Endothelial cells (EC) may represent a major source of cytokines in the bone marrow. In this study we have examined the production and the regulation of the production of leukemia inhibitory factor/human interleukin for DA cells (LIF/HILDA) by EC. Human umbilical venous endothelial cells (HUVEC) were chosen as a working model as they are a well-known source of cytokines. These cells secrete LIF/HILDA (50 pg/mL/10^6 cells/48 h) in basal conditions. This secretion is profoundly altered by interleukin-1α (IL-1α). Secretion of LIF/HILDA is increased threefold on stimulation with IL-1α at a concentration of 100 IU/mL. The secreted protein is bioactive as demonstrated by its proliferative effects on DA1a cells. Modulation of the production of LIF/HILDA by glucocorticoids (GC) was also examined. In striking contrast to what was observed for IL-1α, the synthetic GC dexamethasone (DXM) at a concentration of 10^-8 mol/L inhibited by an average of threefold and suppressed the IL-1α-induced increase of the secretion of this cytokine by HUVEC. In an effort to extend results obtained with HUVEC to the bone marrow endothelium, we have also examined the production of LIF/HILDA by human bone marrow endothelial cells (HBMEC). Our study shows that HBMEC are quantitatively a very important source of this cytokine (above 7.25 ng/mL/10^6 cells/48 h) suggesting that they are a major source of LIF/HILDA in the bone marrow. Again, IL-1α proved to be a very potent stimulus for the secretion of LIF/HILDA and synthetic GC such as DXM when used at a concentration of 10^-8 mol/L inhibited by an average of threefold the basal secretion of LIF/HILDA and had a suppressive effect on the IL-1α-induced increase of this secretion. The downregulation of LIF/HILDA production in the bone marrow by GC may be important to understand the effects of GC on hematopoiesis.

© 1995 by The American Society of Hematology.

In Vitro Biosynthesis of Leukemia Inhibitory Factor/Human Interleukin for DA Cells by Human Endothelial Cells: Differential Regulation by Interleukin-1α and Glucocorticoids

By Christophe Grosset, Bozena Jazwiec, Jean-Luc Taupin, Houqi Liu, Sophie Richard, François-Xavier Mahon, Josy Reiffers, Jean-François Moreau, and Jean Ripoche

THE SELF-RENEWAL, proliferation, and differentiation of multipotent stem cells and committed progenitor cells involves a number of cytokines that act in a complex and largely unknown way. The complexity of the regulation of the proliferative, differentiative, and maturation events of hematopoiesis depends for a good part on the number and the high degree of redundancy of these molecules. Most of the cytokines regulating hematopoiesis are being produced locally by the various cell types constituting the bone marrow stromal microenvironment. Most of the mRNA transcripts for these cytokines have been found in stromal cells and the secretion of bioactive molecules has been demonstrated for some of them such as granulocyte macrophage (GM) and granulocyte (G) colony-stimulating factor (CSF), stem cell factor (SCF), and interleukin-6 (IL-6). In most cases these studies have been using long-term cultures of human bone marrow stromal cells made of a number of different cells, such as macrophages, fibroblasts, adipocytes, and endothelial cells (EC). These studies therefore did not discriminate between these cells to delineate which one(s) is (are) the source of cytokine production. In order to dissect the complex regulatory network of these cytokines in hematopoiesis, it is important to understand which cytokine is produced and secreted by which cell, how their production is regulated, and how each of the cytokine-producing cells is interacting with regards to the hematopoietic cells.

We have initiated an analysis of the production and the regulation of the production of leukemia inhibitory factor/human interleukin for DA cells (LIF/HILDA) by bone marrow stromal cells. LIF/HILDA is a pleiotropic cytokine formerly identified in the supernatants of T-cell clones by its ability to support the proliferation of the murine IL-3-dependent DA1a cell line. This molecule turned out to be identical to the LIF. LIF/HILDA has a wide range of target cells. For instance, LIF/HILDA induces proliferation and suppresses spontaneous differentiation of embryonic stem cells, induces production of several acute phase proteins by hepatocytes, and is a differentiation factor for cholinergic neurons. In addition LIF/HILDA is probably a good candidate as a regulatory molecule for differentiation and proliferation of hematopoietic progenitor cells. However, its effect on these cells is far from clear. Apart from its known differentiation promoting effects on a murine leukemia cell line, M1, LIF/HILDA stimulates platelet formation, stimulates myeloid and erythroid colony formation of human mononuclear phagocyte and T-lymphocyte-depleted bone marrow, and is a synergistic factor for the IL-3-dependent proliferation of early hematopoietic progenitor cells in a blast cell colony assay. But conflicting data also exist and the precise role of LIF, whether it acts directly or indirectly by inducing the release by stromal cells of other mediators or acts only in synergy, remains to be determined.

