HCl buffer (pH 8) containing 0.75 ml of acetic anhydride, and rinsed in 2X SSC.

We used digoxigenin-labelled probes prepared by PCR. Two plasmid vectors containing the human IL-6 and gp130 cDNA were used as a matrix. Specific primers for IL-6 were the same as for RT-PCR experiments. The sense and antisense primers for gp130 were 5'-TTTCCATTGGCTTCAAAAGG-3' and 5'-TGCTGATTGCAAAGCAAAAC-3' respectively. PCR reactions were performed with 400 muM of dNTP-labeled mix (DIG DNA labelling kit (Boehringer Mannheim)), 2 mM $MgCl_2$ (Perkin Elmer), 0.5 pmol/mul of each primer, 3 U of Taq polymerase (Perkin Elmer) and 100 pg of plasmid extracted with Wizard Plus SV miniprep kit (Promega). Reactions were initiated by heating at 94° C for 10 min, then 40 cycles were performed with denaturation at 94° C for 45 sec, annealing at 57° C (IL-6) or 52° C (gp130) for 45 sec and extension at 72° C for 45 sec. A final extension at 72° C for 10 min was then performed.

Hybridisation was carried out overnight at 50° C for IL-6 and gp130. The digoxigenin-labelled probe (8 mug/ml) was diluted in 2X SSC containing 50% deionized formamide, 0.1 mg/ml salmon sperm DNA (Sigma), 0.02% SDS, 1% Denhart's solution and 25% sodium dextran sulphate. The probe was heated for 10 min at 95° C and kept on ice. After overnight hybridisation, sections were thoroughly washed twice in 4X SSC for 10 min at room temperature, twice in 2X SSC for 10 min at 52° C, twice in 2X SSC for 10 min at room temperature, twice in 0.2X SSC for 10 min, once in maleic acid buffer pH7.5 for 5 min and once in 1X blocking reagent (Boehringer Mannheim) for 40 min at room temperature.

For detection of hybridisation, sections were incubated with anti-digoxigenin mAb conjugated with alkaline phosphatase. After three washes in buffer, a substrate consisting of nitroblue tetrazolium and 5-bromocresyl-3-indolylphosphate was layered over the sections. The reaction was allowed to proceed for 1-4 hours in the dark, and development was stopped by dipping slides quickly into tri-ethylenediaminetetraacetic acid buffer pH8. Sections were counterstained with methyl green 0.5% and slides were then washed with distilled water for 1 min and dried.

Immunohistochemistry

A fragment of a pericardial specimen was immediately frozen in liquid nitrogen after removal. Serial 15-mum-thick sections were cut with a cryostat at - 20° C, collected on slides and stored at - 20° C until use. They were stained immunohistochemically by the indirect immunoalkalinephosphatase method.

Briefly, slides were treated for 10 min with 4% paraformaldehyde at room temperature and washed 3 times with phosphate-buffered saline (PBS). Samples were permeabilized for 10 min with 0.5% Triton X100 and washed 3 times with PBS. B-E8, an anti-human IL-6 mAb, and B-R3, an anti-human gp130 mAb (Diaclone, Besançon, France) were used as primary antibodies in 1% BSA 0.1% saponin-PBS. These antibodies were detected with alkaline phosphatase-conjugated goat anti-mouse IgG (Jackson Immunoresearch Laboratory, PA, USA), and fast-red (Sigma Chemical Co., MO, USA), as a chromogen. Slides were counter-coloured with hemalun. Specificity of primary antibodies was confirmed by the absence of signal in serial sections by omission of the primary antibody and its replacement with an irrelevant antibody of the same isotype.

Statistical analysis

Data were expressed as mean ± SEM. The differences between the groups of patients and healthy volunteers were tested by the unpaired Student's t test. Comparison between pericardial and serum parameters with normal distribution was done using the paired Wilcoxon test. Correlation analyses were carried out using Spearman correlation coefficients.

