Expression of IL-19 correlates with Th2 cytokines in uraemic patients

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Abstract

Background. Patients with end-stage renal disease are thought to be in a chronic state of inflammation. They also have an impaired immune response with a dysregulated Th1/Th2 cytokine network. Interleukin (IL)-19, which belongs to the IL-10 family, is a newly discovered proinflammatory cytokine. IL-19 alters the balance of Th1/Th2 cells in favour of Th2. The aims of the present study were to assess the changes in serum levels of IL-19 and their correlation with Th2 cytokine production in uraemic patients.

Methods. Seventy-three uraemic patients with haemodialysis were evaluated; 33 healthy volunteers served as controls. Serum levels of IL-19, -4, -5, -6, -10, -13 and tumour necrosis factor (TNF)-α were analysed using ELISA. Monocytes and T cells isolated from the patients and healthy volunteers were cultured in vitro, and cytokine production was determined.

Results. IL-19 expression in the patients, but not in healthy controls, correlated positively with both the proinflammatory cytokines (IL-6 and TNF-α) and the Th2 cytokines (IL-4, IL-5, IL-6, IL-10 and IL-13). Cultured monocytes from patients with high IL-19 serum levels produced more IL-19 in vitro. Additionally, uraemic serum or oxidized low-density lipoproteins up-regulated the IL-19 transcripts expression in resting monocytes. Compared with T cells from healthy controls, uraemic T cells expressed more endogenous Th2 cytokine transcripts and further responded to IL-19 stimulation in Th2 cytokine production in vitro.

Conclusions. IL-19 expression in uraemic patients correlated with Th2 immune responses which might be involved in the cytokine dysregulation in uraemia.

Keywords: cytokines; haemodialysis; interleukin-19; uraemia

Introduction

Patients with end-stage renal disease have an impaired immune response that leaves them both susceptible to infection and malignancy and resistant to vaccination [1–3]. The immune response defect of uraemic patients correlates with an altered activation of T cells [4,5]. This alteration is associated with an intriguing dysregulation of cytokine production. The cytokine profile produced by the T lymphocytes determines the immune response, and stimulation by antigen exposure causes T-helper lymphocytes to differentiate into two distinct phenotypes, Th1 and Th2 [6]. Recently, several studies [7–11] have reported a change in the profile of Th1/Th2 lymphocytes in uraemic patients. Uraemia on haemodialysis (HD) depressed Th1 cell function and increased Th2 cell function, which dysregulated the cytokine network [8,12,13].

IL-19 is a recently discovered proinflammatory cytokine in the IL-10 family (IL-10, -19, -20, -22, -24 and -26) [14,15]. It is a secreted α-helical protein with amino acid sequences 20% identical to those of IL-10, and it contains four specific positions of cysteine, positions with a structure very similar to that of IL-10 [16]. IL-10 has been considered as one of the most important anti-inflammatory cytokines. HD patients who produce low levels of IL-10 are at a greater risk of cardiovascular mortality than those who produce high levels of IL-10 [17]. In contrast to the anti-inflammatory property of IL-10, IL-19 plays the role of a proinflammatory cytokine [18]. Although the functions of IL-19 are not well understood, we do know that it induces monocytes to produce IL-6 and tumour necrosis factor (TNF)-α [18], and CD4+ T cells to produce Th2 cytokines, which are associated with asthma [19]. IL-19 expression is up-regulated by
IL-19 expression in uraemic patients

Subjects and methods

Patients and healthy controls

We enrolled 73 patients with uraemia and 33 healthy controls in this study (Table 1). All patients received regular HD treatment 4h thrice weekly for at least 1 year with new cuprophane dialysers (membrane surface, 1.3 m²; sterilization, ethylene oxide). Patients with autoimmune diseases, diabetes mellitus, obvious signs of infection, or malignancy and those taking antibiotics or steroids or immunomodulators such as calcitrol, statins, or angiotensin-converting enzyme inhibitors were excluded in this study. The study was approved by our Institutional Review Board and signed consents were obtained from all participants.

