ACADEMIC PRESS

Biochemical and Biophysical Research Communications 296 (2002) 194–200

BBRC

www.academicpress.com

Activation and suppression of renin–angiotensin system in human dendritic cells

Natalia Lapteva,[a,b,1] Kazuki Ide,[c,1] Mie Nieda,[c,d] Yoshitaka Ando,[a] Yoko Hatta-Ohashi,[e] Mutsuhiko Minami,[c] Grigory Dymshits,[b] Koichi Egawa,[d] Takeo Juji,[f] and Katsushi Tokunaga[a,*]

[a] *Department of Human Genetics, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b] *Laboratory of Genome Structure, Institute of Cytology and Genetics, Novosibirsk, Russia*
[c] *Department of Immunology, Yokohama City University, School of Medicine, Tokyo, Japan*
[d] *Laboratory of Molecular Immunology, MEDINET Co., Ltd., Tokyo, Japan*
[e] *Olympus Optical Co., Ltd., Tokyo, Japan*
[f] *Research Section, Japanese Red Cross Central Blood Center, Tokyo, Japan*

Received 9 July 2002

Abstract

We previously identified the gene expression of renin–angiotensin system in human monocyte-derived dendritic cells (DCs). This study was conducted to examine the mechanisms by which angiotensin II and captopril, the inhibitor of the angiotensin-converting enzyme (ACE), affect human DCs. In DCs, lipopolysaccharide (LPS)-induced production of tumor necrosis factor-α (TNF-α), interleukin-(IL)-1α, IL-10, IL-12, and IL-18 was significantly inhibited by captopril. In contrast, angiotensin II treatment resulted in a significant increase in TNF-α and IL-6 protein biosynthesis by DCs. In addition, we have studied the global expression of 2400 genes in DCs from two donors. Here, we demonstrated the specific down-regulation of the ACE gene expression in captopril-treated DCs. Our finding indicates the possible activation of NF-κB through the up-regulation of expressions of MEFV gene (encoding PYRIN protein) and heterogeneous nuclear ribonucleoprotein R in DCs. This is the first study on the modulation of cytokine and gene expression by angiotensin II and captopril in DCs.

Keywords: Dendritic cell; Renin–angiotensin; Angiotensin II; Captopril; cDNA microarray

Dendritic cells (DCs) are professional antigen-presenting cells, which are central to the integration of innate and specific immunity [1]. Dendritic cells that are activated by innate stimuli and loaded with foreign antigens travel to regional lymph nodes to activate the acquired-immune system. Subsequently, the activated acquired-immune cells move into tissues, where the innate immune system sets off the danger signal [2]. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukins (IL)-1, 6, 10, 12, and 18 are critical linkers between the innate and adaptive cell-mediated immunity. They activate growth and differentiation of T- and B-lymphocytes, and macrophages, and thus, inflammatory processes [3,4].

Historically, the renin–angiotensin system was regarded only as important in the regulation of blood volume, peripheral vascular tone, and blood pressure. However, recent studies showed that the renin–angiotensin system is related to other biological processes, such as apoptosis, vascular remodeling, and inflammation [5–7]. Angiotensin II is an octapeptide that is involved in several steps of the inflammatory process. Therefore, this vasoactive peptide is considered as a true cytokine [8]. The precursor of angiotensin II is the angiotensinogen protein, which is subsequently cleaved by renin into angiotensin I. An angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II, which binds specific receptors, namely AT_1 and AT_2, on cell membranes. It was shown that ACE inhibitors

* Corresponding author. Fax: +81-3-5802-2907.
E-mail address: tokunaga@m.u-tokyo.ac.jp (K. Tokunaga).
[1] Authors contributed equally to this work.

0006-291X/02/$ - see front matter
PII: S0006-291X(02)00855-0

(captopril, enalapril, and cilazapril) suppress the synthesis of TNF and IL-1 in mononuclear cells [9]. Moreover, captopril reduces the level of tissue factor expression in endotoxin-stimulated mononuclear leukocytes [10]. In contrast, the stimulation of monocytes with angiotensin II causes the activation of NF-κB and subsequent increase in the TNF-α production [11]. Previously, we reported the mRNA expressions of angiotensinogen, renin-binding protein, ACE, and angiotensin II/vasopressin receptor in DCs [12].

In this study, we investigated the modulation of the functional features of DCs with angiotensin II and captopril, the inhibitor of its production. Our results suggest a novel mechanism by which angiotensin II influences the production of a variety of proinflammatory cytokines in DCs.

