Circulating MCP-1 level and 2518 gene polymorphism as a marker of nephropathy development in Egyptian patients

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Abstract

Objective
Monocyte chemoattractant protein-1 (MCP-1) is a member of CC chemokine that plays an important role in the recruitment of monocytes/macrophages into renal tubulointerstitium. A biallelic A/G polymorphism at position 2518 in the MCP-1 gene was found to regulate MCP-1 expression. MCP-1 and its A/G gene polymorphism have been implicated in the pathogenesis of some renal diseases. The aim of this study was to evaluate the role of circulating MCP-1 level and the relevance of functional genetic variations of MCP-1 as early predictors of the development of glomerulonephropathy (GN) in Egyptian patients.

Methods
This is a case control study that was conducted in 50 GN patients, 20 non-GN cases and 20 ethnically matched healthy controls. MCP-1 serum level was detected by ELISA technique, while genotyping of polymorphisms in the MCP-1 genes was performed using a polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) detection.

Results
High MCP-1 circulating levels and subsequently MCP-1 2518G polymorphism are associated with the developing of nephropathy irrespective to the underlying etiology. MCP-1 serum level was significantly high when compared with healthy controls (P = 0.0007) and non-GN cases (P = 0.01). There was predominance of A allele at 2518 of MCP-1 gene in healthy controls (87.5%) and non-GN cases (77.5%). The frequency of the 2518G MCP-1 polymorphism was significantly higher in GN patients than in healthy controls (P < 0.0001; OR = 15.6) and non-GN cases (P < 0.0001; OR = 7.7). Interestingly, homozygosity for G allele plays the main role in such association.

Conclusion
A/G polymorphism in MCP-1 gene and subsequently high circulating MCP-1 level confer a relevant role in the susceptibility to the development of nephropathy in the Egyptian population denoting that MCP-1 system could be an early predictor of such renal complication.

Abbreviations
GN, glomerulonephropathy; DM, diabetes mellitus; LN, lupus nephritis; MCP-1, monocyte chemoattractant protein-1; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism
1. Introduction

Chemokines form a superfamily of small, inducible and secreted chemoattractant cytokines that play a crucial role in inflammation, infection and immunity [1]. Monocyte chemoattractant protein-1 (MCP-1) is secreted by a variety of cells as a response to several proinflammatory stimuli [2] and [3]. MCP-1 triggers activation, chemotaxis and transendothelial migration of monocytes/macrophages to inflammatory lesions by interacting with the membrane CC chemokine receptor 2 (CCR2) in monocytes [4].

MCP-1 regulatory features are connected with the structure and composition of the promoter region of the MCP-1 gene mapped to chromosome 17q11 [5]. A biallelic A/G polymorphism located at position +2518 in the distal regulatory region regulates MCP-1 expression was detected [6]. Monocytes from individuals carrying G allele at +2518 produce more MCP-1 than monocytes from A/A homozygous subjects [7]. It was hypothesized that polymorphisms that influence the levels of chemokines might play a role in the susceptibility to different diseases such as glomerulonephritis, asthma and atherosclerosis [6], [7] and [8].

Recently, glomerulonephropathy (GN) which is the most common cause of end stage renal disease (ESRD) has been considered as an inflammatory disease in which macrophage infiltration into glomeruli is associated with the progression of glomerular injury [1] and [9]. For the macrophage infiltration MCP-1 plays a central role [10]. They could cause structural damage through the release of proteolytic enzymes and oxygen radicals and glomerular remodelling by the release of growth factors and glomerular functional alterations by cytokines [3], [11] and [12] producing local chronic inflammatory response in arterial walls, contributing to the progression of atherosclerosis, tubular atrophy and interstitial fibrosis [13] and [14].