Table 1. Clinical characteristics of uraemic patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Uraemic patients (n = 73)</th>
<th>Healthy controls (n = 33)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>60.8 ± 12.3</td>
<td>52.4 ± 11.6</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>33/40</td>
<td>16/18</td>
</tr>
<tr>
<td>Duration of HD (months)</td>
<td>53.7 ± 48.9</td>
<td>18.6 ± 1.2</td>
</tr>
<tr>
<td>BUN</td>
<td>66.6 ± 17.8*</td>
<td>16 ± 6.7</td>
</tr>
<tr>
<td>Creatinine</td>
<td>16.9 ± 6.7</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Before HD</td>
<td>9.5 ± 2.7*</td>
<td>3.1 ± 1.0*</td>
</tr>
<tr>
<td>After HD</td>
<td>3.2 ± 0.5</td>
<td>6.2 ± 0.4</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.8 ± 0.5</td>
<td>4.2 ± 0.3</td>
</tr>
<tr>
<td>White blood cells (10³/µl)</td>
<td>6.7 ± 1.9</td>
<td>6.9 ± 1.6</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>60.3 ± 4.4</td>
<td>58.2 ± 5.1</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>32.4 ± 5.6</td>
<td>35.4 ± 6.2</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>8.3 ± 2.1</td>
<td>7.5 ± 1.8</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.2 ± 1.7*</td>
<td>13.8 ± 1.3</td>
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</table>

HD, hemodialysis. Data are means ± SD. *P < 0.05, Student’s unpaired t-test.

Blood samples

Blood samples were collected just before and after the second dialysis session of the week. The serum was prepared and stored at −80°C before analysis. Serum levels of cytokines and C-reactive protein (CRP) and complete blood counts (CBC) were analysed.

Monocyte isolation

Peripheral blood mononuclear cells (PBMCs) were isolated from blood using Ficoll-Paque (Pharmacia, Uppsala, Sweden) density gradient centrifugation. Monocytes were washed twice with warm RPMI-1640 medium and allowed to adhere for 30 min at 37°C in a 5% CO₂ atmosphere. The monocytes were >95% pure, as determined by Liu’s staining, and contained >98% viable cells. The non-adherent cells containing both T and B cells were then removed by washing the monocytes. Total T cells were separated from B cells using negative selection with magnetic beads coated with anti-CD19 Ab (Dynal AS, Oslo, Norway).

Cell cultures

To evaluate the effect of serum on IL-19 expression, we cultured monocytes from peripheral blood (5 × 10⁶ cells/ml in 6 cm plates) in RPMI serum-free medium containing 10% serum from uraemic patients or from healthy controls for 6h. Plates were incubated at 37°C with 5% CO₂. The effect of oxidized low-density lipoprotein (OxLDL) on IL-19 expression was also analysed by incubating monocytes with OxLDL (1, 20 and 100 µg/ml), a gift from Prof. Jen (Department of Physiology, National Cheng Kung University), or LPS (10 ng/ml) for 6h. Total RNA was extracted and analysed using RT–PCR.

To determine the effect of IL-19 on Th2 cytokine responses, T cells (5 × 10⁶ cells/ml in 6 cm plates) were co-cultured with IL-19 (400 ng/ml) in RPMI medium containing 10% fetal bovine serum. After 8h of incubation, total RNA was extracted and analysed using RT–PCR. The supernatants in another culture were collected at 24, 48 and 72h after incubation for cytokine measurement using ELISA.

Reverse transcriptase–polymerase chain reaction (RT–PCR)

The total RNA of monocytes was extracted using an isolaion reagent (RNA-Bee; Tel-Test Inc., Friendswood, TX, USA). The synthesis of oligo(dT)21-primed first-strand cDNA was reverse transcribed in a total volume of 20 µl (Becton, Dickenson Biosciences, Palo Alto, CA, USA). Transcripts of IL-19 in monocytes and transcripts of IL-4 and IL-13 in T cells were amplified using RT–PCR. The sense (5’-gtc gac ccg agg acc tgg tcc-3’) and antisense (5’-tcg ctt gtc gtt tgc ttc cca-3’) primers were used for IL-19. The sense (5’-act gtt ccc ctc tct ggg tgt gtc tgg ttt ggt cca-3’) and antisense (5’-cgg gtt gtt ggt ggt gct cca-3’) primers were used for IL-4. The sense (5’-gcg tct gtt tgg ctc tca gga ccc tga ccc-3’) and antisense (5’-agc acct gct ggt tgg gga cca-3’) primers were used for IL-13.