Materials and methods

Preparation of human DCs and culture with captopril and angiotensin II. Human monocytes were isolated from normal peripheral blood mononuclear cells of healthy donors by magnetic-bead sorting with anti-CD14 mAb (MACS, Miltenyi Biotech, Germany). DCs were prepared from monocytes by culturing for five days in AIM-V medium (Gibco-BRL, Rockville, MD) containing 10% FCS (Hyclone, Logan, UT), 400 U/ml GM-CSF (Kirin Brewery Ltd., Gunma, Japan), and 400 U/ml IL-4 (Becton–Dickinson Labware, Palo Alto, CA). DCs used in this study were CD14-negative, but substantially expressed MHC class I, MHC class II, CD80, CD86, CD1b, CD1c, CD1d, CD40, CD54, and CD86.

In cytokine assays, DCs were first pre-cultured for 24 h with 100 ng/ml lipopolysaccharide (LPS) and then subjected to captopril treatment. DCs were incubated for 24 h (for the cytokine assays) with 2×10^{-5} M captopril (Sigma Chemicals, St. Louis, MO) or with 0.1 M angiotensin II. DCs used for the angiotensin II stimulation were intact. For the microarray experiments, DCs were cultured with captopril or angiotensin II at the same concentrations only for 6 h.

Cytokine assay. TNF-α, IL-1α, IL-6, IL-10, IL-12, and IL-18 levels in the culture supernatant were measured using a commercially available Quantikine ELISA Kit (R&D Systems, Minneapolis, MN) according to manufacturer's instructions.

Isolation of total RNA and DNase I treatment. Total RNAs from DCs were extracted from cells by the isothiocyanate method using the TRIzol Reagent (Gibco-BRL, Rockville, MD) following manufacturer's protocol. DNase I treatment was performed using a DNA-free Kit (Ambion, Austin, TX) according to manufacturer's instructions (12).

Labeling of target cDNAs, microarray hybridization, detection, and quantification analysis. mRNA samples were labeled using a TSA labeling and detection kit (Perkin–Elmer Biosystems, Boston, MA) according to manufacturer's instructions. The first step of labeling was the synthesis of first-strand cDNA using 2 μg total RNA using oligo(dT) primers (3′-AT_{17}-5′, 3′-CT_{17}-5′, and 3′-G T_{17}-5′) in the presence of an optimized dNTP mixture containing biotin-11-dCTP for intact DCs (Perkin–Elmer Biosystems, Boston, MA) and fluorescein-12-dCTP for DCs stimulated with captopril or angiotensin II (Perkin–Elmer Biosystems, Boston, MA). These cDNA targets were mixed and simultaneously hybridized to the Micromax microarray (Perkin–Elmer Biosystems, Boston, MA) under a coverslip in a humid chamber at 65 °C overnight.

After several washings (carried out according to manufacturer's instructions), fluorescein- and biotin-labeled cDNAs were sequentially detected with a series of conjugate reporter molecules according to the instructions for the TSA labeling kit. Glass microarrays were scanned and fluorescent signals (cyanine 3 and cyanine 5) were detected using Scanarray 4000 (Packard Instrument Company, Meriden, CT). The subsequent quantification analysis was carried out using commercially available software (Array Gauge, Fuji Film, Tokyo, Japan).

Semiquantitative RT-PCR analysis. Total RNA (1 μg was mixed with 450 ng random hexanucleotide primers, heated at 70 °C for 3 min, and then chilled on ice. Then, 1× first-strand buffer, 0.01 M DTT, 400 μM dNTP mixture and 200 U reverse transcriptase SuperScript II (Gibco-BRL, Rockville, MD) were added. The mixture was then incubated at 42 °C for 1 h. Multiplex relative RT-PCR quantification was performed using primers (5′-ttccgcaagttcacctacc-3′ and 5′-cgggccggccatgctttacg-3′) for the 15S ribosomal protein sequence as previously described [12]. The gene-specific primer sequences used are shown in Table 1.