In the current study, we have studied the production of LIF/HILDA by human umbilical venous endothelial cells (HUVEC) and the human bone marrow endothelial cells (HBMEC), and analyzed the modulation of this production by IL-1α and glucocorticoids (GC). Results demonstrate that (1) HUVEC and HBMEC produce LIF/HILDA in quantitatively high amounts. High production of LIF/HILDA by HBMEC suggests that these cells are a major source of this cytokine.
cytokine in the bone marrow. (2) IL-1α is a potent stimulus of LIF/HILDA secretion by EC. (3) GC have strikingly opposite effects to those of IL-1α on LIF/HILDA secretion by EC; they decrease the basal secretion of LIF/HILDA by these cells and they suppress its IL-1α-induced increased production.

MATERIALS AND METHODS

EC From Umbilical Cord

Primary cultures of HUVEC were obtained from freshly collected umbilical cords. 0.1% w/v collagenase (Boehringer Mannheim, Meylan, France) was used for treatment of the umbilical vein instead of 0.2%, as originally described. HUVEC were cultured in Iscove’s modified Dulbecco’s medium (IMDM; GIBCO, Cergy-Pontoise, France) supplemented with 20% heat-inactivated fetal calf serum (FCS), 15 μg/mL EC growth factor supplement (ECSG, B0760; Sigma, Saint-Quentin, France), 90 μg/mL heparin (Sigma), penicillin (100 U/mL), streptomycin (50 μg/mL), and amphotericin B (2.5 μg/mL). This culture medium is referred to as standard medium. Cells were grown to confluence in 75 or 25 cm² flasks coated with 100 μg/mL collagen I (Jacques Boy Institute, Paris, France). Cells were passaged after treatment with trypsin-EDTA and routinely used between the second and fourth passages. After the second passage, there was no visible contamination by monocytes. Cells were maintained in a humidified atmosphere at 37°C, 5% CO₂, and were identified by their characteristic morphology and by the expression of factor VIII antigen.

EC From Bone Marrow Microvasculature

EC from human bone marrow (BM) microvasculature were isolated following a two-step procedure with BNH-9 coated microspheres. BNH-9 is a mouse IgM monoclonal antibody recognizing EC specific H and Y antigens (Immunotech, Marseille, France). The whole procedure is essentially the same as that described by Rafii et al11 with slight modifications.

Brieﬂy, normal fresh BM samples were collected from the femoral head or posterior iliac crest from patients undergoing orthopedic surgery or from individuals donating BM for allogeneic BM transplantation. Informed consent was obtained from each donor. The BM sample (5 to 30 mL total) was diluted 1:1 in buffer A (RPMI 1640 medium supplemented with 20% HTF, 100 U/mL E-la, 100 μg/mL streptomycin, 100 μg/mL penicillin, 2.5 μg/mL LIF, 1% FCS), and kept at 4°C until they were assayed for LIF/HILDA. Cells were then incubated for 30 minutes at +4°C and washed twice. Negative controls were cells labeled with appropriate isotypic monoclonal antibodies (mouse IgG₁-PE and mouse IgG₁-FITC). Cells were sorted washed seven times by mixing cells for 1 minute at room temperature on a rotator with 5 mL of buffer B; aggregates were separated from unbound cell supernatant with a magnetic particle concentrator (MPC). After the final wash, EC were collected, washed once with complete medium, and plated in collagen-coated dishes or flasks as above, on collagen I-coated 6-wells Nunc Plastic dishes in IMDM containing 20% FCS, 15 μg/mL ECGF, 90 μg/mL heparin, antibiotics, and fungizone.

HBMEC were characterized by their expression of von Willebrand Factor (vWF) by immunofluorescence and flow cytometry with Epics-Profil II cytometer (Coulter), and the presence of Weibel-Palade bodies by electronic microscopy examination (Philips microscope).