Of notice, diagnosis of GN is based on persistent albuminuria, arterial blood pressure elevation; a relentless decline in glomerular filtration rate (GFR) which is highly variable, so, new tools are needed [15]. Although, increasingly weight of clinical evidence indicates that MCP-1 system is a key factor initiating the inflammatory process of glomerular insult [16], [17] and [18], the role of MCP-1 serum level (sMCP-1) and its gene polymorphism in the development of nephropathy has not been elucidated.

Given this background, and as early prediction of such renal disturbance could prevent the complication as well as the identification of disease promoters is important for the creation of new powerful treatment modalities impeding the development of ESRD [15], the present study aimed to measure circulating levels of sMCP-1 in patients with GN of different etiology, examines whether sMCP-1 levels were correlated with such renal dysfunction and evaluates the influence of underlying disease on MCP-1 level. Since GN represents a heterogeneous group of renal inflammatory diseases with similar features, we also evaluated the role of MCP-1 polymorphism in GN progression and whether different MCP-1 alleles are linked to specific phenotypes.

2. Subjects and methods

2.1. Study population

This case control study was carried out at Tanta University Hospital between August 2008 and February 2009 prospectively. Fifty selected patients suffering from GN, 20 normo-albuminuric patients and 20 healthy subjects with comparable age, sex and male to female ratio were enrolled. GN cases were 21 men and 29 women, aged 46.3 ± 7.4 years (range, 30–59 years). The underlying disease in this group was type 2 diabetes mellitus (DM) [19] in 21 patients (had not been previously treated with an ACEI or AT-II receptor antagonists), hypertension [20] in 16 patients and lupus nephritis in 13 cases (assessed clinically according to the renal Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [21]. Nephropathy was diagnosed clinically by the presence of persistent micro-albuminuria (albumin excretion rate [AER] 20–200 µg/min) and elevated blood pressure (systolic blood pressure >135 mmHg and/or diastolic blood pressure >85 mmHg) [17].

Normo-albuminuric patients (8 males and 12 females; mean age, 44.9 years; range 38–58 years) with AER < 20 µg/min were used as non-GN controls. They included 9 patients with type 2 DM, 6 patients with atherosclerosis and 5 patients with Systemic Lupus Erythematosus (SLE) that was defined according to the American College of Rheumatology (ACR) criteria [22]. Both GN and non-GN cases were recruited from those attending the Nephrology Unit in Internal Medicine Department for follow up. Twenty healthy blood donor volunteers (9 males and 11 females; mean age, 48.4 years; range, 40–57 years) with comparable age, sex and male to female ratio were served as a healthy control group. They had no history of hypertension, renal, cardiac or hepatic diseases. All participants gave written informed consent after approval of the ethical committee.

2.2. Methods

2.2.1. Routine laboratory investigation

Patients and control group were subjected to a thorough history taking and complete clinical examination. Blood urea nitrogen, serum creatinine, AER, fasting serum total cholesterol, serum triglycerides, high-density lipoproteins, low-density lipoproteins, and urine analysis were performed.
2.2.2. MCP-1 serum level

MCP-1 serum level was detected with ELISA technique using kit supplied by R&D systems, Minneapolis, USA according to the manufacture instructions.

2.2.3. MCP-1 genotyping

The −2518 G/A polymorphism of the MCP-1 gene was determined using PCR-RFLP technique as described previously [23].

2.2.3.1. DNA extraction and amplification

Genomic DNA was extracted from EDTA blood by standard techniques using QIA amp blood kit (Qiagen, Germany) according to the manufacturer’s instruction. Amplification was carried out in 50 μl volume containing 300 ng genomic DNA, 0.1 μM of each primer (forward 5' - TCT CTC ACG CCA GC ACT GAC C-3' and reverse 5'-GAG TGT TCA CAT AGG CTG CTG-3'), 200 μM of each dNTP, 3 mM of MgCl₂ and 0.2 U of Taq Gold polymerase (Life technology, USA). Amplification was conducted in Biometra, USA, thermal cycler under the following conditions: one cycle of initial denaturation at 94 °C for 4 min followed by 30 cycles of denaturation at 94 °C for 45 s, annealing at 61 °C for 45 s, extension at 72 °C for 45 s then a final extension cycle at 72 °C for 7 min.