Table 1
Gene specific primers used in semiquantitative RT-PCR

Name of gene	Primers	Length of PCR product
HPV16 E1 protein-binding protein (HPV16)	5′-tgctgattgatgaggtggag-3′ 5′-tttgggtcaagacagcattg-3′	105
Heterogeneous nuclear ribonucleoprotein R (HnrpR)	5′-gagtccacaaagggacctga-3′ 5′-tggaggaccaccatacttcc-3′	105
PYRIN	5′-ttggaaacaagtgggagagg-3′ 5′-caacctccacctcccagtaa-3′	114
Glutamine synthase (GluSyn)	5′-gaaggaatcagcatgggaga-3′ 5′-caggaatgggcttaggatca -3′	106
SnRNP core protein Sm D3 (SmD3)	5′-atacagagatggccgagtgg-3′ 5′-taacatgggtgcgttcttca-3′	103
Coupling protein G(s) α-subunit (α-S1)	5′-tctgtgggaggatgaaggag-3′ 5′-gatcacgtcgatcttgtcca-3′	100
Enteric smooth muscle γ-actin	5′-gggccagaaagacagctatg-3′ 5′-catcccagttggtgatgatg-3′	101
NOF1	5′-tgactgtgatccggaaagtg-3′ 5′-acctgggtgacaggtgtctt-3′	100
Cathepsin D	5′-cttcatcgcagccaagttc-3′ 5′-agcttctgctgcatcaggtt-3′	102
H-2K binding factor-2 (H2-K)	5′-tcaggaacaaaggtggctct-3′ 5′-gctgtgaactggcatgaaaa-3′	100
CD59	5′-ctgctgcaagaaggacctgt-3′ 5′-cagaaatggagtcaccagca-3′	100
Octamer-binding protein Oct-1 (Oct-1)	5′-ccttggacatctccatcagg-3′ 5′-gaatcccccgattcttcatt-3′	102
Calmodulin-dependent protein phosphatase (Calm)	5′-tttgaaggccgagtacgagt-3′ 5′-tttctctgggtccttctcca-3′	100
Aangiotensin converting enzyme (ACE)	5′-agctgcagccactctacctc-3′ 5′-catagcctctgtggtgtcca-3′	200

Results and discussion

Effects of captopril and angiotensin II on cytokine synthesis in DCs

First, we determined by ELISA the effects of captopril (ACE inhibitor) on LPS-induced TNF-α, IL-1α, IL-10, IL-12, and IL-18 production by human DCs. The optimal LPS concentration (100 ng/ml) and culture time (24 h) were determined in preliminary experiments and

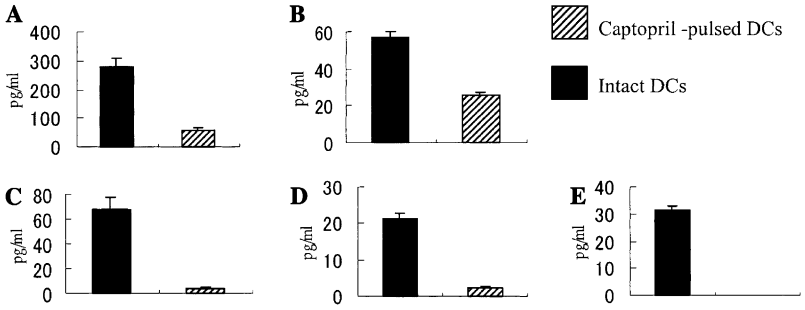

Fig. 1. Effect of captopril on LPS-induced in vitro expression of TNF-α (A), IL-1α (B), IL-10 (C), IL-12 (D), and IL-18 (E) by DCs, as determined by ELISA. Data are means ± SEM, $n = 4$.

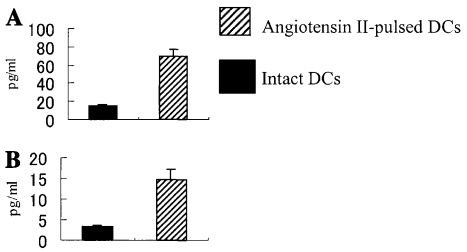

Fig. 2. Angiotensin II-pulsed DCs express TNF-α and IL-6, as determined by ELISA. Data are means ± SEM, $n = 4$.

subsequently used throughout the experiments. As shown in Fig. 1, captopril significantly inhibited LPS-induced production of all examined cytokines in DCs from three different donors. Captopril significantly decreased the levels of secreted TNF-α by 80%, IL-α by 54%, IL-10 by 95%, IL-12 by 90%, and IL-18 by 100%.

As shown in Fig. 2, pre-incubation of DCs with angiotensin II increased the production of TNF-α by 80% and IL-6 by 50%, but did not affect the IL-α, Il-10, IL12, and IL-18 production (data not shown). The expression of TNF-α and IL-6 is regulated by the NF-κB transcription factor. Therefore, our results are consistent with those obtained for monocytes, showing that angiotensin II enhances NF-κB DNA binding [13]. Cell viability was more than 95% in angiotensin II and captopril-treated DCs of these cultures as assessed by flow cytometry. The expression levels of DC cell surface markers, such as HLA-DR, CCR-6, CD40, CD80, CD83, CD86, CD 1b, and CD14, did not show any significant change after the stimulation with either captopril or angiotensin II (data not shown).