Cytokine Preparations and Other Reagents

IL-1 was human rIL-1α purified from Escherichia coli, a gift from Dr PT Lomeo, Hoffman-La Roche, Inc, Nutley, NJ; dexamethasone (DMX) sodium phosphate salt (sterile, apyrogen solution for human therapeutic use) was purchased from Merek, Sharp, and Dohme, Chibret, Paris, France; hydrocortisone (HC) was purchased from Sigma.

LIF/HILDA Proteins and Antisera

Monoclonal antibodies 1F10 and 7D2 (IgG1 mouse monoclonal antibodies) were obtained as previously described. Brieﬂy, mice were immunized with recombinant vaccinia virus harboring the cDNA pC10-6R encoding the complete sequence for human LIF/HILDA.

The resulting monoclonal antibodies were screened by a cytometric antigen assay, in which the LIF/HILDA antigen, as a fusion molecule, was expressed at the membrane of a stably transﬁected P815 cell line.

Puriﬁed LIF is recombiant human protein obtained from CHO cells stably transfected with pC10-6R encoding the complete coding sequence for human LIF/HILDA. Transfected cells produce LIF in the range of 1 to 2 μg/mL in their supernatants.

Experimental Procedures

HUVEC and HBMEC cultures. Confluent HUVEC or HBMEC monolayers were incubated in medium containing the indicated stimuli. Working concentrations were 100 IU/mL for E-la, 10⁻⁸ mol/L for HC, and 10⁻⁴ mol/L for DMX. Cells were stimulated for the indicated time, the supernatants were collected, centrifuged for 15 minutes at 4°C, decanted in a fresh tube, added with Tween 20 0.05% final, and kept at 4°C until they were assayed for LIF/HILDA (addition of Tween prevents denaturation of the LIF/HILDA protein, whereas freezing and thawing the sample tends to give loss of bioactive protein [unpublished observations, June 1993]).

CD34⁺/CD38⁻ isolation. In some experiments, CD34⁺/CD38⁻ hematopoietic progenitors were cocultivated with a HUVEC or a HBMEC monolayer in stroma “non-contact” system with Transwell inserts essentially as described. CD34⁺ cells were isolated from cord blood. MNC were separated by standard Ficol-hypaque centrifugation as described before. Hematopoietic progenitors expressing the CD34 antigen were puriﬁed using the Isolot 59 system (Baxter, Maurepas, France) following the manufacturer’s instructions. To isolate immature CD34⁺/CD38⁺ cells, a two-color staining of immunomagnetically isolated CD34⁺ cells was performed with anti-CD34 fluorescein isothiocyanate (FITC) monoclonal antibody (HPCA-2, Beckton Dickinson, San Jose, CA), anti-CD38 phycoerythrin (PE) and anti-Leu-7 monoclonal antibody (Beckton Dickinson).

Cells were then incubated for 30 minutes at +4°C and washed twice. Negative controls were cells labeled with appropriate isotypic controls (mouse IgG₁-PE and mouse IgG₁-FITC). Cells were sorted
on a FACS (PC 3000, Odam-Brucker, Wissenbourg, France). Selection consisted of (1) gating in side-scatter/forward-scatter bivariate distributions by suppression of background and cell aggregates, and (2) recovering CD34+CD38low cells on a CD34-FITC/CD38-PE bivariate histogram against negative control antibodies.

Cocultures. CD34+ or CD34+/CD38low cells were cocultivated in the presence of HUVEC monolayers in IMDM, 20% FCS, and antibiotics. Two of five of the medium were replaced twice a week. After 7, 14, or 21 days, the culture medium was collected, centrifuged for 10 minutes at 800g, decanted to a fresh tube, added with Tween 20 0.05% final, and kept at +4°C until being assayed for LIFIS/ILDA. Controls were HUVEC cultivated under the same conditions in the absence of CD34+/CD38low progenitors. Where indicated, IL-1α was added.

EIA and DAIα Bioassays

The first antibody 1F10, diluted at 10 μg/mL in carbonate buffer, was coated overnight on 96-well microplates (Maxisorp Nunc, Denmark). After washing with PBS-Tween 20 0.005% (PBS-T), cell supernatants (0.1 mL) were incubated for 90 minutes and further washed with PBS-T. The second biotinylated antibody (7 D2) was diluted in PBS-BSA 0.1% at 1 μg/mL and allowed to react for 90 minutes before washing with PBS-T. The reaction was amplified by peroxidase-linked streptavidin (Amersham, Little Chalfont, UK) and revealed with tetramethyl benzidin (Sigma, France). All incubations were conducted at room temperature. The variations of optical densities were measured with an EIA reader at 450 and 570 nm (Labsystem Multiskan), with a mean of 6 HILDA/LIF negative controls being subtracted for each point. The threshold of detection was determined as the mean of these 6 control measurements plus 2 standard errors, and never exceeded 25 pg/mL in culture supernatants.