2.2.3.2. MCP-1 gene polymorphism

The amplified PCR products were digested with the addition of 2 U PvuII restrictive enzyme (New England BioLab, Beverly, MA, USA) overnight at 37 °C. The digested products were separated by electrophoresis through 3% agarose gel stained with ethidium bromide. Upon digestion with Pvu II of the amplified DNA product (size 234 bp), two fragments of 159 and 75 bp were produced when the polymorphic site was present (G at position −2518) (Fig. 1).

![Figure 1. Agarose gel electrophoresis for RFLP-PCR product of MCP-1 gene, stained with ethidium bromide. M represents DNA marker. Lanes 2 and 5 represent homozygote A/A with single 234 bp band. Lanes 3, 6 and 7 represent heterozygote A/G with 234, 159 and 75 bp bands. Lanes 1 and 4 represent homozygote G/G with 159 and 75 bp bands.](image)

2.3. Statistical analysis

The statistical software package SPSS 15 was used for statistical calculations. Data are presented as mean ± SD for continuous variables and as proportions for categorical variables. Comparisons of means between 2 groups were analyzed by using the Student unpaired T-test while comparisons of means among 3 groups were performed using one-way ANOVA test. The allele and genotype frequencies among cases and controls were compared by Fisher exact test and odds ratio with 95% CI. Two-tailed P-value of < 0.05 was considered significant. Pearson’s correlation coefficient was used to detect the relationship between sMCP-1 level and AER.

3. Results

3.1. Basic characteristics of the study population

Table 1 and Table 2 summarize the basic characteristics of the study population. There was a significant increase in mean values of systolic and diastolic blood pressure, TG, TC, LDL-C, serum creatinine, and AER as well as a significant decrease in mean values of HDL-C and C clearance in GN patients compared with control and normo-albuminuric groups. These changes were related to the severity of their disease. Of notice, there were no differences between subgroups of GN in any of the previous parameters.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age (year)</th>
<th>M:F</th>
<th>Duration (years)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>20</td>
<td>48.4 ± 5.4</td>
<td>9:11</td>
<td>–</td>
<td>117 ± 4</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>Non-GN group</td>
<td>20</td>
<td>44.9 ± 9.1</td>
<td>8:12</td>
<td>14.6 ± 2.8</td>
<td>134 ± 3</td>
<td>84 ± 2</td>
</tr>
</tbody>
</table>

Table 1. Clinical characteristics of patients and control groups.
3.2. MCP-1 serum level in cases and controls

Circulating MCP-1 level increased in accordance with the developing of nephropathy. The mean sMCP-1 concentration was significantly different \((P = 0.001)\) among the studied groups. Inter group analysis revealed that 30\% \((P = 0.0007)\) and 20\% \((P = 0.01)\) increase in sMCP-1 levels in patients with GN (65.8 pg/ml) compared with either of the control and normo-albuminuric groups (50.5 pg/ml and 54.4 pg/ml), respectively. In contrast, no significant difference has been observed in sMCP-1 values between normo-albuminuric and the control groups (Table 3) as well as there was no significant difference between GN subgroups \((P > 0.05)\) (Table 4).
Interestingly, levels of sMCP-1 tended to be positively correlated ($r = 0.87, P < 0.001$) with AER in GN group (Fig. 2). On the other hand, although a tendency of positive correlation between sMCP-1 and TG was found, a negative correlation between sMCP-1 and HDL-C also existed, in both cases the correlation did not achieve statistical significance. Meanwhile, we did not find correlation between sMCP-1 and age, duration of the disease, TG, TC, DBP and SPB (data not shown).