Gene expression profiling in DCs pulsed with captopril and angiotensin II

The function of angiotensin II as a multifunctional hormone with a key role in regulating cardiovascular homeostasis is well known. However, in the past decade, much attention has been focused on the importance of angiotensin II as an immunomodulator and on the study of its immunobiological activity. After we discovered that angiotensin II and captopril (an inhibitor of angiotensin II synthesis) can modulate cytokine synthesis in DCs, we performed a global evaluation of changes in gene expression profiles in intact DCs and DCs incubated with angiotensin II or captopril. Human cDNA microarrays containing 2400 clones (spotted in duplicate) were used to identify differentially expressed genes. Targets from unstimulated DCs and angiotensin II-pulsed DCs of one individual were mixed and hybridized on one microarray slide. Similarly, the targets

Table 2
List of genes up-regulated (>2-fold) in DCs after stimulation with angiotensin II

GenBank No.	Gene name	Ratio angiotensin II-pulsed DC/ intact DCs
U78876	MEK kinase 3*	4.5
X64330	ATP-citrate lyase*	3.6
X15998	Chondroitin sulphate proteoglycan versican*	3.5
M37400	Cytosolic aspartate aminotransferase*	3.5
Y12711	Putative progesterone-binding protein*	3.3
D63807	Lanosterol synthase*	3.3
L06419	Lysyl hydroxylase (PLOD)*	3.2
U75272	Gastricsin*	3.2
U96131	HPV16 E1 protein binding protein	3.0
X04011	X-CGD gene involved in chronic granulomatous disease*	2.9
AF062347	Zinc finger protein 216 splice variant 2 (ZNF216)	2.6
Y00264	Amyloid A4 precursor of Alzheimer's disease	2.5
AF000364	Heterogeneous nuclear ribonucleoprotein R	2.3
AF018080	PYRIN (MEFV)	2.2
L41490	Elongation factor 1-α 1 (PTI-1)*	2.1
X59834	Rearranged mRNA for glutamine synthase	2.1
J02984	Insulinoma rig-analog mRNA encoding DNA-binding protein	2
Y09858	mRNA for unknown protein	2

Note. *Labeled genes are those up-regulated both in angiotensin II- and captopril-pulsed DCs.

Table 3
List of genes down-regulated (>2-fold) in DCs after stimulation with angiotensin II

GenBank No.	Gene name	Ratio intact DCs/angiotensin II-pulsed DC
AF083190	SPF31 (SPF31).	4.3
D16431	Hepatoma-derived growth factor	3.2
M13656	Plasma protease (C1) inhibitor	2.8
X04106	Calcium-dependent protease	2.8
D14041	H-2K binding factor-2	2.6
X74331	DNA primase	2.6
L07807	Dynamin*	2.5
M26880	Ubiquitin	2.4
M34671	Lymphocytic antigen CD59/MEM43	2.3
X59434	Rohu	2.3
J05500	β-Spectrin (SPTB).	2.2
J05036	Cathepsin E.	2.1
M17885	Acidic ribosomal phosphoprotein P0	2.1
U43747	Frataxin (FRDA).	2.1
AF051946	T-type calcium channel α-1*	2.1
J03575	Pyruvate dehydrogenase α	2.1
Z11531	Elongation factor-1-γ	2.0
Z71929	FGFR2*	2.0
X63237	Uba80	2.0
S76730	MM1, clone MM1 product	2.0
X97065	Sec23B isoform	2.0
AF039843	Sprouty 2 (SPRY2)	2.0
L14778	Calmodulin-dependent protein phosphatase*	2.0

Note. * Labeled genes are those down-regulated both in angiotensin II- and captopril-pulsed DCs.