RESULTS

Cytokines and soluble receptors in pericardial fluid and serum

Pericardial and serum IL-6, sIL-6R and sgp130 levels measured by ELISA are shown in Figure 1. IL-6 pericardial levels (mean 132 ± 43 pg/ml; range 9-742 pg/ml) were in every case higher than serum levels (mean 15 ± 7 pg/ml; range 2-113 pg/ml; $p < 0.001$). In contrast, pericardial sIL-6R and gp130 levels were significantly lower (27 ± 12 ng/ml and 50 ± 4 ng/ml, respectively) than serum levels (71 ± 7 ng/ml, $p < 0.01$, and 81 ± 7 ng/ml, $p < 0.001$, respectively). sIL-6R concentrations in the serum of the subjects were not significantly different from those of healthy volunteers (71 ± 26 ng/ml). In contrast, serum IL-6 and CRP levels in patients with coronary pathology (respectively 15 ± 7 pg/ml and 8.1 ± 3.3 mug/ml) were higher ($p < 0.01$ in both cases) than those found in healthy subjects (respectively 5 ± 2.4 pg/ml and < 2.3 mug/ml), whereas sgp130 levels were lower ($p < 0.01$) than those found in healthy subjects (120 ± 42 ng/ml). OSM and CNTF were not detected in serum of healthy volunteers nor in the serum and pericardial fluid of these patients.

As expected, correlations between serum and pericardial albumin ($r = 0.65$; $p < 0.01$) or CRP levels ($r = 0.60$; $p < 0.01$) were observed (Figure 2A, B). In contrast, serum and pericardial IL-6, sIL-6R, and sgp130 concentrations did not correlate (Figure 2C, D, E). IL-6 and CRP concentrations correlated in serum ($r = 0.51$; $p < 0.03$), but not in pericardial fluid (Figure 2F, G).

Cytokines in pericardium culture supernatants

As indicated in Figure 3A, very high IL-6 levels were detected in culture supernatants of freshly excised, normal pericardium. Although half of the medium was changed every day, IL-6 levels increased up to day 3, which demonstrated massive IL-6 production by pericardial tissue incubated in culture medium alone; methylprednisolone (MP) strongly inhibited this production. Short-term cultures showed that IL-6 levels were detected as soon as 4 h following the beginning of culture (data not shown). When cultured in RPMI 1640 alone, the production of IL-6 was only 12% of the production obtained in the presence of FCS. RT-PCR studies further demonstrated the presence of IL-6 mRNA in cultured pericardium samples. In contrast, this mRNA was weakly detected in fresh pericardium samples, and in samples cultured for 2 days in the presence of MP (Figure 4). When compared to IL-6 concentrations in culture supernatants, sIL-6R and sgp130 levels were moderately elevated (Figure 3B, C). In any event, cumulative data taking into account daily culture medium changes suggest moderate sIL-6R and sgp130 production during the time course of the culture. Until day 4, sgp130 concentrations in culture supernatants were almost the same in the presence or absence of MP. At days 5 and 6, sgp130 levels further increase in the presence of MP. sIL-6R levels were always higher in the presence of MP than in control conditions. In addition, sIL-6R levels became undetectable from day 5 in control cultures. OSM and CNTF were not detected in these pericardial culture supernatants.

Analysis of IL-6 and gp130 mRNA and proteins on pericardium by in situ *hybridisation and immunohistochemistry*

The expression of IL-6 and gp130 mRNA transcripts was present on pericardium, signals being mainly localised in mesothelial cells (Figure 5D, E). A control with an irrelevant probe showed the absence of a positive signal (Figure F). In accordance with *in situ* hybridisation studies, immunohistochemical expression of IL-6 and gp130 was also detected on mesothelial cells (Figure 5A, B).