PCR was performed for 30 cycles (20 sec at 94°C, 20 sec at 60°C and 20 sec at 72°C). PCR products were visualized on 1.5% agarose gels containing ethidium bromide. The relative

lipopolysaccharide (LPS) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [14] and has been induced in acute systemic inflammation, for example, after cardiac surgery using a cardiopulmonary bypass (CPB) [20]. Furthermore, IL-19 dose-dependently up-regulated IL-4 and down-regulated interferon (IFN)γ [21], which suggested that IL-19 altered the balance of Th1 and Th2 cells in favour of Th2 cells.

Uraemic patients are thought to be in a chronic state of inflammation [22]. Other studies [23,24] found that the proinflammatory cytokines, such as IL-6, TNF-α and IL-1β, in monocytes were produced in greater amounts in patients undergoing HD. Changes in serum levels of IL-19 in uraemia have not, however, been reported. We wanted to test our hypothesis that expression of IL-19 might be involved in Th2 cytokine responses in uraemia. We, therefore, assessed the changes in serum levels of IL-19 and their correlation with Th2 cytokine production in uraemic patients on HD.
quantity of PCR products was analysed using the Bio-Profil program (Vilbert Lourmat, Torcy, France).

**Expression and purification of IL-19 recombinant protein**

A cDNA clone coded for the human IL-19 sequence from leucine to leucine (aa 25–176) was inserted into the expression vector of *Pichia pastoris* (pPICZ-a; Invitrogen, San Diego, CA, USA). IL-19 was expressed and purified from the culture medium of the yeast cells using affinity chromatography. This protein was used in biological function analysis in vitro and for the generation of polyclonal and monoclonal antibodies as previously described [19].

**Cytokine measurements**

ELISA kits (R&D Systems, Minneapolis, MN, USA) were used to analyse levels of IL-4, -5, -6, -10, -13 and TNF-α in serum. Concentrations of IL-19 were determined using ELISA with pairs of specific monoclonal or polyclonal antibodies as previously described [19,25]. Results are expressed as the means of duplicate assays.

**Statistical analysis**

Statistical analysis was performed with GraphPad prism 4.0 (GraphPad Software Inc, San Diego, CA) and SigmaPlot 9.0 (Systat Software Inc., Richmond, CA, USA). Data are mean ± SD or median with the corresponding intra-quartile ranges as indicated. Student’s unpaired t-test or the Mann–Whitney U-test was used, where appropriate, to compare data. Coefficients of correlation between the production of cytokines were calculated using the Spearman correlation analysis. The Kruskal-Wallis test and then Dunn’s test was used to compare the differences in cytokine levels between groups of patients. Statistical significance was set at *P* < 0.05.

**Results**

**IL-19 was up-regulated in uraemia patients on HD**

In order to determine the inflammatory status of the uraemia patients, we collected serum from 73 uraemia patients and 33 healthy controls. Serum levels of CRP, TNF-α and IL-6 in patients were significantly higher than in healthy controls (Table 2). Our previous study [18,20] showed that IL-19 was induced and correlated with IL-6 and TNF-α production in acute inflammation, IL-19 also induced monocytes to produce IL-6 and TNF-α. Therefore, we wanted to analyse the changes of IL-19 in uraemic patients. IL-19 levels in patients were statistically higher than in healthy controls (*P* < 0.05). The range of the serum levels of IL-19 in uraemic patients was wide (Figure 1). The levels of IL-19 did not correlate with clinical characteristics such as age, gender, duration of HD, or levels of CRP and WBC (data not shown). To determine acute dialysis effect on changes of IL-19, we tested and compared the serum levels of IL-19 in blood samples drawn immediately before (349 ± 339 ng/ml) and after (338 ± 311 ng/ml) HD and did not find significant difference.