![Correlation between sMCP-1 level and AER in 50 GN cases. Significant positive correlation was detected.](image)

3.3. Polymorphism frequency distribution between the case and the control groups

The distribution of wild (AA) and mutant (AG/GG) genotypes was 80% and 20% in control group with low frequency of GG genotype (5%) and G allele (12.5%). We found nearly similar distribution in genotype and allele frequencies in normo-albuminuric cases. The exact test of population distribution indicated that the distributions of MCP-1G allele frequencies were significantly higher in GN-patients (69%) compared to both control subjects (12.5%, $P < 0.0001$, OR = 15.6) and normo-albuminuric cases (22.5%, $P < 0.0001$, OR = 7.7) (Table 5).

<table>
<thead>
<tr>
<th>Subject groups</th>
<th>Genotypes frequency</th>
<th>Alleles frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild</td>
<td>Mutant</td>
</tr>
<tr>
<td>Controls ($n = 20$)</td>
<td>A A</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Non-GN cases ($n = 20$) (vs. controls)</td>
<td>n (%)</td>
<td>13 (65)$^a$</td>
</tr>
<tr>
<td>GN cases ($n = 50$) (vs. controls)</td>
<td>n (%)</td>
<td>10 (20)$^b$</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.1 (0.02–0.2)</td>
<td>1.6 (0.4–6.5)</td>
</tr>
<tr>
<td>GN cases ($n = 50$) (vs. non-GN)</td>
<td>n (%)</td>
<td>10 (20)$^c$</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.1 (0.04–0.4)</td>
<td>0.8 (0.3–2.9)</td>
</tr>
</tbody>
</table>

Non-GN: non-glomerulonephropathy; GN: glomerulonephropathy. OR: Odds ratio. 95% CI: 95% confidence interval.

$^a$ Non-GN cases vs. controls by Fisher exact test, $P > 0.05$ (non significant).

$^b$ GN cases vs. controls by Fisher exact test, $P < 0.0001$ (highly significant).
The genotype frequency showed significant increase in mutant genotypes (80% vs. 20%, $P < 0.0001$, OR = 16) with the predominance of homozygote mutant (GG) genotype (58% vs. 5%, $P < 0.0001$, OR = 26.2) in GN patients group compared with healthy controls. Similarly, there is significant increase in mutant genotypes (80% vs. 35%, $P = 0.0006$, OR = 7.4) with the predominance of homozygote mutant (GG) genotype (58% vs. 10%, $P = 0.0004$, OR = 12.4) in GN group compared to normo-albuminuric group. Moreover, the higher OR in homozygotes (26.2) than in heterozygotes (1.6) in comparing GN cases with other two groups suggests a dominant mode of action of the homozygote MCP-1 -2518 polymorphism in the development of GN (Table 5).

By analyzing the link of different MCP-1 alleles and genotypes to specific disease background, no significant difference in the allele or genotype frequencies between different causes of GN with $P$ values of >0.05 was found (Table 6).

### Table 6. Distribution of -2518 A/G genotype and allele frequency of MCP-1 gene in diseased groups.

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 21)</th>
<th>HT (n = 16)</th>
<th>LN (n = 13)</th>
<th>$P$-value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>4</td>
<td>19</td>
<td>3</td>
<td>18.8</td>
</tr>
<tr>
<td>AG</td>
<td>4</td>
<td>19</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>GG</td>
<td>13</td>
<td>62</td>
<td>9</td>
<td>56.2</td>
</tr>
<tr>
<td><strong>Allele</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12</td>
<td>28.6</td>
<td>10</td>
<td>31.2</td>
</tr>
<tr>
<td>G</td>
<td>30</td>
<td>71.4</td>
<td>22</td>
<td>68.8</td>
</tr>
</tbody>
</table>

DM: diabetes mellitus; HT: hypertension; LN: lupus nephritis; AA: wild genotype; AG and GG: mutant genotype.

$^a$ By using Fisher-exact test.