DISCUSSION

The present study demonstrates the presence of high IL-6 levels in pericardial fluid obtained from patients undergoing cardiac surgery. Pericardial IL-6 levels were 2 to 185 fold higher than serum levels, with no correlation between them. These results confirm previous studies showing that IL-6 could be detected using a biological assay in pericardial fluid from certain patients undergoing cardiac surgery [16]. In the biological assay, 1 U/ml could be estimated to represent 1 pg/ml of IL-6 [17]. In the Riemann *et al.* study [16], IL-6 was undetectable (< 10 U/ml) in half of the fluids tested and the highest level was 4,500 U/ml. In contrast, we detected IL-6 in all the pericardial fluid samples analysed. These differences could be due to experimental procedures. Moreover, we cannot exclude the presence of other inhibitory, stimulatory or synergistic factors which are able to play a role in target cell responses in a biological assay. For example, IL-6 displays some redundancy with related cytokines including LIF, OSM, CNTF, IL-11 and CT-1 [17]. Among them, CNTF and OSM were not detected in these fluids. Another study reported the presence of 3,000 pg/ml of IL-6 in the pericardial fluid and 9,200 pg/ml in the serum of a child with fatal adenoviral pericarditis [18]. These authors suggest that the presence of high levels of IL-6 in these fluids was consistent with the inflammation due to adenovirus infection. They hypothesise extra-pericardial production of IL-6. In our study, CRP and albumin concentrations in serum were close to normal values. However, these subjects developed heart valve disease as the result of prior atherosclerotic and/or inflammatory processes or chronic ischemic heart disease. Nevertheless, these studies were impossible to extend to healthy subjects for ethical reasons.

Whereas serum and pericardial levels of albumin or CRP correlated, no correlation was found between serum and pericardial IL-6 levels, which argues for local IL-6 production in the pericardial interstitium, contrasting with the previously mentioned hypothesis of Mistenchko *et al.* [18]. On the other hand, cultured normal pericardial fragments produced high levels of IL-6, even in the absence of FCS. It is an open question as to whether the 8-fold increase in IL-6 synthesis potentiated by FCS is due to specific factors or to its general trophic and nutritive effects. We have shown that MP strongly inhibits IL-6 synthesis by pericardium *ex vivo*. This was in agreement with the demonstration that glucocorticoids directly inhibited IL-6 gene expression in monocytes, endothelial cells and fibroblasts [19, 20]. Furthermore, RT-PCR studies provided

evidence that IL-6 mRNA was strongly expressed in cultured pericardial fragments, and inhibited by MP. These studies also demonstrated that IL-6 mRNA was weakly expressed in fresh tissue, but could be strongly expressed in pericardium cultured in medium alone. Despite the fact that the induction of IL-6 synthesis by pericardium remains to be characterised, it demonstrates the potential of this tissue to produce high amounts of IL-6. Pericardium is mainly made up of fibroblasts and mesothelial cells, two candidates for IL-6 production. We have shown that expression of protein and mRNA transcript for IL-6 is mainly detected in mesothelial cells. On the other hand, Topley *et al.* [15] showed that cultured human mesothelial peritoneal cells expressed specific mRNA, and released IL-6. We also demonstrated the presence of high levels of IL-6 in supernatants of normal pleura in culture (unpublished observations). We recently showed that the main inducer of IL-6 release during cardiac surgery was linked to surgical trauma [21]. Despite this, we cannot conclude from these indirect findings that pericardium is the source of the IL-6 detected in the pericardial fluid.

In contrast to IL-6, sIL-6R and sgp130 levels in pericardial fluid were lower than in serum, as previously reported for pleural effusions [12]. However, the sera and pericardial levels did not correlate, suggesting a local origin. *In vitro* studies demonstrated sIL-6R and sgp130 release, confirming this hypothesis. In the presence of MP, previously described to upregulate these receptors [22], their production was enhanced. As for IL-6, the presence of gp130 mRNA and protein was detected on mesothelial cells. Although IL-6 and its receptors were present in pericardial fluid and pericardium, it remains to further investigate their biological roles in these tissues. In pleura, it has been suggested that IL-6 could be an autocrine growth factor for mesothelial cells [23]. An increasing body of evidence supports the existence of paracrine and autocrine regulatory pathways in the heart [24]. Both coronary vascular and endocardial endothelium release several diffusible agents that acutely modify cardiac myocyte functions [25]. Corda *et al.* [26] reported that pericardial fluids contain myocardial growth factors that exert paracrine action on cardiac myocytes. They demonstrated the presence of fibroblast growth factor 2 (FGF2) in pericardial fluid, which was able to induce normal myocyte growth and suggested the presence of unidentified factors able to participate in the development of ventricular hypertrophy. IL-6 could be one of those uncharacterised factors. On the other hand, Ichinose *et al.* [27] reported that pericardial fat pad tissue also produced a large amount of IL-6 *in vitro*, and suggested that it could be related to tissue repair and

neovascularization in patients who underwent pericardial fat pad reinforcement to prevent bronchopleura fistula. The role of IL-6 in pericardium remains to be further elucidated.