Table 4
List of genes up-regulated (>2-fold) in DCs after stimulation with captopril

GenBank No.	Gene name	Ratio captopril-pulsed DC/intact DCs
M11233	Cathepsin D	7.4
D63807	Lanosterol synthase*	3.9
X64330	ATP-citrate lyase*	3.8
Y12711	Putative progesterone-binding protein*	3.7
U15009	SnRNP core protein Sm D3	3.6
U78876	MEK kinase 3*	3.5
L06419	Lysyl hydroxylase*	3.4
X04409	Coupling protein G(s) α-subunit	3.3
X16940	Enteric smooth muscle γ-actin	3.0
X87949	BiP protein	3.0
X04011	X-CGD gene involved in chronic granulomatous disease*	2.9
L41490	Elongation factor 1-α 1*	2.8
U39400	NOF1	2.7
S80562	Acidic calponin	2.6
X15998	Chondroitin sulphate proteoglycan versican*	2.4
M37400	Cytosolic aspartate aminotransferase*	2.2
U75272	Gastricsin*	2.1
X13694	Osteopontin	2.0

Note. * Labeled genes are those up-regulated both in captopril- and angiotensin II-pulsed DCs.

from intact DCs and captopril-pulsed DCs from the same individual were hybridized to another microarray. The cDNA microarray analysis was performed for two different donors. As a result, about 1333 (55%) of 2400 genes spotted onto the array were detected. In the case of stimulation with angiotensin II, the expression levels of 18 genes increased (Table 2) and those of 23 decreased (Table 3). On the other hand, the expression of 18 genes was up-regulated (Table 4) and that of 26 genes down-regulated (Table 5) after captopril stimulation. Interestingly, we found that the expression of 10 genes, encoding proteins such as lanosterol synthase, ATP-citrate lyase, putative progesterone-binding protein, MEK 3 kinase, lysyl hydroxylase, X-CGD protein, elongation factor 1-α1, chondroitin sulfate proteoglycan versican, cytosolic aspartate aminotransferase and gastricsin, was nonselectively up-regulated, following the stimulation with angiotensin II and captopril. Similarly, the expression levels of four genes encoding dynamin,

Table 5
List of genes down-regulated (>2-fold) in DCs after stimulation with captopril

GenBank No.	Gene name	Ratio intact DCs/captopril-pulsed DC
X51521	Ezrin	4.5
AF051946	T-type calcium channel α-1 subunit*	3.5
M26657	Angiotensin converting enzyme	2.8
L41816	Cam kinase I	2.7
L07807	Dynamin*	2.7
M34175	β-Adaptin	2.6
M31158	cAMP-dependent protein kinase subunit RII-β	2.6
X13403	mRNA for octamer-binding protein Oct-1	2.5
L03558	Cystatin B	2.4
Z11566	Pr22 protein	2.4
U04209	Associated microfibrillar protein	2.4
M15796	Cyclin protein gene	2.4
V00497	β-Globin	2.3
L14778	Calmodulin-dependent protein phosphatase*	2.3
J00068	Adult skeletal muscle α-actin mRNA	2.3
U23942	Lanosterol 14-demethylase cytochrome P450	2.3
J04173	Phosphoglycerate mutase	2.3
D87434	KIAA0247 gene	2.3
U69546	RNA binding protein Etr-3	2.3
M27492	Interleukin 1 receptor	2.2
AF044209	Nuclear receptor co-repressor N-CoR	2.2
Z71929	FGFR2 mRNA*	2.2
X74070	Transcription factor BTF 3	2.2
M90656	γ-Glutamylcysteine synthetase (GCS)	2.2
U87460	Putative endothelin receptor type B-like protein	2.2
D45887	Calmodulin	2.1

Note. * Labeled genes are those down-regulated both in captopril- and angiotensin II-pulsed DCs.

T-type calcium channel α-1 subunit, FGFR2, and calmodulin-dependent protein phosphatase decreased in DCs after treatment with angiotensin II and captopril. Generally, both angiotensin II and captopril are recognized and captured by DCs as exogenous antigens. Thus, they may cause nonspecific up- and down-regulations of the expression of genes that play important roles in a network integrating cellular responses (enhancing antigen presentation, cell metabolism, rearrangements in cytoskeleton) to a number of stimuli. For instance, lanosterol synthase catalyzes the cyclization of squalene-2,3-epoxide lanosterol, which is the parental compound of all steroids in mammals [14]. Recently, it has been shown that steroids are the major components of sphingolipid- and cholesterol-rich plasma membrane microdomains, termed membrane rafts. The membrane raft structure plays an integral role in early events of CD40 signaling and MHC class I antigen presentation in DCs [15,16]. Therefore, we suggest that the nonspecific up-regulation of the lanosterol synthase in DCs stimulated with antigens (angiotensin II and captopril) indicates the activation of DCs to produce more steroids to enhance the antigen-presenting and activating T-cell costimulatory features of DCs.