**Serum levels of IL-19 correlated with expression levels of IL-6 and TNF-α**

To assess the relation of up-regulated IL-19, IL-6 and TNF-α, we analysed the correlation between their expression levels. IL-19 serum level was positively correlated with IL-6 (correlation coefficient $r = 0.619$, *P* < 0.001) and TNF-α ($r = 0.776$, *P* < 0.001) in uraemia patients (Figure 2) but not in healthy controls (data not shown).

![Fig. 1. The IL-19 levels in the serum of 73 uraemic patients and 33 healthy controls were analysed using ELISA. There were significant differences between the uraemic patients and healthy controls (*P* < 0.05, Mann–Whitney U-test). The median value is shown as a horizontal line within the box. The median levels of IL-19 were 271 ng/ml (25th–75th percentile value, 94–619 ng/ml) in uraemic patients and 176 ng/ml (25th–75th percentile value, 68–271 ng/ml) in healthy controls.](image-url)
Serum levels of the Th2 cytokines IL-4, -5, -10 and -13 increased in uraemic patients

The Th cell function is polarized toward the Th2 phenotype in uraemic patients [8]. To determine whether circulating Th2 cytokines also increased in HD patients, we examined the serum levels of IL-4, -5, -10 and -13 using ELISA. We found that all four cytokines were significantly higher in uraemic patients than in healthy controls (Table 3).

IL-19 levels correlated with IL-4, -5, -10 and -13 levels

IL-19 and Th2 cytokines were statistically higher in our patients than in healthy controls (Figure 1 and Table 3). It has been reported that IL-19 could induce Th2 cytokines in vitro and in vivo [19,21]. To determine whether IL-19 expression was correlated with Th2 cytokine expression in uraemic patients, we analysed the correlation between the expression levels of IL-19 and IL-4, -5, -10 and -13. Up-regulated IL-19 was positively correlated with IL-4 (ρ = 0.775, P < 0.001), IL-5 (ρ = 0.523, P < 0.001), IL-10 (ρ = 0.678, P < 0.001) and IL-13 (ρ = 0.743, P < 0.001) (Figure 3). Furthermore, we grouped our patients into three categories according to serum levels of IL-19: low-IL-19-expressing patients (low IL-19: <50 ng/ml, n = 16); moderate-IL-19-expressing patients (moderate IL-19: 50–500 ng/ml, n = 34); high-IL-19-expressing patients (high IL-19: >500 ng/ml, n = 23) and compared the difference of Th2 cytokine expression between groups of patients. We found that the serum levels of IL-4, -5, -10 and -13 were significantly different between groups of patients and correlated with IL-19 expression. However, there was no difference in CRP levels between groups of patients (data not shown).

Expression of IL-19 in monocytes correlated with serum IL-19 levels in uraemia patients

Monocytes were one of the major sources of circulating IL-19 [14,20]. To test whether the IL-19 expression of monocytes from uraemic patients correlated with their circulating level of IL-19, we collected an identical number of monocytes from patients with the lowest IL-19 level (15 ± 12 ng/ml, n = 6) and highest IL-19 level (2154 ± 433 ng/ml, n = 6) and analysed IL-19 transcripts by RT–PCR. IL-19 transcripts in monocytes from the latter patients were three times higher than those in the former patients (Figure 4). After the monocytes had been cultured in vitro for 24 h, the supernatants were collected and IL-19 protein levels were analysed using ELISA. Monocytes from the six high-IL-19-expressing patients secreted more IL-19 protein than did those from the six low-IL-19-expressing patients (132.5 ± 58.4 vs 46.6 ± 23.8 ng/ml; P < 0.05). These data indicated that monocytes were one of the sources of IL-19 and that they correlated with serum IL-19 levels in uraemic patients.