The DAIα proliferative assay, has already been described, and is based on the LIF-induced proliferation of the murine DAIα cell line. In this assay, one unit is the quantity of LIF able to provide 50% of the maximal DAIα proliferation. Where indicated, IL-1α was added.

Northern Blot Analysis

Total cellular RNA was extracted from HUVEC monolayers as described.22 RNA was denatured using formamide and formaldehyde and electrophoresis was performed on gels containing formaldehyde. Double-stranded cDNA probes were the human LIF cDNA excised as a 0.6 kb Xhol/Xhol insert from the plasmid pC10-6R7 and an actin cDNA probe (chicken cytoskeleton actin) from ATCC. Probes were labeled with 32P by random priming (Boehringer Mannheim). RNA loading was checked by ethidium bromide staining and control hybridization of the blot with the actin probe.

Statistical Methods

Significant differences between values obtained in each assay were determined by paired Student’s t-test. The difference was considered significant when P < .05.

RESULTS

LIF/HILDA Production by HUVEC: Differential Regulation by IL-1α and GC

Biosynthesis of LIF/HILDA was investigated by EIA in the supernatants of HUVEC grown in IMDM, 20% FCS, and antibiotics. The HUVEC were grown at confluence and stimulated with either IL-1α and/or DXM for 48 hours. ECGF was omitted to avoid any possible contamination by a protein that would have interfered with the assay. We chose IL-1α as it has been shown to be a potent inducer of cytokine secretion by EC. The effects of DXM were also investigated to study the potential downregulation of EC-derived cytokines by this synthetic glucocorticoid. Results summarized in Fig 1, show that HUVEC spontaneously secreted LIF/HILDA in their supernatants. The mean level of five experiments for basal secretion was 90 pg/mL/10⁶ cells/48 h. Production of LIF/HILDA was significantly increased by threefold (P = .01) when HUVEC were being stimulated by IL-1α at a final concentration of 100 IU/mL. Other concentrations were not investigated. We next studied the potential regulatory activity of synthetic glucocorticoids on the production of LIF/HILDA. We found that DXM at a final concentration of 10⁻⁶ mol/L consistently inhibited the basal production of LIF/HILDA by an average of threefold (P = .005). Furthermore, there was a striking suppressing effect of DXM on the IL-1α-induced increase in LIF/HILDA production (P = .005). In the presence of both DXM (10⁻⁶ mol/L) and IL-1α (100 IU/mL), the production of LIF/HILDA is close to control levels (P = .20) (Fig 1).
LIF/HILDA Is Produced by HBMEC: Quantitative Importance of This Secretion and Modulation by IL-1α and GC

In an effort to understand whether EC from the bone marrow microvasculature also produce LIF/HILDA and to study the regulation of this production, we isolated HBMEC from normal bone marrow. These cells are thought to play an important role in the local production of cytokines necessary for hematopoiesis. Secretion of LIF/HILDA in the supernatants of these cells was analyzed in basal conditions and after 48 hours of stimulation by IL-1α (100 IU/mL). Results indicated that HBMEC are a quantitatively important source of LIF/HILDA (median level was 7.25 ng/mL/10^6 cells/48 h, n = 4) (Fig 2). These results show that basal production of LIF/HILDA by HBMEC is quantitatively strikingly more important in HBMEC than in HUVEC (approximately 80-fold). Again, IL-1α profoundly increased the production of this cytokine. In the presence of IL-1α, the secretion of LIF/HILDA by HBMEC was significantly increased by an average of threefold (P = .03). Again, as observed with HUVEC, DXM at a final concentration of 10^{-6} mol/L inhibited by threefold the basal secretion of LIF/HILDA (P = .01) and suppressed the IL-1α-induced increase of LIF/HILDA secretion (Fig 2). HC at 10^{-6} mol/L gave the same results (not shown).