We identified a subset of genes, the expression levels of which in DCs were specifically regulated in the presence of angiotensin II. It has been shown previously that angiotensin II, like TNF-α, causes rapid activation of NF-κB in human mononuclear cells [13]. Moreover, in our study, we showed for the first time that the angiotensin II stimulation up-regulates PYRIN (family member of PYRIN-containing Apaf1-like proteins) mRNA in DCs (Fig. 3). The family of PYRIN-containing Apaf1-like proteins participates in inflammatory signaling by regulating the activation of NF-κB and cytokine processing [17]. In addition, heterogeneous nuclear ribonucleoproteins can bind to the NF-κB enhancer motif, which stimulates its phosphorylation in vitro by an associated serine/threonine kinase [18]. We provide here the first direct evidence that angiotensin II increases the expression levels of PYRIN and heterogeneous nuclear

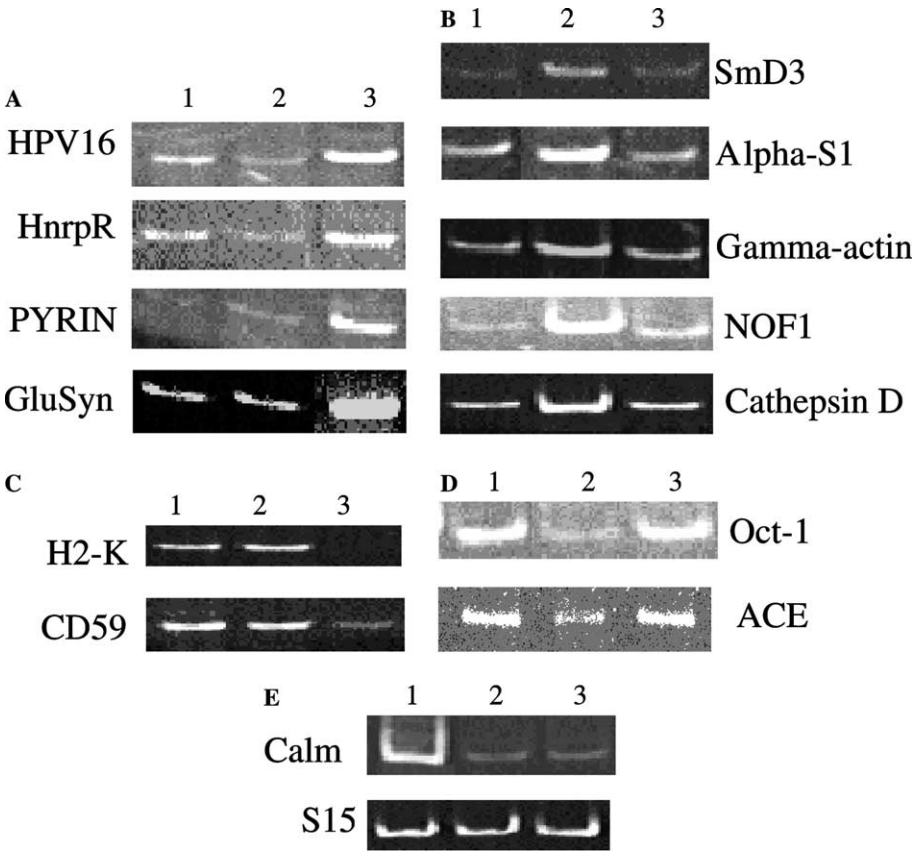

Fig. 3. Semiquantitative RT-PCR with gene-specific primers, confirming the results of cDNA microarray analysis in angiotensin II- and captopril-pulsed DCs. Genes specifically up-regulated by angiotensin II (A), up-regulated by captopril, down-regulated by angiotensin II (C), down-regulated by captopril (D), and down-regulated by both angiotensin II and captopril. 1, intact DCs; 2, captopril-pulsed DCs; 3, angiotensin II-pulsed DCs. These results are representative of three experiments using mRNA from DCs of unrelated donor. Primers for S15 ribosomal protein served as internal standard.

ribonucleoprotein R. Therefore, our finding indicates the possible activation of NF-κB through the up-regulation of expressions of these genes in DCs. We confirmed the up-regulation of PYRIN and heterogeneous nuclear ribonucleoprotein R gene expressions in intact and angiotensin II-stimulated DCs by semiquantitative RT-PCR (Fig. 3).