### Table 7. Serum level of MCP-1 in different genotypes in the studied groups.

<table>
<thead>
<tr>
<th>Studied groups</th>
<th>MCP-1 (g/ml) in different genotypes</th>
<th>$T$-test</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>AG/GG</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Range</td>
<td>30–55</td>
<td>41–90</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>45.3 ± 6.8</td>
<td>56.4 ± 9.1</td>
</tr>
<tr>
<td>Non-GN group</td>
<td>Range</td>
<td>34–60</td>
<td>46–102</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>47.6 ± 8.2</td>
<td>62.3 ± 13.2$^*$</td>
</tr>
<tr>
<td>GN group</td>
<td>Range</td>
<td>43–69</td>
<td>55–120</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>51.8 ± 8.5</td>
<td>84.6 ± 11.5$^*$</td>
</tr>
<tr>
<td></td>
<td>$F$</td>
<td>2.179</td>
<td>19.508</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>0.128</td>
<td>&lt;0.0001$^*$</td>
</tr>
</tbody>
</table>

Non-GN: non-glomerulonephropathy; GN: glomerulonephropathy; AA: wild genotype; AG/GG: mutant genotype.
4. Discussion

In this study we demonstrated that up-regulation of sMCP-1 is probably involved in the development of GN. This concept is based on: (1) sMCP-1 levels were significantly elevated in GN patients compared to the healthy controls, and normo-albuminuric cases, (2) MCP-1 serum level was nearly similar within GN subgroups and (3) significant positive correlation was detected between GN group and AER. Thus, we suggest that this marker reflects the progression of albuminuria in nephropathy and could be a predictor of the development of GN irrespective of the underlying etiology.

The role of circulating MCP-1 in renal damage in different glomerular diseases, such as DM [13], SLE [7], IgA nephropathy [24] and polycystic kidney [25] has been intensively investigated. Although many studies have focused on the association between circulating or urinary MCP-1 level and such renal disorders, only few of them were concerned with its role in nephropathy which seems to be controversial. Of these, Chiarelli et al. [26] highlighted a possible role of circulating MCP-1 in the development of early nephropathy in patients with type 1 diabetes. A result that was further supported by Takebayashi et al. [13] who suggested that serum MCP-1 correlates not only with macroalbuminuria, but also with UAE in their type 2 diabetic patients. This is explained by the pivotal role played by increased MCP-1 production due to stimulation by cytokines [27] and exposure to urinary proteins [28] in the progressive tubulointerstitial damage which is thought to be the common pathological finding resulting in ESRD in spite of causes of renal damages [29].

On the other hand, Kiyici et al. [3] demonstrated that serum MCP-1 levels were significantly increased in type 1 diabetic patients but not correlated with development of nephropathy. Ihm et al. [30] reported that peripheral blood mononuclear cells produced more MCP-1 in patients with or without diabetic nephropathy than cells from controls. This result was explained by Ha et al. [31] who verify that high glucose-induced generation of reactive oxygen species (ROS) and protein kinase C (PKC) activation seem to be involved in NF-aB activation and subsequently influence serum MCP-1 concentration.

Banba et al. [32] and Wada et al. [33] noticed that urine levels, but not serum levels, of MCP-1 increased in accordance with the extent of albuminuria in their studies on type 1 and 2 diabetic patients. Morii et al. [17] added that urine levels, but not serum levels, of MCP-1 correlates with the development of diabetic nephropathy. Interestingly, Qiu-yue and Fen-qin concluded that both serum and local MCP-1 had an impact on kidney affection a superior role of urinary MCP-1 as early predictor before appearance of proteinuria [1].