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**Table 3. Serum levels of Th2 cytokines in uraemic patients and healthy individuals**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Uraemic patients (n = 73)</th>
<th>Healthy individuals (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4 (pg/ml)</td>
<td>638 (161, 3180)*</td>
<td>190 (171, 275)</td>
</tr>
<tr>
<td>IL-5 (pg/ml)</td>
<td>23 (15, 57)*</td>
<td>13 (11, 23)</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>147 (7, 475)*</td>
<td>58 (0, 252)</td>
</tr>
<tr>
<td>IL-13 (pg/ml)</td>
<td>1323 (278, 3561)*</td>
<td>122 (61, 216)</td>
</tr>
</tbody>
</table>

Data are medians (q1, q3). *P < 0.05, Mann–Whitney U-test.

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**Fig. 2.** The serum level of IL-19 was positively correlated with IL-6 (A) and TNF-α (B) in uraemic patients (n = 73). The correlation coefficient was estimated using the Spearman rank order correlation method.
Serum from uraemic patients up-regulated IL-19 transcripts of healthy monocytes in vitro

The serum levels of IL-19 in uraemic patients correlated with proinflammatory cytokines. The upstream inducers trigger IL-19 expression in monocytes which could be the elevated levels of cytokines (TNF-α, IL-6 and IL-10) or other unidentified factors in serum of uraemic patients. If so, serum from uraemic patients may induce IL-19 expression in healthy monocytes. To test this possibility, we analysed the effect of uraemic serum on IL-19 transcripts in resting monocytes in vitro. Healthy peripheral monocytes were cultured with serum isolated from uraemic patients (uraemic serum, n = 6) or from healthy controls (control serum, n = 6). We found that uraemic serum, but not control serum, up-regulated the IL-19 transcripts in monocytes (Figure 5). This result suggests the serum factors may contribute to the up-regulation of IL-19 in uraemic patients.

OxLDL induced monocytes to express IL-19

OxLDL is one of the uraemic toxins that causes endothelial dysfunction and contribute to atherosclerosis in uraemic patients [26,27]. To examine whether OxLDL also stimulated IL-19 expression, we used RT-PCR to determine the transcript of IL-19 in OxLDL-treated resting human monocytes from healthy controls (n = 6). We found that OxLDL, but not native LDL, induced IL-19 expression in human peripheral monocytes (Figure 6). This result suggested that OxLDL was one factor contributing to the induction of serum IL-19 in uraemic patients.
IL-19 expression in uraemic patients

**Discussion**

Uraemic patients are thought to be in a chronic state of inflammation. The consequence of chronic inflammation in uraemia may involve malnutrition, anaemia and cardiovascular complications [22]. Similar to patients in other studies [22,24], the HD patients in this study were in a chronic systemic inflammatory state with elevated CRP and increased IL-6, IL-10 and TNF-α production. We found that IL-19 was differentially expressed in uraemic patients, but statistically higher than healthy controls. In addition, the expression pattern of IL-19 in uraemia positively correlated with other proinflammatory cytokine production, which appears to be a novel finding.

Recently, we reported [20] that IL-19 was induced in surgery using a CPB and concomitant with induction of IL-6 and TNF-α. However, HD also involves contact between the blood and the artificial surfaces of the extracorporeal circuit, complement activation [29] and LPS fragments and cytokine-inducing substances from the dialysate [30]; these cause an aberrant expression of cytokines [24,31]. While cytokine levels were generally elevated in most post-CPB patients, they were unevenly expressed in uraemic patients on HD. Moreover, the serum levels of IL-19 before and after HD did not show significant difference in this study. These data indicate that HD might affect chronic rather than acute induction of IL-19. Although our study did not include data from patients in chronic renal failure without HD treatment, we found that OxLDL, one of the uraemic toxins, could induce IL-19 production in vitro. Thus, we believe that uraemic toxin, HD-related chronic inflammation and pro-inflammatory cytokines all contribute to the production of IL-19.

Many patients in the present study expressed high levels of circulating IL-19 and Th2 cytokines, while some of them expressed low levels of circulating IL-19 and Th2 cytokines. Notably, low IL-19-group patients also had increased CRP levels; same levels as the other two groups. One possible reason for this is that most uraemic patients develop an immunodeficiency with diminished cellular immune activation and impaired cytokine response after stimulation [8,24]. However, the cause of the varied pattern of cytokine production in uraemic patients awaits further investigation.

