ORIGINAL ARTICLE

Serum levels of the Th1 chemoattractant interferon-gamma-inducible protein (IP) 10 are elevated in patients with essential hypertension

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Growing evidence shows that inflammation has a pivotal role in the pathophysiology of essential hypertension (EH). Although it has been acknowledged that target organ damage involves an inflammatory response, most work has focused on the role of macrophages, but T lymphocytes have recently become the center of interest. The goal of our study was to evaluate the role of T-cell-specific cytokines in the pathogenesis of EH. The study examined 39 patients with EH (57.7 ± 6.8 years, systolic blood pressure (SBP) 157.5 ± 11.8 mm Hg, diastolic blood pressure 92.2 ± 12.9 mm Hg, mean arterial pressure 113.9 ± 12.6 mm Hg) and 30 healthy, normotensive controls (55.2 ± 4.9 years). Blood was drawn from a peripheral vein, and serum levels of interferon-inducible protein (IP)-10 and interleukins (IL)-4, -7 and -13 were measured by a multiplexing assay. Hypertensive patients had significantly higher levels of IP-10, IL-4, IL-7 and IL-13 than control subjects. When the patients were classified into tertiles according to their serum IP-10 levels (T1: $41.2\text{--}94.1$ pg ml⁻¹; T2: $103.4\text{--}162.5$ pg ml⁻¹; T3: $171.7\text{--}443.5$ pg ml⁻¹), the patients classified into the highest tertile also had the highest blood pressure. In a correlation analysis, plasma IP-10 concentration was significantly associated with SBP ($r=0.59$, $P<0.001$). Furthermore, hypertensives with microalbuminuria, an early sign of hypertensive target organ damage, had the highest IP-10 levels. A stepwise multivariate regression analysis revealed IP-10 as the strongest independent predictor of SBP ($P=0.01$). In conclusion, our study provides new insights into the pathophysiological mechanisms in EH linking inflammation and IP-10. However, these preliminary results need to be confirmed in larger trials.

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INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular diseases. It markedly increases the risk of death from stroke, ischemic heart disease and other vascular diseases. Because of its high prevalence in almost all populations, hypertension has become a major healthcare concern. Clinical data have demonstrated that essential hypertension (EH) is clearly linked to inflammation: C-reactive protein levels have been associated with future development of hypertension.^{1,2} In addition, basic and clinical researches have also demonstrated the upregulation of genes related to inflammation, such as tumor necrosis factor- α and intercellular adhesion molecule-1, in the target organs and the circulation of hypertensive animals and patients. Recently, we have shown that inflammatory pathways have already been activated in young patients with mild hypertension before there are even signs of target organ damage.³

In an attempt to assess global risk in EH, increasing attention has been given to the identification of the critical inflammatory pathways

involved in the mechanisms associated with subclinical atherosclerotic disease.^{4,5}

In this context, Guzik *et al.*⁶ identified the crucial role of T cells in the genesis of hypertension. They showed that angiotensin II markedly increased T cells in the perivascular adipose tissue. Mice lacking T cells had blunted hypertension, and did not develop abnormalities of vascular function during angiotensin II infusion or desoxycorticosterone acetate salt. Transfer of T cells restored these abnormalities.

This possible new role of T cells in the pathophysiology of hypertension further raises questions. The role of T cell-dependent cytokines and chemokines in patients with EH is not currently fully understood.

In this study, we focused on interferon-inducible protein-10 (IP-10), also referred to as CXCL10, a chemokine that promotes the migration of activated T cells (T-helper 1 (Th1) lymphocytes).⁷ IP-10 belongs to the C-X-C chemokine superfamily and is produced and released by monocytes and endothelial cells. Increased serum IP-10

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levels have been reported in atherosclerotic patients⁸ and, furthermore, have been shown to indicate T-cell activity.^{9–11} IP-10 protein has been shown to be transiently induced in the reperfused myocardium in an experimental myocardial infarction model.¹² However, no reports have examined the role of IP-10 in hypertensive patients.

On the basis of these results, we hypothesized that IP-10 contributes to the inflammatory milieu in patients with EH. To investigate this hypothesis further, we performed this pilot study in patients with moderate hypertension.