MCP-1 activates tubular epithelial cells leading to increase in secretion of the proinflammatory cytokine interleukin-6 (IL-6) and expression of intracellular adhesion molecule -1 (ICAM-1) via Gi-protein, protein kinase C (PKC) and intracellular Ca\textsuperscript{2+} dependent mechanisms. MCP-1 activated: (i) the transcription factor nuclear factor-xB (NF-xB), a transcription factor involved in inflammatory and immune responses and (ii) activating protein-1 (AP-1) a transcription factor involved in inflammatory and growth responses. Both NF-xB

Table 8. Serum level of MCP-1 in different genotypes break down by GN etiology.

<table>
<thead>
<tr>
<th>GN group</th>
<th>MCP-1 (pg/ml) in different genotypes</th>
<th>T-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>AG/GG</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>Range 46–58</td>
<td>61–115</td>
<td>5.679</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 51.7 ± 5.9</td>
<td>87.8 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>Range 45–59</td>
<td>65–120</td>
<td>4.626</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 51.2 ± 6.1</td>
<td>89.4 ± 13.7</td>
<td></td>
</tr>
<tr>
<td>LN</td>
<td>Range 43–55</td>
<td>63–110</td>
<td>5.501</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 49.3 ± 6.5</td>
<td>88.6 ± 11.6</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.139</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.873</td>
<td>0.942</td>
<td></td>
</tr>
</tbody>
</table>
| DM: diabetes mellitus; HT: hypertension; LN: lupus nephritis.
and AP-1 were involved in the MCP-1 mediated induction of IL-6 [34].
Another finding in this work was that G allele frequency was significantly higher in GN group than other two groups. This is in agreement with the study done by Ye DQ et al. [35] and Moon et al. [36] who found that the 2518 G frequency is obviously over-represented in Asian, Mexican, Korean and Chinese populations, reflecting variations between different ethnic populations which probably has an impact on disease processes, or a patient’s response to infections or drugs.

Finally, our results demonstrated that patient’s carriers for the G allele especially the homozygotes were at increased risk for GN with positive association between MCP-1 mutant genotype and G allele and high serum MCP-1 level irrespective of the underlying cause. These results suggest that G allele carriage is responsible for increased production of serum MCP-1 in our GN patients and predisposes to the development of nephropathy rather than the occurrence of the disease itself.

Human MCP-1 gene transcription appears to be under the control of 2 distinct areas of the 5′-flanking region of the gene. The distal regulatory region is located 1.8 through 2.7 kb upstream of the transcriptional start site. This segment contains 2 nuclear factor-κB binding motifs essential for cytokine induction of MCP-1 expression. The 2518 A to G polymorphism might affect the transcriptional activity of this region and is correlated with individual differences in monocyte MCP-1 production [37] and [38].

Rovin et al. [37] suggested that the 2518 G allele produced more MCP-1 in interleukin-1-stimulated peripheral blood mononuclear cells, the effect of A/G MCP-1 gene polymorphism on MCP-1 production is controversial. Simeoni et al. [38] showed that the presence of the 2518 G allele was associated with decreased plasma MCP-1, decreased prevalence of insulin resistance, and decreased risk of DM. Although, Kouyama et al. failed to detect an association between MCP-1A/G polymorphism and type 2 diabetes, they noticed that the 2518 AA genotype was associated with higher serum MCP-1 concentration [39]. Kim et al. [40] also reported that urinary excretion of MCP-1 was greater in AA homozygotes than in other genotypes in Korean patients with lupus nephritis. Moon et al. [36] added that carriage of 2518 A allele in the MCP-1 gene was associated with the susceptibility of kidney failure in Korean patients with type 2 DM. These inconsistent results might be population-dependent and/or phenotype specific.

In conclusion, the present study implicates the role of circulatory MCP-1 and its 2518 G gene polymorphism as a predictor of the development of GN in Egyptian patients. As MCP-1 plays an important role in the stimulation of the inflammatory infiltrate, and probably, it might also have immunomodulatory effects, thus, we suggest that preventing MCP-1 secretion or inhibiting its effects might be a useful approach for the research on new therapeutic tools.

Conflicts of interest
The authors declare that there is no conflict of interest.

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