IL-1α Enhancement of LIF/HILDA Messenger RNA

The level of LIF/HILDA mRNA and regulation of its expression by IL-1α was examined by Northern hybridization on HUVEC grown and stimulated in standard growth medium. The blot was first hybridized with LIF/HILDA cDNA probe and was subsequently re-hybridized with a chicken actin cDNA probe as an internal control. Results (Fig 3) show that the level of LIF message is difficult to detect in basal conditions and that IL-1α induces a strong increase in the expression of this message. These results suggest that the IL-1α modulation of LIF/HILDA expression in EC occurs primarily at the mRNA level.

LIF/HILDA Secreted by EC is Biologically Active

Bioactivity of LIF/HILDA secreted by HUVEC was measured by a DA1a proliferative assay based on the LIF/HILDA-induced proliferation of the murine DA1a cell line. Fifty microliters of culture supernatants’ dilutions were incubated for 72 hours at 37°C with 50 μL of 1.5 10^4 DA1a cells. The LIF/HILDA biologic activity in the supernatants of control HUVEC reached 36 DA1a U/24 h. This activity was increased to 80 U/24 h in the supernatants of IL-1α-stimulated cells. These results are in agreement with the EIA assay and suggest that no other cytokines besides LIF/HILDA, which might interfere with the DA1a cell proliferation assay, are being secreted by these cells (Fig 4).
LIF IS PRODUCED BY EC

Fig 4. LIF/HILDA produced by EC is bioactive. Values are those of a typical experiment representative of three. Bioactivity of LIF/HILDA was measured by its ability to induce the proliferation of the murine DA1a cell line. (B) Control cell supernatants; (C) IL-1α-stimulated cells supernatants.

Kinetic Analysis of LIF/HILDA Production in Cocultures of Hematopoietic Progenitor Cells With HUVEC

To analyze the production and regulation of the production of LIF/HILDA in an experimental system that would reflect more closely the physiologic hematopoiesis, we set up experiments in which human hematopoietic progenitor cells were cocultivated with EC as a stromal layer. A non-contact system was used in which EC can be separated but soluble molecules allowing communication between stromal cells and the differentiating and proliferating hematopoietic cells diffuse freely within the two compartments. We asked the question whether LIF/HILDA was being produced in such a system and how its concentration was varying during the coculture. As shown in Fig 5, LIF/HILDA is being produced in increasing amounts over a period of 21 days in cocultures of HUVEC and CD34+. However, the kinetics of LIF/HILDA production in the cocultures is not significantly different to the LIF/HILDA (grown without CD34+ progenitors) control HUVEC. Whether IL-1α is present or not. These results indicate that the differentiating and proliferating hematopoietic cells do not influence the production of LIF/HILDA by the HUVEC stroma layer. Cocultures of HUVEC with CD34+/38loW progenitors gave identical results (not shown).

DISCUSSION

The local mechanism by which the bone marrow microenvironment exerts its control over hematopoiesis still remains to be clarified. One form of this control is based on the secretion of a wide array of growth factors in the immediate environment of the proliferating and maturing hematopoietic cells. The regulation of the expression of these growth factors in hematopoiesis. An absence of demonstrative proliferative effects of LIF/HILDA on CD34+ progenitors has been reported.14,15,24-26 In vivo data tend to suggest that LIF/HILDA plays an important function in hematopoiesis. There is an elevation of progenitor cells in the spleen of mice after injection of LIF/HILDA, with a noticeable increase in megakaryocyte progenitors.32

The current hypothesis is that the effects of LIF/HILDA might be directed at a very primitive compartment as is suggested, for instance, by the increase in size of CFU-Mix and BFU-E colonies after bone marrow progenitor cultures in the presence of LIF/HILDA13 or by the LIF/HILDA-induced augmentation of the IL-3-dependent proliferation of early human hematopoietic cell line.14