METHODS

Subjects

The clinical research competence unit in Erlangen-Nuremberg recruited 39 participants. Baseline characteristics are listed in Table 1. Patients were enrolled when they had EH and were drug resistant, that is, on more than three antihypertensives. Normotensive control subjects (blood pressure <130/85 mm Hg; $n=30$) with normal physical examination results and without a history of medical illness were enrolled in the study after exclusion of any significant risk factors for cardiovascular disease. Patients and controls were included simultaneously. Healthy controls were selected to approximate the age and sex distribution of the patient group. Exclusion criteria for all subjects included diabetes mellitus, hyperthyroidism, significant renal disease, malignancy, treatment with immunosuppressive or antiinflammatory drugs, connective tissue disease, infection and any acute illness. Moreover, in the patient group, secondary forms of hypertension were excluded by appropriate tests. Healthy volunteers were recruited (1) among medical students and (2) in the outpatient clinic, and were selected to approximate the age and sex distribution

of the patient group. Volunteers recruited in the outpatient clinic came for checkup examinations or physical fitness tests.

Before enrollment in the study, written informed consent was obtained from each participant. The study protocol was approved by the clinical investigations ethics committee of the University of Erlangen-Nuremberg, Germany. The study was performed in adherence to the principles of the Declaration of Helsinki and according to Good Clinical Practice standards.

Blood sampling protocol

Peripheral venous blood was drawn into blood collection tubes containing 106 mmol l^{-1} sodium citrate in a highly standardized manner. All blood samples were collected under minimal tourniquet pressure from the antecubital vein using a large-caliber puncture needle (21 gauge) under resting conditions (subjects had rested for more than 15 min). All blood tubes were immediately transferred to the laboratory. After centrifugation (1500 g and 4°C for 10 min), the serum supernatant was stored at -80°C until analysis. Samples were thawed only once.

Multiplexing

Cytokines in samples were measured with a multiplexing method using the assay and protocol developed by Linco Research (St Charles, MO, USA). Briefly, after blocking the filter plate with assay buffer, samples, standards and controls were added to the wells of the plate ($25 \mu\text{l}$ per well) in duplicate, followed by application of premixed beads. After 1 h of incubation at room temperature on a shaker, the content of the wells was removed using a vacuum, and the wells were washed twice with washing buffer. Detection antibody cocktail ($25 \mu\text{l}$ per well) was then applied, and the plate was incubated for 30 min at room temperature. After $25 \mu\text{l}$ of streptavidin-phycoerythrin solution was added and incubated for 30 min, the content of the wells were removed by vacuum. The plates were washed with washing buffer, and $100 \mu\text{l}$ of sheath fluid was added to each well. The plate was incubated for 5 min. The signal was read using a Luminex 100 IS Reader (Luminex, Austin, TX, USA).

Statistical analysis

The statistical analyses were carried out using SPSS software (release 16.0, SPSS, Chicago, IL, USA). Results are given as means $\pm$ s.d. or as median and 25–75th percentile, if otherwise stated. Paired samples were compared using the Student's *t*-test. Comparisons between groups were performed using one-way ANOVA and the Bonferroni's *post hoc* test. Correlation analyses were performed using Pearson's test for parametric data and the Spearman's ρ test for nonparametric data. Two-tailed values of $P<0.05$ were considered statistically significant.

RESULTS

Demographic and clinical data for the patients and the control subjects are summarized in Table 1. There were no significant differences in age, sex or body mass index (kg m^{-2}) between the hypertensive patients and the normotensive controls. Hypertensives had higher systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure and pulse pressure levels (all $P<0.001$) than normotensive controls. Significant microalbuminuria level was identified in 21 (56%) of the hypertensive patients, which is defined as albuminuria $\geq 15 \mu\text{g min}^{-1}$ and $<200 \mu\text{g min}^{-1}$ (30–300 mg per 24 h).

Levels of interleukin (IL)-4 were significantly higher in hypertensive patients (median 141.4 pg ml^{-1} , range $66.5\text{--}168.6 \text{ pg ml}^{-1}$) than in the healthy control group (median 33.3 pg ml^{-1} , range $18.2\text{--}57.3 \text{ pg ml}^{-1}$; $P<0.05$; Figure 1a). IL-7 was also found to be higher in the hypertensive group (median 12.2 pg ml^{-1} , range $11.4\text{--}14.2 \text{ pg ml}^{-1}$) than in the control group (median 10.2 pg ml^{-1} , range $9.5\text{--}10.4 \text{ pg ml}^{-1}$; $P<0.05$; Figure 1b). The median IL-13 level was higher in the hypertensive group (median 225.7 pg ml^{-1} , range $61.3\text{--}445.3 \text{ pg ml}^{-1}$) compared with the control group (median 97.6 pg ml^{-1} , range $36.3\text{--}164.7 \text{ pg ml}^{-1}$; $P<0.05$; Figure 1c). Whereas IL-4 and IL-13 significantly correlated with SBP (IL-4: $r=0.48$, $P<0.05$; IL-13:

Table 1 Patients' characteristics

	Hypertensives	Controls
<i>n</i>	39	30
Age (years)	57.7 ± 6.8	55.2 ± 4.9
Male (%)	79.5	76
Disease duration (years)	15.6 ± 13.4	—
Body mass index (kg m^{-2})	28.8 ± 3.5	26.5 ± 2.6
Waist circumference (cm), M	106.8 ± 12.9	102.7 ± 10.3
Waist circumference (cm), F	93.4 ± 13.6	92.5 ± 11.7
Fasting glucose (mg dl^{-1})	94.8 ± 12.5	—
Cholesterol	234.3 ± 45.1	—
HDL-cholesterol	56.3 ± 12.6	—
LDL-cholesterol	157.3 ± 36.5	—
Smoking (%)	51.3	40
ACE inhibitors (%)	18	—
(ARB) (%)	25	—
Beta-blockers (%)	29	—
Calcium channel blockers (%)	22	—
Diuretics	39	—
Heart rate	63.3 ± 11.8	65.7 ± 12.9
Office SBP (mm Hg)	157.5 ± 19.0	125.3 ± 10.3
Office DBP (mm Hg)	92.2 ± 12.9	76.7 ± 8.5
MAP (mm Hg)	113.9 ± 12.6	92.4 ± 9.8
24-h SBP (mm Hg)	142.1 ± 28.8	—
24-h DBP (mm Hg)	83.6 ± 11.5	—
Sokolow-Lyon index	2.4 ± 0.9	—
Serum creatinine (mg dl^{-1})	0.91 ± 0.2	0.95 ± 0.7
HbA1c (%)	5.6 ± 0.3	—
Microalbuminuria (<i>n</i> , %)	21, 56%	—

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; DBP, diastolic blood pressure; F, female; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male; MAP, mean arterial pressure. Values are shown as mean $\pm$ s.e.m.

Figure 1 Relationship of serum IL-4 (a), IL-7 (b) and IL-13 (c) in hypertensives and normotensive controls.

$r=0.43$, $P<0.05$), IL-7 did not significantly correlate with SBP ($r=0.24$, $P=\text{nonsignificant}$).

Hypertensive patients had significantly higher IP-10 levels (median 57.0 pg ml^{-1} , range $42.1\text{--}63.5 \text{ pg ml}^{-1}$ vs. median 162.5 pg ml^{-1} , range $116.5\text{--}285.8 \text{ pg ml}^{-1}$, respectively; $P<0.001$; Figure 2). When the patients were classified into tertiles according to their serum IP-10 levels (T1: $41.2\text{--}94.1 \text{ pg ml}^{-1}$; T2: $103.4\text{--}162.5 \text{ pg ml}^{-1}$; T3: $171.7\text{--}443.5 \text{ pg ml}^{-1}$), the patients classified into the highest tertile also had the highest blood pressure (Figure 3).

Furthermore, the plasma IP-10 concentration was significantly associated with SBP ($r=0.47$, $P<0.005$; Figure 4).

To further evaluate the relationship between IP-10 and hypertensive target organ damage, patients were stratified on the basis of having signs of microalbuminuria. Interestingly, hypertensives with microalbuminuria had the highest IP-10 levels (Figure 5).

On the basis of these results, we performed a stepwise multivariate regression analysis, and IP-10 was the strongest independent predictor of SBP ($P=0.01$).

The influence of RAS blockade on IP-10 levels was also examined in a subanalysis. However, there was no significant difference between patients with and without ACE inhibitor therapy (median 100.3 pg ml^{-1} , range $82.4\text{--}156.1 \text{ pg ml}^{-1}$ vs. median 147.1 pg ml^{-1} , range $93.2\text{--}257.9 \text{ pg ml}^{-1}$; $P=0.24$).

High-sensitivity C-reactive protein levels were also measured as a basal marker of inflammation. As expected, CRP levels were

Figure 2 Serum IP-10 levels in hypertensives and normotensive controls, $*P<0.001$.

Figure 3 Relationship of serum IP-10 levels and mean arterial pressure (MAP), $*P<0.05$, $**P<0.01$.

Figure 4 Correlation analysis of IP-10 and systolic blood pressure (SBP), $r=0.47$, $P<0.005$.

significantly higher in hypertensives as compared with healthy control subjects ($2.7 \pm 3.8 \text{ mg l}^{-1}$ vs. $0.6 \pm 0.9 \text{ mg l}^{-1}$, $P<0.01$). When CRP was included in the multivariate analysis, IP-10 was still an independent predictor of SBP ($P=0.02$).

Figure 5 Relationship of serum IP-10 levels in hypertensives with and without microalbuminuria, $P < 0.01$.