CONCLUSION

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Figures











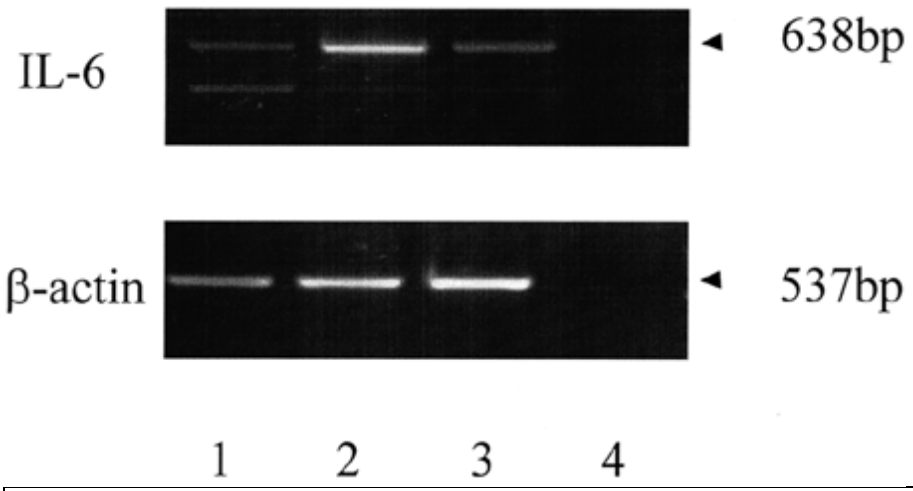
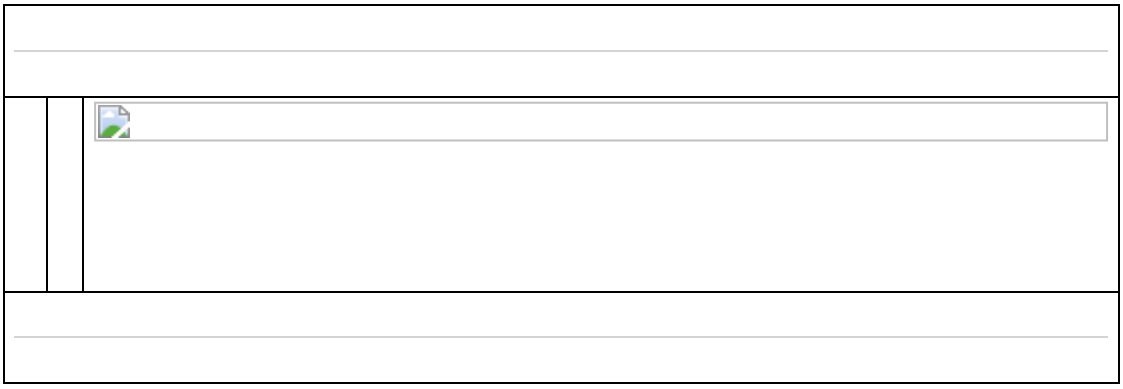


Figure 4
Expression of IL-6 and β-actin transcripts by RT-PCR in fresh (1) or 48 hours cultured pericardium in medium alone (2) or MP (3).
Negative control (absence of cDNA) (4). The size of the PCR products is 638 bp for IL-6 and 537 bp for β-actin.





Authors

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

FRE CNRS 2224, IBMIG, 40, avenue du recteur-Pineau, 86022 Poitiers Cedex, France.

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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.

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

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Eric Lelièvre, Isabelle Corre

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