In the present study we show that LIF/HILDA might be a major source of all cytokines in the bone marrow. The good correlation between the EIA and the DA1a biologic activity is not produced by HUVEC. In vitro, expression of LIF/HILDA by human bone marrow stromal cells has been demonstrated in recent studies. The LIF mRNA was detected in long-term bone marrow cultures and IL-1 or TNF-α also increased expression of this messenger; LIF/HILDA protein was found in the supernatants of long-term bone marrow stroma culture.27 However the nature of the cells involved in this production remained to be determined. The bone marrow stroma is made of approximately 60% to 70% fibroblasts, 10% to 20% EC, and other cells present in small amounts but with potential functional importance, such as adipocytes, macrophages, and osteoclasts. Fibroblasts may be one source of LIF/HILDA in the bone marrow since its mRNA has been found in bone marrow- derived stromal fibroblast cells.29 Our data support the idea that EC are the major source of LIF/HILDA produced in the bone marrow. EC have been shown to produce (almost nearly) all of the cytokines that are believed to play a role in the proliferation and maturation of the hematopoietic cells.30 More recently, SCF mRNA has been shown to be expressed31 and IL-11 protein to be produced by EC.32 These experiments further emphasize the fact that EC produce all the necessary factors to support hematopoiesis. In the current study we show that results obtained for LIF production by HUVEC can be extrapolated to HBMEC. The significantly higher production of LIF by HBMEC on a per cell basis might represent specialization of the EC of bone marrow toward the production of the cytokines neces-
Fig 5. Coculture of EC with hematopoietic progenitor cells. LIF/HILDA production. Hematopoietic progenitor cells CD34+ were grown in the presence of a HUVEC monolayer in a non-contact system for 3 weeks, with two of five of the medium being replaced twice a week with fresh medium containing or not containing IL-1α. The concentration of LIF/HILDA was measured by EIA as described in section 2-6. (B) control HUVEC (without CD34+ cells); (□) HUVEC cocultivated with CD34+ cells; (□) IL-1α-stimulated HUVEC (without CD34+ cells); (O) IL-1α-stimulated HUVEC cocultivated with CD34+ cells. Values are the mean ± SD for duplicate measurements of three independent experiments. Working concentrations were 100 IU/mL for IL-1α.

IL-1α is a potent stimulus for LIF secretion by EC, and this phenomenon might be important to understand the effects of IL-1 on the growth and differentiation of purified hematopoietic progenitors. IL-1 has been shown to induce the production of CSFs both in vitro and in vivo. IL-1 has also been shown to play an essential role in promoting the proliferation of very immature progenitor cells as represented, for instance, by high proliferative potential colony forming cells. It is therefore tempting to speculate that the modulation of expression of LIF/HILDA by IL-1 is important to explain the direct enhancing effect of IL-1 on progenitor growth and proliferation. As a possible relevant example, a dysregulated stimulation of LIF by high levels of IL-1 may be of importance in the pathophysiology of chronic myelogenous leukemia. IL-1 stimulation of LIF production might also be of operational importance in emergency situations in which an increase in the proliferation of hematopoietic progenitors is desirable such as in inflammatory disorders, sepsis, etc. In these situations, IL-1 is brought to the bone marrow by the circulation.

In this study, we also report that GC downregulate LIF/HILDA secretion by EC. Inhibition of the biosynthesis of LIF/HILDA by DXM is another example of the more general properties of synthetic glucocorticoids to downregulate the expression of a number of cytokines, among which there are some believed to play an important role in hematopoiesis such as IL-1, IL-3, or IL-6. Downregulation of the production of cytokines such as IL-1 or LIF/HILDA, which are believed to play a role in the proliferation of the more primitive compartments of hematopoietic cells, may explain for instance the reduced frequency of LTC-IC in coculture of CD34+/38− cells on human bone marrow LTC-derived adherent cells in the presence of hydrocortisone. Finally, production of LIF/HILDA by EC provides a potentially useful model in delineating the synthesis, processing, and control of secretion of this protein.

ACKNOWLEDGMENT

We thank Drs Bosredon and Bernard (Orthopedic Surgery Department, Bordeaux Hospital) for providing bone marrow samples and the staff from the Maternity Department for providing cord blood and umbilical cords.

REFERENCES


30. Mantovani A, Dejana E: Cytokines as communication signals between leukocytes and endothelial cells. Immuno Today 10:370, 1989


43. Hestdal KH, Ruscetti FW, Chizzonite R, Ortiz M, Gooya JM, Longo DL, Keller JR: Interleukin-1 (IL-1) directly and indirectly promotes hematopoietic cell growth through type 1 IL-1 receptor. Blood 84:125, 1994


In vitro biosynthesis of leukemia inhibitory factor/human interleukin for DA cells by human endothelial cells: differential regulation by interleukin-1 alpha and glucocorticoids

C Grosset, B Jazwiec, JL Taupin, H Liu, S Richard, FX Mahon, J Reiffers, JF Moreau and J Ripoche