DISCUSSION

In this pilot study, we observed increased plasma levels of IP-10 among patients with moderate hypertension. We detected a positive correlation between IP-10 and SBP. Furthermore, hypertensive patients with microalbuminuria, an early sign of target organ damage, presented the highest IP-10 levels. In a multivariate analysis, IP-10 was shown to be the strongest independent predictor of SBP. This is, to our knowledge, the first report of elevated IP-10 levels in moderate hypertension and target organ damage.

Recently accumulated evidence has demonstrated an elevated serum IP-10 level in various diseases, including inflammatory disease, and has shown its utility as a clinically useful biomarker.^{13–15} For instance, Tang *et al.*¹⁶ demonstrated that IP-10 is an independent predictor of outcome for severe acute respiratory syndrome patients. Another group has demonstrated elevated IP-10 levels in patients with coronary artery disease.⁸ Furthermore, Aukrust *et al.*¹⁷ recently reviewed the usefulness of serum plasma chemokine levels to predict the risk of cardiovascular events and suggested an important pathogenic role of chemokines in atherogenesis and plaque destabilization.

Several studies published in the past three decades have already suggested that the adaptive immune system contributes to hypertension. Although it is often acknowledged that target organ damage in hypertension involves an inflammatory response, most work has focused on the role of macrophages. The accumulation of these cells in various tissues, such as the kidney, is often viewed as a nonspecific response to elevated blood pressure. About 30 years ago, Svendsen¹⁸ demonstrated that the delayed phase of desoxycorticosterone acetate salt hypertension was blunted in thymectomized animals. The T-cell-modulating agent mycophenolate mofetil lowers blood pressure in Dahl salt-sensitive rats.¹⁹ Mofetil also lowers blood pressure in humans with psoriasis and rheumatoid arthritis, which are both T-cell-dependent autoimmune disorders.^{20,21} The most recent data for the crucial role of T cells in hypertension has been provided by Guzik.⁶ They showed that mice lacking T- and B cells have a blunted hypertensive response to chronic low-dose ANG II infusion or desoxycorticosterone acetate salt challenge. Furthermore, these animals demonstrated preserved endothelium-dependent vasodilatation and had only a minimal increase in vascular superoxide production compared with wild-type animals. Very interestingly, restoring B cells by a transplant procedure had no effect, whereas adoptive transfer of T cells completely restored the blood pressure elevation and increase in vascular superoxide production caused by ANG II. Obviously, T cells have an underestimated role in the pathogenesis and progression of hypertension. Therefore, evaluation of T-cell reactivity in the case of hypertension could be a tool for risk stratification. In this situation,

IP-10 has attracted attention as an indicator of Th1 activity.²² As IP-10 selectively upregulates human T-cell cytokine synthesis and induces migration of Th1 cells to local lesions, it could be used as a marker of Th1 activity in target organ damage (for example, kidney).^{11,23}

In this study, we found that hypertensive patients with microalbuminuria, one early sign of renal target organ damage, had the highest IP-10 levels. Recently, Crowley *et al.*²⁴ demonstrated that hypertensive target organ damage lesions are associated with renal T-cell infiltration. Another group demonstrated an attenuation of experimental hypertensive renal damage by a lymphocyte migration inhibitor.²⁵ In addition, elevated IP-10 levels have been reported to reflect active disease in patients with inflammatory diseases.^{26–28} On the basis of our results, IP-10 seems to have a role in progressive essential hypertension, which suggests a role for lymphocytes in the inflammatory milieu in hypertension. In addition to elevation of the Th1 cell chemokine IP-10, we also observed an upregulation of the Th2 cell cytokines IL-4 and IL-13, as well as the T-cell activator IL-7. We chose these cytokines because of their important roles as Th2 activators: IL-4 and IL-7 induce T-cell proliferation and differentiation of naive T cells to Th2 cells; IL-13 is released by activated Th2 cells leading to further cell activation. Additionally, these cytokines have an important role in orchestrating inflammatory reactions in general: both IL-4 and -13 have been shown to induce endothelial expression of vascular cell adhesion protein-1, thus facilitating the transmigration of leukocytes across vascular endothelial cells into the target organ. This mechanism is thought to have an important role in hypertensive target organ damage.

Furthermore, IL-4 and IL-13 also enhance levels of the vascular endothelial growth factor.^{29,30} We only recently demonstrated a role for vascular endothelial growth factor as an inflammatory mediator in young hypertensive patients without signs of target organ damage.³¹

In conclusion, our study provides new insights into the pathophysiological mechanisms in EH linking inflammation and IP-10. However, these preliminary results need to be confirmed in larger trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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