ACE inhibitors are widely used in the treatment of systemic hypertension. Aside from its blood pressure-lowering properties, captopril has various immunomodulatory functions. The drug exhibits beneficial effects on rheumatoid arthritis, prevention of complications in insulin-dependent diabetes mellitus, and inhibition of inflammation in experimental lupus diseases [19–21]. Some ACE inhibitors including captopril are capable of suppressing the production of monocytes/macrophage-derived proinflammatory cytokines [22]. These immunomodulatory actions of captopril have been explained by several mechanisms, including antiproliferation, anti-oxidant activity, inhibition of metalloproteases, and elevation of prostaglandin synthesis [23–26]. To our knowledge, we demonstrated for the first time by cDNA microarray analysis the specific down-regulation of ACE in captopril-treated DCs (Table 5). These data were confirmed by semiquantitative RT-PCR (Fig. 3). The inhibitory properties of captopril may be related to the presence of thiol groups in the captopril structure (providing specific binding sites for ACE) as well as the indirect suppression of expression of the gene encoding ACE.

In addition, we found the increased level (3.3-fold) of coupling protein G(s) α-subunit in DCs after stimulation with captopril (Table 4). These data are consistent with previous data, in which captopril restored the levels of Gi-α proteins to the base levels and also enhanced the levels of Gi α-2 and Gi α-3 in the hearts of hypertensive rats [27].

In conclusion, ACE converts angiotensin I into angiotensin II, which binds specific receptors on cell membranes. Previously, we found that DCs can express the receptor of angiotensin II/vasopressin [12], angiotensinogen, and ACE. Therefore, it is conceivable that under appropriate conditions, angiotensin II is formed and occupancy of its receptor on DCs occurs in vivo. Here, we showed that angiotensin II-stimulated DCs produce proinflammatory cytokines and express genes enhancing the activity of NF-κB transcription factor. Moreover, we showed using cDNA microarray and RT-PCR analyses that the proinflammatory cytokine inhibitory function of captopril in DCs can be induced by suppression of gene expression of ACE. Our result is consistent with the hypothesis that the induction of expression of proinflammatory cytokines by blood cells (including DCs) can be regulated by angiotensin II. Finally, the gene expression profiles in angiotensin II- and captopril-treated DCs obtained in the present study clarify further the effects of angiotensin II and captopril on blood cells and may provide an immunological platform, based on which specific cellular therapies using DCs may be developed.

References

[1] L.H. Stockwin, D. Mcgonagle, I.G. Martin, G.E. Blair, Dendritic cells: immunological sentinels with a central role in health and disease, Immunol. Cell Biol. 78 (2000) 91–102.
[2] B.N. Lambrecht, Allergen uptake and presentation by dendritic cells, Curr. Opin. Allergy Clin. Immunol. 1 (2001) 51–59.
[3] R.M. Steinman, Cytokines amplify the function of accessory cells, Immunol. Lett. 17 (1988) 197–202.
[4] F. Biet, C. Locht, L. Kremer, Immunoregulatory functions of interleukin 18 and its role in defense against bacterial pathogens, J. Mol. Med. 80 (2002) 147–162.
[5] L. Rossig, S. Dimmeler, A.M. Zeiher, Apoptosis in the vascular wall and atherosclerosis, Basic Res. Cardiol. 96 (2001) 11–22.
[6] J.P. Wesselman, J.G. De Mey, Angiotensin and cytoskeletal proteins: role in vascular remodeling, Curr. Hypertens Rep. 4 (2002) 63–70.
[7] G. Wolf, U. Wenzel, K.D. Burns, R.C. Harris, R.A. Stahl, F. Thaiss, Angiotensin II activates nuclear transcription factor-κB through AT1 and AT2 receptors, Kidney Int. 61 (2002) 1986–1995.
[8] M. Ruiz-Ortega, O. Lorenzo, Y. Suzuki, M. Ruperez, J. Egido, Proinflammatory actions of angiotensins, Curr. Opin. Nephrol. Hypertens 10 (2001) 321–329.
[9] M. Fukuzawa, J. Satoh, M. Sagara, G. Muto, Y. Muto, S. Nishimura, S. Miyaguchi, X.L. Qiang, Y. Sakata, T. Nakazawa, F. Ikehata, S. Ohta, T. Toyota, Angiotensin converting enzyme inhibitors suppress production of tumor necrosis factor-α in vitro and in vivo, Immunopharmacology 36 (1997) 49–55.
[10] E. Napoleone, A. Di Santo, M. Camera, E. Tremoli, R. Lorenzet, Angiotensin-converting enzyme inhibitors downregulate tissue factor synthesis in monocytes, Circ. Res. 86 (2000) 139–143.
[11] M. Ruiz-Ortega, O. Lorenzo, M. Ruperez, S. Konig, B. Wittig, J. Egido, Angiotensin II activates nuclear transcription factor κB through AT(1) and AT(2) in vascular smooth muscle cells: molecular mechanisms, Circ. Res. 86 (2000) 1266–1272.
[12] N. Lapteva, M. Nieda, Y. Ando, K. Ide, Y. Hatta-Ohashi, G. Dymshits, Y. Ishikawa, T. Juji, K. Tokunaga, Expression of renin-angiotensin system genes in immature and mature dendritic cells identified using human cDNA microarray, Biochem. Biophys. Res. Commun. 285 (2001) 1059–1065.
[13] R. Kranzhofer, M. Browatzki, J. Schmidt, W. Kubler, Angiotensin II activates the proinflammatory transcription factor nuclear factor-κB in human monocytes, Biochem. Biophys. Res. Commun. 257 (1999) 826–828.
[14] M. Young, H. Chen, M.D. Lalioti, S.E. Antonarakis, The human lanosterol synthase gene maps to chromosome 21q22.3, Hum Genet. 97 (1996) 620–624.
[15] P.O. Vidalain, O. Azocar, C. Servet-Delprat, C. Rabourdin-Combe, D. Gerlier, S. Manie, CD40 signaling in human dendritic cells is initiated within membrane rafts, EMBO J. 19 (2000) 304–3313.
[16] P. Machy, K. Serre, M. Baillet, L. Leserman, Induction of MHC class I presentation of exogenous antigen by dendritic cells is controlled by CD4+ T cells engaging class II molecules in cholesterol-rich domains, J. Immunol. 168 (2002) 1172–1180.
[17] L. Wang, G. Manji, J.M. Grenier, A. Al-Garawi, S. Merriam, J.M. Lora, B.J. Geddes, M. Briskin, P.S. Distefano, J. Bertin, PYPAF7: a novel PYRIN-containing Apaf1-like protein that