In the present study, IL-19 transcripts in monocytes were also up-regulated and correlated with serum levels of IL-19 in HD patients, indicating that monocytes are one of the important sources of IL-19. In addition, in vitro cultures of monocytes from high-IL-19-group patients produced more IL-19 protein in supernatants. It is interesting that the in vitro culture of monocytes...
from the six lowest IL-19-expressing patients, whose serum IL-19 levels were undetectable or extremely low, produced one-third as much IL-19 as produced by monocytes from the six highest IL-19-expressing patients. We speculate that the in vivo condition of the uraemic state of low-IL-19-expressing patients may inhibit IL-19 production from monocytes.

On the other hand, IL-19 transcripts were up-regulated in resting monocytes incubated with uraemic serum (Figure 5). Some stimuli molecules may be present in the uraemic serum. The stimuli involved in the induction of IL-19 could be circulating TNF-α, IL-6 or LPS. There is a bi-directional stimulatory effect between IL-19 and either IL-6 or TNF-α in monocytes [20]. We speculate that cytokine interactions are important for up-regulating the induction of IL-19 in uraemic patients on HD.

Additionally, OxLDL might also be a factor involved in the up-regulation of IL-19 in monocytes. Prolonged dialysis results in elevated oxidative stress, which causes a decrease in vitamin E concentration in LDL and increases their susceptibility to oxidation in uraemic patients [26,27]. Our previous results also demonstrated IL-19 induced reactive oxygen species (ROS) production in monocytes [18]. ROS production might contribute to the elevation of oxidative stress and the oxidation of LDL. OxLDL but not native LDL induced IL-19 expression. Therefore, if uraemic patients have an increased OxLDL level, there may be an amplification loop which contributes to the expression of IL-19 and further oxidative stress in the uraemic patients. Because OxLDL causes endothelial dysfunction and contributes to atherosclerosis in uraemic patients, it is worthwhile to further investigate
the significance of OxLDL and IL-19 levels for the cardiovascular prognosis of uraemic patients.

In uraemic patients, the immune-response defect correlates with the altered activation of T cells [4,5] associated with a dysregulation of cytokine production. Recently, several studies [7–10] reported a change in the profile of Th1/Th2 lymphocytes in uraemic patients. The principal immunological defects of uraemic patients consist of impairment of cell-mediated immunity and phagocytic activity, functions sustained by Th1 cells and opposed by Th2 cells [32,33]. In addition, IL-4 and IL-10 possess direct anti-inflammatory properties, down-regulate LPS-induced inflammatory cytokine production by macrophage, inhibit macrophage cytotoxic activity and block rescue of monocytes from apoptosis [34–37]. In the present study, the up-regulated Th2 cytokines also positively correlated with IL-19 expression in uraemia. The function of IL-19 in Th2 cytokine production has been reported [19,21,28]. In a murine asthma model, IL-19 induced activated CD4+ T cells to produce IL-13 [19]. Exposing T cells to IL-19 down-regulated IFN-γ but up-regulated IL-4 and -13 and supported the polarization of naive T cells to Th2-like cells [28]. In the present study, IL-19 induced IL-4 and IL-13 expression in T cells in vitro, which is consistent with a previous report [28]. IL-19 also induced IL-5 and IL-10 with expression patterns similar to those of IL-4 and IL-13 (data not shown). Moreover, compared with control T cells, uraemic T cells expressed more endogenous Th2 cytokine transcripts. These findings indicate that IL-19 was up-regulated in vivo and primed T cells in HD patients, and IL-19 could further induce Th2 cytokine production in vitro. Thus, we hypothesize that uraemic patients on HD are in a chronic state of inflammation and that their production of pro-inflammatory cytokines increases, which further induces monocytes to produce IL-19. Consequently, up-regulated IL-19 contributes to the Th2 cytokine response in these patients.

In summary, expression of IL-19 correlates with proinflammatory cytokines and Th2 cytokine production in uraemic patients on HD. Monocytes are one of the sources of IL-19 production. Uraemic serum or OxLDL up-regulated IL-19 expression in resting monocytes. These results indicated that IL-19 expression might be involved in cytokine dysregulation in uraemia.

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Conflict of interest statement. None declared.

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