regulates activation of NF-κB and caspase-1-dependent cytokine processing, J. Biol. Chem. 17 (2002) 17.
[18] I. Van Seuningen, J. Ostrowski, K. Bomsztyk, Description of an IL-1-responsive kinase that phosphorylates the K protein. Enhancement of phosphorylation by selective DNA and RNA motifs, Biochemistry 34 (1995) 5644–5650.
[19] M.F. Martin, K.E. Surrall, F. Mckenna, J.S. Dixon, H.A. Bird, V. Wright, Captopril: a new treatment for rheumatoid arthritis? Lancet 1 (1984) 1325–1328.
[20] E.J. Lewis, L.G. Hunsicker, R.P. Bain, R.D. Rohde, The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group, N. Engl. J. Med. 329 (1993) 1456–1462.
[21] H. Herlitz, A. Tarkowski, C. Svalander, R. Volkmann, G. Westberg, Beneficial effect of captopril on systemic lupus erythematosus-like disease in MRLlpr/lpr mice, Int. Arch. Allergy Appl. Immunol. 85 (1988) 272–277.
[22] R. Schindler, C.A. Dinarello, K.M. Koch, Angiotensin-converting-enzyme inhibitors suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells, Cytokine 7 (1995) 526–533.
[23] H. Bauer, A. Lametschwandtner, M. Steiner, H.C. Bauer, Influence of angiotensin converting enzyme inhibitor (captopril) on kidney epithelial cells in vitro: studies on potassium (86Rb) influx and cellular proliferation, Clin. Chim. Acta 187 (1990) 47–53.
[24] D. Jay, Captopril and glutathione inhibit the superoxide dismutase activity of Hg(II), Arch. Inst. Cardiol. Mex. 68 (1998) 457–461.
[25] T. Nakagawa, T. Kubota, M. Kabuto, T. Kodera, Captopril inhibits glioma cell invasion in vitro: involvement of matrix metalloproteinases, Anticancer Res. 15 (1995) 1985–1989.
[26] S.A. Johnsen, M. Aurell, Immunosuppressive action of captopril blocked by prostaglandin synthetase inhibitor, Lancet 1 (1981) 1005.
[27] S.K. Pandey, M.B. Anand-Srivastava, Modulation of G-protein expression by the angiotensin converting enzyme inhibitor captopril in hearts from spontaneously hypertensive rats. Relationship with adenylyl cyclase, Am. J. Hypertens 9 (1996) 833–837.